Assessment of Methodological Practices Implemented in Pfizer's COVID-19 mRNA Vaccine Trials with respect Good Clinical Practice

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Abstract:
This report evaluates the methodological practices and clinical data from the mRNA COVID-19 vaccine trials sponsored by Pfizer, focusing on Good Clinical Practice (GCP), efficacy, and safety outcomes. It has been established by examining
- the pivotal study clinical reports on adults over 16 years of age (December 2020 -interim analysis at 3 months, New England Journal of Medecine publication - six-month interim analysis, July 2023 – final analysis)
- the trial results in the adolescent population aged 12 to 15 years (April 2021),
- the trial results in children aged 5 to 11 years (October 2021)
- the trial results regarding hildren aged 6 months to less than 5 years (June 2022)
- the results on third dose or booster (September 2021)
- the results from trials on bivalent vaccines,
- the trial results involving pregnant women,
- the successive Risk Management Plans,
- the publicly released database of the pivotal trial due to a court ruling,
- the Periodic Safety Update Reports (PSURs) …

The report highlights incomplete results (efficacy on transmission, asymptomatic cases, mortality not tested and not statistically proven), multiple risks, missing information regarding both efficacy, safety and immunogenicity data (protection conferred by antibodies).
It demonstrates **multiple methodological bias and major violations to GCP** across all clinical trials that invalidate the conclusions regarding efficacy, safety, and immunogenicity.

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1 Introduction

Since December 2019, Coronavirus, Severe Acute Respiratory Syndrome (SARS-COV-2) has spread rapidly across the globe from Wuhan Province, China.

The World Health Organization (WHO) has declared a global pandemic on March 11, 2020.

Many pharmaceutical companies have been racing to find a vaccine since the publication of the SARS-COV-2 genome by China on January 12, 2020, when the complete sequence of the coronavirus genome was detected in samples taken from their first patients. On January 29, 2020, the Pasteur Institute announced the virus' genome sequencing based on material collected from two of the first three confirmed cases in France.

Source : https://www.pasteur.fr/fr/espace-presse/documents-presse/institut-pasteur-sequence-genome-complet-du-coronavirus-sars-cov-2

On March 16, 2020, the U.S. National Institute of Health began a trial of an "experimental" vaccine in collaboration with the biotechnology company Moderna Inc, with the trial involving 45 healthy adults, ages 18-55.

Source : https://fr.euronews.com/2020/06/30/coronavirus-les-dates-cles-de-la-course-au-vaccin

As of April 8, 2020, at least 115 vaccines were already in the pipeline worldwide, with 73 already in the exploratory or preclinical stage, with Inovio, Moderna, CanSino Biologicals, and the Shenzhen Genoimmune Medical Institute leading the way.

Source : https://www.nature.com/articles/d41573-020-00073-5

In May 2020, Operation Warp Speed in the United States, initially a public/private partnership initiated by the U.S. government, was transferred to the White House covid-19 response team in order to promote mass production of several vaccines and new technologies.

This has presented unique practical and ethical challenges for those working in the clinical trials industry.

This report is intended to be an objective analysis of clinical trials practices compared to those used in the COVID-19 trials and specifically in the Pfizer/BioNtech Phase 1-2-3 trial.

It does not argue about the regulatory processes of vaccine manufacturing or preclinical studies, each of which would deserve a full report.

It does not call into question the competence or the involvement of the thousands of people involved in the trials, but rather the **respect of Good Clinical Practice, an essential element in the world of the pharmaceutical industry in order** to obtain honest and reliable statistical results and to be able to evaluate the benefit/risk ratio.

2 My expertise

Christine Cotton

Founder and director of Statitec, a Contract Research Organization specialized in data management & biostatistics
Participation in Data Safety Management Boards as an expert biostatistician
Participation in international trials and FDA submissions
Expert in clinical trial methodology
Quality assurance officer at my company
Biostatistician
SAS ® programmer

Experience in all phases of clinical trials and in numerous therapeutic areas: osteoarthritis, osteoporosis, diabetes, influenza, hepatitis C, tuberculosis, ovarian cancer, colorectal cancer, breast cancer, follicular lymphoma, lymphocytic leukemia, multiple myeloma, kidney transplantation, depression, cognitive disorders, Alzheimer's disease, sinusitis, eczema, psoriasis, hemangioma, ulcerative colitis, Crohn's disease, rheumatoid arthritis, chronic bronchitis, allergies, gout, hypertension, heart failure, menopause, incontinence, benign prostatic hyperplasia, impotence, child nutrition...

Personal

Birth date : 27/April/1970

Education

1993-1997	Master degree (Magistere) of Economy and Statistics Toulouse School of Economics / University Paul Sabatier (Toulouse)
1992-1993	Bachelor of Sciences degree in econometrics Toulouse School of Economics

Language

French	Mother tongue
English	Good knowledge
Spanish	Good knowledge

Professional experience

2023	**Consultant for the pharmaceutical industry - clinical trials, observational studies:** methodology, sample size, protocol writing, statistical analyses
Since 2020	**Whistleblower** Author of an expert report on the Pfizer clinical trial for its Covid vaccine in relation to Good Clinical Practice, highlighting multiple methodological and statistical biases invalidating its efficacy and safety conclusions Author of the book "Tous vaccinés, tous protégés? Vaccins Covid-19, chronique d'une catastrophe sanitaire annoncée", with a preface by Senator Laurence Muller-Bronn, MEP Michèle Rivasi, MEP Virginie Joron and former MEP Martine Wonner.
2018-2019	**Freelance consultant for pharmaceutical industry** Protocol methodology, protocol writing, sample size, statistical analysis, Compliance to pharmaceutical industry guidelines

1995-2018	**CEO Statitec – Clinical Research Organisation** Expert in Data Safety Management Board Quality Assurance Officer • Maintenance and update of Standard Operating Procedures • Respect of standard and quality • Protocol writing, CRF writing • Scientific advice Head of biometry • Planning management • Supervision of data-managers and biostatisticians • Expertise in statistics and its applications in clinical trials • Management of observational studies • Management of ATUs/RTUs • Validation of statistical activities (programming, reports ..) Biostatistician, • Randomization's list • Sample size calculation and writing of Statistical section of protocol • Writing of Statistical Analysis Plan (SAP) • Developing of SAS ® programs • Participation in Validation Committee meeting • Statistical analysis: descriptive statistics, usual tests, variance and covariance analysis, survival analysis, multivariate models, various study designs (parallel groups, cross-over ...), genomic studies • Clinical study report written in compliance with ICH E3
1995-1996	**Laboratoire Statistiques et Probabilités/ Statistics and Probabilities Laboratory** Biostatistician for Pierre Fabre laboratory SAS ® programmer
1994-1995	Traductor English to French software manual "Data analysis with student Systat" – International Thomson Publishing France

Technical skills

Systems	Windows XP/NT, SBS 2003, SBS 2008, SBS 2011
Langages	SAS® : SAS base, macro, stat, graph ....
Hardware	PC
Softwares	Word, Excel, Powerpoint, Qualigram, NQuery, East, PASS, Capture System

Clients

Archimedes Pharma, AstraZeneca, Aventis, Bauch&Lomb, Bayer, Ceva, Danone, Debiopharm, Ferring, Forenap, Galderma, Ipsen, Janssen-Cilag, LPG System, Mayoli Spindler, Medtronic, Menarini, Merck Lipha Santé, Novagali Pharma, Novartis, Orfagen, Pherecydes Pharma Menarini, Roche, , Pierre Fabre, Sanofi, Synthélabo, Servier, Takeda, Théa, Yamanouchi, hospitals, associations...

Examples of direct Publications or publications on studies managed by Statitec

An 8-week, randomized, controlled, clinical study of the use of a 0.1% chlorhexidine mouthwash by chronic periodontitis patients
Tenenbaum H, Luc J, Schaaf JF, Federlin-Ducani M, Cotton C, Elkaim R, Cuisinier FJ, Roques C. An 8-week, randomized, controlled, clinical study of the use of a 0.1% chlorhexidine mouthwash by chronic periodontitis patients. J Investig Clin Dent. 2011 Feb;2(1):29-37. doi: 10.1111/j.2041-1626.2010.00031.x. Epub 2010 Nov 8. PMID: 25427325. https://pubmed.ncbi.nlm.nih.gov/25427325/

Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study.
Diabetes Care. 2009 Dec;32(12):2245-50. doi: 10.2337/dc09-0750. Epub 2009 Sep 18. PMID: 19767384; PMCID: PMC2782985. Raccah D, Sulmont V, Reznik Y, Guerci B, Renard E, Hanaire H, Jeandidier N, Nicolino M. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2782985/

Pomalidomide plus low-dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4;14): IFM 2010-02 trial results
Leleu X, Attal M, Arnulf B, Moreau P, Traulle C, Marit G, Mathiot C, Petillon MO, Macro M, Roussel M, Pegourie B, Kolb B, Stoppa AM, Hennache B, Bréchignac S, Meuleman N, Thielemans B, Garderet L, Royer B, Hulin C, Benboubker L, Decaux O, Escoffre-Barbe M, Michallet M, Caillot D, Fermand JP, Avet-Loiseau H, Facon T; Intergroupe Francophone du Myélome. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. Blood. 2013 Mar 14;121(11):1968-75. doi: 10.1182/blood-2012-09-452375. Epub 2013 Jan 14. PMID: 23319574. https://pubmed.ncbi.nlm.nih.gov/23319574/

Lenalidomide Maintenance after Stem Cell Transplantation for Multiple Myeloma
Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, Stoppa AM, Hulin C, Benboubker L, Garderet L, Decaux O, Leyvraz S, Vekemans MC, Voillat L, Michallet M, Pegourie B, Dumontet C, Roussel M, Leleu X, Mathiot C, Payen C, Avet-Loiseau H, Harousseau JL; IFM Investigators. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012 May 10;366(19):1782-91. doi: 10.1056/NEJMoa1114138. PMID: 22571202 https://pubmed.ncbi.nlm.nih.gov/22571202/

A prospective, international, randomized, noninferiority study comparing an implantable titanium vertebral augmentation device versus balloon kyphoplasty in the reduction of vertebral compression fractures (SAKOS study)
AM, Kaya JM, Touta A, Noriega D, Marcia S, Theumann N, Blondel B, Simon A, Hassel F, Maestretti G, Petit A, Weidle PA, Gonzalez Fuentes S, Pflugmacher R. A prospective, international, randomized, noninferiority study comparing an titanium implantable vertebral augmentation device versus balloon kyphoplasty in the reduction of vertebral compression fractures (SAKOS study). Spine J. 2020 Dec;20(12):2039-2040. doi: 10.1016/j.spinee.2020.08.021. Epub 2020 Sep 12. PMID: 32927099.
https://pubmed.ncbi.nlm.nih.gov/32927099/

Pegylated interferon-a2a plus ribavirin for chronic hepatitis C in a real-life setting: the Hepatys French cohort (2003-2007)
Bourlière M, Ouzan D, Rosenheim M, Doffoël M, Marcellin P, Pawlotsky JM, Salomon L, Fagnani F, Rouanet S, Pinta A, Vray M. Pegylated interferon-a2a plus ribavirin for chronic hepatitis C in a real-life setting: the Hepatys French cohort (2003-2007). Antivir Ther. 2012;17(1):101-10. doi: 10.3851/IMP1935. PMID: 22267474. https://pubmed.ncbi.nlm.nih.gov/22267474/

Blood memory B cells are disturbed and predict the response to rituximab in patients with rheumatoid arthritis
Sellam J, Rouanet S, Hendel-Chavez H, Abbed K, Sibilia J, Tebib J, Le Loët X, Combe B, Dougados M, Mariette X, Taoufik Y. Blood memory B cells are disturbed and predict the response to rituximab in patients with rheumatoid arthritis. Arthritis Rheum. 2011 Dec;63(12):3692-701. doi: 10.1002/art.30599. PMID: 22127692. https://pubmed.ncbi.nlm.nih.gov/22127692/

Patient satisfaction with treatment of breakthrough pain with fentanyl pectin nasal spray in cancer
Caroline Maindet, Alain Serrie, Philippe Janoray, Xavier Amores, Antoine Lemaire, Satisfaction des patients au traitement des accès douloureux paroxystiques par le fentanyl nasal pectiné dans le cancer, Douleurs : Evaluation - Diagnostic - Traitement, Volume 18, Issue 1, 2017, Pages 15-23, ISSN 1624-5687, https://doi.org/10.1016/j.douler.2017.01.005.
(https://www.sciencedirect.com/science/article/pii/S1624568717300069)

Factors predictive of medication nonadherence after renal transplantation: a French observational study
Couzi L, Moulin B, Morin MP, Albano L, Godin M, Barrou B, Alamartine E, Morelon E, Girardot-Seguin S, Mendes L, Misdrahi D, Cassuto E, Merville P. Factors predictive of medication nonadherence after renal transplantation: a French observational study. Transplantation. 2013 Jan 27;95(2):326-32. doi: 10.1097/TP.0b013e318271d7c1. PMID: 23149477. https://pubmed.ncbi.nlm.nih.gov/23149477/

Abstract P6-11-04: Capecitabine Therapy for Locally Advanced or Metastatic Breast Cancer: A Difference between Reported Clinical Trials and Routine Clinical Practice?

Results from the ELIXIR Study in Routine Oncology Practice - P Dalivoust; M Debled; B Asselain; X Pivot; L Bobadilla; A Riviere; D Gedouin; J Dauba; I Marquis; I. Ray-Coquard https://aacrjournals.org/cancerres/article/70/24_Supplement/P6-11-04/560776/Abstract-P6-11-04-Capecitabine-Therapy-for-Locally

Clinical pilot study to evaluate the efficacy of a preservative-free hypertonic ophthalmic solution for patients with symptomatic corneal edema
Clinical pilot study to evaluate the efficacy of a preservative-free hypertonic ophthalmic solution for patients with symptomatic corneal edema]. J Fr Ophtalmol. 2015 Nov;38(9):800-8. French. doi: 10.1016/j.jfo.2015.04.011. Epub 2015 Oct 9. PMID: 26443383. https://pubmed.ncbi.nlm.nih.gov/26443383/

Characteristics and management of gout patients in Europe: data from a large cohort of patients
Richette P, Flipo RN, Patrikos DK. Characteristics and management of gout patients in Europe: data from a large cohort of patients. Eur Rev Med Pharmacol Sci. 2015 Feb;19(4):630-9. PMID: 25753881. https://pubmed.ncbi.nlm.nih.gov/25753881/

Gastric emptying evaluation by ultrasound prior colonoscopy: an easy tool following bowel preparation

Coriat R, Polin V, Oudjit A, Henri F, Dhooge M, Leblanc S, Delchambre C, Esch A, Tabouret T, Barret M, Prat F, Chaussade S. Gastric emptying evaluation by ultrasound prior colonoscopy: an easy tool following bowel preparation. World J Gastroenterol. 2014 Oct 7;20(37):13591-8. doi: 10.3748/wjg.v20.i37.13591. PMID: 25309090; PMCID: PMC4188911.
https://pubmed.ncbi.nlm.nih.gov/25309090/

A Multicentre Randomised Controlled Study Evaluating the Effect of a Standardised Education Programme on Quality of Life, Disease Severity, and Disease Knowledge in Patients with Moderate-To-Severe Psoriasis: The EDUPSO Study

Jendoubi F, Balica S, Richard MA, Chiaverini C, Bernier C, Quiles N, Bachelez H, Beylot-Barry M, Mallet S, Goujon C, Parier J, Misery L, Carrere F, Lauwers-Cances V, Paul C; French Psoriasis Research Group. A Multicentre Randomised Controlled Study Evaluating the Effect of a Standardised Education Programme on Quality of Life, Disease Severity, and Disease Knowledge in Patients with Moderate-To-Severe Psoriasis: The EDUPSO Study. Dermatology. 2022;238(4):630-639. doi: 10.1159/000520289. Epub 2021 Dec 9. PMID: 34883480.
https://pubmed.ncbi.nlm.nih.gov/34883480/

Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial

Jault P, Leclerc T, Jennes S, Pirnay JP, Que YA, Resch G, Rousseau AF, Ravat F, Carsin H, Le Floch R, Schaal JV, Soler C, Fevre C, Arnaud I, Bretaudeau L, Gabard J. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. Lancet Infect Dis. 2019 Jan;19(1):35-45. doi: 10.1016/S1473-3099(18)30482-1. Epub 2018 Oct 3. PMID: 30292481. https://pubmed.ncbi.nlm.nih.gov/30292481/

Management of the European clinical trial Phagoburn, the first clinical trial in the world on phagotherapy (use of bacteria-eating viruses), Pherecydes Pharma, subsidized to the tune of 5 million euros

Temporary Authorization for use (ATU) or Temporary Recommendations for Use (RTU)

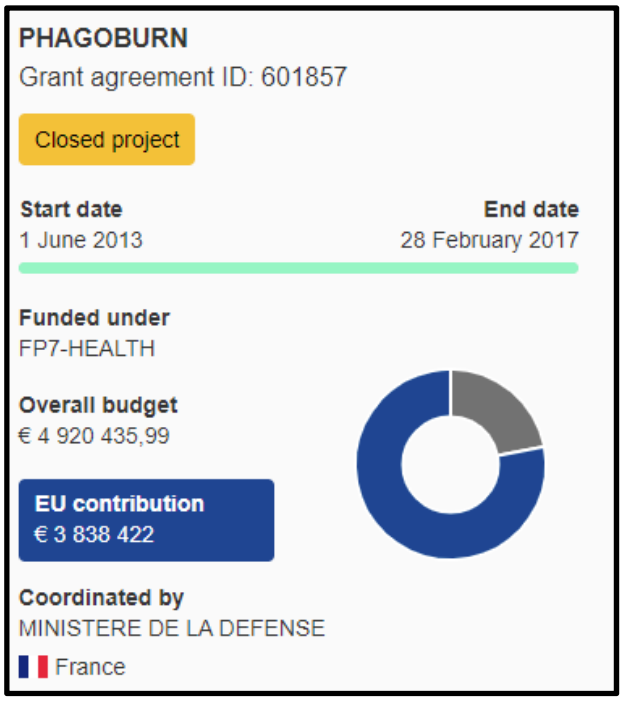
Management and statistical analysis of data for several ATUs and RTUs.

Relapsed or refractory mantle cell lymphoma or chronic lymphocytic leukaemia, metastatic prostate cancer, chronic hepatitis C genotype 1, VIH, multidrug-resistant pulmonary tuberculosis, Non-IgM AL amyloidosis and Randall's disease, Active ulcerative colitis, Crohn's disease, proliferative infantile haemangiomas.

Last study managed

PHAGOBURN, a project conducted from 2013 to 2017 and funded by the European Commission with 4.9 million euros. It is the first study in the world to have rigorously evaluated, compared to a reference treatment, the efficacy of bacteriophages produced according to pharmaceutical standards to treat bacterial infections. The patients were hospitalized in 11 burn centers in France, Belgium and Switzerland and were suffering from burns (due to P. aeruginosa). The Percy BTC alone included 40% of the patients. In the end, bacteriophages have effectively demonstrated their capacity to eliminate target bacteria, with several limitations that are instructive.

Illustration 1 : Phagoburn project financing by Europe



Source : https://cordis.europa.eu/project/id/601857/reporting

Clinical trial registration :

https://clinicaltrials.gov/ct2/show/NCT02116010?term=phagoburn&draw=2&rank=1

Articles about this trial :

https://www.mypharma-editions.com/la-cro-statitec-pilote-les-essais-cliniques-du-projet-europeen-phagoburn

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30482-1/fulltext

https://www.defense.gouv.fr/sante/actualites/phagoburn-des-virus-pour-traiter-des-infections-bacteriennes

Illustration 2 : Example of managed studies

Title of the study
Phase III, multicenter, randomized, European trial - Efficacy, pharmacokinetics and safety of X in infants less than 90 days old with **clinical sepsis**
Phase III, randomized, 3-arm, parallel patient trial of X versus Y efficacy and safety in **osteoporotic postmenopausal women**: a 2-year open-label study
Randomized, multicenter, phase III trial comparing two strategies brain radiotherapy followed by chemotherapy to chemotherapy alone in patients with **non-squamous non-small cell lung cancer** with asymptomatic brain metastases
Phase III, randomized, multicenter, placebo-controlled study evaluating the effect of monthly oral X on in vivo bone micro-architecture parameters, measured by peripheral micro CT scan in **osteopenic postmenopausal women**
Phase III trial, X versus Y as induction therapy prior to Autologous Stem Cell Transplantation in patients with newly diagnosed **multiple myeloma**
Phase III, randomized, open-label, parallel-group trial - Equivalence, efficacy and safety of X versus Y in **seborrheic dermatitis** of the face
Phase III, multicenter, randomized, double-blind, placebo-controlled trial - Efficacy of X in the recovery of **neurological disorders after stroke**
Phase III, randomized, double-blind, equivalence study of X versus placebo for the treatment of **seasonal allergic rhinitis**
Randomized Phase III Trial - The Value of Maintenance Treatment with X after Autologous Stem Cell Transplantation in **Myeloma Patients** Under 65 Years of Age
Phase II, multicenter, open-label trial - Efficacy of Y in patients with progressively relapsed or **refractory multiple myeloma** with a karyotypic abnormality by 17p deletion or translocation (4;14)
Phase II, multicenter, open-label, randomized, parallel-group trial - Efficacy of X versus placebo in the treatment of **anal fissure**
Phase II, randomized, double-blind, controlled, efficacy versus efficacy trial in patients with **Friedreich's ataxia**
Phase II, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial - Efficacy and safety of X for **migraine prophylaxis**
Phase II, single-center, randomized, double-blind, parallel group trial - Efficacy and safety of X versus placebo in patients with active **ophthalmopathy**
Phase II, randomized, double-blind, effect of X versus placebo on cerebral glucose metabolism in elderly patients with memory impairment, **mild Alzheimer's disease**
Randomized, open-label, non-comparative, multicenter phase II trial of sequential X plus Y versus Z alone as second-line therapy in patients with progressing stage IV **non-small cell lung cancer**
Phase I-II, multicenter, randomized, European trial. Safety of X in infants less than 90 days old with **meningitis**
Phase I/II trial – Randomized. Determination of the maximum tolerated dose, safety, pharmacokinetics and antitumor activity of X combined with concurrent chemoradiotherapy in patients with **squamous cell carcinoma of the head and neck**

Title of the study
Effects of X, Y, Z and placebo on driving performance in 16 healthy volunteers, double-blind Latin square
Phase II, multicenter, trial to evaluate the efficacy and safety of X in stabilizing tumor growth in patients with **neuroendocrine tumors**
Phase I, open-label trial to study the influence of repeated doses of X on the pharmacokinetic profile in healthy volunteers
Phase I, randomized, placebo-controlled trial to study the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple oral doses of Y
Phase I trial:Pharmacodynamic effects on alertness of a single oral dose of X (20 mg, 50 mg or 100 mg) versus Y (200 mg) in healthy subjects during **sleep deprivation**
Pharmacodynamic study of the effect of oral alpha2 antagonist X with or without exercise on lipolysis in **obese subjects**". Double-blind, cross-over, randomized, placebo-controlled study
Open-label, non-comparative, multicenter study of the efficacy, safety, and pharmacokinetics of the 22.5 mg formulation of X in patients with **central precocious puberty**
Evaluation of gastric emptying rate during **colonic preparation** with Y®
Open-label, non-controlled, multicenter, long-term follow-up study of insulin therapy in patients with **type 1 diabetes**
Impact of continuous glucose monitoring system on glycemic control in **diabetic hemodialysis patients**
An open-label, non-comparative, multi-center study of the efficacy, safety, and pharmacokinetics of the 22.5 mg formulation of X in patients with **central precocious (gonadotropin-dependent) puberty**
Bioequivalence study of x (30 mg) after single oral administration: comparison of two tablets manufactured by different processes. Single-dose, open-label, randomized, crossover study in healthy young male volunteers
Evaluation of the efficacy of X 10% against natural infestations of Neotrombicula autumnalis in dogs
Effect of X versus placebo on detrusor overactivity in **women with mixed incontinence**. A double-blind randomized controlled trial
Tolerance and efficacy of X in the treatment of moderate to **severe obstructive sleep apnea syndrome** in adults
Treatment of adult patients with **locally advanced or metastatic non-small cell lung cancer** with EGFRm+ and T790M mutations who have progressed during or after treatment with an EGF receptor tyrosine kinase inhibitor
Efficacy and tolerance of X in adult **seborrheic dermatitis**
Open-label, multicenter, randomized clinical trial comparing the efficacy and safety of X in subjects with **type 1 diabetes mellitus**
Medico-economic evaluation of the value of X in treated **multiple myeloma** patients under 65 years of age
Study of the effect of X on the **salivary bacterial load**

Title of the study
Efficacy and safety of X versus Placebo in **telogenous effluvium** - Multicenter, double-blind, randomized study in two parallel groups
Efficacy and safety study of X versus placebo in the local treatment of adult **periodontitis**
Efficacy and safety study of X versus Y in the treatment of **contact dermatitis, psoriasis and lichenification**
Evaluation of the analgesic effect of X- Study on capsaicin-induced **pain model**
Phase IV, open-label, multicenter, non-comparative trial of the efficacy and safety of X in **cervical dystonia**
Phase IV, multicenter, open-label, non-comparative trial to evaluate the efficacy and tolerability of X in the treatment of **dynamic equinus foot deformity** in young children with cerebral palsy
Randomized, parallel-group, open-label study of local tolerance and **behavior** in patients using nicotine chewing gum versus X
Efficacy and tolerance of X on vulvitis observed in cases of **vulvovaginal candidiasis**
Study of intestinal permeability and rectal sensitivity in patients with **irritable bowel syndrome** with visceral hypersensitivity treated by X
Efficacy, local tolerance and acceptability of a moisturizing emollient in patients undergoing maintenance **renal dialysis with xerosis**
…..
Observational study : Clinical, bacteriological and respiratory functional profiles of patients consulting a general practitioner for an exacerbation of **chronic bronchitis**
Observational study: Real-life conditions of use of sodium phosphate tablets for **colon cleansing before colonoscopy**
Observational study in medicine of the priority handicap and behavior of patients suffering from **painful osteoarthritis** of the lower limbs
Observational study of the criteria determining the adaptation of estradiol dosage during the first 9 months of hormone replacement therapy
Observational study: Evaluation of Therapeutic Strategies in **Coronary Patients** and Observation of the Influence of Risk
Observational Study Description of **Recurrent Sinusitis**
Observational study Management of lower limb **osteoarthritis** flare-ups in private practice
Observational Study: Description of prognostic factors for the occurrence of febrile neutropenia during Granulocyte-Cellular Growth Factor (G-CSF) initiation in patients receiving chemotherapy for **Breast Cancer**
Observational study: Description of risk and protective factors at the time of diagnosis of **Alzheimer's disease**
Observational study: Determination of the profile of patients with a **pregnancy** under treatment X®
Observational study: Description of the semiology of **chronic cancer pain** in patients with background opioid treatment and paroxysmal pain attacks

Title of the study
Observational study Management of memory complaints and diagnosis of **Alzheimer's disease**
Observational study: Description of psychotic symptomatology in the elderly
Observational study: Description of depressive symptomatology at the initial diagnosis of **Alzheimer's disease**
Observational study: Initiation of appropriate symptomatic treatment in patients with **Alzheimer's disease**
Observational study: Interest of a therapeutic contract in **diabetic patients** treated with Proton Pump Inhibitors "on demand"
Observational study describing the role of the caregiver in the accompaniment of patients with **multiple sclerosis** treated with subcutaneous X from three perspectives: neurologist, patient and caregiver
Observational study: Prevalence of oropharyngeal events according to type of inhaled corticosteroid therapy
Observational study: Assessment of **asthma and COPD** control by use of inhaled rescue bronchodilator therapy by X
Observational study on **mucovisidosis**
Evaluation in real situation of use of the new formula X cream
Observational study - Study of physicians' therapeutic attitudes in **hypertensive patients** who have failed a calcium channel blocker monotherapy
Observational study: Cohort study of patients treated with X combined with a diuretic, for non-controlled **hypertension** in general practice and cardiology
Observational, descriptive, cross-sectional study with real patients conducted among a sample of the population of dermatologists and their patients with predominantly **erythematotelangiectatic rosacea**
Observational study - Risk factors for **bullous pemphigoid**
Large-scale study of DNA copy number variations and gene expression profile of bone marrow plasma cells from monoclonal gammopathies of undetermined significance (MGUS) and indolent myeloma (IMM). Search for correlations with evolutionary risk in order to establish a predictive model of early malignant transformation
Study of the immunological function and phenotype of peripheral Natural Killer cells and other blood subsets from healthy volunteers
Observational study - Management of patients with breast cancer: evaluation of the supported pathway implemented at the Institut du Sein
Observational study on compliance with immunosuppressive therapy after **renal transplantation** in patients with access to a software to manage organ transplants
…..
TUA - Treatment of adult patients with **locally advanced or metastatic non-small cell lung cancer**, carrying EGFRm+ and T790M mutations, who have progressed during or after treatment with an EGF receptor tyrosine kinase inhibitor

Title of the study
TUA - Treatment of **advanced metastatic prostate cancer** (castration-resistant) in adult patients who have received prior X
TUA - Treatment of **chronic hepatitis C** due to HCV genotype 1, in adult patients with compensated liver disease and documented cirrhosis (F4)
TUA - Treatment of **HIV-1** infection in adults
TUA - Treatment of multidrug-resistant pulmonary **tuberculosis** (MDR-TB) in adult patients, when the use of another effective treatment regimen is impossible due to resistance or intolerance
TUA - Treatment of **chronic hepatitis** C due to genotype 1 or 4 virus, in combination with other drugs, in adult patients with advanced disease (with F3/F4 hepatic fibrosis or with extrahepatic manifestations of HCV)
TUA - Treatment of adult patients with relapsed or refractory **mantle cell lymphoma** with chronic lymphocytic leukemia who have received at least one prior therapy, or as first line therapy in case of 17p deletion or TP53 mutation
TUA - Treatment of proliferative childhood **hemangiomas** with life-threatening or functional risks, and ulcerated hemangiomas not responding to simple care, in children not eligible for inclusion in a clinical trial
TUA - Treatment of adult patients with active, moderate to severe **ulcerative colitis or Crohn's disease** who have had an inadequate response or loss of response to conventional therapy and anti-TNFα (tumor necrosis factor-alpha antagonist) or who have been intolerant to these treatments

Note:

TAU: Temporary Use Authorization
French procedure created in 1986 that allows certain categories of patients to use drugs that have not yet been marketed. It was split into early access authorizations and compassionate access authorizations (AAC) in July 2021, is a

TRFU: Temporary recommendations for use
Same mechanism as for TAU for products that have been granted marketing authorization but are not yet covered by the health insurance system

3 From molecule to drug, the obstacle course

3.1 The phases of drug development

Medicines undergo an extremely long and tedious life cycle, passing through several regulated stages to ensure their quality, safety and effectiveness for patients.

3.1.1 Basic research

Out of 10,000 molecules screened during the exploratory research stage, only 10 drug candidates will be patented and one will pass all the stages of testing and clinical trials to become a drug: the path from innovation to patient is thus long, complex and costly.

Basic research is the stage during which thousands of molecules likely to be of therapeutic interest are selected in order to retain only those that could become potential drug candidates. It is during this phase that the galenic development begins, which defines the formulation and manufacturing choices.

This stage can last from 2 to 3 years.

3.1.2 Pre-clinical studies

Preclinical studies are an essential step in the development of drugs or vaccines and are part of a multi-stage testing strategy. This phase evaluates the efficacy and safety of the vaccine in animal and cell models (in vitro) before moving on to human trials.

Preclinical trials consist of the following

- **Toxicity studies** on the potential of the product to cause
    - and possible effects on the lymph nodes,
    - systemic toxicity (effects on different organs) and on the immune system.
- **Pharmacokinetic studies** studying the distribution of the product after injection in the different organs, its metabolism and its elimination**.**

This phase can be completed by studies on development and fertility, as well as studies on genotoxicity and carcinogenicity. Mutagenicity is also considered in the case of new adjuvants or additives.

This preclinical phase is important because it will determine the indicators to be followed in future clinical trials in humans.

These animal models are not perfect and often fail to predict immunogenicity (ability to develop immunity) and efficacy in humans, which will only be assessed in subsequent clinical trials. Furthermore, the absence of detectable toxicity in animal studies does not mean that a drug/vaccine will be safe for humans.

According to the Johns Hopkins University, a typical vaccine development timeline **takes 5 to 10 years, and sometimes longer,** to assess whether the vaccine is safe and efficacious in clinical trials involving preclinical studies.

3.1.3 Clinical trials in human

There are four distinct evaluation phases, each of which results in a different clinical trial.

- **Phase I :**

Phase I clinical trials involve a small number of healthy volunteers and are designed to test the safety of the drug in humans. These are proof-of-concept studies of the mechanism of action. They mainly study the pharmacological effects (dose ranges, Maximum Tolerated Dose) and pharmacokinetic parameters in humans. They can last from several weeks to several months.

For a vaccine, according to the Johns Hopkins University, "*Phase 1 trials can be completed in two to three months, allowing for two doses three to four weeks apart"*.

- **Phase II :**

Phase II clinical trials take place if the results of Phase I are conclusive and safe for humans. They consist of testing the efficacy of the drug and determining its optimal dosage (several doses tested) in sick patients, the dose chosen being an effective dose with the least possible harmful side effects.

For a vaccine, according to the Johns Hopkins University, "*Phase 2 trials can be completed in three to four months, allowing for longer follow-up to better assess safety and immunogenicity. This timeline is shortened when phase 1 and phase 2 trials are combined*."

- **Phase III :**

The purpose of Phase III clinical trials is to confirm efficiency by comparing the efficiency of the new drug to the reference treatment (when it exists) and/or to a placebo (when no treatment exists) and to evaluate its tolerance.

This phase involves a large number of patients recruited in several countries, by dozens of different doctors, and may last several years. The aim is to evaluate the benefit/risk ratio of the drug being tested and the precautions to be taken when using it due to its various side effects. During this phase, trials relating to industrial development and the mode of administration and packaging (capsules, tablets, syrup, etc.) are also carried out.

It is at the end of Phase III that the reports are submitted to the health authorities for marketing authorization (MA), the verification process by the regulatory authorities generally last from 12 to 18 months. The marketing of the drug is not authorized until the authorities are satisfied and issue a marketing authorization.

Many countries also require cost-effectiveness studies of the new drug, which will help the government or insurance companies to make recommendations and decide whether the drug

should be obtained by prescription, and whether it should be reimbursed by the country's health insurance system.

The marketing process also requires the communication of the information collected on the new drug to physicians and other health professionals, so that they are informed of its effects and can prescribe it in the cases they consider appropriate.

For a vaccine, 2 to 4 Years are necessary to assess the relevant parameters.

- **Phase IV :**

These trials are carried out once the drug is marketed. They allow us to learn more about the drug under real conditions of use and to evaluate its tolerance on a large scale and over the long term in order to detect undesirable effects of the drug that were not detected during the previous phases, and thus to understand **its <u>real</u> benefit/risk ratio**.

Phases I to III generally last 4 to 7 years.

Illustration 3 : Johns Hopkins University - The different stages of drug development

Source : https://coronavirus.jhu.edu/vaccines/timeline

In summary, while there is no fixed development time for a drug to be tested and approved, it is common for all phases of development from research to market to take 10 to 15 years.

The development of vaccines is identical to that of a drug, the patient not being ill, is called a participant.

The usual time of development is 5 to 10 years (Johns Hopkins University).

3.2 Clinical research stakeholders

In order to carry out a clinical trial, there are many stakeholders

- **Sponsor** : an individual, a company, an institution, or an organization that takes responsibility for the research: pharmaceutical company …

- **Center** : place where one person is responsible for the conduct of the clinical trial, the investigator. If a trial is conducted by a team of people at one site, the investigator is the leader of the team and may be called the principal investigator.

- **Clinical Research Associates (CRAs):** they ensure the follow-up of the trial through regular visits to the investigating centers in order to verify the documents kept by the investigator and the reporting of the measured parameters in the database. They also ensure that GCP is respected. These tasks are grouped under the name of monitoring.

- **Data-managers** : they are in charge of data management, they develop a secured website in which the centers will enter the measurements made during the trial, they also ensure the control in order to obtain reliable data and the coding of adverse events according to validated dictionaries.

- **Statisticians** : they are involved as soon as the clinical study protocol (document containing all the information about the trial) is written, since they calculate the number of subjects to be included in order to be able to conclude on the efficacy, write the methodology of the analyses that will be carried out, ensure the programming of these analyses and provide all the tables, listings and graphs that will be inserted in the clinical report

- **The medical writer**: generally with a medical background, he/she writes the clinical report of the study often in collaboration with the statistician.

- **Pharmacovigilants** : they assess the seriousness of all adverse events reported to them by investigators and the causal link with the study product.

- **Quality Assurance**: they are in charge of writing the working methods to be followed (Standard Operating Procedures). They carry out audits of the various parties involved in order to check that the working methods comply with the laboratory's internal procedures, recommendations and legislative and regulatory provisions in force.

All services can be located **within the laboratory or outsourced to subcontractors** or contract research organizations called CROs (Clinical Research Organizations).

All participants, whether they are internal to the laboratory or external companies, are subject to the same regulations and must follow the working methods, reference documents, guidelines, etc., all of these rules being grouped together under the name of **Good Clinical Practice (GCP)** as well as all the recommendations issued by the health authorities relating to its activity, whether they are global, from the World Health Organization (WHO), European, American or local.

The sponsor retains full responsibility for the trial, and must ensure that it is adequately monitored, depending on the objective, purpose, complexity, whether or not there is randomization, whether or not products are kept "blind", the number of subjects to be included, the trial's evaluation criteria, etc. **On-site monitoring, before, during and after the trial is therefore necessary to ensure the progress of the study, to control and validate the documents and data collected.**

3.3 Regulation in clinical trials

Every clinical trial is governed by a set of principles whose purpose is to ensure the safety of the persons participating in the research as well as the integrity and accuracy of the data, which are grouped under the name of **Good Clinical Practice (GCP).**

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), originally founded in 1990, became a non-profit legal entity in 2015, and assumes the role of **centralizing practices** by having as members health agencies from most of the world, EMA (European Medicines Agency), MHLW/PMDA (Japan), FDA (Food and Drug Administrations), Swissmedic (Switzerland), Health Canada (Canada), ANVISA (Brazil), HSA (Singapore), MFDS (Republic of Korea), NMPA (China), SFDA (Saudi Arabia)….(https://www.ich.org/)

Its mission is **to draft and maintain guidelines or recommendations** and technical documents to be followed by clinical research stakeholders in order to homogenize practices at the global level in terms of safety, quality and efficacy, in order to facilitate the work of health agencies when pharmaceutical companies apply for marketing authorization for new products.

The Good Clinical Practice reference document - "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) - Guidance for Industry" is available at

- The ICH website

https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

- Health agency websites

FDA : https://www.fda.gov/media/93884/download

EMA : https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

Ministry of Health Canada : https://www.cpp-sudmed2.fr/IMG/pdf/e6_f.pdf

This document is THE reference for all those involved in Clinical Research as it is defined as "an international **ethical and scientific quality standard for the design and conduct of trials** involving human subjects and for the recording and reporting of trial data. **Adherence to such a standard assures the public that the rights, safety, and well-being of trial subjects are**

protected, consistent with the principles of the Declaration of Helsinki, and that clinical trial data are reliable.

The ICH recommendations concerning efficacy, tolerance, quality ... have been in place for years, the list is in the following tables, the column corresponds to the version, the data being the date of last revision.

Tableau 1 : Efficacy guidelines

Title	Step	Date
E1 - The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions	Step 5	27 October 1994
E10 - Choice of Control Group and Related Issues in Clinical Trials	Step 5	20 July 2000
E11(R1) - Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population	Step 5	18 August 2017
E11A EWG - Paediatric Extrapolation	Step 1	-
E12 - Principles for Clinical Evaluation of New Antihypertensive Drugs	-	-
E14 - The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	Step 5	12 May 2005
E14 Q&As (R3) - Questions & Answers: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	Step 5	10 December 2015
E14/S7B IWG - Questions & Answers: Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential	Step 3	27 August 2020
E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories	Step 5	1 November 2007
E16 - Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions	Step 5	20 August 2010
E17 - General principles for planning and design of Multi-Regional Clinical Trials	Step 5	16 November 2017
E18 - Genomic Sampling and Management of Genomic Data	Step 5	6 September 2017
E19 EWG - Optimisation of Safety Data Collection	Step 3	4 April 2019
E20 EWG - Adaptive Clinical Trials	Step 1	-
E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting	Step 5	27 October 1994
E2B(R3) - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs)	Step 5	1 November 2012
E2B(R3) EWG/IWG - Electronic Transmission of Individual Case Safety Reports (ICSRs)	-	-
E2B(R3) Q&As - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports	Step 5	1 June 2019
E2C(R2) - Periodic Benefit-Risk Evaluation Report	Step 5	17 December 2012
E2C(R2) Q&As - Questions & Answers: Periodic Benefit-Risk Evaluation Report	Step 5	31 March 2014
E2D - Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting	Step 5	12 November 2003

Title	Step	Date
E2D(R1) EWG - Post Approval Safety Data Management: Definition and Standards for Expedited Reporting	Step 1	-
E2E - Pharmacovigilance Planning	Step 5	18 November 2004
E2F - Development Safety Update Report	Step 5	17 August 2010
E3 - Structure and Content of Clinical Study Reports	Step 5	30 November 1995
E3 Q&As (R1) - Questions & Answers: Structure and Content of Clinical Study Reports	Step 5	6 July 2012
E4 - Dose-Response Information to Support Drug Registration	Step 5	10 March 1994
E5 Q&As (R1) - Questions & Answers: Ethnic Factors in the Acceptability of Foreign Clinical Data	Step 5	2 June 2006
E5(R1) - Ethnic Factors in the Acceptability of Foreign Clinical Data	Step 5	5 February 1998
E6(R2) - Good Clinical Practice (GCP)	Step 5	10 November 2016
E6(R3) EWG - Good Clinical Practice (GCP)	Step 1	-
E7 - Studies in Support of Special Populations: Geriatrics	Step 5	24 June 1993
E7 Q&As - Questions & Answers: Studies in Support of Special Populations : Geriatrics	Step 5	16 July 2010
E8 - General Considerations for Clinical Trials	Step 5	17 July 1997
E8(R1) EWG - Revision on General Considerations for Clinical Studies	Step 5	6 October 2021
E9 - Statistical Principles for Clinical Trials	Step 5	5 February 1998
E9(R1) EWG - Addendum: Statistical Principles for Clinical Trials	Step 5	20 November 2019

Tableau 2 : Safety guidelines

Title	Step	Date
S10 - Photosafety Evaluation of Pharmaceuticals	Step 5	13 November 2013
S11 - Nonclinical Safety Testing in Support of Development of Paediatric Medicines	Step 5	14 April 2020
S12 EWG - Non-clinical Biodistribution Considerations for Gene Therapy Products	Step 3	3 June 2021
S1A - Need for Carcinogenicity Studies of Pharmaceuticals	Step 5	29 November 1995
S1B - Testing for Carcinogenicity of Pharmaceuticals	Step 5	16 July 1997
S1B(R1) EWG - Rodent Carcinogenicity Studies for Human Pharmaceuticals	Step 3	10 May 2021
S1C(R2) - Dose Selection for Carcinogenicity Studies of Pharmaceuticals	Step 5	11 March 2008
S10 - Photosafety Evaluation of Pharmaceuticals	Step 5	13 November 2013
S2(R1) - Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use	Step 5	9 November 2011
S3A - Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies	Step 5	27 October 1994

Title	Step	Date
S3A Q&As - Questions and Answers: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure - Focus on Microsampling	Step 5	16 November 2017
S3B - Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies	Step 5	27 October 1994
S4 - Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)	Step 5	2 September 1998
S5(R2) - Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility	Step 5	1 November 2005
S5(R3) - Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals	Step 5	18 February 2020
S5(R4) Maintenance EWG - Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals	-	-
S6(R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals	Step 5	12 June 2011
S7A - Safety Pharmacology Studies for Human Pharmaceuticals	Step 5	8 November 2000
S7B - The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals	Step 5	12 May 2005
S8 - Immunotoxicity Studies for Human Pharmaceuticals	Step 5	15 September 2005
S9 - Nonclinical Evaluation for Anticancer Pharmaceuticals	Step 5	18 November 2009
S9 Q&As - Questions and Answers: Nonclinical Evaluation for Anticancer Pharmaceuticals	Step 5	27 April 2018

3.4 Conduct of a clinical trial

Each clinical trial begins with the writing of a document, the **protocol**, which stipulates the objectives of the research, the type of population (choice of subjects in terms of age, sex, comorbidities, etc.), the follow-up time of the participants (duration of the study), the number of visits, the efficacy criteria, the tolerance criteria, the quality control and assurance procedures, etc. It also details the statistical methodology that will be used to analyze all the criteria collected during the trial.

In agreement with the laboratory and certain health professionals specialized in the field studied, the **biostatistician** writes the **statistical methodology** and calculates the number of subjects to be included in order to be able to conclude on the efficacy based on hypotheses on the expected efficacy of the experimental product, particularly for phase 3 trials.

Writing such a document requires several months of work depending on the complexity of the trial and a certain amount of back and forth with the health agencies in order to obtain a consensus on the statistical methodology, the choice of the clinical criteria that will be analyzed and in particular the primary efficacy criterion on which the number of subjects is calculated.

The protocol is accompanied by the Case Report Form (CRF) which includes, in the form of checkboxes, free text, tables of values, date fields, times, etc., all the information required in the protocol and which must be reported to the sponsor on each participant in the trial.

It is also a question of recruiting the centers participating in the trial, the final list of which is most often included in the protocol. Out of habit and convenience, the laboratories contact the hospital services with which they are used to working.

Once the trial has been approved by the health authorities and the centers have been identified, the study can be set up in the investigating centers.

The tasks of each stakeholder are explained below.

- **The Sponsor**

Prior to the start of the trial, the Sponsor must prepare and provide the participating centers with the regulatory documents :

- The investigator's brochure which contains a description of the product and its properties as well as the results of all non-clinical studies on pharmacology;
- The Case Report Form (CRF) which includes all the information required in the protocol to be reported to the sponsor on each trial participant,
- The informed consent form for participants to sign,
- Financial contracts between the center and the laboratory, with the centers being paid for each participant included in the trial
- The letters of approval of the study by the authorities

…

It is also a question of **developing the distribution chains for the tested products**, which must be transported under the right conditions of storage, temperature, etc., from the production site to the pharmacies of the sites recruiting the patients, and the pharmacies must ensure proper conservation according to the manufacturer's standards.

During the trial, the project manager in charge of the study must ensure its progress by coordinating the various departments or subcontractors

- **Data-management Service :**

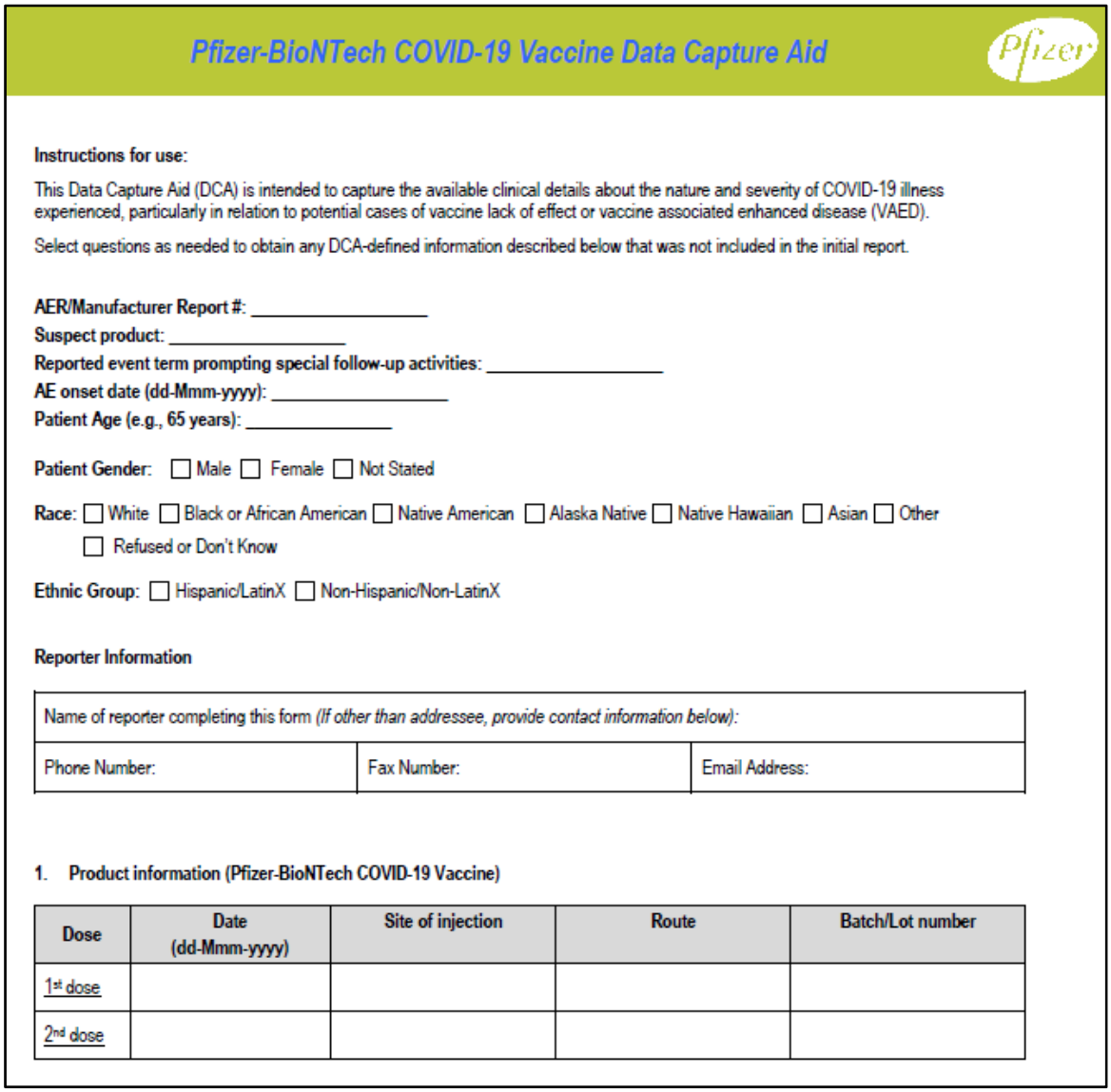
Data management activities are governed by the **Good Data Management Practices** and other technical documents mentioned below.

Prior to the start of the trial the data manager(s) must complete the following documents:

- The data-management plan, which explains the working methods that will be implemented to manage the test, the software that will be used
- The Data Validation Plan, which details all the controls that will be implemented during data entry by the centers to detect missing data and data entry errors

They must also ensure the development of the trial-specific website, named e-CRF for electronic CRF, which contains the data entry screens defined in the patient's booklet (Case Report Form).

Illustration 4 : Example of a CRF page



Pfizer-BioNTech COVID-19 Vaccine Data Capture Aid

Instructions for use:

This Data Capture Aid (DCA) is intended to capture the available clinical details about the nature and severity of COVID-19 illness experienced, particularly in relation to potential cases of vaccine lack of effect or vaccine associated enhanced disease (VAED).

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____
Suspect product: _____
Reported event term prompting special follow-up activities: _____
AE onset date (dd-Mmm-yyyy): _____
Patient Age (e.g., 65 years): _____

Patient Gender: ☐ Male ☐ Female ☐ Not Stated

Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian ☐ Other ☐ Refused or Don't Know

Ethnic Group: ☐ Hispanic/LatinX ☐ Non-Hispanic/Non-LatinX

Reporter Information

Name of reporter completing this form *(If other than addressee, provide contact information below)*:		
Phone Number:	Fax Number:	Email Address:

1. Product information (Pfizer-BioNTech COVID-19 Vaccine)

Dose	Date (dd-Mmm-yyyy)	Site of injection	Route	Batch/Lot number
1st dose				
2nd dose				

The data manager(s) must also **program the correct allocation of treatments (randomization)** for each new participant included in the study. For example, the first participant might receive Product A, the second participant also receives Product A, while participants three and four receive Product B, participant five receives Product B, participant six receives Product A, and so on. This ensures that the groups maintain an equal distribution, in this case, every four participants.

Randomization prevents investigators from personally deciding the treatment for new patients, as such decisions are often influenced by subjective criteria. This bias can distort the study's results, such as when patients with more severe conditions are preferentially assigned to one treatment group over another.

The data manager(s) program the order of the fields to be entered in the electronic data capture (EDC) system to guide the investigator efficiently through the next relevant field. For example, if the patient has no prior medical history, the system automatically navigates to the next page. Conversely, if the patient has at least one medical history entry, the system requires the investigator to complete mandatory fields detailing the nature of the history before proceeding.

They also program consistency checks or validation tests to identify missing or inconsistent data within the dataset. These checks are crucial for maintaining data quality and integrity. All checks must be clearly defined in advance in a formal document known as the Data Validation Plan (DVP), which outlines the specific rules, processes, and thresholds to be applied during data review.

Since multiple individuals will have access to the electronic case report form, it is essential to create **distinct access profiles** with predefined read, write, and modify permissions. These profiles should accommodate various roles, such as the project manager, investigators, data managers, and clinical research associates. Each individual is assigned a unique username and password, known only to them.

To ensure **security**, the system should deactivate a user's access after repeated incorrect password entries. However, the system must also include a secure password recovery mechanism to minimize disruption and restore access efficiently.

Additionally, all personnel at trial sites involved in the study must be trained in the proper completion of the electronic patient records prior to the study's initiation. This training ensures consistent and accurate data entry across all centers.

The tools used for data management in clinical trials must comply with the **FDA 21 CFR Part 11** standard, which regulates electronic records and signatures to ensure data integrity, security, and traceability. This regulation mandates robust systems for data validation, audit trails, and controlled access. In compliance with these requirements, clinical trial data entry is not performed using spreadsheet software like Microsoft Excel®. Instead, specialized electronic data capture (EDC) systems or validated clinical trial management systems (CTMS) are employed. These platforms are specifically designed for clinical data management, offering built-in compliance with regulatory standards, comprehensive audit trails, and enhanced security features, ensuring that trial data is both reliable and legally admissible.

Source : Guidance for Industry Part 11, Electronic Records; -Electronic Signatures — Scope and Application - https://www.fda.gov/media/75414/download

In summary, the **FDA 21 CFR Part 11** standard requires, among other things:

- Validation of systems used for developing electronic case report forms (e-CRFs) within the user's operational environment to ensure they perform as expected under real-world conditions.
- Full traceability of data entries, which includes recording the user’s name who entered the data, the date and time of entry, as well as the user who modified the data, the date/time of modification, and the reason for modification (such as data entry error or corrections requested by a data manager or clinical research associate). This complete record for all fields in the electronic notebook, across all patients, is known as an **audit trail**.

The **audit trail review** serves as a crucial tool for detecting any undocumented data corrections, thus allowing identification of any unauthorized changes made by investigators, data managers, clinical research associates, or other personnel involved in the study. The audit trail ensures compliance with regulatory standards by maintaining transparency and data integrity throughout the trial process.

The data manager(s) check that the website setup has been correctly parameterized by creating "false patients" called "test patients". The aim is to create enough patients to ensure that the randomization assigns treatments correctly, and **to validate that all the programmed tests detect all the possible problems** (missing data, wrong date, biological value not compatible with the standard entered, start date of an event later than the end date, time between visits compatible with the protocol ....). It is common practice to enter all the data required for at least 50 patients in order to cover all the possibilities. The test patients should be kept as well as all the results of the tests performed in order to prove the proper functioning of the website in case of an audit.

The e-CRF can only be made available to centers (from test mode to production mode) once it has been fully tested and validated.

This step can take up to 3 months in the case of a complex CRF, numerous visits, multiple examinations including laboratory data (blood tests), imaging examinations...

As the investigating centers recruit participants and ensure data entry into the electronic case report form (e-CRF), the data manager(s) runs the programmed checks in **order to send correction requests to the centers so that they can complete the missing data and correct the inconsistent data** from the patient documents available on the site (demographic data, concomitant medications, adverse events, biological check-ups, PCR test results, etc.)

According to ICH recommendations, all participant medical histories, adverse events, previous and concomitant medications should be coded to facilitate analysis.

As with any activity that is part of drug development, the coding of adverse reactions is regulated. To help pharmacovigilance services as well as health authorities to evaluate the adverse events of a product, **a medical dictionary for regulatory activities (MedDRA)** was developed in the late 1990s by the ICH.

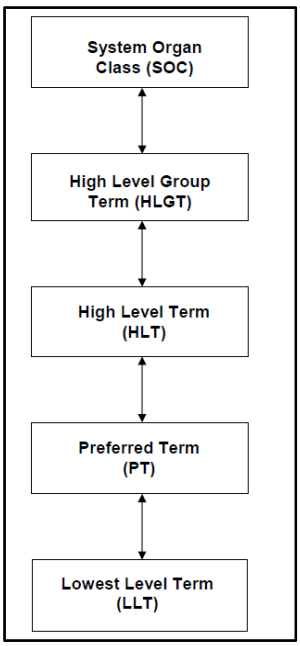
The MedDRA coding system uses keywords representing the medical condition(s) described in the reported case and converts them into standardized codes. In order to be used worldwide, it includes multilingual databases to avoid translation.

Coding of adverse events is performed by the data manager(s) when they are reported in clinical trials.

MedDRA has a hierarchical structure, from the most specific to the most general.

The lowest level term (LLT) provides maximum specificity. High Level Terms (HLT) and High Level Group Terms (HLGT) facilitate data retrieval and presentation by providing a grouping of clinically relevant terms. Preferred terms (PT) should be unambiguous, as specific and self-descriptive as possible in the context of international requirements. The System Organ Class (SOC) is the highest level of the hierarchy that provides the broadest concept for data retrieval.

Illustration 5 : MedDRA hierarchical structure



The validation of the coding must be carried out by the Pharmacovigilance department. The two departments therefore go back and forth until the coding is fully validated.

The data manager is also responsible for i**mplementing the extraction of the data entered into the e-CRF into a database** that can be used by the statistician. This database consists in several files, with the parameters measured during the trial put in columns and the individuals in rows. Since it would be unreadable and therefore unusable to create a single file containing all the data of all the participants in a trial, the data are arranged by type in different files.

Here again, **the database format must follow specifications** in terms of file names, variable names, data organization, etc. The Clinical Data Interchange Standards Consortium (CDISC), a worldwide non-profit organization, develops data standardization systems. Their reference documents constitute the standards to be implemented to define the format of the files or tables to be parameterized.

Special recommendations have been written for the COVID-19 databases.

https://www.cdisc.org/standards/therapeutic-areas/covid-19

Source : https://www.cdisc.org/system/files/members/standard/ta/TAUG-COVID-19_v1.0_0.pdf

It goes without saying that the data export process must be validated in order to put all the fields of the e-CRF in the right place.

At the end of the study, the data must have been 100% checked and cleaned by the data manager(s). When the database is documented as error-free, it can be "frozen", i.e. it cannot be modified afterwards. Any "unlock" of the database is an indicator of poor quality of the work of the data manager(s), since it means that errors have not been corrected despite the checks made.

The data manager export the data at the end of the process to create the files that will be sent to the statistician.

- **The monitoring service**

Monitoring activities are governed by the **Good Monitoring Practices** and other technical documents mentioned below.

Prior to the start of the trial the clinical research officer(s) must complete the following document the monitoring plan which contains the key data to be checked, the schedule of visits …

CRAs should ensure that the investigator site has received the trial and investigational product management documents, and that site personnel who will be working on the study have been trained in the protocol and its required practices.

During the study, like the data manager(s) with whom they work closely, the clinical research associates (CRAs) also perform **some checks on the data and visit the sites** that have included participants in order to verify that the data reported in the e-CRF are indeed those of the local examinations (source data) to which the data manager does not have access.

They check that the patients included in the study respect the inclusion criteria in terms of age, associated pathologies .... that the consent has been signed by the patients... They must also verify that the centers respect the storage conditions of the study products as foreseen by the Sponsor, that all the entries, exits, returns of the products are traced, that the patients have been correctly followed ....

Like the data manager(s), they can issue requests for corrections to the centers, which must respond to them. **They also verify that adverse events have been identified and reported to the pharmacovigilance department.**

In recent years, in order **to limit the costs and duration of trials**, it has become increasingly common, particularly in the context of **fast-track** process, for CRAs to carry out part of their checks remotely, in what is known as **remote monitoring**. The CRA schedules telephone or video conferences with the center's staff, who transmit the source medical documents to the CRA via a secure area so that the CRA can compare the source data with the data entered in the e-CRF. Although this practice is accepted at the regulatory level, it is still less effective than on-site visits, which is why it is common to keep face-to-face visits in order to compare the quality of the audit with on-site monitoring.

It is therefore often also necessary to have a document exchange platform for remote monitoring but also for any type of confidential document exchange, including statistical results, as the secure platform prevents confidential documents from being sent by e-mail.

At the end of the study, the source documents must be 100% verified.

- **The pharmacovigilance service :**

Pharmacovigilance activities are governed by **Good Pharmacovigilance Practice**s.

Prior to the start of the trial, the pharmacovigilance department should prepare the Pharmacovigilance Plan.

As adverse events are reported by the investigating sites, the pharmacovigilance staff assess the severity of the events and the causal link with the tested product. They are the ones who establish the responsibility of the product in the occurrence of adverse events (imputability).

- **The statistical service :**

Prior to the start of the trial the statistician(s) shall:

  - Develop the randomization list, which should be developed by a laboratory statistician and kept secret until the end of the trial
  - Write the statistical analysis plan according to the protocol methodology.

The statistician **will program the statistical analyses** based on all the data exported from the electronic patient case form in a format compatible with the chosen statistical analysis software (SAS® type or other).

When **intermediate** analyses are planned, since the laboratory staff should not know which products have been given to the participants (due to the blind design), the analyses are sent to experts outside the laboratory, the so-called IRC (Independent Review Committee).

As with any stakeholder, the working methods and documents to be provided by IRCs are regulated.

The statistical analyses are carried out by the Committee's expert biostatistician, who programs the planned analyses using one or more **software programs validated in clinical research** (SAS® or other) and provides the results, which will be examined by the other members of the Committee, generally physicians or professors working in the field of research.

Within the framework of his activities, the **biostatistician must follow very strict regulations** and must respect a very large number of reference documents concerning the statistical analysis methods to be used according to the type of study (parallel groups, crossover studies, equivalence studies, non-inferiority studies, etc.) and the parameters to be analysed (quantitative and qualitative parameters) .... One of the reference documents is the ICH E9 "Statistical Principles for Clinical Trials".

Source : https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

A second statistician must validate all programs for critical data including the calculation of the primary endpoint on which the efficacy conclusion of a phase 3 study is based. The programs are executed and the records of the execution of the programs (log) are kept as evidence in case of audit, a file containing the list of programs, the name of the programmer, the day of the programming, the name of the "validator", the date of validation, the date of execution ...

Once the database frozen by the data manager and the regulatory certificates issued, it is possible to obtain the decoding of the experimental products since the knowledge of the treatment actually given to each patient is necessary to provide the results.

The decoding of the products is therefore transmitted to the biostatistician so that he can execute his programs.

As with the interim analyses, the “logs” are recorded as evidence in the event of an audit. Any changes from what was planned in the protocol must be documented. Tables, graphs and listings are integrated into the clinical report, which will be commented on by a medical writer.

During the study, the various participants must maintain and keep all the evidence of their actions on the study by filling in all the documents drawn up beforehand. All these documents and records constitute a file to be kept, either at the investigator site, or at the Sponsor's, or at both, depending on the type of data concerned. The complete file is called **Trial Master File** (TMF).

This paper or dematerialized file allows the operational staff as well as the auditors and inspectors to evaluate the respect of the protocol, the good progress of the test and the quality of the obtained data.

The documents to be included in the TMF are referenced in the "**Guideline on the content, management and archiving of the clinical trial master file**".

Sources : Guideline on the content, management and archiving of the clinical trial master file- 06 December 2018 - Good Clinical Practice Inspectors Working Group (GCP IWG)
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

https://www.ijclinicaltrials.com/index.php/ijct/article/view/442

In summary, in any center, the personnel involved in the trial must be trained to the study practices before starting the study. Each person, investigator, nurse, staff in charge of the management of the trial products, staff in charge of the laboratory analyses... must sign the **sign-in sheet** to prove that the training has been carried out.

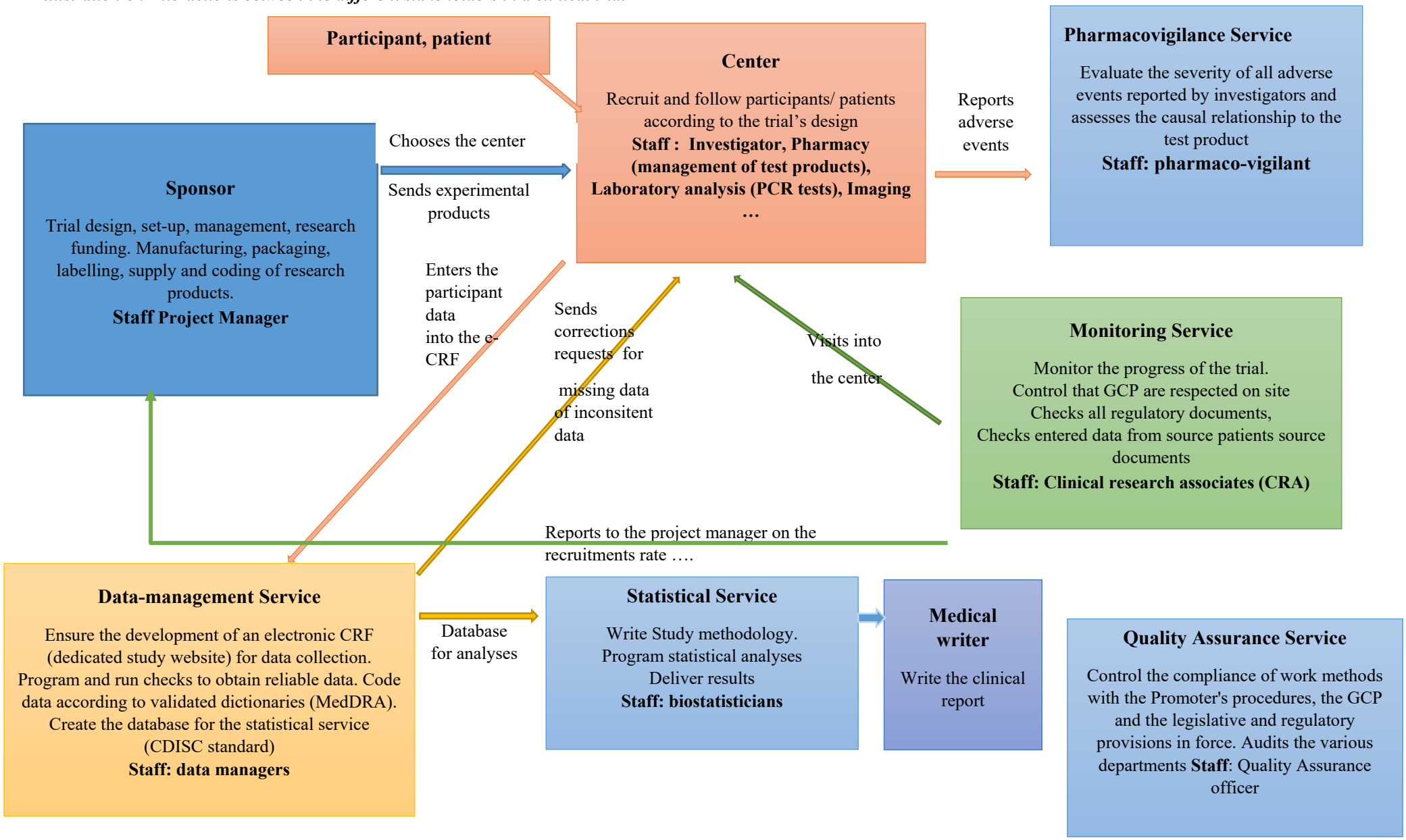
All workers must be trained in Good Clinical Practice and be familiar with all documents regulating their activities.

The sponsor is responsible for the coordination of its trial and for ensuring that the working procedures comply with GCP and applicable laws and regulations.

The Quality Assurance department oversees audits of the various departments and subcontractors in order to evaluate the quality of work.

The interactions between the different participants in a trial are shown in the following figure.

Illustration 6 : Interactions between the different stakeholders in a clinical trial



3.5 Risks and bias

All the guidelines have only one goal, to minimize the risk of error in the evaluation of the benefit-risk in order to avoid any risk of using a potentially ineffective or even dangerous product in real life.

It is therefore necessary to identify the elements that may cause the results to deviate from their true value, these elements are called biases.

Some biases come from, among other things,

- Non-randomization, e.g., treatment assignment such that low-risk subjects are systematically assigned to a treatment.
- From **unequal distribution** of subjects per treatment at each center, trials with large differences in the number of subjects between centers or with very few participants may induce heterogeneity in treatment effect across centers.
- The calculation of the criteria themselves
- The definition of analysis populations. For example, protocol violations and exclusion of subjects from the analysis based on knowledge of the subject's outcome are possible sources of bias that may affect the accurate assessment of the treatment effect.
- Poor quality of participant follow-up within the centers reducing the quality of reported data

Therefore, it is necessary to take precautions to reduce bias and ensure the ability of the trial to conclude correctly.

In summary,

Clinical trials are governed by a complex set of global guidelines designed to standardize and regulate the roles and practices of all involved participants. The intricate nature of trials, including their design, the variety of data collected (such as clinical exams, lab results, imaging, and tests like PCR), the large number of participants, and the long-term follow-up required, necessitates the involvement of many staff members. This complexity demands continuous coordination to ensure the trial runs smoothly and adheres to regulatory requirements.

Throughout a clinical trial, **all stakeholders must create and maintain detailed documentation of every action taken**, following the established guidelines.

Auditing these documents allows for the continuous evaluation of the quality of the work performed. As the number of patients increases, the workload of project managers, data managers, and Clinical Research Associates (CRAs) becomes more demanding. They must ensure that data entry is completed promptly to meet the trial's deadlines, especially when intermediate analyses are scheduled. **Accurate data is crucial, as it is unthinkable to conduct analyses on computer databases that may contain errors, which could compromise the integrity of the trial results.**

Failure to adhere to the technical and methodological recommendations designed to minimize bias—collectively known as Good Clinical Practice (GCP)—by any participant in the trial process can have serious consequences.

This includes individuals at the patient recruitment centers (such as investigators, nurses, pharmacists, and laboratory staff), as well as stakeholders responsible for trial management (such as Clinical Research Associates, data managers, pharmacovigilance officers, and biostatisticians).

Non-compliance can result in erroneous data, leading to unreliable results regarding the efficacy, immunogenicity, and safety of a product. This, in turn, poses a significant risk of misjudging the benefit/risk ratio, potentially allowing an ineffective and life-threatening product to reach the market.

4 The Importance of Adhering to Good Clinical Practice (GCP)

A large number of regulatory documents, as well as publications on agency websites, refer to Good Clinical Practice (GCP), which are a crucial component of clinical research as they ensure the reliability of results.

On the FDA's website, there is an extensive collection of reference documents for the management of clinical trials, where Good Clinical Practice (GCP) are frequently mentioned.

The article, ***'Descriptive Analysis of Good Clinical Practice Inspection Findings from U.S. Food and Drug Administration and European Medicines Agency*** ,' published on May 24, 2022—after the emergency authorizations in the United States and the numerous conditional Marketing Authorizations—states in its introduction that 'inspections related to Good Clinical Practice (GCP) are conducted by regulatory agencies to assess the integrity of data, protect the rights, safety, and well-being of study participants, and ensure that trials are conducted in compliance with GCP and applicable laws and regulations

Illustration 7 : Article – Descriptive Analysis of Good Clinical Practice Inspection Findings from U.S. Food and Drug Administration and European Medicines Agency

Introduction Go to:

Good clinical practice (GCP) inspections are conducted by regulatory agencies to assess data integrity and to safeguard the rights, safety, and well-being of study participants as well as to ensure trials are conducted in compliance with GCP and applicable laws and regulations [1–6]. challenges associated with the globalization of clinical trials, FDA and EMA began a GCP collaboration in 2009 to conduct collaborative GCP inspections; conduct periodic information exchanges on GCP-related activities; and share information on interpretation of GCP. This collaboration allowed for a better understanding of each other's inspection procedures [13]. Over time, this collaboration has expanded to include the regular exchange of inspection related information and the sharing of best inspection practices [14].

Source : https://pubmed.ncbi.nlm.nih.gov/35610469/

Sellers JW, Mihaescu CM, Ayalew K, Kronstein PD, Yu B, Ning YM, Rodriguez M, Williams L, Khin NA. Descriptive Analysis of Good Clinical Practice Inspection Findings from U.S. Food and Drug Administration and European Medicines Agency. Ther Innov Regul Sci. 2022 Sep;56(5):753-764. doi: 10.1007/s43441-022-00417-w. Epub 2022 May 24. Erratum in: Ther Innov Regul Sci. 2022 May 30;: Erratum in: Ther Innov Regul Sci. 2022 Jun 6;: PMID: 35610469; PMCID: PMC9356921.

This article also mentions that « GCP inspections utilize a data-focused approach and verify **individual subject level data and clinical trial conduct** at investigator sites as well as assess sponsor/contract research organizations oversight responsibilities »

The authors refer to key reference documents, including ICH E6, which we discussed extensively in Section 3.4 - Regulations in Clinical Trials of this report

« For FDA's Center for Drug Evaluation and Research, the assessment of ***GCP compliance and data integrity for marketing applications*** *is performed by the Office of Scientific Investigations in collaboration with the Office of New Drugs and the Office of Regulatory Affairs. The GCP inspections are conducted by the FDA investigators under the agency wide bioresearch monitoring program using the 21 Code of Federal Regulations for clinical investigators and sponsors/contract research organizations.*

For FDA, ***ICH E6 is guidance****. In the European Union, in the context of the centralized procedure, GCP inspections are requested by the Committee for Medicinal Products for Human Use (CHMP), coordinated by EMA, and conducted by inspectors from the individual European Union member states following European Union laws, applicable national/local laws, and the International Council for Harmonization (ICH) guideline on good clinical practice (ICH E6). The basis for the majority of EMA inspection findings is the ICH E6 guideline****. EMA's inspections cover GCP systems and processes*** *in addition to data verification. »*

Illustration 8 : Article – Descriptive Analysis of Good Clinical Practice Inspection Findings from U.S. Food and Drug Administration and European Medicines Agency

> FDA and EMA operate under different regulatory frameworks for GCP inspections. For FDA's Center for Drug Evaluation and Research, the assessment of GCP compliance and data integrity for marketing applications is performed by the Office of Scientific Investigations in collaboration with the Office of New Drugs and the Office of Regulatory Affairs. The GCP inspections are conducted by the FDA investigators under the agency wide bioresearch monitoring program using the 21 Code of Federal Regulations for clinical investigators and sponsors/contract research organizations. The basis for FDA inspection findings is 21 Code of Federal Regulations [1, 15]. These GCP inspections utilize a data-focused approach and verify individual subject level data and clinical trial conduct at investigator sites as well as assess sponsor/contract research organizations oversight responsibilities [1, 16]. For FDA, ICH E6 is guidance. In the European Union, in the context of the centralized procedure, GCP inspections are requested by the Committee for Medicinal Products for Human Use (CHMP), coordinated by EMA, and conducted by inspectors from the individual European Union member states following European Union laws, applicable national/local laws, and the International Council for Harmonization (ICH) guideline on good clinical practice (ICH E6) [2, 6]. The basis for the majority of EMA inspection findings is the ICH E6 guideline. EMA's inspections cover GCP systems and processes in addition to data verification [6, 16].

Source : https://pubmed.ncbi.nlm.nih.gov/35610469/

Sellers JW, Mihaescu CM, Ayalew K, Kronstein PD, Yu B, Ning YM, Rodriguez M, Williams L, Khin NA. Descriptive Analysis of Good Clinical Practice Inspection Findings from U.S. Food and Drug Administration and European Medicines Agency. Ther Innov Regul Sci. 2022 Sep;56(5):753-764. doi: 10.1007/s43441-022-00417-w. Epub 2022 May 24. Erratum in: Ther Innov Regul Sci. 2022 May 30;: Erratum in: Ther Innov Regul Sci. 2022 Jun 6;: PMID: 35610469; PMCID: PMC9356921.

The WHO references them in its Fiftieth Report of the Expert Committee on Specifications for Pharmaceutical Preparations, dated 2016

« *In recent years the number of observations made regarding good data management practices during inspections of GMP, good clinical practice (GCP) and good laboratory practices (GLP) has been increasing. There is increased regulatory awareness of the need for integrity of data submitted as a basis for regulatory decisions. Good data management in line with scientific advances and regulatory developments is crucial for all stakeholders in regulation of health products, including patients, industry and regulators.* »

Illustration 9 : OMS – WHO Expert Committee on Specifications for Pharmaceutical Preparations – Report 50 - GCP

8.6 **Guidance on good data and record management practices**

In recent years the number of observations made regarding good data management practices during inspections of GMP, good clinical practice (GCP) and good laboratory practices (GLP) has been increasing. There is increased regulatory awareness of the need for integrity of data submitted as a basis for regulatory decisions. Good data management in line with scientific advances and regulatory developments is crucial for all stakeholders in regulation of health products, including patients, industry and regulators.

Source : https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y

They reaffirm the importance of Good Manufacturing Practices and Good Clinical Practice in their 53rd report in 2019:

*« Validation is an essential part of good practices, including **GMP and Good Clinical Practice**, and is therefore an element of the pharmaceutical quality system. Validation incorporates qualification and should be applied over the life cycle of a product, process, method or system. WHO published Supplementary guidelines on good manufacturing practices: validation in 2006 (20). The main text of these guidelines is supported by several appendices, listed as follows:*

- *Appendix 1: Validation of heating, ventilation and air-conditioning systems;*
- *Appendix 2: Validation of water systems for pharmaceutical use;*
- *Appendix 3: Cleaning validation;*
- *Appendix 4: Analytical method validation;*
- *Appendix 5: Validation of computerized systems;*
- *Appendix 6: Qualification of systems and equipment;*
- *Appendix 7: Non-sterile process validation »*

Illustration 10 : OMS – WHO Expert Committee on Specifications for Pharmaceutical Preparations – Report 53 – GMP- GCP

11.2 **Good manufacturing practices for validation**

11.2.1 **General main text**

Validation is an essential part of good practices, including GMP and good clinical practices, and is therefore an element of the pharmaceutical quality system. Validation incorporates qualification and should be applied over the life-cycle of a product, process, method or system.

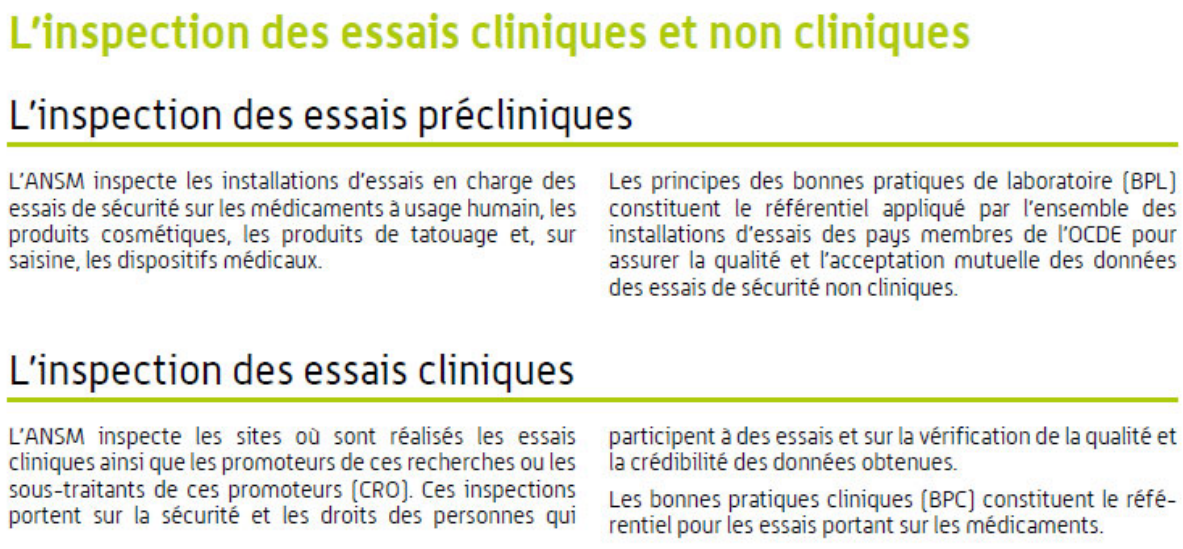
WHO published *Supplementary guidelines on good manufacturing practices: validation* in 2006 (*20*). The main text of these guidelines is supported by several appendices, listed as follows:

- Appendix 1: Validation of heating, ventilation and air-conditioning systems;
- Appendix 2: Validation of water systems for pharmaceutical use;
- Appendix 3: Cleaning validation;
- Appendix 4: Analytical method validation;
- Appendix 5: Validation of computerized systems;
- Appendix 6: Qualification of systems and equipment;
- Appendix 7: Non-sterile process validation.

Source : https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y

In its 2020 report, the French National Agency for the Safety of Medicines and Health Products (ANSM) also references Good Clinical Practice as a **benchmark** for drug trials.

Illustration 11 : ANSM – 2020 Report - GCP



L'inspection des essais cliniques et non cliniques

L'inspection des essais précliniques

L'ANSM inspecte les installations d'essais en charge des essais de sécurité sur les médicaments à usage humain, les produits cosmétiques, les produits de tatouage et, sur saisine, les dispositifs médicaux.

Les principes des bonnes pratiques de laboratoire (BPL) constituent le référentiel appliqué par l'ensemble des installations d'essais des pays membres de l'OCDE pour assurer la qualité et l'acceptation mutuelle des données des essais de sécurité non cliniques.

L'inspection des essais cliniques

L'ANSM inspecte les sites où sont réalisés les essais cliniques ainsi que les promoteurs de ces recherches ou les sous-traitants de ces promoteurs (CRO). Ces inspections portent sur la sécurité et les droits des personnes qui participent à des essais et sur la vérification de la qualité et la crédibilité des données obtenues.

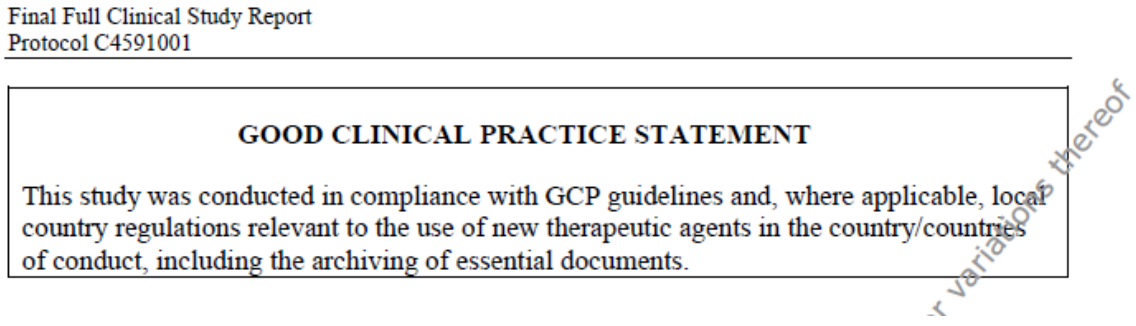
Les bonnes pratiques cliniques (BPC) constituent le référentiel pour les essais portant sur les médicaments.

Source : https://ansm.sante.fr/uploads/2022/10/10/rapport-dactivite-2020-fr.pdf

The Pfizer report dated July 28, 2023, which we will examine later, even mentions on page 2:

« ***This study was conducted in accordance with Good Clinical Practice (GCP) guidelines and, where applicable, local regulations regarding the use of new therapeutic agents in the relevant country or countries***. »

Illustration 12 : Pfizer – July 28, 2023 – GCP Statement



Final Full Clinical Study Report
Protocol C4591001

GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

We will demonstrate in this report that this is not the case.

5 COVID-19 Clinical Trial Development Milestones - The Pfizer/BioNtech Case

5.1 Timeline of the trials that led to the selection and marketing of the BNT162b2 vaccine candidate

Pfizer's own press releases and their timeline show key dates in the development of the product.

On March 13, 2020, Pfizer announced a five-pronged plan in the fight against COVID-19, calling on biopharmaceutical industry players to begin an unprecedented collaboration alongside Pfizer. Pfizer outlined five commitments to enable researchers to accelerate the development of solutions and vaccines

1. Sharing tools and knowledge
2. Mobilization of employees
3. Application of our expertise in drug development
4. Adaptation of our manufacturing capacities
5. Improved emergency response

Source: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-outlines-five-point-plan-battle-covid-19

On April 9, 2020, Pfizer and German biotech company BioNTech joined forces to develop a vaccine.
"BioNTech will contribute multiple mRNA vaccine candidates as part of its BNT162 COVID-19 vaccine program, which are expected to enter human testing in April 2020
fizer will contribute its leading global vaccine clinical research and development, regulatory, manufacturing and distribution infrastructure and capabilities."

Source: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-further-details-collaboration

On April 22, 2020, the Paul-Ehrlich Institute, Germany's vaccine certification authority, gave BioNTech and Pfizer the green light to **begin the first clinical trial of a COVID-19 vaccine candidate a Phase 1/2 trial**, testing a variety of investigational vaccines in **200 healthy volunteers**, ages 18 to 55 with dose escalations ranging from 1 µg to 100 µg with the goal of determining the optimal dose for further studies as well as assessing the safety and immunogenicity of the vaccine.
They also announced that they had completed preclinical studies in Germany.

Source: https://www.pfizer.com/news/press-release/press-release-detail/biontech_and_pfizer_announce_regulatory_approval_from_german_authority_paul_ehrlich_institut_to_commence_first_clinical_trial_of_covid_19_vaccine_candidates

On April 29, 2020, twelve participants in the German study had already been treated with the BNT162 vaccine candidates **since the trial began on April 23, 2020.** Pfizer and BioNTech then planned to initiate trials for BNT162 in the U.S. after regulatory approval, which is expected soon.

Source : https://www.pfizer.com/news/press-release/press-release-detail/biontech-and-pfizer-announce-completion-dosing-first-cohort

According to the regulations, all clinical trials must be registered prior to the start of the trial on the public Internet registry referenced by the World Health Organization (WHO), the U.S. site www.clinicaltrials.gov or the European site www.clinicaltrialsregister.eu set up by the European Medicines Agency (EMA) or another national or WHO-approved registry, in accordance with the applicable regulations and no later than 21 days after the recruitment of the first person.

Also on April 29, 2020, Pfizer registered its Phase 1-2-3 trial at www.clinicaltrias.gov,

https://clinicaltrials.gov/ct2/show/NCT04368728?term=pfizer&cond=Covid19&draw=2

under the title "*Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals*"

On May 5, 2020, Pfizer/BioNtech announced that the first phase 1/2 participants had been treated at New York University Grossman School of Medicine and the University of Maryland School of Medicine.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_biontech_dose_first_participants_in_the_u_s_as_part_of_global_covid_19_mrna_vaccine_development_program

In June 2020, after the trials had begun, the U.S. Department of Health and Human Services, the Food and Drug Administration (FDA) with the Center for Biologics Evaluation and Research issued Recommendations for Vaccine Development.

Page 13 therefore **defined post hoc how to determine the primary efficacy endpoint for a phase 3 trial**, which was to have a confirmed SARS-COV2 infection with at least one of the following symptoms

- Fever,
- Coughing,
- Shortness of breath or difficulty breathing,
- Fatigue,
- Muscle or body aches,
- Headache
- New Loss of taste or smell,
- Sore throat,
- Congestion or runny nose
- Nausea or Vomiting
- Diarrhea,

Illustration 13 : FDA Recommendations for Vaccine Development - Definition of Primary Efficacy Endpoint

- Standardization of efficacy endpoints across clinical trials may facilitate comparative evaluation of vaccines for deployment programs, provided that such comparisons are not confounded by differences in trial design or study populations. To this end, FDA recommends that either the primary endpoint or a secondary endpoint (with or without formal hypothesis testing) be defined as virologically confirmed SARS-CoV-2 infection with one or more of the following symptoms:
  - Fever or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

Source: Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (fda.gov) - U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research June 2020 - https://www.fda.gov/media/139638/download

On page 6 of the same document, the FDA stated that

Illustration 14 : FDA Recommendations for Vaccine Development - Theoretical risk of respiratory disease

- Data from studies in animal models administered certain vaccine constructs against other coronaviruses (SARS-CoV and MERS-CoV) have raised concerns of a theoretical risk for COVID-19 vaccine-associated enhanced respiratory disease (ERD). In these studies, animal models were administered vaccine constructs

To monitor this risk, page 12 stated that follow-up of participants in the COVID-19 trials, particularly for severe cases, **should be at least 1 to 2 years to assess the duration of protection and to evaluate potential acute respiratory illnesses associated with the vaccine as immune responses wane**.

Illustration 15 : FDA Recommendations for Vaccine Development – Follow-up

- Follow-up of study participants for COVID-19 outcomes (in particular, for severe COVID-19 disease manifestations) should continue as long as feasible, ideally at least one to two years, to assess duration of protection and potential for vaccine-associated ERD as immune responses to the vaccine wane.

Source : Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (fda.gov) - U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research June 2020 - https://www.fda.gov/media/139638/download

On July 1, 2020, Pfizer/BioNtech announced encouraging results for its Phase 1/2 versus placebo vaccine candidate BNT162b1 in the United States.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-early-positive-data-ongoing

On July 13, 2020, Pfizer/BioNtech obtained approval from the FDA to file its application via an accelerated procedure called Fast Track.
Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-granted-fda-fast-track-designation-two

On July 20, 2020, Pfizer/BioNtech announced its preliminary results for the **BNT162b1** candidate being evaluated in the German Phase 1/2 trial including 60 healthy adults aged 18-55. Of the 60 participants, 48 had received 2 doses of BNT162b1 on days 1 and 22, with 12 subjects receiving a 1 µg dose, 12 a 10 µg dose, 12 a 30 µg dose, and 12 a 50 µg dose; 12 participants received a single 60 µg injection.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate

On July 27, 2020, after review of preclinical and clinical data from the Phase 1/2 clinical trials, and in consultation with the FDA's Center for Biologics Evaluation and Research (CBER) and other global regulatory agencies, **Pfizer/BioNTech selected its BNT162b2 vaccine candidate in the Phase 2/3 study at a dose of 30 µg in a 2-dose regimen**.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate

On August 20, 2020, Pfizer/BioNTech announced additional Phase 1 safety and immunogenicity results on BNT162b2 at 30 µg from their ongoing U.S. study. They also announced that, with respect to the Phase 2/3 trial that began in July 2020, more than 11,000 participants had been enrolled.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-share-positive-early-data-lead-mrna

On October 6, 2020, based on preliminary results from preclinical and early clinical studies in adults suggesting antibody production following injection of the BNT162b2 vaccine candidate, Pfizer/BioNtech announced the start of discussions with the European Medicines Agency (EMA) for the **BNT162b2** vaccine candidate.

It was also reported that the global Phase 3 study of BNT162b2 included 37,000 participants enrolled at 120 clinical sites including the U.S., Brazil, South Africa and Argentina, and more than 28,000 participants had received their second dose.

Source : https://www.pfizer.com/news/press-release/press-release-detail/biontech-and-pfizer-initiate-rolling-submission-european

On November 20, 2020, Pfizer/BioNtech submitted its application to the FDA, and announced that it had already begun submitting applications around the world, including Australia, Canada, Europe, Japan and the United Kingdom.
Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-submit-emergency-use-authorization

On December 2, 2020, the U.K. Medicines and Healthcare products Regulatory Agency (MHRA), based on the results of the interim analysis, granted emergency marketing authorization for the Pfizer/BioNtech vaccine under Regulation 174, with the companies ready to deliver the first doses to the U.K. immediately.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-achieve-first-authorization-world

On December 10, 2020, Pfizer/BioNtech announced **efficacy results on the selected primary endpoint of COVID-19 infections from 7 days after the second dose (95% vaccine efficacy)** as well as safety results from the interim analysis of **BNT162b2** in 43,448 Phase 3 clinical trial participants enrolled from more than 150 clinical trial sites in the U.S., Germany, Turkey, South Africa, Brazil and Argentina.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-publication-results-landmark

On the same day, the results were presented to the FDA's Vaccine and Related Biologics Advisory Committee (VRBPAC), which voted 17-4 in favor of granting **an emergency use authorization** (EUA) for the BNT162b2 vaccine.

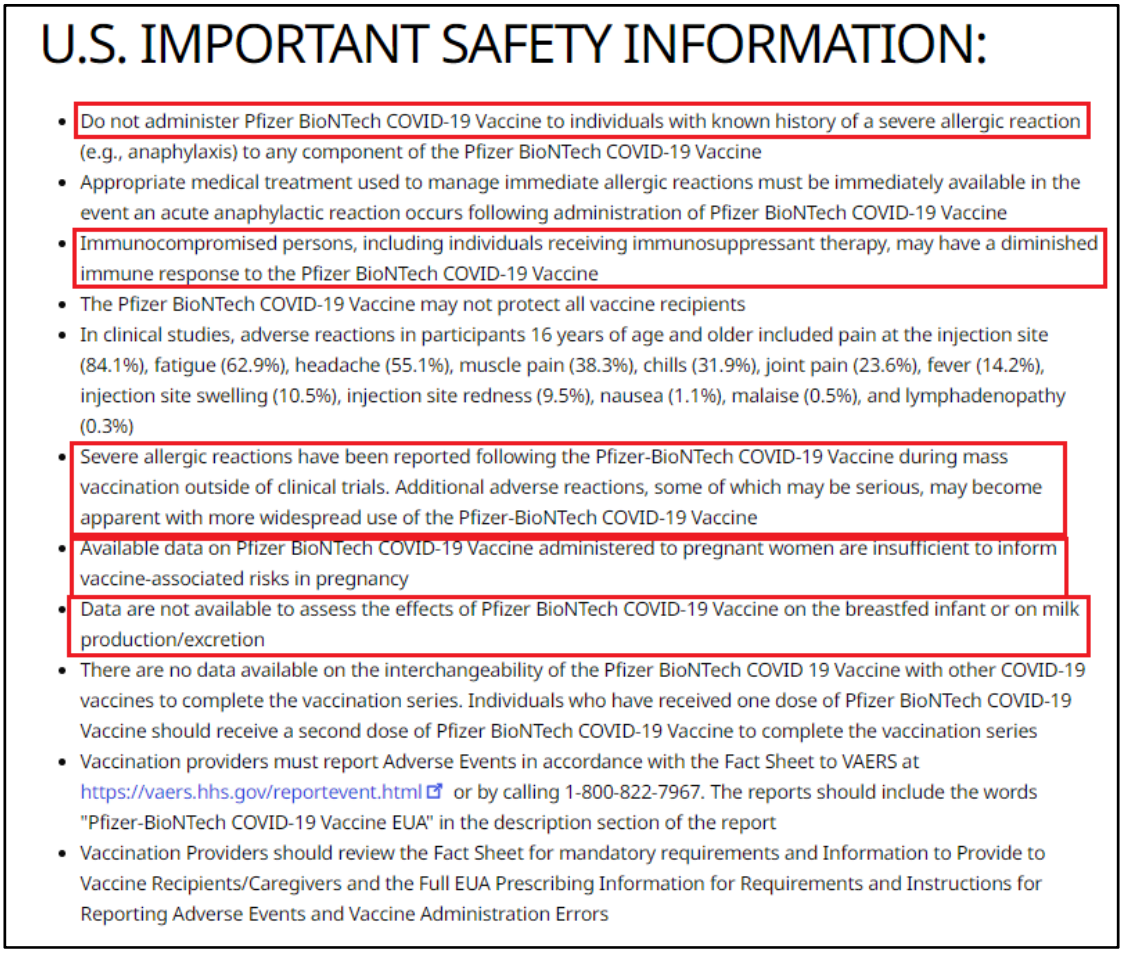
Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-fda-advisory-committee-vote

On December 14, 2020, Pfizer presented the results of the ongoing German Phase 1/2 study, "Analysis of the 37 participants immunized with BNT162b2 showed a broad immune response with SARS-CoV-2 specific neutralizing antibodies, TH1-like CD4+ T cells and a strong expansion of CD8+ T cells of the early effector memory phenotype. The data confirmed previous results from the U.S. trial demonstrating a good safety profile and robust induction of antibody responses **with a longer follow-up period of 85 days**."

In the same press release, Pfizer/BioNtech expressed a number of reservations and precautions for real-life use (see Illustration 16 : Pfizer - Press releases – December 14, 2020.).

- Do not administer Pfizer BioNTech COVID-19 vaccine to persons with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of Pfizer BioNTech COVID-19 vaccine.
- Immunocompromised individuals, including those on immunosuppressive therapy, may have a decreased immune response to Pfizer BioNTech COVID-19 vaccine.
- Pfizer BioNTech COVID-19 vaccine may not protect all vaccine recipients
- There are no data available to assess the effects of Pfizer BioNTech COVID-19 vaccine on breastfeeding infants or on milk production/excretion.
- There are no data available on the interchangeability of Pfizer BioNTech COVID-19 vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Pfizer BioNTech COVID-19 vaccine should receive a second dose of Pfizer BioNTech COVID-19 vaccine to complete the vaccination series.

Illustration 16 : Pfizer - Press releases – December 14, 2020



U.S. IMPORTANT SAFETY INFORMATION:

- Do not administer Pfizer BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer BioNTech COVID-19 Vaccine
- Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer BioNTech COVID-19 Vaccine
- Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer BioNTech COVID-19 Vaccine
- The Pfizer BioNTech COVID-19 Vaccine may not protect all vaccine recipients
- In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%)
- Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials. Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine
- Available data on Pfizer BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy
- Data are not available to assess the effects of Pfizer BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion
- There are no data available on the interchangeability of the Pfizer BioNTech COVID 19 Vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Pfizer BioNTech COVID-19 Vaccine should receive a second dose of Pfizer BioNTech COVID-19 Vaccine to complete the vaccination series
- Vaccination providers must report Adverse Events in accordance with the Fact Sheet to VAERS at https://vaers.hhs.gov/reportevent.html or by calling 1-800-822-7967. The reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report
- Vaccination Providers should review the Fact Sheet for mandatory requirements and Information to Provide to Vaccine Recipients/Caregivers and the Full EUA Prescribing Information for Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors

Source: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-data-german-phase-12-study

On December 21, the European Commission (EC) granted conditional marketing authorization (CMA) to Pfizer and BioNTech for its vaccine, now called Comirnaty®.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-authorization-european-union

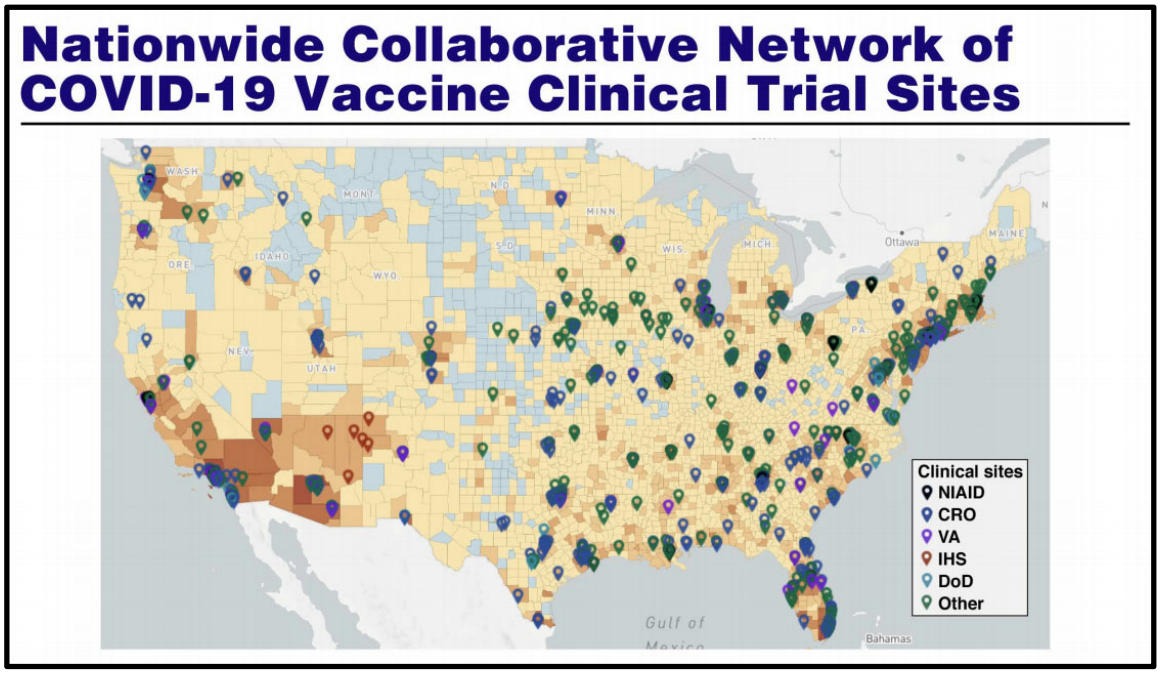
A simple calculation, based on the enrolment figures cited in the press releases, can be used to reconstruct the progress of enrolment in the Phase 2/3 clinical trial that concluded the proof of efficacy of the **BNT162b2** vaccine candidate.

Illustration 17 : Calculated rate of recruitment of participants in the Phase 3 trial

Date	Number of participants	Number of centers	Number of days	Recruitment rate per day	Recruitment rate per hour
27/07/2020	360				
20/08/2020	11000		25	426	53
06/10/2020	37000	120	48	541,7	67,7
14/11/2020	44000	150	40	175,0	21,9

The map below shows stakeholders throughout the United States involved in COVID-19 testing.

Illustration 18 : U.S. National Collaborative Network of Clinical Investigation Sites



Source: NIH activities in the development of vaccines against COVID-19 - Hilary Marston, M.D., M.P.H. / Medical Officer and Policy Advisor for Pandemic Preparedness / National Institute of Allergies and Infectious Diseases - https://www.fda.gov/media/143559/download

On the October 22, 2020, the presentation by Robert Johnson at the Vaccines and Related Biologics Advisory Committee Meeting available on the FDA website clearly summarizes the strategy being taken to accelerate development.

Illustration 19 : Normal development of a trial

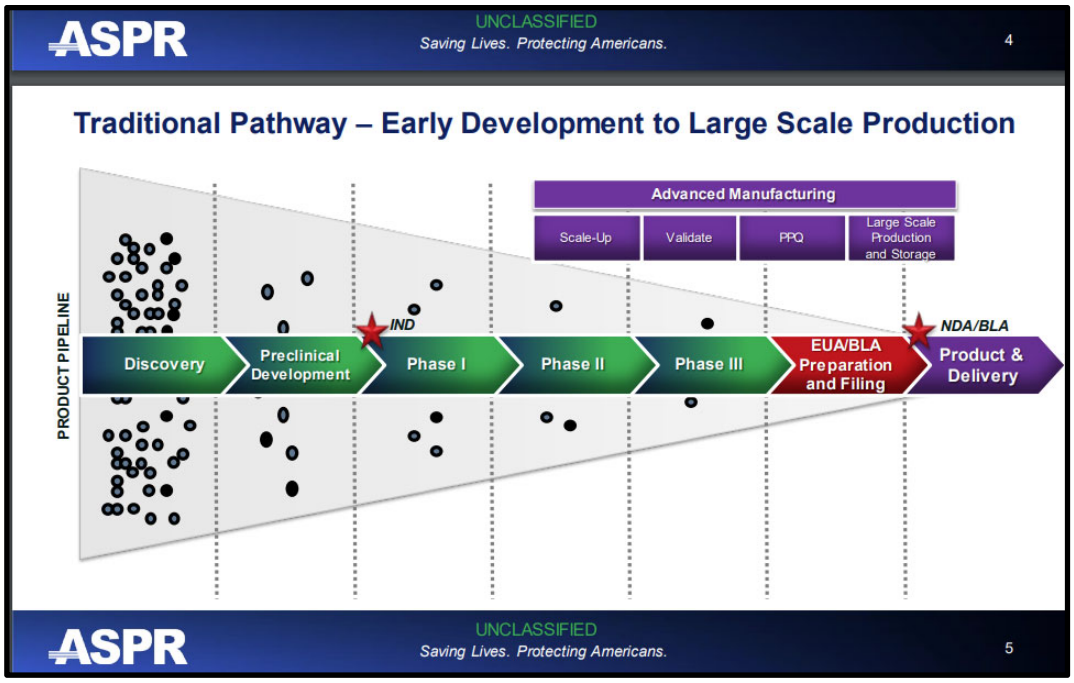
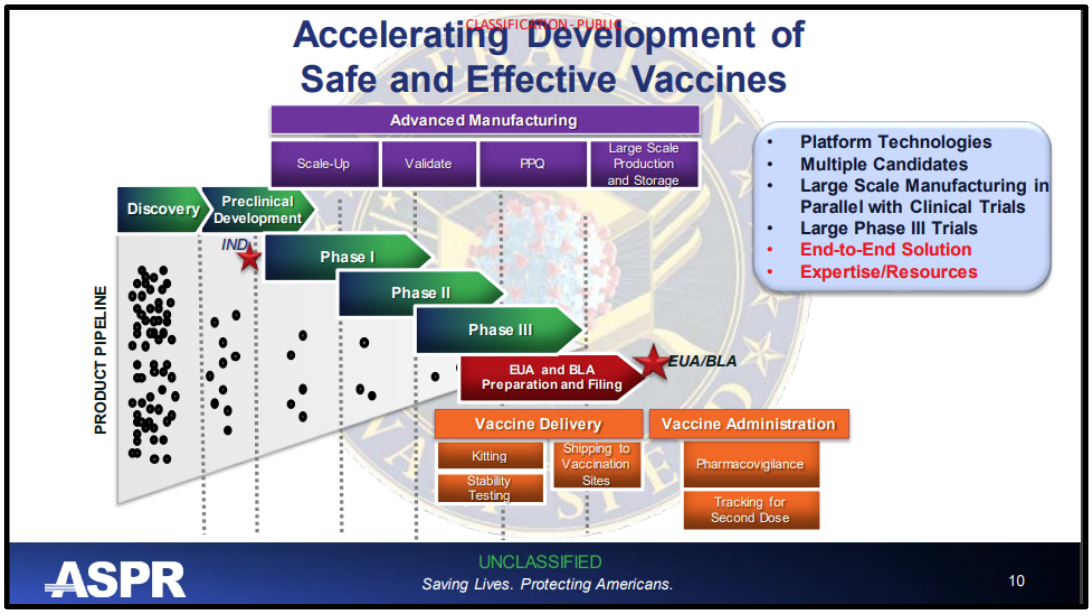


Illustration 20 : Accelerated development of COVID-19 trial



Source: Vaccines and Related Biological Products Advisory Committee, COVID-19 Vaccine Development Portfolio, - Robert Johnson, PhD Director, Division of Influenza and Emerging Infectious Diseases BARDA/ASPR/HHS - https://www.fda.gov/media/143560/download

In summary, between January 12, 2020, the publication of the genome by China, and the beginning of April 2020, BioNtech has therefore developed RNA vaccine candidates, a period of two and a half months.

The first human trial was approved by German authorities 11 days later, and by April 29, 12 patients had already received the vaccine candidates.

In this very short time, the laboratory had to ensure the manufacture of the products according to the regulations in force and to set up the distribution channels, which already appears to be a feat that we will not discuss in this report but which would require some clarification.

On July 27, 2020, phase 1/2 results, led to the selection of the BNT162b2 vaccine candidate for the phase 2/3 study, at a dose of 30 µg in a 2-dose regimen.

As of August 20, 2020, less than a month into the **BNT162b2** trial, 11,000 participants had already been recruited, with the number of participating centers not provided in the release, a rate of approximately **440 participants recruited per day, or 55 per hour.**

As of October 6, 2020, the Phase 2/3 study of BNT162b2 included 37,000 participants enrolled at 120 clinical sites including the United States, Brazil, South Africa and Argentina, and more than 28,000 participants had already received their second dose. Between October 6 and August 20, 26,000 participants were enrolled over a 48-day period, **at a rate of 542 per day, or nearly 68 per hour**.

As of November 14, 2020, the database provided for the interim analysis to the Independent Expert Panel contained nearly 44,000 participants recruited from 150 clinical trial sites across the United States, Germany, Turkey, South Africa, Brazil, and Argentina. This means that **13,000 participants were enrolled over a 40-day period, at a rate of 175 per day, or nearly 22 per hour**.

The results of the interim analysis were presented on December 10 and the FDA voted the same day for emergency use of Pfizer's vaccine candidate, BNT162b2 versus placebo

This tremendous rate of recruitment of participants (44,000) spread over 150 centers throughout the United States as well as in Germany, Turkey, South Africa, Brazil and Argentina already raises the question of compatibility with

* proper training of investigating centers,

* a homogeneous practice of the centers

* adequate follow-up of participants

5.2 Characteristics of the Pfizer-BioNtech Phase 1-2-3 trial (main or pivotal)

This is a randomized, controlled Phase 1-2-3 study testing several doses of vaccines candidates; the BNT162b2 vaccine candidate at the 30 µg dose selected in Phase 2 versus placebo, 0.9% saline. The trial is multicenter, meaning that it is taking place at several clinical sites.

Source : Protocole de la phase 1- 2-3

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf

The study is composed of 2 parts.

- Phase 1: to determine the best vaccine candidate (choice of dose and dosage)
- Phase 2/3: Expanded cohort and an efficacy portion.

The primary objective of Phase 2-3 is to evaluate the efficacy of BNT162b2 in preventing the development of symptomatic COVID-19 from 7 days after the second dose of vaccine in participants without pre-vaccination COVID-19 infection.

The second objective is identical to the first one but in participants with or without infection before vaccination.

It is also a question of studying tolerance in terms of local reactions to the injections as well as so-called systemic events (fever, fatigue, chills, vomiting, diarrhea, etc.) and any other serious or non-serious events.

As an exploratory measure, the immune response and its persistence will also be evaluated.

The participant initially had to be over 18 years of age to be included in the trial; Amendment 6 on September 8 allows 16-17 year olds to be included and Amendment 7 on October 6, 2020 expands the population to 12-15 year olds.

As for all clinical trials, pregnant or lactating women are excluded, as they are part of a protected population under patient protection laws.

8 visits were foreseen by the protocol,

- Visit 1: first dose of the experimental product on Day 1
- Visit 2: second dose of the experimental product which was to take place between days 19 and 23 after the first visit
- *Visit 3: 1 week after dose 2 –only phase 1-2*
- *Visit 4: 2 weeks after dose 2 – only phase 1-2*
- Visit 5: visit at 1 month, between 28 and 35 days after visit 2 (2nd dose),
- Visit 6: visit at 6 months, between 175 and 189 days after 2nd dose
- Visit 7: visit at 12 months, between 350 and 378 days after 2nd dose
- Visit 8: visit at 24 months, between 714 to 742 days after 2nd dose

The total duration of the trial was therefore 25 months.

The list of parameters collected during each visit can be seen on the following 3 diagrams.

Illustration 21 : Phase 1-2-3 Pfizer Clinical Study Protocol - Detailed Visit Schedule - - 1

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	

Illustration 22: Phase 1-2-3 Pfizer Clinical Study Protocol - Detailed Visit Schedule -2

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄—►	◄—►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
Collect e-diary or assist the participant to delete application						X		

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf

Illustration 23 : Phase 1-2-3 Pfizer Clinical Study Protocol - Detailed Visit Schedule - 3

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf

In order not to introduce **bias** into the investigator's selection of participants, the study was **blinded**, as the physical appearance of the experimental vaccine candidates and the placebo could be different. The participant was not aware of the product he or she was receiving, nor were the investigator, study coordinator, or other site personnel.

At the investigator site, only the personnel in charge of storage, distribution, preparation and administration of the experimental products were not "blinded" and knew the contents of the vials handled.

Antibody samples (line "Collect Blood sample for immunogenicity" in Illustration 13 were to be taken on Day 1, the day on which the participant received his/her first dose of the experimental product, at Visit 3 (1 month after the second dose), at Visit 4 (6 months after the second dose), at Visit 5 (12 months after the second dose), at Visit 6 (at 24 months after the second dose).

No follow-up visits to participants were planned between 1 and 6 months after injection of the second dose, either to measure antibodies, or to collect tolerance data or COVID-19 infections.

Vaccine efficacy was to be assessed **based on the major clinical endpoint of interest, the so-called primary endpoint, by counting the number of confirmed symptomatic COVID-19 cases**.

In order to classify the participant as symptomatic COVID-19, the diagnosis had to take place as specified in the trial protocol, in its sections "*8.1. Efficacy and/or Immunogenicity Assessments*" and "*8.13. COVID-19 Monitoring*".

Illustration 24 : Phase 1-2-3 Pfizer Clinical Study Protocol (April 15th, 2020) – Determination of COVID-19 cases

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, a telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. Four definitions of potential SARS-CoV-2–related cases will be considered:

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf

Illustration 25 : Phase 1-2-3 Pfizer Clinical Study Protocol (April 15th, 2020) - COVID-19 Surveillance

8.13. COVID-19 Disease Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately, and if confirmed, participate in a telehealth visit as soon as possible, optimally within 3 days of symptom onset. Note that this does not substitute for a participant's routine medical care. Therefore participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- New or increased sore throat;
- New or increased wheezing;
- New or increased sputum production;
- New or increased nasal congestion;
- New or increased nasal discharge;
- Loss of taste/smell.

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf

According to 8.1, efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19.
If the participant experienced at least one of the symptom in the Illustration 25, he should contact the site to plan an in-person visit or a telehealth in order to have a nasal swab, which will be tested at a central laboratory to detect SARS-CoV-2.
The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used.

It is important to note that, as planned in most trials, in addition to the test result provided by the local laboratory (laboratory in the participant's locality), the nasal swab had to be sent to a central laboratory to confirm or not the initial result and to avoid having heterogeneous diagnostic methods.

In the fourth Amendment of the protocol (30 June 2021), the symptoms for diagnosing COVID-19 were modified to approximate the June 2020 FDA "Development and Licensure of Vaccines to Prevent COVID-19" recommendations as shown in the amendment history page 134 of the pdf document (Illustration 26).

Illustration 26 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Summary of changes

Document	Version Date	Summary and Rationale for Changes
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment.

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf (page 134 of the pdf document)

This amendment changes the 6-month visit initially planned by simple telephone contact (teleconsultation) into a face-to-face visit allowing a blood sample to be taken for antibody testing.

The amendment also allows that the surveillance visit for COVID-19 was conducted via teleconsultation and no in person at the investigator site.

At the time of the start of the Phase 2/3 trial on July 27, 2020, it was therefore the second definition of symptoms that was underway to determine the occurrence of a COVID-19 as explained in sections 8.1 (Illustration 27), 8.14 (Illustration 33) and 8.13 (Illustration 32) of the protocol.

Illustration 27 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Determination of COVID-19 cases

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf (page 201 of the pdf document)

According to this new definition, by confirmed symptomatic COVID-19, it should therefore be understood:

- **Presence of at least one of the following symptoms**
    - Fever,
    - New or increased cough,
    - New or increased shortness of breath,
    - Chills,
    - New or increased muscle pain,
    - New loss of taste or smell,
    - Sore throat,
    - Diarrhea,
    - Vomiting.

and

- **Positive PCR Test** during or within the 4 days before or after the symptomatic. The nasal swab should be sent to a central laboratory in order to get homogenous results for all participants.

  If no central result was available, the result of a local laboratory should be used to confirm a COVID-19 case.

The severe cases were defined into the protocol as follows :

- **Confirmed COVID-19**
- **And presence of at least 1 of the following :**
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
    - Significant acute renal, hepatic, or neurologic dysfunction*;
    - Admission to an ICU;
    - Death.

In order to monitor reactions to the injection of the investigational products (reactogenicity) remotely, some participants had access to the study website, as explained in section "**8.2.2 Electronic Diary**" of the protocol. The participant himself/herself or his/her legal representatives could report certain information regarding his/her health status after injection of the investigational vaccine tested during the trial via an application installed on their personal devices.

The participant was trained in the use of this tool on the day of his first injection, cf line "Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required (Illustration 22).

The following items were to be assessed and reported by the first 6000 participants included in the Phase 3 trial (reactogenicity population) from one day after injection to 7ème days after injection, i.e., for approximately 14 days:

- ***Local reactions:***
  - Pain at the injection
  - Swelling
  - Redness

- ***Systemic events :***
  - **Vomiting**
  - **Diarrhea**
  - Headache
  - Fatigue/ tiredness
  - **Chills**
  - **New or worsened muscle pain**
  - New or worsened joint pain
- **Maximal oral temperature**

These possible reactions to vaccine are called “Solicited Eventss”.

The patient was required to alert their investigator in case of:

- **Grade 3** on the local reaction grading scale or grade 3 systemic event (cf Illustration 28 and Illustration 29), the event had to be reported to the investigator in order to plan a possible visit to the center. Grade 4 could only be determined by the investigator who had to inform the Sponsor and remove the patient from the trial
- **Fever ≥ 39 degres**. In case of the fever exceeded 40 degrees, it was imperative that the investigator inform the Sponsor and remove the patient from the trial.

The investigator remained responsible for detecting other serious or non-serious events by interviewing participants during their visit to the center.

Illustration 28 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Local reaction grading scale

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf (page 207 du document pdf)

Illustration 29 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) - Systemic event grading scale

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf (page 207 du document pdf)

The participant was also asked to record the use of antipyretic medication.

Illustration 30 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) - Antipyretic medication

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the e-diary daily during the reporting period (Day 1 to Day 7).

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf

In July 2020, the clinical trial was supposed to end in January 2023 as indicated on the clinical trial registration site.

Illustration 31 : Pfizer - Trial registration

Study Details

Study Identification

Unique Protocol ID	C4591001
Brief Title	Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults
Official Title	A PHASE 1/2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO DESCRIBE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND POTENTIAL EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY ADULTS
Secondary IDs	2020-002641-42

Study Status

Record Verification	2020-07
Overall Status	Active, not recruiting
Study Start	2020-04-29 [Actual]
Primary Completion	2021-06-28 [Estimated]
Study Completion	2023-01-23 [Estimated]
First Submitted	2020-04-27
First Submitted that Met QC Criteria	2020-04-29
First Posted	2020-04-30 [Actual]
Last Update Submitted that Met QC Criteria	2020-07-15
Last Update Posted	2020-07-17 [Actual]

Source : https://clinicaltrials.gov/study/NCT04368728?tab=history&a=7#version-content-panel

When analyzing these elements, we observe **several inaccuracies and methodological issues** in the evaluation of the primary efficacy criterion, specifically the number of confirmed symptomatic COVID-19 cases.

To calculate this criterion, it was necessary to determine, for each participant, whether they exhibited symptoms, whether they were a confirmed case (yes or no), and, if yes, the date of confirmation. This assessment was particularly important from seven days after the second injection for the main analysis and only during the observation period prior to database extraction.

To document symptoms indicative of a potential COVID-19 case, participants could use an electronic diary, as illustrated in Illustration 32. It is important to note that this method of data collection is more suitable for a younger population accustomed to using digital tools than for an older population.

Illustration 32 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Determination of COVID-19 cases

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf (pages 241-242 du document pdf)

In order to correctly report his symptoms, the participant had the following means at his disposal (Illustration 33)

- Contact with the investigator, including the opportunity for the participant or the participant's parents/legal guardians, as appropriate, ***to report whether or not the participant has experienced symptoms that could represent potential COVID-19-related illness*** *(COVID-19 Electronic Illness Diary; see Section 8.13).*

- *An alert in case of hospitalization of the participant.*
- *Visit reminders.*
- *Messages of thanks and encouragement from the study team.*
- *A platform for recording local reactions and systemic events (electronic reactogenicity diary)*

Illustration 33 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Communication between the participant and the investigator site

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf (page 244 du document pdf)

Participants were **encouraged** to contact the study site immediately but were also advised to consult their physician if they experienced any of the following symptoms: fever, onset or worsening of cough, onset or worsening of shortness of breath, chills, onset or worsening of muscle aches, loss of taste or smell, sore throat, diarrhea, or vomiting.

If a participant consulted their primary care physician, the physician would presumably perform a nasal swab for analysis by a local laboratory. However, it is unclear whether the physician was required to take two swabs so that one could be sent to the central laboratory, as this is not specified in the protocol.

Once the test result was obtained, the participant was instructed to contact the investigator site to ensure the result was recorded in the database.

If the participant chose to contact the site directly and not to make an appointment with his usual doctor, it is specified in the protocol (see Illustration 24) that symptoms that could be possible **reactions** to the experimental product (fever, chills, muscle aches ...) should not trigger a visit for a potential COVID-19 disease, **unless**

- *If, in the opinion of the investigator, such a visit was necessary.*
- *If, in the opinion of the investigator, the clinical picture was more indicative of possible COVID-19-related disease than vaccine reactogenicity.*
- *If, in the opinion of the investigator, the symptoms were more likely to be vaccine reactogenicity, **a local test for SARS-CoV-2** could be performed.*

This diagnostic method also relies on the participant's accurate assessment of their symptoms.

It is worth noting that participants who completed the electronic diary to assess reactogenicity were also required to complete the COVID-19 electronic symptom diary, where they had to report identical symptoms, including fever, chills, muscle aches, diarrhea, and vomiting.

This approach further necessitated that center staff respond promptly to participant calls reporting symptoms so that PCR testing could be conducted as quickly as possible. Considering the number of participants recruited per clinical investigation center (an average of 293) in record time during the COVID-19 pandemic and under travel restrictions, it is unclear whether the investigative sites had sufficient capacity to respond to all participant calls.

It is was also planned that "*if a participant or the participant's parents/legal guardians, as appropriate, did not actively complete the electronic reactogenicity log or the COVID-19 electronic disease log, the investigator or designee was to contact the participant or the participant's parents/legal guardians, as appropriate, to determine the reason for this and to obtain details of the missed events.*"

The Pfizer laboratory was thus well aware of the importance of the postponement of symptoms since section 8.14 of the protocol insists on this point (see Illustration 33)
"***In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her***

***parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed*.”**

Clearly, **any incomplete or erroneous reporting of symptoms could lead to an inaccurate assessment by the investigator,** particularly if the participant is engaging through a teleconsultation and not in person.

It is also important to note that the use of antipyretics suppresses fever and reduces or even eliminates pain—symptoms that serve as initial indicators of COVID-19 and should prompt testing to confirm the presence of the virus. Thus, the use of antipyretics introduces a significant bias by masking symptoms and potentially excluding COVID-19 cases from identi **Furthermore, it is well known that some symptoms, such as fever, chills, muscle aches, diarrhea, and vomiting, can be both reactions to the vaccination and symptoms of COVID-19.**

How could an investigator, relying solely on participant-reported data during teleconsultations, differentiate between vaccine-related reactions and COVID-19 symptoms without examining the participant? **Logically, any participant presenting symptoms of interest should have undergone immediate PCR testing to classify the symptoms as either adverse events or COVID-19 cases, leaving no room for the investigator’s subjective interpretation**.

This approach introduces a **significant bias in evaluating the occurrence of COVID-19**. It is evident that if no PCR test is performed, no symptomatic COVID-19 case is recorded, meaning that **any symptomatic participant without a PCR test is automatically classified as a therapeutic success.**

Even more concerning, a symptomatic participant who tests positive via a local laboratory’s PCR test but is unable to contact the investigator site is also classified as a therapeutic success.

In order to overcome this major bias, it would have been much more appropriate to perform PCR tests not only for participants reporting symptoms, but for **all** participants, this would also have allowed the detection of asymptomatic COVID-19 who are also vectors of the disease.

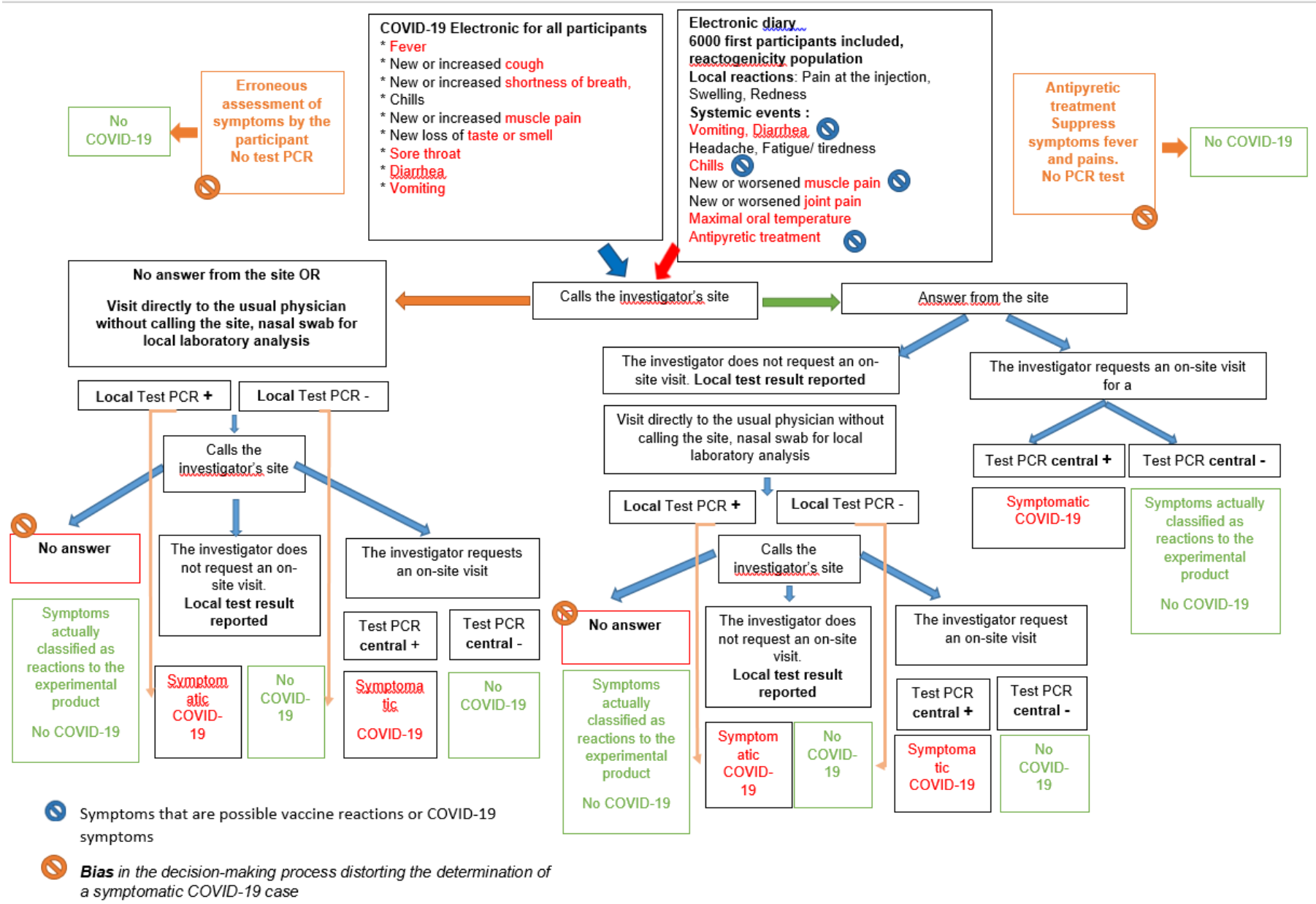
Considering the choice of the primary endpoint itself, we can already conclude that the Pfizer vaccine cannot claim to prevent transmission of COVID-19 since the efficacy is only evaluated on symptomatic cases and not all COVID-19 cases.

The diagnostic method chosen (summarized in the diagram on the following page), although usual in the clinical trials on vaccines, is very surprising in the context of a pandemic where any person infected with COVID-19 could contaminate those around him or her, transmitting a potentially fatal disease.

This obviously did not worry the laboratory much, which left the participants on their own without offering them systematic and regular tests as one might have expected.

From the protocol, it is already clear that the method used to determine the occurrence of a symptomatic COVID-19 case confirmed by PCR test, the main criterion of the trial, presents multiple biases that can seriously compromise the results obtained.

Illustration 34 : Main criterion diagnosis, symptomatic COVID-19 confirmed by PCR test



To conclude efficacy without waiting for the trial's completion, the protocol outlined several interim analyses of the primary endpoint described above. These analyses were planned to occur after the identification of 62, 92, and finally 120 evaluable symptomatic COVID-19 cases.

The final analysis of all efficacy endpoints (both primary and secondary) was to be conducted after at least 164 evaluable symptomatic COVID-19 cases had been identified.

Furthermore, Protocol Amendment 10, dated December 1, 2020, allowed participants who had received the placebo to switch to receiving BNT162b2 (see Illustration 35 page 129 of the pdf document).

This amendment effectively eliminates the possibility of comparing the BNT162b2 and placebo groups for both efficacy and safety, as will be discussed.

Illustration 35 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) –Summary of changes

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf

In summary,

Certain symptoms of COVID-19 overlap with vaccine reactions (reactogenicity), making it difficult for both the participants and the recruiting center to identify COVID-19 cases.

Participants are responsible for assessing and reporting their symptoms to the investigator who recruited them in order to undergo PCR testing.
The use of electronic diaries is not suitable for an elderly population, which is the group most susceptible to contracting SARS-CoV-2.

The use of antipyretic treatments suppresses fever and alleviates, or even eliminates, pain, which are among the early signs that could indicate a COVID-19 infection. These measures deprive patients of their ability to assess their symptoms and undergo PCR testing, as they become asymptomatic.
Thus, the use of antipyretics introduces a statistical bias by masking symptoms and potential COVID-19 cases.

Regular PCR testing is not provided, which, although common in vaccine clinical trials, is quite surprising in the context of a pandemic, where any COVID-19 patient could infect those around them with a potentially deadly disease. This did not seem to greatly concern the laboratory, which left participants to manage on their own without offering systematic and regular testing, as might have been expected.

This approach introduces a significant bias in the assessment of COVID-19 occurrence. Indeed, the absence of a PCR test in a symptomatic patient will be interpreted as the absence of symptomatic COVID-19 and classified as a therapeutic success.
The absence of a PCR test in asymptomatic patients allows uncounted cases to go unreported. This artificially inflates the number of therapeutic successes and skews the results of vaccine efficacy.

The method used to determine the occurrence of symptomatic COVID-19 cases confirmed by PCR testing, which is the primary endpoint of the trial, contains multiple biases that invalidate the results obtained.

Furthermore, efficacy against transmission is not demonstrated, as it was not studied.

6 Clinical trial results – Clinical study report on the adult population (more than 16 years old)

6.1 December 10, 2020 Clinical Study Report - 3-Month Interim Analysis

6.1.1 Initial results

As of November 14, 2020, 43,548 participants had been randomized from the 44,820 selected, 21,220 participants received the vaccine and 21,728 received the placebo.

At the time of the interim analysis reviewed with the health authorities, **the data included are those for the period July 72, 2020, through November 14, 2020**, the date of the interim database freeze, referred to as Cuttoff as indicated under the report's results tables.

At that date, 37,706 participants were analysed in the safety population (18,860 BNT162b2 and 18,846 placebo), half of whom had been followed for more than 2 months after the second dose of vaccine (50.6% exactly), 91.6% had been followed for more than 1 month after the first injection.

Details of participant follow-up times are presented in Table 3 of the clinical report (page 30).

Illustration 36 : December 10, 2020 Clinical Study Report – Participants follow-up

Table 3. Follow-Up Time After Dose 2 – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Subjects (%) with length of follow-up of:			
<2 Months	9329 (49.5)	9310 (49.4)	18639 (49.4)
<2 Weeks	363 (1.9)	388 (2.1)	751 (2.0)
≥2 to <4 Weeks	1223 (6.5)	1200 (6.4)	2423 (6.4)
≥4 to <6 Weeks	3239 (17.2)	3235 (17.2)	6474 (17.2)
≥6 to <8 Weeks	4504 (23.9)	4487 (23.8)	8991 (23.8)
≥2 Months	9531 (50.5)	9536 (50.6)	19067 (50.6)
≥8 to <10 Weeks	6296 (33.4)	6329 (33.6)	12625 (33.5)
≥10 to <12 Weeks	2853 (15.1)	2809 (14.9)	5662 (15.0)
≥12 to <14 Weeks	382 (2.0)	398 (2.1)	780 (2.1)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 18NOV2020 (05:34) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adsl_s005_fup_time_d2_saf

Source: https://www.fda.gov/media/144246/download

Of the 37,706 participants, **only 780 were followed for more than 3 months at the time of the interim analysis, or 2.1%** of the population analyzed.

The 2010 World Health Organization (WHO) recommendations, in section "*2.13 Follow-up in clinical trials*", called for a **follow-up period of one year for efficacy and 6 months for safety**.

Illustration 37 : 2010 WHO Recommandations

> **2.13 Follow-up in clinical trials**
> It is expected that there will be a follow-up of at least 6-months in clinical trials after the last dose of the vaccine, for safety assessment. This should be active and not reliant on spontaneous reports.
> For efficacy and immunogenicity assessment longer follow-up, of at least one year, may be expected depending on the clinical endpoint requirements. Applicants are directed to guidance documents on specific vaccines for further information.
> Immunogenicity assessment before and after the booster dose will be required for vaccines given as a booster dose.

Source :
https://web.archive.org/web/20131031205225/https://www.who.int/immunization_standards/vaccine_quality/clinical_considerations_oct10.pdf

In October 2020, the FDA wrote special recommandations for COVID-19 vaccines in a document called, "*Emergency Use Authorization for Vaccines to Prevent COVID-19*."

Source : https://www.fda.gov/media/142749/download

The preface indicates in the Public Comment section that this document was implemented **without public review as is customary**.

This document reduces the minimum duration of participant follow-up time to a median of 2 months, i.e., 50% may be followed for less than 2 months to establish efficacy and tolerability as clearly stated in paragraph c. on page 11

Illustration 38 : FDA Emergency Use Authorization for Vaccines to Prevent COVID-19 - Section C-3.c. Information Tolerance and efficacy

> c. Data from Phase 3 studies should include a median follow-up duration of at least two months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile, including: adverse events; cases of severe COVID-19 disease among study subjects; and cases of COVID-19 occurring during the timeframe when adaptive (rather than innate) and memory immune responses to the vaccine would be responsible for a protective effect.

Source : https://www.fda.gov/media/142749/download

These new recommendations issued in a hurry are therefore not consistent with all previous recommendations, even the FDA's own recommendations written in June 2020 which were defined to provide valid and reliable results.

The results on page 55 of the clinical report (see Illustration 39) focus on the first appearance of COVID-19 from 7 days after dose 2 in participants without infection before 7 days after dose 2. They indicate that of the 18,198 participants who received BNT162b2, 8 were diagnosed with symptomatic COVID-19 by the definition and diagnostic method used, or 0.0439%, versus 162 in the placebo group, or 0.884%.

The efficacy was calculated as follows

$$\text{Relative risk (RR)} = \frac{8 / 18\,198}{162 / 18\,328} = \frac{0.0439}{0.8840} = 0.0497\ \%$$

Vaccine Efficacy = 1- RR = 1-0.0497=95 %

The 95% credible interval for VE was 90.3% to 97.6% (95% confidence interval shown in the table below), indicating that the true VE is at least 90.3% with a probability of 97.5% (2.5% error threshold to conclude efficacy) given the observed data.

Illustration 39 : December 10, 2020 Clinical Study Report –Efficacy results – Main criterion – Symptomatic COVID-19 – 92 pages Report

Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_wo_eval

Source: https://www.fda.gov/media/144246/download

A second report was presented by the laboratory during the "*Vaccines and Related Biological Products Advisory Committee*" of December 10, 2020, this one comprising only 53 pages instead of the 92 of the other report.

Source https://www.fda.gov/media/144245/download

The non-numbered page 24 shows exactly the same results as the first report but including results by age strata, confirming that these are the same results over the same observation periods.

Illustration 40 : December 10, 2020 Clinical Study Report – Efficacy results – Main criterion – Symptomatic COVID-19 – 53 pages report

5.2.5. Vaccine Efficacy

Primary Efficacy Analyses

Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 6). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Source : https://www.fda.gov/media/144245/download

This document mentions (page 42) **suspected cases of COVID but not confirmed by PCR test**, this part of the report has disappeared from the other 92 pages report presented the same day.

Illustration 41 : December 10, 2020 Clinical Study Report – Suspected COVID-19 cases – 53 pages report

Pfizer-BioNTech COVID-19 Vaccine
VRBPAC Briefing Document

Suspected COVID-19 Cases

As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness. Two serious cases of suspected but unconfirmed COVID-19 were reported, both in the vaccine group, and narratives were reviewed. In one case, a 36-year-old male with no medical comorbidities experienced fever, malaise, nausea, headache and myalgias beginning on the day of Dose 2 and was hospitalized 3 days later for further evaluation of apparent infiltrates on chest radiograph and treatment of dehydration. A nasopharyngeal PCR test for SARS-CoV-2 was negative on the day of admission, and a chest CT was reported as normal. The participant was discharged from the hospital 2 days after admission. With chest imaging findings that are difficult to reconcile, it is possible that this event represented reactogenicity following the second vaccination, a COVID-19 case with false negative test that occurred less than 7 days after completion of the vaccination series, or an unrelated infectious process. In the other case, a 66-year-old male with no medical comorbidities experienced fever, myalgias, and shortness of breath beginning 28 days post-Dose 2 and was hospitalized one day later with abnormal chest CT showing a small left-sided consolidation. He was discharged from the hospital 2 days later, and multiple nasopharyngeal PCR tests collected over a 10-day period beginning 2 days after symptom onset were negative. It is possible, though highly unlikely, that this event represents a COVID-19 case with multiple false negative tests that occurred more than 7 days after completion of the vaccination regimen, and more likely that it represents an unrelated infectious process.

Among 3410 total cases of suspected but unconfirmed COVID-19 in the overall study population, 1594 occurred in the vaccine group vs. 1816 in the placebo group. Suspected COVID-19 cases that occurred within 7 days after any vaccination were 409 in the vaccine group vs. 287 in the placebo group. It is possible that the imbalance in suspected COVID-19 cases occurring in the 7 days postvaccination represents vaccine reactogenicity with symptoms that overlap with those of COVID-19. Overall though, these data do not raise a concern that protocol-specified reporting of suspected, but unconfirmed COVID-19 cases could have masked clinically significant adverse events that would not have otherwise been detected.

Source : https://www.fda.gov/media/144245/download

It states that during the trial, 3410 COVID 19 were suspected but not confirmed, 1594 occurred in the vaccine group versus 1816 in the placebo group.

Suspected cases that occurred within 7 days of any vaccination were **409** in the vaccine group versus **287** in the placebo group.

The remaining question is why 3410 cases were not confirmed by PCR test.

Were the cases unconfirmed because the PCR test was negative or unconfirmed because the PCR test was not performed by the center?

Therefore, the number of PCR tests performed for the 3410 suspected but non confirmed COVID 19 cases should be available.

If the primary endpoint had been based on the number of symptomatic participants, which is a relevant endpoint since the symptomatic patients are those who are hospitalized, we

would have had, at a minimum, 417 cases for BNT162b2 (8+409) and 449 cases for placebo (162+287), which would have resulted in a VE of 6.5% !

Assuming that 30% of these cases were positive from 7 days after dose 2, this would add 123 cases to the 8 cases for the BNT162b2 group, or 131 cases. For the placebo group, we would obtain 86 additional cases to be added to the 162 already observed, i.e. 248 cases.

The efficacy calculation would then be 46.8%, far from the 95% announced.

When the percentage of COVID-19 cases is decreased, the efficacy is increased (see Illustration 3 Vaccine Effectiveness Simulation). This suggests an underestimation of the number of COVID-19 cases due to lack of PCR testing.

This suggests an underestimation of the number of COVID-19 cases due to lack of PCR testing.

Illustration 42 : Simulation Vaccine Efficacy according to positive % rate among the non confirmed cases

Hypothèse % de cas +	BNT162b2	Placebo	BNT162b2	Placebo	IRR	VE
30%	122,7	86,1	0,720	1,353	0,532	46,8 %
25%	102,25	71,75	0,604	1,277	0,473	52,7%
20%	81,8	57,4	0,495	1,195	0,414	58,6%
15%	12,27	8,61	0,110	0,933	0,118	88,2%
10%	1,227	0,861	0,049	0,889	0,056	94,4%

With less than 50% efficacy, the vaccine would not have been suitable for emergency use as the "*Development and Licensure of Vaccines to Prevent COVID-19*" document specified that a vaccine efficacy greater than 50% is necessary to obtain an emergency use. **This makes the suspected but unconfirmed cases of covid-19 even more suspect.**

Illustration 43 : FDA - Development and Licensure of Vaccines to Prevent COVID-19 – Efficacy threashold

E. Statistical Considerations

- To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%.
  - The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.
  - A lower bound ≤30% but >0% may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.

Source: Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (fda.gov) - U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research June 2020 - https://www.fda.gov/media/139638/download

It is interesting to note that the vaccine efficacy was lower, **82%**, when taking into account **symptomatic COVID-19 cases from dose 1**.

This shows how much the choice of the primary efficacy criterion affects the result since there is a 13% loss when counting from dose 1 and not from dose 2.

Illustration 44 : Pfizer - December 10, 2020 Clinical Study Report – Résultats d'efficacité COVID-19 symptomatiques à partir de la dose 1 - Rapport de 92 pages

Table 11. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 18NOV2020 (17:06)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: /nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_pd1_aai

Source: https://www.fda.gov/media/144246/download

For severe cases within 7 days after dose 2 (page 65 of the report), the reported vaccine efficacy (VE) results were 66.4%, however, the VE confidence interval of (-124.8, 96.3) **did not support a difference between BNT162b2 and placebo for this endpoint**.

Illustration 45 : Pfizer December 10, 2020 Clinical Study Report – Efficacy results – Severe COVID-19 – 92 pages Report

Table 16. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:47)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_7pd2_wo_eval

Source: https://www.fda.gov/media/144246/download

As of December 10, 2020, it was therefore incorrect to conclude that BNT162b2 protected against severe cases as defined in the protocol.

Concerning the reactions reported by the participant on the electronic diary, only the 53-page report gives the numbers and proportions of participants with an event, the 92-pages report presenting only graphs making the percentages difficult to read.

In the subpopulation of participants aged 18-55 years with access to electronic diaries, 2045 BNT162b2 and 2053 placebo after dose 2 (pages 35 and 36 of the report), there was significantly more use of antipyretics in the BNT162b2 group (45%) than in the placebo group (12.6%).

The presence of a fever ≥ 38, chills, muscle pain are also much more reported with, respectively 15.8%, 35.1% and 37.3% versus 0.5%, 3.8% and 8.2% for placebo.

The results were similar for those over 55 years of age (pages 37 and 38 of the report) in terms of the difference between BNT162b2 and placebo but with less symptom reported, possibly due to the use of the electronic diary, which may indicate an underestimation of symptoms in older participants.

Illustration 46 : December 10, 2020 Clinical Study Report – Solicited events after dose 2 – 18-55 years Population / > 55 years old Population

	18 to 55 Years of Age		>55 Years of Age and Older	
Adverse Event	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Fever				
≥38.0°C	331 (15.8)	10 (0.5)	181 (10.9)	4 (0.2)
>38.0°C to 38.4°C	194 (9.2)	5 (0.2)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	110 (5.2)	3 (0.1)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	26 (1.2)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chills[a]				
Any	737 (35.1)	79 (3.8)	377 (22.7)	46 (2.8)
Mild	359 (17.1)	65 (3.1)	199 (12.0)	35 (2.1)
Moderate	333 (15.9)	14 (0.7)	161 (9.7)	11 (0.7)
Severe	45 (2.1)	0 (0.0)	17 (1.0)	0 (0.0)
New or worsened muscle pain[a]				
Any	783 (37.3)	173 (8.2)	477 (28.7)	87 (5.3)
Mild	326 (15.5)	111 (5.3)	202 (12.2)	57 (3.5)
Moderate	410 (19.5)	59 (2.8)	259 (15.6)	29 (1.8)
Severe	47 (2.2)	3 (0.1)	16 (1.0)	1 (0.1)
Use of antipyretic or pain medication	945 (45.0)	266 (12.6)	625 (37.7)	161 (9.8)

Source : https://www.fda.gov/media/144245/download

It should be noted that the reactogenicity population is a subpopulation of the general population, so **it would have been important to ensure that it represents the general population in terms of age, sex, comorbidities**...

Regarding the duration of protection assessed by antibody assay, Illustration 47 shows the average neutralizing antibody assay for participants aged 18 to 55 years (page 26 of the report), while Illustration 47 (page 27 of the report) shows the average neutralizing antibody assay for participants over 65 years of age for phase 1/2.

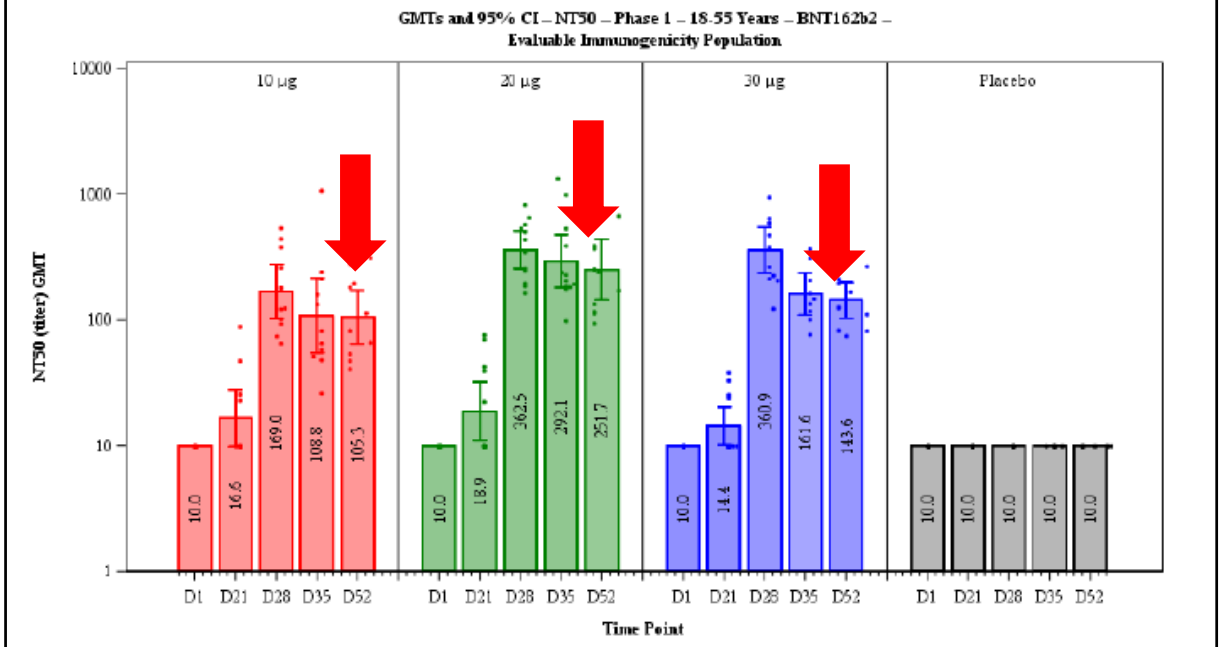
It is important to note that the laboratory was aware of the products administered to each participant since it was not blinded (see section 6.3.3-*Blinding of the Sponsor* of the protocol).

It can be noted that, under the 2 graphs, the cutoff date was August 24, 2020 and not November 14 (date of the database extraction) as for the other results. The neutralizing antibody assays were presented for days D1, D21, D28, D35 and D52, D28 to 52 being performed after dose 2.

A decrease in immunity was already observed at D52 whatever the dose 10 µg, 20 µg or 30 µg, the dose finally chosen on July 27. It is very surprising that no results were available after August 24 for the unfinished Phase 1 when one sees the laboratory's eagerness to manage the progress of its clinical trials.

Illustration 47 : Pfizer - December 10, 2020 Clinical Study Report –Immunogenicity results – Phase 1,2 – 18-55 years old – 92 pages report

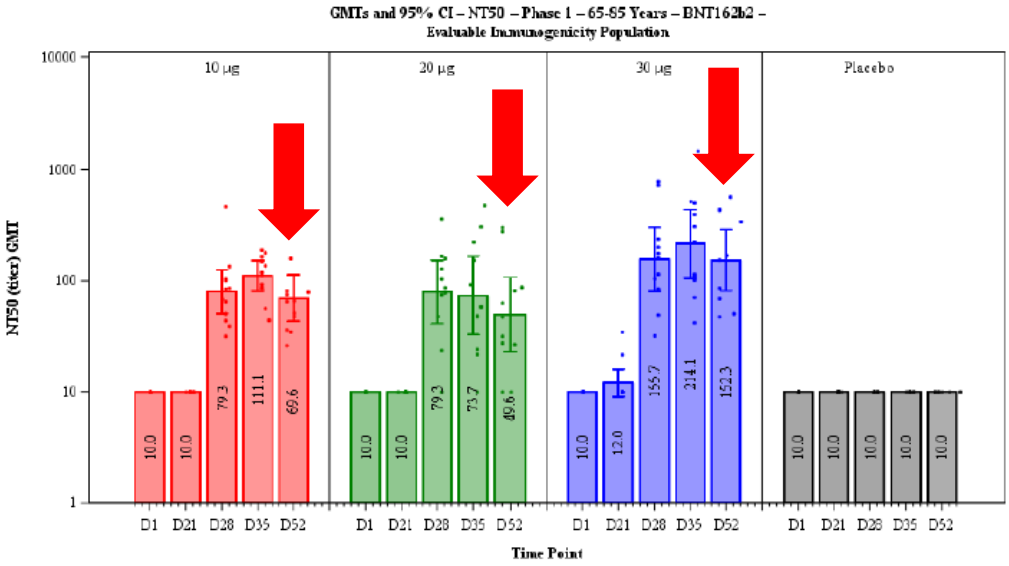
Figure 6. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001 [A P1 Serology/adva f002 sars 50 18 b2 p1

Illustration 48 : Pfizer - December 10, 2020 Clinical Study Report – Immunogenicity results – Phase 1,2 – 65-85 years old – 92 pages report

Figure 7. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Evaluable Immunogenicity Population

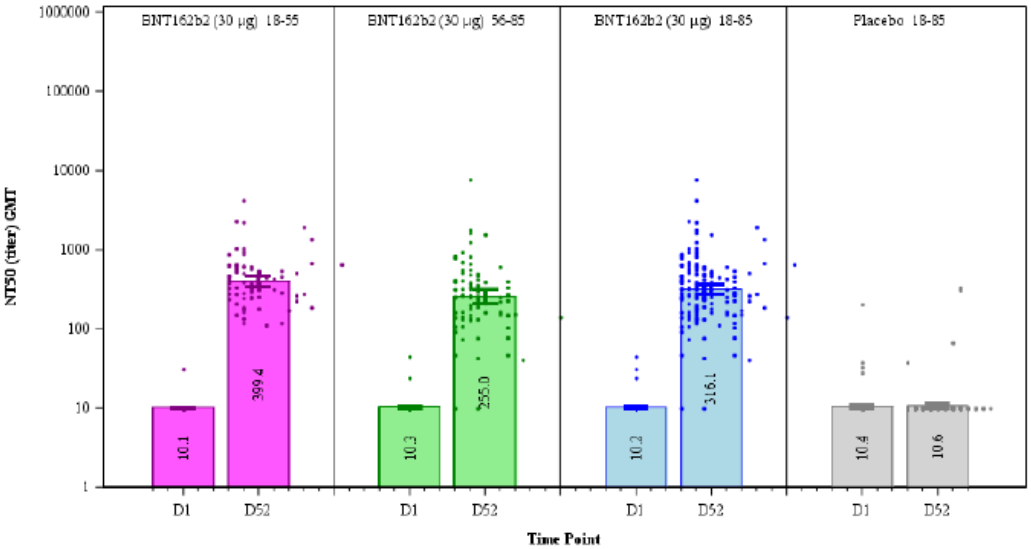


Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: ./nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_65_b2_p1

For phase 2, results were presented only for D1 and D52, as intermediate assays were suppressed for an unknown reason (see below page 35 of the report).

Illustration 49 : Pfizer - December 10, 2020 Clinical Study Report – Immunogenicity results – 65-85 ans – 92 pages-report

Figure 8. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Evaluable Immunogenicity Population – Phase 2



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 02NOV2020 (19:23) Source Data: adva Table Generation: 12NOV2020 (00:12)
(Cutoff Date: 12OCT2020, Snapshot Date: 02NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P2_Serology/adva_f002_sars_50_p2

Source : https://www.fda.gov/media/144245/download

It should be noted that the FDA's Emergency Use Authorization for Vaccines to Prevent COVID-19 states that **no immune markers have been identified to establish protection against COVID-19**. Therefore, neutralizing antibodies were used, for lack of a better term, to assess immunogenicity.

Illustration 50 : FDA – Emergency Use Authorization to prevent COVID-19 - Prélèvements pour Immunogenicity endpoints

> **4. Assays for assessment of immunogenicity endpoints**
>
> The assays used to assess immunogenicity endpoints of clinical studies should be identified. Even though an immune marker predictive of protection against COVID-19 has not been established to date, depending on the vaccine construct, neutralizing antibody may be considered a relevant measure of immunogenicity.

Source : « Emergency Use Authorization for Vaccines to Prevent COVID-19 - Guidance for Industry » *https://www.fda.gov/media/142749/download*

In summary,

On the basis on the results presented into the December 2020 Clinical Study Report, we can conclude:

- No efficacy statistically proven on SARS-CoV-2 transmission as not studied
- No efficacy statistically proven on severe case
- No efficacy statistically proven on the more than 75 years old population
- No efficacy statistically proven on asymptomatic cases
- Wrong results on main efficacy criterion due to multiple statistical biases
- No efficacy statistically proven against COVID -19 mortality

- No measurements of antibodies after 2 months after dose 2 although the neutralizing antibodies started to decrease in phase 2
- No immune marker identified to predict a protection against COVID-19 according to the Emergency Use Authorization Guidelines

https://www.fda.gov/media/142749/download

- Duration of Protection **UNKNOWN**

6.1.2 Analysis of the trial database

In the United States, attorney Aaron Siri initiated legal proceedings to compel the FDA to release the documents used in the evaluation of the vaccine for the issuance of emergency use authorization.
The documents related to this legal case are available on the website

https://phmpt.org/pfizer-court-documents

Illustration 51 : Transcript of Scheduling Conference - Aaron Siri - Judge Mark Pittman - December 14th, 2021

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF TEXAS

FORT WORTH DIVISION

PUBLIC HEALTH AND MEDICAL PROFESSIONALS FOR TRANSPARENCY	)	CASE NO. 4:21-CV-01058-P
vs.	)	FORT WORTH, TEXAS
FOOD AND DRUG ADMINISTRATION	)	DECEMBER 14, 2021 9:05 A.M.

VOLUME 1
TRANSCRIPT OF SCHEDULING CONFERENCE
BEFORE THE HONORABLE MARK T. PITTMAN
UNITED STATES DISTRICT COURT JUDGE

A P P E A R A N C E S:

FOR THE PLAINTIFF:	AARON SIRI Siri & Glimstad, LLP 200 Park Avenue New York, New York 10166 Telephone: 212.532.1091 JOHN HOWIE Howie Law, PC 2608 Hibernia Street Dallas, Texas 75204 Telephone: 214.622.6340
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COURT REPORTER:	MONICA WILLENBURG GUZMAN, CSR, RPR 501 W. 10th Street, Room 310 Fort Worth, Texas 76102 Telephone: 817.850.6681 E-Mail: mguzman.csr@yahoo.com

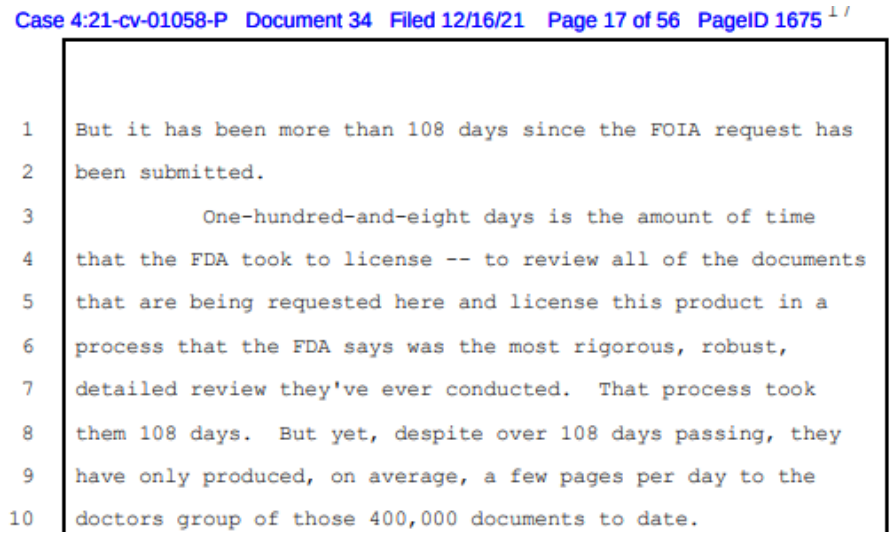
Proceedings reported by mechanical stenography, transcript produced by computer.

Source :Transcript of Scheduling Conference (December 14, 2021).pdf
https://phmpt.org/pfizer-court-documents/

We have extensively discussed in this report the rapid development of COVID vaccines in general, and Pfizer's Comirnaty® vaccine in particular. Attorney Siri revisits this unprecedented achievement, noting that the FDA reviewed 400,000 documents in 108 days in order to grant this emergency use authorization.

« One-hundred-and-eight days is the amount of time that the FDA took to license -- to review all of the documents that are being requested here and license this product in a process that the FDA says was the most rigorous, robust, detailed review they've ever conducted. That process took them 108 days. But yet, despite over 108 days passing, they have only produced, on average, a few pages per day to the doctors group of those 400,000 documents to date. »

Illustration 52 : Transcript of Scheduling Conference - Aaron Siri - Judge Mark Pittman - December 14th, 2021



Case 4:21-cv-01058-P Document 34 Filed 12/16/21 Page 17 of 56 PageID 1675

But it has been more than 108 days since the FOIA request has been submitted.

One-hundred-and-eight days is the amount of time that the FDA took to license -- to review all of the documents that are being requested here and license this product in a process that the FDA says was the most rigorous, robust, detailed review they've ever conducted. That process took them 108 days. But yet, despite over 108 days passing, they have only produced, on average, a few pages per day to the doctors group of those 400,000 documents to date.

Source : https://phmpt.org/wp-content/uploads/2022/03/034-Transcript-of-Scheduling-Conference-December-14-2021.pdf

On February 2, 2022, Judge Pittman ordered the gradual release of the documents submitted by Pfizer to the FDA, a decision that included the clinical trial database used by biostatisticians to provide all expected and planned results outlined in the trial protocol.

In accordance with the Parties' agreed production schedule detailed in the Joint Status Report, the Court ORDERS that:

1. The Food and Drug Administration's ("FDA") rolling productions will each be due on the first business day of each month, instead of once every thirty days.
2. The FDA will produce 10,000 pages for the first two productions, which will be due on or before March 1 and April 1, 2022.
3. The FDA will produce 80,000 pages on or before May 2, June 1, and July 1, 2022; 70,000 pages on or before August 1, 2022; and then 55,000 pages on or before the first business day of each month thereafter.
4. The FDA can "bank" any processed pages in excess of its monthly quota, such that, for example, if the FDA produces 90,000 pages in May 2022 (or 65,000 pages in September 2022), it would bank 10,000 pages. Then, in a subsequent month, if the FDA is unable to produce the full amount of pages required, it can apply the banked pages toward its quota for that month.

5. For the SAS files that duplicate the data in CRF files, the FDA will count every 40 rows as one page instead of every 20 rows as one page.

Illustration 53 : ORDER-GRANTING-IN-PART-THE-MOTION-TO-MODIFY-THE-PRODUCTION-SCHEDULE-AND-ADDOPTS-THE-JOINT-STATUS-REPORT-MODIFIED-AGREED-PRODUCTION-SCHEDULE

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
FORT WORTH DIVISION

PUBLIC HEALTH AND MEDICAL PROFESSIONALS FOR TRANSPARENCY,

Plaintiff,

v. **No. 4:21-cv-1058-P**

FOOD AND DRUG ADMINISTRATION,

Defendant.

ORDER

Before the Court is Defendant Food and Drug Administration's Motion to Partially Modify Scheduling Order ("Motion"). ECF No. 36. Also before the Court is a Joint Status Report that articulates the Parties' agreed production schedule. ECF No. 55. Having considered the Joint Status Report, the Court will adopt the Parties' agreed-upon terms; the Motion is therefore **GRANTED in part**.

In accordance with the Parties' agreed production schedule detailed in the Joint Status Report, the Court **ORDERS** that:

1. The Food and Drug Administration's ("FDA") rolling productions will each be due on the first business day of each month, instead of once every thirty days.
2. The FDA will produce 10,000 pages for the first two productions, which will be due on or before March 1 and April 1, 2022.
3. The FDA will produce 80,000 pages on or before May 2, June 1, and July 1, 2022; 70,000 pages on or before August 1, 2022; and then 55,000 pages on or before the first business day of each month thereafter.
4. The FDA can "bank" any processed pages in excess of its monthly quota, such that, for example, if the FDA produces 90,000 pages in May 2022 (or 65,000 pages in September 2022), it would bank 10,000 pages. Then, in a subsequent month, if the FDA is unable to produce the full amount of pages required, it can apply the banked pages toward its quota for that month.

5. For the SAS files that duplicate the data in CRF files, the FDA will count every 40 rows as one page instead of every 20 rows as one page.

SO ORDERED on this **2nd day** of **February, 2022.**

Mark T. Pittman
UNITED STATES DISTRICT JUDGE

Source : https://phmpt.org/wp-content/uploads/2022/02/056-ORDER-GRANTING-IN-PART-THE-MOTION-TO-MODIFY-THE-PRODUCTION-SCHEDULE-AND-ADDOPTS-THE-JOINT-STATUS-REPORT-MODIFIED-AGREED-PRODUCTION-SCHEDULE.pdf

6.1.2.1 Database structure

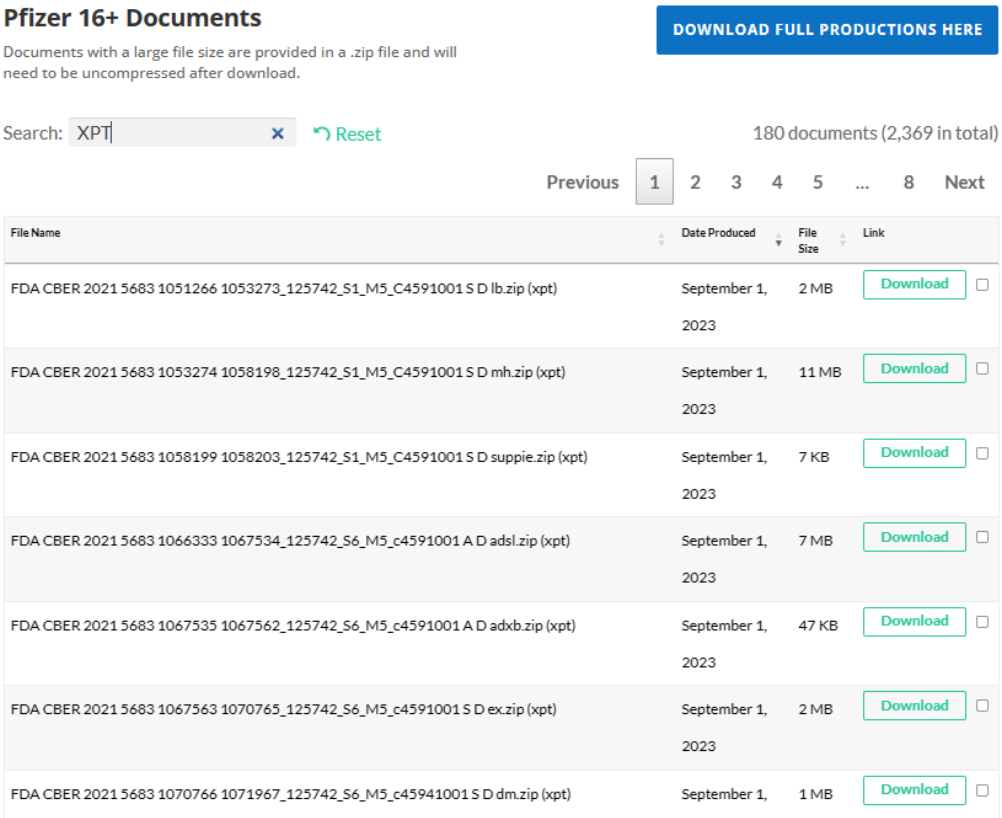
Following the disclosure mandate, the FDA provided, according to the established timeline, the Pfizer database (DB) along with a number of documents related to this database. The DB contains all data on the measured parameters during the trial for all participants: demographics, vaccination dates, visit dates, adverse effects, efficacy or immunogenicity data, and more.

The documents are made available to the public on the website: https://phmpt.org/pfizer-16-plus-documents

The database is provided in the form of multiple XPT files, which are standard SAS® transport files that can be easily imported into SAS® software with just a few lines of programming, a process that is quite common in clinical trials.

In total, 180 XPT files are available, covering several clinical trials, including the one that led to the first emergency use authorization and various Marketing Authorizations in Europe. The data from the pivotal trial is dated March 13, 2021 (cutoff date).

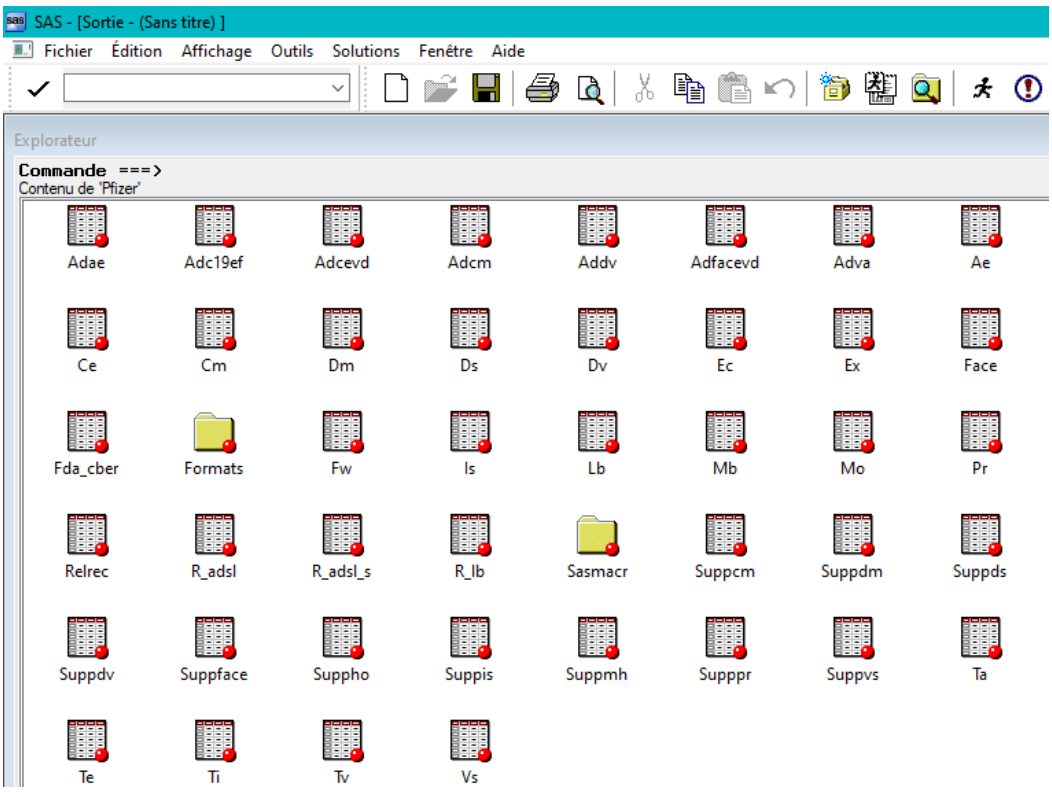
Illustration 54 : Excerpt from the XPT files constituting the database



Once the XPT files are imported into SAS® version 9.4, the database contains the following SAS tables. The import instructions are available on the CDC website.

https://wwwn.cdc.gov/nchs/data/tutorials/file_download_import_SAS.sas

Illustration 55 : SAS® datasets constituant la base de données



The details of the tables can be obtained after a few lines of code.

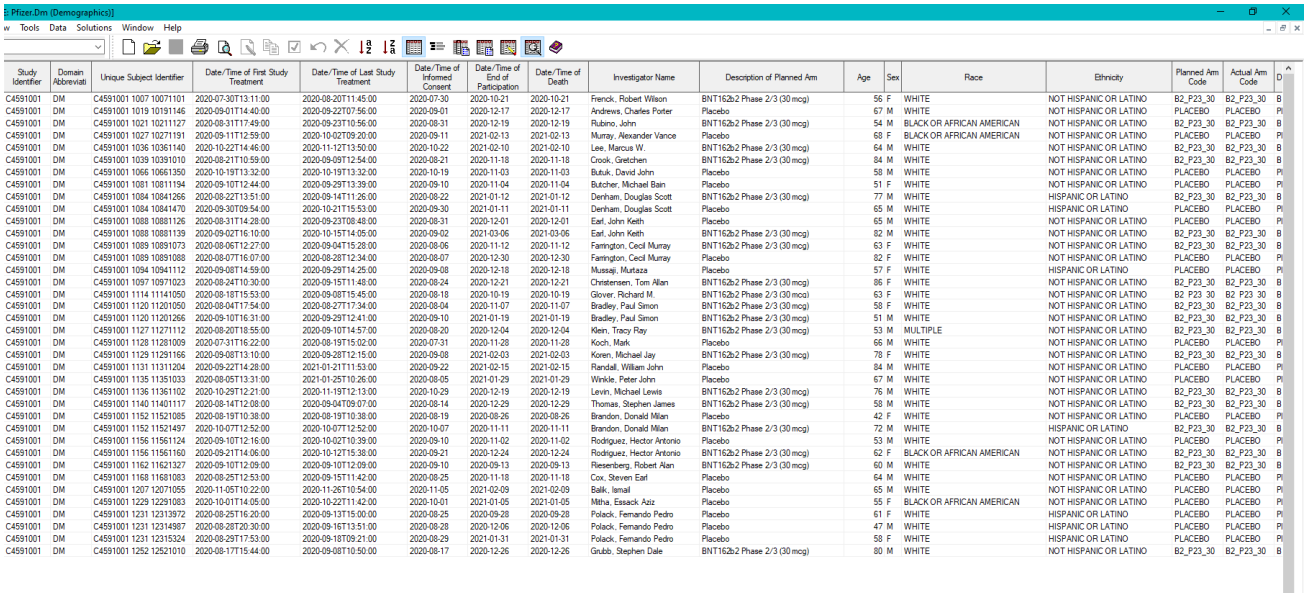
```
proc contents data=pfizer._all_ varnum;
run;
```

Illustration 56 : List of the SAS® datasets

#	Nom	Type de membre	Taille du fichier	Modifié(e) le
1	ADAE	DATA	85MB	24/04/2024 22:14:54
2	ADC19EF	DATA	1GB	24/04/2024 22:14:42
3	ADCEVD	DATA	432MB	24/04/2024 22:11:23
4	ADCM	DATA	47MB	24/04/2024 22:11:50
5	ADDV	DATA	44MB	24/04/2024 22:10:14
6	ADFACEVD	DATA	4GB	24/04/2024 22:12:49
7	ADMH_EXA	DATA	371MB	24/04/2024 22:15:01
8	ADSYMPT	DATA	199MB	24/04/2024 22:14:15
9	ADVA	DATA	164MB	24/04/2024 22:11:15
10	ADXB	DATA	640KB	24/04/2024 22:15:07
11	AE	DATA	37MB	24/04/2024 22:14:54
12	C4591001	DATA	16MB	24/04/2024 22:14:56
13	CE	DATA	367MB	24/04/2024 22:11:45
14	CM	DATA	4MB	24/04/2024 22:12:52
15	CO_2	DATA	49MB	24/04/2024 22:15:01
16	DD	DATA	128KB	24/04/2024 22:14:55
17	DI	DATA	128KB	24/04/2024 22:14:46
18	DM	DATA	16MB	24/04/2024 22:14:56
19	DS	DATA	128KB	24/04/2024 22:14:48
20	DV	DATA	12MB	24/04/2024 22:11:28
21	EC	DATA	47MB	24/04/2024 22:11:30
22	EX	DATA	45MB	24/04/2024 22:15:08
23	FACE	DATA	1GB	24/04/2024 22:14:05
24	FAHO	DATA	2MB	24/04/2024 22:15:01
25	FDA_CBER	DATA	44MB	24/04/2024 22:15:02
26	FORMATS	CATALOG	21KB	08/04/2024 21:41:36
27	FW	DATA	192KB	24/04/2024 22:14:48
28	HO	DATA	22MB	24/04/2024 22:15:02
29	IE	DATA	576KB	24/04/2024 22:12:52
30	IS	DATA	30MB	24/04/2024 22:11:32
31	LB	DATA	3MB	24/04/2024 22:14:49
32	MB	DATA	49MB	24/04/2024 22:12:52
33	MH	DATA	154MB	24/04/2024 22:15:04
34	MO	DATA	192KB	24/04/2024 22:12:53
35	PE	DATA	9MB	24/04/2024 22:12:53
36	PR	DATA	128KB	24/04/2024 22:13:05
37	RELREC	DATA	640KB	24/04/2024 22:12:53
38	R_ADSL	DATA	121MB	24/04/2024 22:15:07
39	R_ADSL_S	DATA	121MB	24/04/2024 22:14:53
40	R_LB	DATA	11MB	24/04/2024 22:14:49

Here is an excerpt from the SAS® DM table containing demographic data as well as a number of variables related to vaccine administration, group (Placebo or BNT162b2), and important dates such as the date of death.

Illustration 57 : DM (démography) SAS® dataset



Study Identifier	Domain Abbreviati	Unique Subject Identifier	Date/Time of First Study Treatment	Date/Time of Last Study Treatment	Date/Time of Informed Consent	Date/Time of End of Participation	Date/Time of Death	Investigator Name	Description of Planned Arm	Age	Sex	Race	Ethnicity	Planned Arm Code	Actual Arm Code	D
C4591001	DM	C4591001 1007 10071101	2020-07-30T13:11:00	2020-08-20T11:45:00	2020-07-30	2020-10-21	2020-10-21	Frenck, Robert Wilson	BNT162b2 Phase 2/3 (30 mcg)	56	F	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1019 10191146	2020-09-01T14:40:00	2020-09-22T07:56:00	2020-09-01	2020-12-17	2020-12-17	Andrews, Charles Porter	Placebo	67	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1021 10211127	2020-08-31T17:49:00	2020-09-23T10:56:00	2020-08-31	2020-12-19	2020-12-19	Rubino, John	BNT162b2 Phase 2/3 (30 mcg)	54	M	BLACK OR AFRICAN AMERICAN	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1027 10271191	2020-09-11T12:59:00	2020-10-02T09:20:00	2020-09-11	2021-02-13	2021-02-13	Murray, Alexander Vance	Placebo	68	F	BLACK OR AFRICAN AMERICAN	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1036 10361140	2020-10-22T14:46:00	2020-11-12T13:50:00	2020-10-22	2021-02-10	2021-02-10	Lee, Marcus W.	BNT162b2 Phase 2/3 (30 mcg)	64	M	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1039 10391010	2020-08-21T10:59:00	2020-09-09T12:54:00	2020-08-21	2020-11-18	2020-11-18	Crook, Gretchen	BNT162b2 Phase 2/3 (30 mcg)	84	M	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1066 10661350	2020-10-19T13:32:00	2020-10-19T13:32:00	2020-10-19	2020-11-03	2020-11-03	Butuk, David John	Placebo	58	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1081 10811194	2020-09-10T12:44:00	2020-09-29T13:39:00	2020-09-10	2020-11-04	2020-11-04	Butcher, Michael Bain	Placebo	51	F	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1084 10841266	2020-08-22T13:51:00	2020-09-14T11:26:00	2020-08-22	2021-01-12	2021-01-12	Denham, Douglas Scott	BNT162b2 Phase 2/3 (30 mcg)	77	M	WHITE	HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1084 10841470	2020-09-30T09:54:00	2020-10-21T15:53:00	2020-09-30	2021-01-11	2021-01-11	Denham, Douglas Scott	Placebo	65	M	WHITE	HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1088 10881126	2020-08-31T14:28:00	2020-09-23T08:48:00	2020-08-31	2020-12-01	2020-12-01	Earl, John Keith	Placebo	65	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1088 10881139	2020-09-02T16:10:00	2020-10-15T14:05:00	2020-09-02	2021-03-06	2021-03-06	Earl, John Keith	BNT162b2 Phase 2/3 (30 mcg)	82	M	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1089 10891073	2020-08-06T12:27:00	2020-09-04T15:28:00	2020-08-06	2020-11-12	2020-11-12	Farrington, Cecil Murray	BNT162b2 Phase 2/3 (30 mcg)	63	F	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1089 10891088	2020-08-07T16:07:00	2020-08-28T12:34:00	2020-08-07	2020-12-30	2020-12-30	Farrington, Cecil Murray	Placebo	82	F	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1094 10941112	2020-09-08T14:59:00	2020-09-29T14:25:00	2020-09-08	2020-12-18	2020-12-18	Mussaji, Murtaza	Placebo	57	F	WHITE	HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1097 10971023	2020-08-24T10:30:00	2020-09-15T11:48:00	2020-08-24	2020-12-21	2020-12-21	Christensen, Tom Allan	BNT162b2 Phase 2/3 (30 mcg)	86	F	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1114 11141050	2020-08-18T15:53:00	2020-09-08T15:45:00	2020-08-18	2020-10-19	2020-10-19	Glover, Richard M.	BNT162b2 Phase 2/3 (30 mcg)	63	F	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1120 11201050	2020-08-04T17:54:00	2020-08-27T17:34:00	2020-08-04	2020-11-07	2020-11-07	Bradley, Paul Simon	BNT162b2 Phase 2/3 (30 mcg)	58	F	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1120 11201266	2020-09-10T16:31:00	2020-09-29T12:41:00	2020-09-10	2021-01-19	2021-01-19	Bradley, Paul Simon	BNT162b2 Phase 2/3 (30 mcg)	51	M	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1127 11271112	2020-08-20T18:55:00	2020-09-10T14:57:00	2020-08-20	2020-12-04	2020-12-04	Klein, Tracy Ray	BNT162b2 Phase 2/3 (30 mcg)	53	M	MULTIPLE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1128 11281009	2020-07-31T16:22:00	2020-08-19T15:02:00	2020-07-31	2020-11-28	2020-11-28	Koch, Mark	Placebo	66	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1129 11291166	2020-09-08T13:10:00	2020-09-28T12:15:00	2020-09-08	2021-02-03	2021-02-03	Koren, Michael Jay	BNT162b2 Phase 2/3 (30 mcg)	78	F	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1131 11311204	2020-09-22T14:28:00	2021-01-21T11:53:00	2020-09-22	2021-02-15	2021-02-15	Randall, William John	Placebo	84	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1135 11351033	2020-08-05T13:31:00	2021-01-25T10:26:00	2020-08-05	2021-01-29	2021-01-29	Winkle, Peter John	Placebo	67	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1136 11361102	2020-10-29T12:21:00	2020-11-19T12:13:00	2020-10-29	2020-12-19	2020-12-19	Levin, Michael Lewis	BNT162b2 Phase 2/3 (30 mcg)	76	M	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1140 11401117	2020-08-14T12:08:00	2020-09-04T09:07:00	2020-08-14	2020-12-29	2020-12-29	Thomas, Stephen James	BNT162b2 Phase 2/3 (30 mcg)	58	M	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1152 11521085	2020-08-19T10:38:00	2020-08-19T10:38:00	2020-08-19	2020-08-26	2020-08-26	Brandon, Donald Milan	Placebo	42	F	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1152 11521497	2020-10-07T12:52:00	2020-10-07T12:52:00	2020-10-07	2020-11-11	2020-11-11	Brandon, Donald Milan	BNT162b2 Phase 2/3 (30 mcg)	72	M	WHITE	HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1156 11561124	2020-09-10T12:16:00	2020-10-02T10:39:00	2020-09-10	2020-11-02	2020-11-02	Rodriguez, Hector Antonio	Placebo	53	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1156 11561160	2020-09-21T14:06:00	2020-10-12T15:38:00	2020-09-21	2020-12-24	2020-12-24	Rodriguez, Hector Antonio	BNT162b2 Phase 2/3 (30 mcg)	62	F	BLACK OR AFRICAN AMERICAN	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1162 11621327	2020-09-10T12:09:00	2020-09-10T12:09:00	2020-09-10	2020-09-13	2020-09-13	Riesenberg, Robert Alan	BNT162b2 Phase 2/3 (30 mcg)	60	M	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B
C4591001	DM	C4591001 1168 11681083	2020-08-25T12:53:00	2020-09-15T11:42:00	2020-08-25	2020-11-18	2020-11-18	Cox, Steven Earl	Placebo	64	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1207 12071055	2020-11-05T10:22:00	2020-11-26T10:54:00	2020-11-05	2021-02-09	2021-02-09	Balik, Ismail	Placebo	65	M	WHITE	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1229 12291083	2020-10-01T14:05:00	2020-10-22T11:42:00	2020-10-01	2021-01-05	2021-01-05	Mitha, Essack Aziz	Placebo	55	F	BLACK OR AFRICAN AMERICAN	NOT HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1231 12313972	2020-08-25T16:20:00	2020-09-13T15:00:00	2020-08-25	2020-09-28	2020-09-28	Polack, Fernando Pedro	Placebo	61	F	WHITE	HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1231 12314987	2020-08-28T20:30:00	2020-09-16T13:51:00	2020-08-28	2020-12-06	2020-12-06	Polack, Fernando Pedro	Placebo	47	M	WHITE	HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1231 12315324	2020-08-29T17:53:00	2020-09-18T09:21:00	2020-08-29	2021-01-31	2021-01-31	Polack, Fernando Pedro	Placebo	58	F	WHITE	HISPANIC OR LATINO	PLACEBO	PLACEBO	Pl
C4591001	DM	C4591001 1252 12521010	2020-08-17T15:44:00	2020-09-08T10:50:00	2020-08-17	2020-12-26	2020-12-26	Grubb, Stephen Dale	BNT162b2 Phase 2/3 (30 mcg)	80	M	WHITE	NOT HISPANIC OR LATINO	B2_P23_30	B2_P23_30	B

The details provided by the SAS® Contents procedure for the DM table allow for the retrieval of the file creation date (03/21/2023), the number of observations in the table, which is 48,091 corresponding to the number of participants, the file size (16 MB), the number of variables (26), and the names of the variables containing the participants' data.

Nom de la table	PFIZER.DM	**Observations**	48091
Type de membre	DATA	**Variables**	26
Moteur	V9	**Index**	0
Créée	21/03/2023 13:10:51	**Longueur d'observation**	352
Dernière modification	21/03/2023 13:10:51	**Observations supprimées**	0
Protection		**Compressée**	NON
Type de table		**Triée**	NON
Libellé	Demographics		
Représentation des données	WINDOWS_64		
Codage	wlatin1 Western (Windows)		

Informations dépendantes de la machine/de l'hôte	
Taille de la page	65536
Nombre de pages	259
Première page de données	1
Nb max. d'obs. par page	186
Obs. sur première page de données	174
Nombre de corrections dans la table	0
ExtendObsCounter	YES
Nom du fichier	F:\Vaccine\exp\Pfizer\BDD\dm.sas7bdat
Version de création	9.0401M7
Hôte de création	
Nom du propriétaire	
Taille du fichier	16MB
Taille de fichier (octets)	17039360

Variables par ordre de création					
#	Variable	Type	Long.	Format	Libellé
1	STUDYID	Texte	8		Study Identifier
2	DOMAIN	Texte	2		Domain Abbreviation
3	USUBJID	Texte	22		Unique Subject Identifier
4	SUBJID	Texte	8		Subject Identifier for the Study
5	RFSTDTC	Texte	19		Subject Reference Start Date/Time
6	RFENDTC	Texte	10		Subject Reference End Date/Time
7	RFXSTDTC	Texte	19		Date/Time of First Study Treatment
8	RFXENDTC	Texte	19		Date/Time of Last Study Treatment
9	RFICDTC	Texte	10		Date/Time of Informed Consent
10	RFPENDTC	Texte	10		Date/Time of End of Participation
11	DTHDTC	Texte	10		Date/Time of Death
12	DTHFL	Texte	1		Subject Death Flag
13	SITEID	Texte	4		Study Site Identifier
14	INVID	Texte	7		Investigator Identifier
15	INVNAM	Texte	37		Investigator Name
16	BRTHDTC	Texte	10		Date/Time of Birth
17	AGE	Num.	8	BEST12.	Age
18	AGEU	Texte	5		Age Units
19	SEX	Texte	1		Sex
20	RACE	Texte	41		Race
21	ETHNIC	Texte	22		Ethnicity
22	ARMCD	Texte	9		Planned Arm Code
23	ARM	Texte	29		Description of Planned Arm
24	ACTARMCD	Texte	9		Actual Arm Code
25	ACTARM	Texte	29		Description of Actual Arm
26	COUNTRY	Texte	3		Country

The list of all tables can be found in the appendices.

Like all clinical trial databases, the structure of the Pfizer database appears to follow the CDISC (Clinical Data Interchange Standards Consortium) standards mentioned on page 27 of this report, which, as a reminder, are the reference standards for clinical trial databases.

The document « **Analysis Data Reviewer Guide (ADRG) - BLA Analysis for Participants ≥16 Years of Age BioNTech SE and PFIZER INC. Study C459100** »' is particularly relevant for quality managers, as **it covers the methods and anomalies that need to be documented** (such as subjects enrolled at multiple sites…):

This document details the calculations of the criteria so that health agencies can reprogram the calculations to verify the results submitted by the laboratory.

Illustration 58 : PFIZER/BioNTech- Study C4591001- Analysis Data Reviewer Guide - BLA Analysis for Participants ≥16 Years of Age – Extract of the SAS® database

No. Objectives on VE against asymptomatic infection and Phase 1 booster are not assessed. The booster and variant strain assessment in Protocol amendment 14 and SAP V5 are also not included.

Additional Content of Interest

No additional content of Interest.

5.2 Analysis Datasets

Dataset Label	Class	Efficacy	Safety	Baseline or other subject PK/PD	Primary	Structure
ADSL Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET			X		One record per subject
ADAE Adverse Events Analysis Dataset	OCCURRENCE DATA STRUCTURE		X		X	One record or multiple records per subject per adverse event per event start date
ADCEVD Diary and CRF Event Analysis Dataset	OCCURRENCE DATA STRUCTURE		X			One record or multiple records per subject per clinical event
ADFACEVD Diary and Non-event Analysis Dataset	BASIC DATA STRUCTURE		X		X	One record or multiple records per subject per analysis parameter per analysis timepoint
ADCM Concomitant Medications Analysis Dataset	OCCURRENCE DATA STRUCTURE		X			One record or multiple records per subject per recorded medication occurrence or constant-dosing interval
ADDS Disposition Analysis Dataset	OCCURRENCE DATA STRUCTURE			X		One record or multiple records per subject per disposition status or protocol milestone
ADDV Protocol Deviation Analysis Dataset	OCCURRENCE DATA STRUCTURE			X		One record or multiple records per subject per protocol deviation per event start date
ADMH Medical History Analysis Dataset	OCCURRENCE DATA STRUCTURE			X		One record or multiple records per subject per medical history event

Dataset Label	Class	Efficacy	Safety	Baseline or other subject PK/PD	Primary	Structure
ADC19EF Covid-19 Efficacy Analysis	BASIC DATA STRUCTURE	X			X	One record or multiple records per subject per analysis parameter per analysis timepoint
ADSYMPT Covid-19 Signs and Symptoms	BASIC DATA STRUCTURE	X			X	One record or multiple records per subject per analysis parameter per analysis timepoint
ADVA Immunogenicity Analysis Dataset	BASIC DATA STRUCTURE	X				One record or multiple records per subject per analysis parameter per analysis visit

Source : Documents rendus publics par décision de justice aux Etats-Unis

https://phmpt.org/wp-content/uploads/2022/03/125742_S1_M5_c4591001-A-adrg.pdf

This document details the calculations of the criteria so that health agencies can reprogram the calculations to verify the results submitted by the laboratory.

6.1.2.2 Issues in Participant Recruitment Centers

The number of participants per investigator site can be easily calculated from the SAS® ADSL dataset.

Once a participant is randomized, a product is randomly assigned to him/her by the computer system managing the randomization. The tables below provide the number of participants by country and by investigator site.

Illustration 59 : Number of vaccinated participants per country

COUNTRY	BNT162b2 Phase 2/3 (30 mcg)	Placebo	Total
USA	16493	16520	33013
ARGENTINA	2883	2881	5764
BRAZIL	1452	1448	2900
SOUTH AFRICA	401	399	800
GERMANY	249	250	499
TURKEY	249	249	498

The table below presents the number of participants recruited by investigator site.

Illustration 60 : Number of vaccinated participants per center classified by decreasing number

SITEID	BNT162b2 Phase 2/3 (30 mcg) Number of patients vaccinated	Placebo Number of patients vaccinated	Total Number of patients vaccinated
1231	2883	2881	5764
1241	774	774	1548
1226	678	674	1352
1013	400	391	791
1008	373	372	745
1056	304	306	610
1133	307	303	610
1087	298	296	594
1152	286	288	574
1162	283	285	568
1177	282	282	564
1109	275	277	552
1135	266	268	534
1090	265	265	530
1084	261	260	521
1170	248	248	496
1232	213	214	427
1134	212	209	421
1123	196	197	393
1066	192	195	387
1005	193	192	385

SITEID	BNT162b2 Phase 2/3 (30 mcg) Number of patients vaccinated	Placebo Number of patients vaccinated	Total Number of patients vaccinated
1091	189	189	378
1096	189	189	378
1110	186	188	374
1128	188	186	374
1146	187	187	374
1085	184	185	369
1120	184	183	367
1007	177	180	357
1057	177	176	353
1037	174	173	347
1089	173	174	347
1112	170	171	341
1046	168	169	337
1149	167	167	334
1018	163	164	327
1047	165	162	327
1019	157	156	313
1178	157	156	313
1116	154	157	311
1079	156	153	309
1016	153	154	307
1171	153	151	304
1142	148	148	296
1140	147	144	291
1028	144	145	289
1095	141	143	284
1156	137	140	277
1204	139	135	274
1092	134	138	272
1088	132	131	263
1015	130	131	261
1077	130	131	261
1083	127	129	256
1098	127	129	256
1251	128	128	256
1141	127	128	255
1021	126	126	252
1247	125	124	249
1223	122	126	248
1042	122	123	245
1055	122	122	244
1129	122	120	242
1168	119	120	239
1071	119	117	236

SITEID	BNT162b2 Phase 2/3 (30 mcg) Number of patients vaccinated	Placebo Number of patients vaccinated	Total Number of patients vaccinated
1124	118	117	235
1131	118	117	235
1147	118	117	235
1248	117	116	233
1009	113	116	229
1167	114	114	228
1011	114	113	227
1039	111	113	224
1044	111	113	224
1264	111	112	223
1235	111	110	221
1125	109	108	217
1027	109	107	216
1080	107	108	215
1082	105	106	211
1229	105	106	211
1230	105	105	210
1081	105	101	206
1126	103	103	206
1254	104	102	206
1111	103	102	205
1054	100	102	202
1093	100	101	201
1107	100	100	200
1012	93	92	185
1094	93	92	185
1117	91	91	182
1265	91	87	178
1052	88	87	175
1179	87	86	173
1157	86	85	171
1006	83	86	169
1022	83	83	166
1224	82	84	166
1195	80	78	158
1030	79	77	156
1270	78	77	155
1036	70	70	140
1269	68	72	140
1163	68	71	139
1048	66	65	131
1260	64	67	131
1246	66	64	130
1118	64	65	129

SITEID	BNT162b2 Phase 2/3 (30 mcg) Number of patients vaccinated	Placebo Number of patients vaccinated	Total Number of patients vaccinated
1024	64	64	128
1038	63	64	127
1114	62	63	125
1139	62	63	125
1150	62	63	125
1073	62	62	124
1003	59	61	120
1097	60	60	120
1121	59	61	120
1068	59	57	116
1101	57	59	116
1127	54	54	108
1166	53	53	106
1145	53	52	105
1194	52	52	104
1136	51	52	103
1072	50	51	101
1197	50	50	100
1130	51	48	99
1261	42	41	83
1205	40	39	79
1169	36	39	75
1258	37	37	74
1207	35	34	69
1001	34	34	68
1174	34	34	68
1185	32	33	65
1210	31	31	62
1217	31	31	62
1203	29	31	60
1213	30	30	60
1208	27	28	55
1214	28	27	55
1122	26	26	52
1161	21	22	43
1219	17	23	40
1252	19	20	39
1220	18	18	36
1212	17	18	35
1221	15	17	32
1218	10	15	25
1209	10	11	21
1202	6	6	12

This table informs us that the five largest sites recruited over 10,000 participants, representing one-quarter of the total population analyzed for the December 2020 report, with the record being held by site 1231, the only center in Argentina

It concerns a military hospital that began vaccinations on August 6, 2020, with a significant increase starting on August 14, 2020. Between August 6, 2020, and September 27, 2020, this center recruited **5,764 participants, averaging between 10 and 280 individuals per day**!

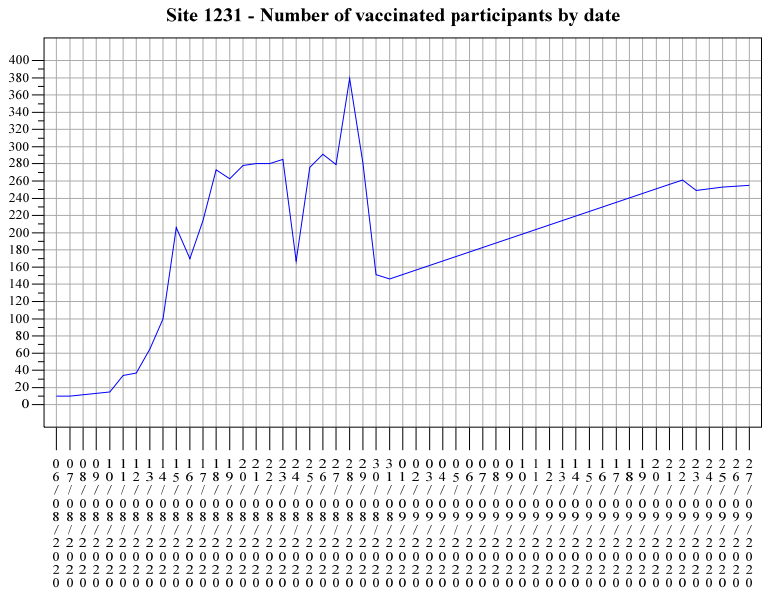
This daily number of participants, ranging from 2 to 35 patients to be vaccinated and trained in study practices per hour, requires a minimum team of 15 people, assuming 8 hours of work and 30 minutes per patient.

Illustration 61 : Number of vaccinated participants per center – Center 1231

Vaccination Date 01	Number of patients vaccinated
06AUG2020	10
07AUG2020	10
10AUG2020	15
11AUG2020	34
12AUG2020	37
13AUG2020	65
14AUG2020	100
15AUG2020	206
16AUG2020	170
17AUG2020	214
18AUG2020	273
19AUG2020	263
20AUG2020	278
21AUG2020	280
22AUG2020	280

Vaccination Date 01	Number of patients vaccinated
23AUG2020	285
24AUG2020	167
25AUG2020	276
26AUG2020	291
27AUG2020	279
28AUG2020	379
29AUG2020	281
30AUG2020	151
31AUG2020	146
21SEP2020	256
22SEP2020	261
23SEP2020	249
25SEP2020	253
27SEP2020	255

Illustration 62 : Nombre de participants vaccinés par date – Site 1231 – Représentation graphique



Furthermore, it appears that participant numbers from the center, instead of containing the center's number as required by Good Data Management Practice, contain the number 4444.

The center recruited 4,501 participants until 08/31/2020, and then 1,275 through a virtual site identified by the number 4444 starting from 09/20/2020. This three-week pause in recruitment corresponds to the time needed for all previously enrolled participants to receive their second dose.

In the database, participants recruited under the number 4444 are identified not by the SAS® SITEID variable, which always equals 1231, but because the participant code contains 4444 instead of 1231, despite existing regulations.

Illustration 63 : Pfizer : SAS® database - Example of participants – Site 1231

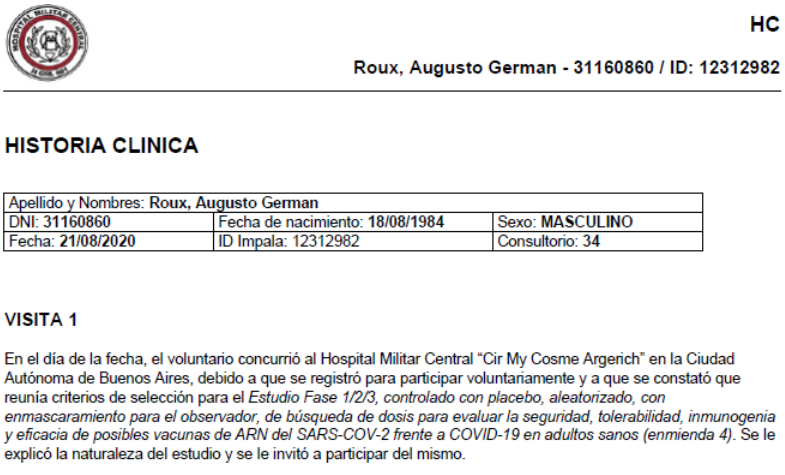
Unique Subject Identifier	Study Site Identifier	Country	Description of Actual Arm	Date of Randomization	Side ID calculated from the participant number (15 to 19)
C4591001 1231 12315664	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315665	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315666	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315667	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315670	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315671	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315676	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315677	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315679	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315680	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 1231 12315684	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	31AUG2020	1231
C4591001 4444 44441001	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441003	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441006	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441008	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441010	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441011	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441016	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441018	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441020	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441022	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441023	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441026	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444
C4591001 4444 44441027	1231	ARG	BNT162B2 PHASE 2/3 (30 MCG)	21SEP2020	4444

The creation of a virtual site to increase recruitment at a single site is not part of Good Clinical Practice, especially considering that this is far from the only issue at this site.

In fact, one of the center's volunteers, the lawyer at the High Court of Justice of Buenos Aires, Augusto Roux, claims to have suffered from pericarditis following his vaccination with BNT162b2, with medical evidence to support his claim.

He is recorded under the number 12312982 in the database, and the documents submitted confirm that he participated in the clinical trial under this number.

Illustration 64 : Augusto Roux - Document Visit 1



HC

Roux, Augusto German - 31160860 / ID: 12312982

HISTORIA CLINICA

Apellido y Nombres: **Roux, Augusto German**		
DNI: **31160860**	Fecha de nacimiento: **18/08/1984**	Sexo: **MASCULINO**
Fecha: **21/08/2020**	ID Impala: 12312982	Consultorio: **34**

VISITA 1

En el día de la fecha, el voluntario concurrió al Hospital Militar Central "Cir My Cosme Argerich" en la Ciudad Autónoma de Buenos Aires, debido a que se registró para participar voluntariamente y a que se constató que reunía criterios de selección para el *Estudio Fase 1/2/3, controlado con placebo, aleatorizado, con enmascaramiento para el observador, de búsqueda de dosis para evaluar la seguridad, tolerabilidad, inmunogenia y eficacia de posibles vacunas de ARN del SARS-COV-2 frente a COVID-19 en adultos sanos (enmienda 4)*. Se le explicó la naturaleza del estudio y se le invitó a participar del mismo.

There is no record of Mr. Roux's pericarditis in the database; the staff responsible for managing the clinical trial recorded him as having pneumonia, which was later changed to COVID-19, despite a negative PCR test. In the SAS® table of adverse effects (ADAE), psychological disorders diagnosed by the head of the Argentine center, Mr. Fernando Pollack, are also mentioned.

Illustration 65 : Listing of adverse events recorded for Participant Augusto Roux in the database

Subject Identifier for the Study	Study Site Identifier	Planned Arm Code	Description of Actual Arm	Ag	Age Units	Race	Sex	Ethnicity	Country	Date of First Exposure to Treatment	Time of First Exposure to Treatment	Vaccination Date 01	Vaccination Date 02	Se Nu	Category for Adverse Event	Spo Iden	Reported Term for the Adverse Event	Body System or Organ Class
12312982	1231	B2_P23_30	BNT162b2 Phase 2/3 (30 mcg)	36	YEARS	WHITE	M	NOT HISPANIC OR LATINO	ARG	21AUG2020	18:50:00	21AUG2020	09SEP2020	1	ADVERSE EVENT	3	severe anxiety	PSYCHIATRIC DISORDERS
12312982	1231	B2_P23_30	BNT162b2 Phase 2/3 (30 mcg)	36	YEARS	WHITE	M	NOT HISPANIC OR LATINO	ARG	21AUG2020	18:50:00	21AUG2020	09SEP2020	2	ADVERSE EVENT	2	mild pain at the injection site	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
12312982	1231	B2_P23_30	BNT162b2 Phase 2/3 (30 mcg)	36	YEARS	WHITE	M	NOT HISPANIC OR LATINO	ARG	21AUG2020	18:50:00	21AUG2020	09SEP2020	3	ADVERSE EVENT	1	Suspected COVID-19 Illness	INFECTIONS AND INFESTATIONS

Mr. Roux informed the Argentine health agency, as well as the European and American agencies, including the CDC.

Here is a brief excerpt from the email he sent to the « Compliance issues with pharmacovigilance obligations » department of the EMA on March 27, 2021, in which Mr. Roux clearly explains his symptoms to the agency.

Illustration 66 : Augusto Roux – E-mail to EMA - March 27, 2021

27 de marzo de 2021 02:40

Rv: URGENT COMPLAINT PFIZER VACCINE BNT162B2

De: Augusto Roux <augustoroux@gmail.com>

Para: qdefect@ema.europa.eu <qdefect@ema.europa.eu>

Enviado desde mi teléfono Huawei

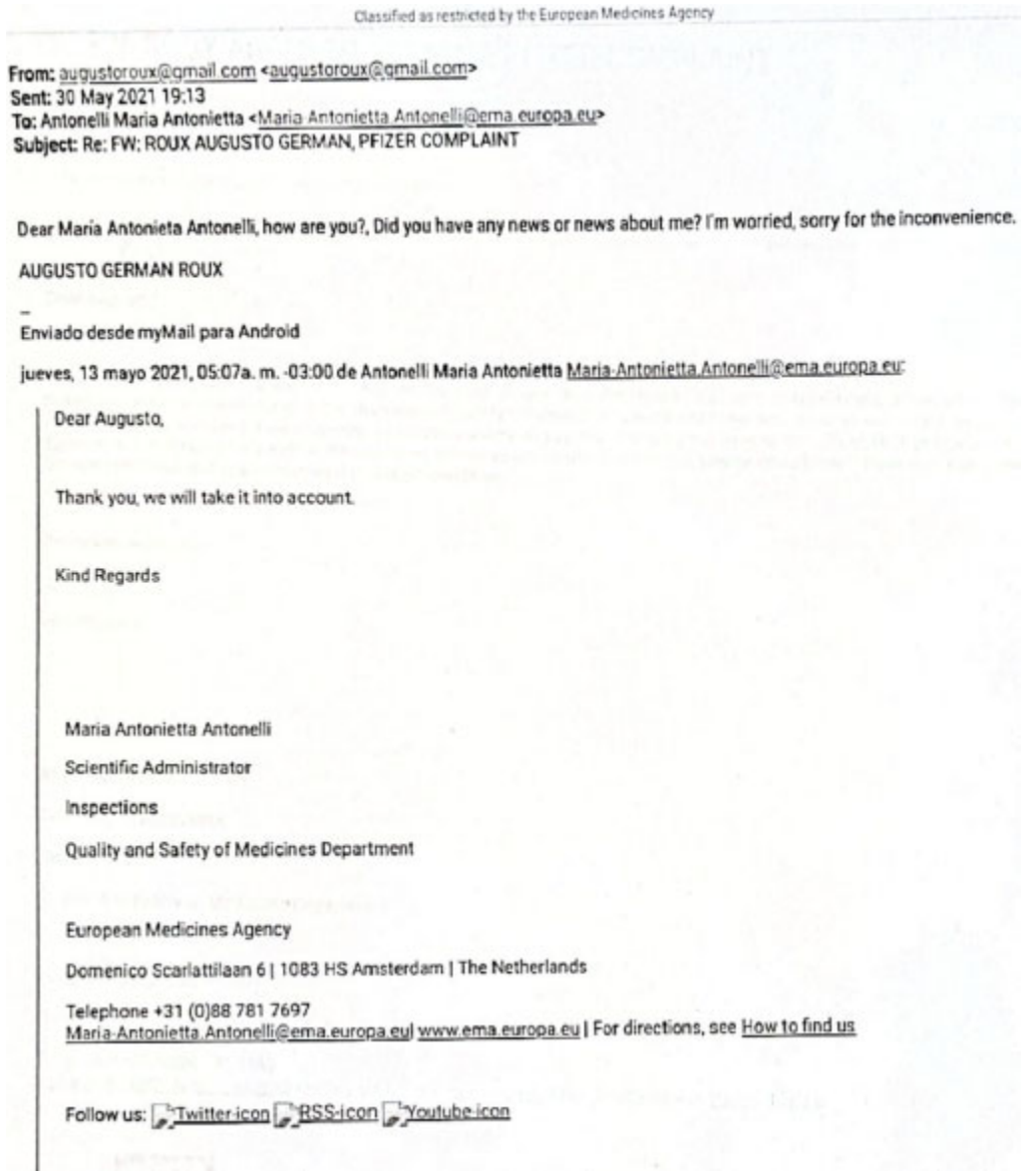
-------- Mensaje original --------
De: Augusto Roux <augustoroux@gmail.com>
Fecha: sáb., 27 mar. 2021 02:06
Para: phv-noncompliance@ema.europa.eu
Asunto: URGENT COMPLAINT PFIZER VACCINE BNT162B2

Attached complaint made to the FDA inspector's office, I hope that one day someone can read me, it is a disgrace to all this and not have to go to the television channels, it is requested that the severity of the case that is used with other laboratories be applied.

COMPLAINT ADVERSE EFFECTS OF THE PFIZER BNT162B2 VACCINE, ALTERATION OF THE RESULTS OF THE CLINICAL TRIAL INVESTIGATION PHASE 2/3, REQUESTS OPENING OF THE INVESTIGATION REPORT BY THE AUTHORITIES

Dear Office of Inspector General´ s, my name is Augusto German Roux, 36 years old, born on August 18, 1984, domiciled in Buenos Aires City, Argentina.
I wanted to file a complaint regarding the adverse effects I suffered after volunteering for the SarsCov2 Pfizer vaccine, having been a volunteer at the Cosme Argerich Central Military Hospital in Buenos Aires City, carried out by Dr. Fernando Polack.
The first dose was on August 19, 2020, and the second application was on September 9 of the same year.
After the second dose I began to feel fevers greater than 40 degrees Celsius temperature (which lasted for several weeks), I suffered loss of consciousness, fainting, a tachycardia that almost left me near death, and extremely dark urine that they were referred on September 12 to be admitted to the German Hospital in Buenos Aires.
The reason for admission was because, according to an X-ray, my lungs had found grinding teeth compatible with incipient bilateral pneumonia, which is why I had to be admitted to an emergency room to perform the corresponding swab.
The coronavirus swab gave a negative result, so I asked the medical team to perform a complete hepatogram in order to find out the reasons for the urine staining.
I have many suspicions about everything that happened and I believe that the German Hospital laboratory under the influence of the medical research team of the Pfizer laboratory altered the results of the analysis in the hospitalization´s day, since supposedly they came out perfect,

Illustration 67 : Response from the EMA to Augusto Roux



Classified as restricted by the European Medicines Agency

From: augustoroux@gmail.com <augustoroux@gmail.com>
Sent: 30 May 2021 19:13
To: Antonelli Maria Antonietta <Maria Antonietta.Antonelli@ema.europa.eu>
Subject: Re: FW: ROUX AUGUSTO GERMAN, PFIZER COMPLAINT

Dear Maria Antonieta Antonelli, how are you?, Did you have any news or news about me? I'm worried, sorry for the inconvenience.

AUGUSTO GERMAN ROUX

–
Enviado desde myMail para Android

jueves, 13 mayo 2021, 05:07a. m. -03:00 de Antonelli Maria Antonietta Maria-Antonietta.Antonelli@ema.europa.eu:

> Dear Augusto,
>
> Thank you, we will take it into account.
>
> Kind Regards
>
> Maria Antonietta Antonelli
>
> Scientific Administrator
>
> Inspections
>
> Quality and Safety of Medicines Department
>
> European Medicines Agency
>
> Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
>
> Telephone +31 (0)88 781 7697
> Maria-Antonietta.Antonelli@ema.europa.eu| www.ema.europa.eu | For directions, see How to find us
>
> Follow us: Twitter-icon RSS-icon Youtube-icon

In summary,

The number of participants recruited at the Argentina center and the imbalance among the centers should have drawn the attention of health authorities to request clarifications from the laboratory regarding the management of the clinical trial in Argentina.

The creation of a virtual center number (4444) is entirely unusual. This center was established immediately after the administration of the first two doses at the recruited participants.

The laboratory and health agencies should have initiated an audit as soon as possible to clarify the case of Augusto Roux, a volunteer accusing the laboratory of fraud.

Nothing was done. **Attempting to discredit the participant by diagnosing him with imaginary psychological disorders is also not in accordance with the Declaration of Helsinki, as Mr. Pollack has no expertise in psychology.**

This serious matter, which seeks to minimize the tolerance issues of the product under investigation, confirms the invalidity of the data in the database as well as the results obtained.

6.1.2.3 Missing participants

In the declassified documents, we have two versions of the lists of investigators who recruited participants; the first version dates from November 26, 2020, and the second from March 29, 2021. The table below summarizes the numbers of participants selected and randomized on these two dates by country.

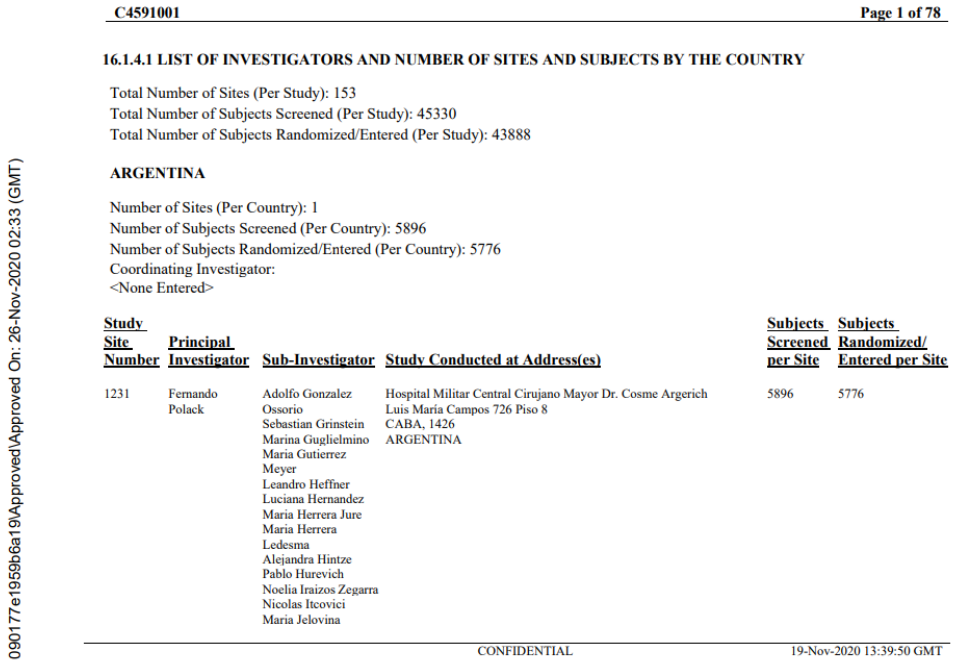
Illustration 68 : Pfizer – Comparatif des documents listes des investigateurs et nombre de sujets par pays au 26 novembre 2021 et 29 mars 2021

	Document dated November 26, 2020	**Document dated March 29, 2021**	**Number of missing participants**
Total number of sites (per study)	153	153	
Total number of subjects screened (per study)	45330	48092	
Total number of randomised subjects /entered (per study)	43888	45121	
Argentina			
Total number of sites (per country)	1	1	
Total number of subjects screened (per country)	5896	5896	
Total number of randomised subjects /entered (per country) :	5776	5615	**161**
Brazil			
Total number of sites (per country)	2	2	
Total number of subjects screened (per country)	2927	2927	
Total number of randomised subjects /entered (per country) :	2900	2880	**20**
Germany			
Total number of sites (per country)	6	6	
Total number of subjects screened (per country)	514	514	
Total number of randomised subjects /entered (per country) :	500	492	**8**
South Afriqua			
Total number of sites (per country)	4	4	
Total number of subjects screened (per country)	842	842	
Total number of randomised subjects /entered (per country) :	800	788	**12**
Turkey			
Total number of sites (per country)	9	9	
Total number of subjects screened (per country)	500	500	

Total number of randomised subjects /entered (per country) :	500	487	**13**
ÉTATS-UNIS			
Total number of sites (per country)	131	131	
Total number of subjects screened (per country)	34651	37413	
Total number of randomised subjects /entered (per country) :	33412	34859	

Note : the figures are provided by site; it has not been verified that the total indicated by country corresponds to the sum of the investigator sites in the country."

Illustration 69 : BioNTech / PFIZER - Study C4591001- 16.1.4.1 List of investigators and number of sites and subjects by the country - Document dated November 26, 2020



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16.1.4.1 LIST OF INVESTIGATORS AND NUMBER OF SITES AND SUBJECTS BY THE COUNTRY

Total Number of Sites (Per Study): 153
Total Number of Subjects Screened (Per Study): 45330
Total Number of Subjects Randomized/Entered (Per Study): 43888

ARGENTINA

Number of Sites (Per Country): 1
Number of Subjects Screened (Per Country): 5896
Number of Subjects Randomized/Entered (Per Country): 5776
Coordinating Investigator:
<None Entered>

Study Site Number	Principal Investigator	Sub-Investigator	Study Conducted at Address(es)	Subjects Screened per Site	Subjects Randomized/ Entered per Site
1231	Fernando Polack	Adolfo Gonzalez Ossorio Sebastian Grinstein Marina Guglielmino Maria Gutierrez Meyer Leandro Heffner Luciana Hernandez Maria Herrera Jure Maria Herrera Ledesma Alejandra Hintze Pablo Hurevich Noelia Iraizos Zegarra Nicolas Itcovici Maria Jelovina	Hospital Militar Central Cirujano Mayor Dr. Cosme Argerich Luis Maria Campos 726 Piso 8 CABA, 1426 ARGENTINA	5896	5776

CONFIDENTIAL 19-Nov-2020 13:39:50 GMT

090177e1959b6a19\Approved\Approved On: 26-Nov-2020 02:33 (GMT)

Source : https://phmpt.org/wp-content/uploads/2023/10/125742_S1_M5_5351_c4591001-fa-interim-investigators.pdf

Illustration 70 : BioNTech / PFIZER – Study - C4591001- 16.1.4.1 List of investigators and number of sites and subjects by the country - Document dated March 29, 2021

16.1.4.1 LIST OF INVESTIGATORS AND NUMBER OF SITES AND SUBJECTS BY THE COUNTRY

Total Number of Sites (Per Study): 153
Total Number of Subjects Screened (Per Study): 48092
Total Number of Subjects Randomized/Entered (Per Study): 45121

ARGENTINA

Number of Sites (Per Country): 1
Number of Subjects Screened (Per Country): 5896
Number of Subjects Randomized/Entered (Per Country): 5615
Coordinating Investigator:
<None Entered>

Study Site Number	Principal Investigator	Sub-Investigator	Study Conducted at Address(es)	Subjects Screened per Site	Subjects Randomized/ Entered per Site
1231	Fernando Polack	Diego Tourn Virginia Trias Uriarte Anabel Vaca Lizzi Rita Valdez Antonela Valente Emmanuel Valls Mercedes Vazquez Elizabeth Ventrice Maria Vera Morandini Ana Liss Vergez Alejandra de Lourdes Vigliano Vanina Vilaseca Florencia Virili Juan Voievdca	Hospital Militar Central Cirujano Mayor Dr. Cosme Argerich Luis María Campos 726 Piso 8 CABA, 1426 ARGENTINA	5896	5615

Source : https://phmpt.org/wp-content/uploads/2023/10/125742_S1_M5_5351_c4591001-interim-mth6-investigators.pdf

In total, 214 randomized participants have gone missing, with 161 from the Argentine center.

As in many clinical trials, it is the electronic notebook or eCRF that is used by the investigator to randomise participants. The randomisation process is explained in section 6.3.1 of the protocol.

"Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. ***The site personnel will then be provided with a vaccine assignment and randomization number****. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.*"

Illustration 71 : BioNTech / PFIZER – Trial protocol - Randomization process

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel,

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Each participant is therefore assigned an automatic number by the system upon the creation of his/her record. The connection information, randomization, and other details are recorded in the audit trail previously mentioned in this document.

It is therefore completely impossible for participants to be « de-randomized ».

These 214 participants have clearly been purely and simply deleted from the database, which is entirely abnormal under Good Data Management Practices, especially since appropriate rights are required to engage in such practices.

It is necessary to obtain explanations from the laboratory on this matter.

6.1.2.4 Potential COVID-19 illness visit not done when required per protocol

The SAS® ADDV table containing protocol deviations allows for the frequency of the ten categories of protocol deviations, namely:

- Inclusion/Exclusion
- Informed Consent
- Study Product
- Laboratory
- Procedures/Tests
- Concomitant Treatments
- Randomization
- Safety Reports
- Visit Schedule
- Other

Excluding deviations occurring after November 14, 2020, the cutoff date, we find that there are more participants with potential COVID-19 visits not completed for the BNT162b2 group than for the placebo group, with 652 participants versus 517, resulting in 135 fewer individuals untested for potential COVID-19 in the vaccine group.

Illustration 72 : Pfizer – Database –SAS® ADVV dataset- Protocol deviation – Potential COVID-19 illness visit

	BNT162b2 Phase 2/3 (30 mcg)	**Placebo**	**Total**
Potential COVID-19 illness visit not done when required per protocol.	652	517	1169

With the vaccinated group being tested less frequently, the number of COVID cases confirmed by PCR tests is underestimated for the vaccine, which constitutes **a major bias** in the assessment of the primary efficacy endpoint, distorting the result.

This could partly explain the difference in the number of cases identified by the counting method and PCR tests versus anti-nucleocapsid serology.

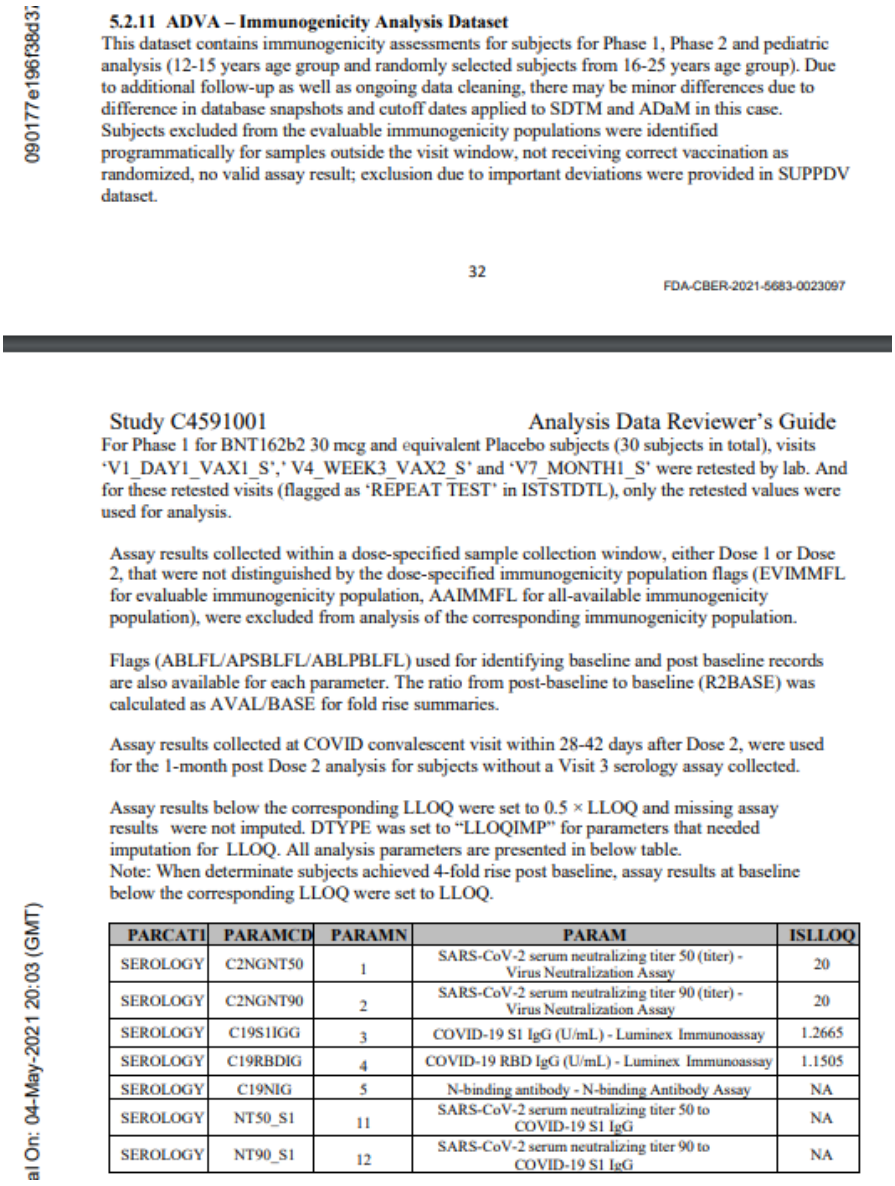
Note that concerning the Safety Reporting category

	BNT162b2 Phase 2/3 (30 mcg)	**Placebo**	**Total**
AE/SAE not recorded in clinical database	1	3	4
SAE not reported to IRB per local regulations		1	1
SAE report delayed or not reported to Sponsor	8	5	13

6.1.2.5 Anti-nucleocapsid serology

As indicated in the guide, the SAS® ADVA table 'contains immunogenicity assessments for subjects in Phase 1, Phase 2, and the pediatric analysis (age group 12-15 years and subjects randomly selected from the age group 16-25 years)

Illustration 73 : BioNTech/PFIZER - Study C4591001- Analysis Data Reviewer Guide - BLA Analysis for Participants ≥16 Years of Age –SAS® ADVA dataset – Immunogenicity criteria



090177e196f38d3

5.2.11 ADVA – Immunogenicity Analysis Dataset

This dataset contains immunogenicity assessments for subjects for Phase 1, Phase 2 and pediatric analysis (12-15 years age group and randomly selected subjects from 16-25 years age group). Due to additional follow-up as well as ongoing data cleaning, there may be minor differences due to difference in database snapshots and cutoff dates applied to SDTM and ADaM in this case. Subjects excluded from the evaluable immunogenicity populations were identified programmatically for samples outside the visit window, not receiving correct vaccination as randomized, no valid assay result; exclusion due to important deviations were provided in SUPPDV dataset.

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Study C4591001 Analysis Data Reviewer's Guide

For Phase 1 for BNT162b2 30 mcg and equivalent Placebo subjects (30 subjects in total), visits 'V1_DAY1_VAX1_S',' V4_WEEK3_VAX2_S' and 'V7_MONTH1_S' were retested by lab. And for these retested visits (flagged as 'REPEAT TEST' in ISTSTDTL), only the retested values were used for analysis.

Assay results collected within a dose-specified sample collection window, either Dose 1 or Dose 2, that were not distinguished by the dose-specified immunogenicity population flags (EVIMMFL for evaluable immunogenicity population, AAIMMFL for all-available immunogenicity population), were excluded from analysis of the corresponding immunogenicity population.

Flags (ABLFL/APSBLFL/ABLPBLFL) used for identifying baseline and post baseline records are also available for each parameter. The ratio from post-baseline to baseline (R2BASE) was calculated as AVAL/BASE for fold rise summaries.

Assay results collected at COVID convalescent visit within 28-42 days after Dose 2, were used for the 1-month post Dose 2 analysis for subjects without a Visit 3 serology assay collected.

Assay results below the corresponding LLOQ were set to 0.5 × LLOQ and missing assay results were not imputed. DTYPE was set to "LLOQIMP" for parameters that needed imputation for LLOQ. All analysis parameters are presented in below table.
Note: When determinate subjects achieved 4-fold rise post baseline, assay results at baseline below the corresponding LLOQ were set to LLOQ.

PARCATI	PARAMCD	PARAMN	PARAM	ISLLOQ
SEROLOGY	C2NGNT50	1	SARS-CoV-2 serum neutralizing titer 50 (titer) - Virus Neutralization Assay	20
SEROLOGY	C2NGNT90	2	SARS-CoV-2 serum neutralizing titer 90 (titer) - Virus Neutralization Assay	20
SEROLOGY	C19S1IGG	3	COVID-19 S1 IgG (U/mL) - Luminex Immunoassay	1.2665
SEROLOGY	C19RBDIG	4	COVID-19 RBD IgG (U/mL) - Luminex Immunoassay	1.1505
SEROLOGY	C19NIG	5	N-binding antibody - N-binding Antibody Assay	NA
SEROLOGY	NT50_S1	11	SARS-CoV-2 serum neutralizing titer 50 to COVID-19 S1 IgG	NA
SEROLOGY	NT90_S1	12	SARS-CoV-2 serum neutralizing titer 90 to COVID-19 S1 IgG	NA

al On: 04-May-2021 20:03 (GMT)

Source : https://phmpt.org/wp-content/uploads/2022/03/125742_S1_M5_c4591001-A-adrg.pdf

For this SAS® table, the contents procedure of SAS® provides the following information: 114,365 observations corresponding to the various parameters measured for immunogenicity at different visits.

Nom de la table	PFIZER.ADVA	**Observations**	114365
Type de membre	DATA	**Variables**	126
Moteur	V9	**Index**	0
Créée	21/03/2023 13:09:32	**Longueur d'observation**	1496
Dernière modification	21/03/2023 13:09:32	**Observations supprimées**	0
Protection		**Compressée**	NON
Type de table		**Triée**	NON
Libellé			
Représentation des données	WINDOWS_64		
Codage	wlatin1 Western (Windows)		
Variables par ordre de création			

COVID-19 RBD IgG (U/mL) - Luminex Immunoassay	1074
COVID-19 S1 IgG (U/mL) - Luminex Immunoassay	1897
N-binding antibody - N-binding Antibody Assay	102281
SARS-CoV-2 serum neutralizing titer 50 (titer) - Virus Neutralization Assay	2814
SARS-CoV-2 serum neutralizing titer 50 to COVID-19 S1 IgG	1748
SARS-CoV-2 serum neutralizing titer 90 (titer) - Virus Neutralization Assay	2809
SARS-CoV-2 serum neutralizing titer 90 to COVID-19 S1 IgG	1742

We therefore have a total of 102,281 measurements for the serology that interests us.

When calculating the number of participants who became positive for COVID (seroconversion) during the trial up to November 14, 2020, the cutoff date used for the first interim analysis, we find 235 positive participants while retaining all participants.

If we exclude those indicated as non-evaluable in the database (variable EVALEFFL=Y).

Illustration 74 : Number of participants with a COVID calculated from SAS® ADVA – Total Population– Subgroup of participants without a history of SARS-CoV-2.

	BNT162b2 Phase 2/3 (30 mcg)	**Placebo**	**Total**
NEG / NEG	15914	15709	31623
NEG / POS	75	160	235
Total	15989	15869	31858

The efficacy of the vaccine is calculated as follows:
VE = (1 - (attack rate in vaccinated individuals / attack rate in placebo)) x 100
In the total population,

VE= (1- (75 / 15 989) / (160 / 15 869)) x 100= (1-0,0047/0,01008) x 100=53,5%

We are far from the announced 95% efficacy.
To recall, there were 8 vaccinated participants who contracted COVID starting 7 days after the second dose out of a total of 36,523 participants.

Illustration 75 : Pfizer - Clinical Study Report of December 10, 2020 – Efficacy results – Symptomatic COVID-19 – 92-page report

Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:46)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_wo_eval

Nearly 10 times more COVID cases are detected in the vaccinated group using serology than with PCR testing, regardless of whether the participants are symptomatic or not.

This confirms the questionable choice of the primary efficacy endpoint, which therefore does not account for all individuals with COVID but only a subset, thus distorting the actual efficacy.

The results of this endpoint have never been presented by the Pfizer laboratory in ANY of the interim clinical reports that led to market authorization for unknown reasons.

Why was the serological criterion, much easier to assess than a PCR test on symptomatic participants, not prioritized for evaluating efficacy?

This is all the more curious since Serologic assays to accurately detect anti–SARS-CoV-2 nucleocapsid antibodies, which would be elicited by naturally acquired infection but not by SARS-CoV-2 spike protein–based vaccination, have been developed and validated, providing the technology required to enable evaluation of efficacy against the infection endpoint. The nesting of endpoints and their partitioning into mutually exclusive and exhaustive categories aid in the interpretation of results. Every infection endpoint is either a COVID-19 endpoint or an asymptomatic infection endpoint, and a harmonized analysis of these 3 endpoints can assess the overall vaccine effect on infection and the proportion of this effect on each component endpoint. Similarly, every COVID-19 endpoint is either a non severe or severe COVID-19

endpoint, and a harmonized analysis of these 3 endpoints can elucidate the proportion of the vaccine effect on each component endpoint»[1]

According to the publication 'Performance Characteristics of the Abbott Architect SARS-CoV-2 IgG Test and Seroprevalence in Boise, Idaho,' the authors report a sensitivity and specificity of 100%, meaning that the Abbott serology test can indeed detect all COVID cases[2],

Illustration 76 : Publication – Clinical Endpoints for Evaluating Efficacy in COVID-19 Vaccine Trials

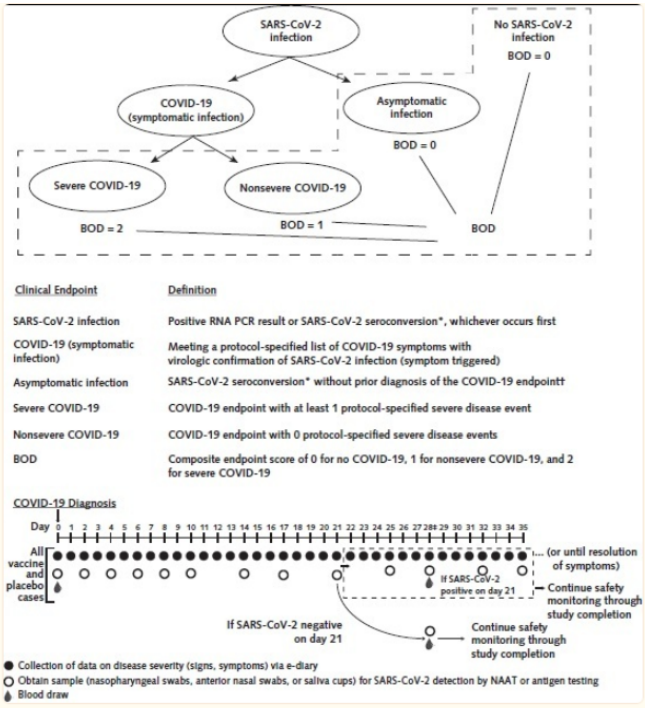

Figure 1.

Clinical endpoint relationships, definitions, and example sampling scheme for diagnosed COVID-19 cases.

Serologic assays to accurately detect anti–SARS-CoV-2 nucleocapsid antibodies, which would be elicited by naturally acquired infection but not by SARS-CoV-2 spike protein–based vaccination, have been developed and validated (8), providing the technology required to enable evaluation of efficacy against the infection endpoint. The nesting of endpoints and their partitioning into mutually exclusive and exhaustive categories aid in the interpretation of results (Figure 1 , *top)*. Every infection endpoint is either a COVID-19 endpoint or an asymptomatic infection endpoint, and a harmonized analysis of these 3 endpoints can assess the overall vaccine effect on infection and the proportion of this effect on each component endpoint. Similarly, every COVID-19 endpoint is either a nonsevere or severe COVID-19 endpoint, and a harmonized analysis of these 3 endpoints can elucidate the proportion of the vaccine effect on each component endpoint.

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7596738/

[2] https://pubmed.ncbi.nlm.nih.gov/32381641/

6.1.2.6 Death not reported at the time of the analysis

The first interim analysis in December 2020 was conducted on a database that was « frozen » (data-management exact term) as of November 14, 2020, which is referred to as a cutoff date. The clinical report presented to the FDA during the meeting on December 10, 2020, reported 6 deaths, 2 in the BNT162b2 group and 4 in the placebo group.

Illustration 77 : Pfizer - Clinical Study Report of December 10, 2020 – Safety results – Participants with at least 1 adverse event from Dose 1 to Data Cutoff date

Table 8. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to Data Cutoff Date (14NOV2020) – Phase 2/3 (All Subjects) – Safety Population

Adverse Event	Vaccine Group (as Administered) BNT162b2 (30 µg) (N[a]=21621) n[b] (%)	Placebo (N[a]=21631) n[b] (%)
Any event	5770 (26.7)	2638 (12.2)
Related[c]	4484 (20.7)	1095 (5.1)
Severe	240 (1.1)	139 (0.6)
Life-threatening	21 (0.1)	24 (0.1)
Any serious adverse event	126 (0.6)	111 (0.5)
Related[c]	4 (0.0)	0
Severe	71 (0.3)	68 (0.3)
Life-threatening	21 (0.1)	23 (0.1)
Any adverse event leading to withdrawal	37 (0.2)	30 (0.1)
Related[c]	16 (0.1)	9 (0.0)
Severe	13 (0.1)	9 (0.0)
Life-threatening	3 (0.0)	6 (0.0)
Death	2 (0.0)	4 (0.0)

Note: Data for subjects randomized on or after 10OCT2020 are included to comprehensively show all data reported but are subject to change with additional follow-up.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_all_p23_saf

Source: https://www.fda.gov/media/144246/download

The report states that

There were 6 participants, all in Phase 3, who died through the data cutoff date of 14 November 2020. This included 2 participants in the BNT162b2 group and 4 participants in the placebo group. None of these deaths were assessed by the investigator as related to study intervention.

Details of the 6 reported deaths among all enrolled participants include:

- One participant in the older BNT162b2 group experienced an SAE of arteriosclerosis and **died 3 days after Dose 1**.
  After searching the database, this refers to **patient 11621327, a 60-year-old male.** Vaccinated on September 10, 2020, he died on the 13th from arteriosclerosis, and this death was not assessed as being related to the vaccine.

- One participant in the older BNT162b2 group experienced an SAE of cardiac arrest 60 days after Dose 2 and died 3 days later.
  After searching the database, this refers to patient **10071101, a 56-year-old woman**, vaccinated on July 30, 2020, and August 20, 2020. She died on October 21, 2020, from **cardiac arrest, 62 days after her second dose.**

Illustration 78 : Pfizer : SAS® database – ADAE dataset – Death report into the Clinical Study Report of December 10, 2020 for BNT162b2

Unique Subject Identifier	Subject Identifier for the Study	Study Site Identifier	Description of Actual Arm	Age	Age Units	Race	Sex	Country	Vaccination Date 01	Vaccination Date 02	Baseline SARS-CoV-2 Status	HIV Positive Subjects Flag	Double Blinded Follow-up Censor Date	Reported Term for the Adverse Event	Body System or Organ Class	Start Date/Time of Adverse Event	Study Day of Start of Adverse Event	End Date/T Adverse Ev
C4591001 1007 10071101	10071101	1007	BNT162b2 Phase 2/3 (30 mcg)	56	YEARS	WHITE	F	USA	30JUL2020	20AUG2020	NEG	N	21OCT2020	Cardiac Arrest	CARDIAC DISORDERS	2020-10-18	81	2020-10-21
C4591001 1162 11621327	11621327	1162	BNT162b2 Phase 2/3 (30 mcg)	60	YEARS	WHITE	M	USA	10SEP2020	.	POS	N	13SEP2020	Atherosclerotic Disease	VASCULAR DISORDERS	2020-09-13	4	2020-09-13

Illustration 79 : Pfizer : Clinical Study Report of December 10, 2020 – Discussion on deaths

6.3.3.2.3. Deaths in Study C4591001 Phase 2/3

There were 6 participants, all in Phase 3, who died through the data cutoff date of 14 November 2020. This included 2 participants in the BNT162b2 group and 4 participants in the placebo group. None of these deaths were assessed by the investigator as related to study intervention.

Details of the 6 reported deaths among all enrolled participants include:

- One participant in the older BNT162b2 group experienced an SAE of arteriosclerosis and died 3 days after Dose 1.
- One participant in the older BNT162b2 group experienced an SAE of cardiac arrest 60 days after Dose 2 and died 3 days later.
- One participant in the younger placebo group experienced an SAE of unevaluable event (unknown of unknown origin; no additional information currently available at the time of this report) 8 days after Dose 1 and died the same day.
- One participant in the older placebo group experienced an SAE of hemorrhagic stroke 15 days after Dose 2 and died the next day.
- One participant in the younger placebo group experienced an SAE of death (cause unknown; no additional information currently available at the time of this report) 34 days after Dose 2.
- One participant in the older placebo group experienced an SAE of myocardial infarction 16 days after Dose 1 and died the same day.

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Regarding the deaths in the placebo group, the report noted the following deaths:

- One participant in the younger placebo group experienced an SAE of unevaluable event (unknown of unknown origin; no additional information currently available at the time of this report) 8 days after Dose 1 and died the same day.
- One participant in the older placebo group experienced an SAE of hemorrhagic stroke 15 days after Dose 2 and died the next day.

- One participant in the younger placebo group experienced an SAE of death (cause unknown; no additional information currently available at the time of this report) 34 days after Dose 2.
- One participant in the older placebo group experienced an SAE of myocardial infarction 16 days after Dose 1 and died the same day.

Reviewing the database, it appears that participant **11201050**, **a 58-year-old woman** vaccinated with the BNT162b2 on August 4 and August 27, 2020, died from **cardiac arrest on November 7, 2020, 72 days after the second dose**, with this death not attributed to the vaccine.

<u>This death is not mentioned</u> in the table of deceased patients nor in the list, even though she is part of the tolerance population to be analyzed.

Illustration 80 : Pfizer : SAS® database – ADAE dataset – Death not reported into the Clinical Study Report of December 10, 2020 - Participant 11201050

	Unique Subject Identifier	Subject Identifier for the Study	Study Site Identifier	Description of Actual Arm	Age	Age Units	Race	Sex	Country	Vaccination Date 01	Vaccination Date 02	Baseline SARS-CoV-2 Status	HIV Positive Subjects Flag	Double Blinded Follow-up Censor Date	Reported Term for the Adverse Event	Body System or Organ Class	Start Date/Time of Adverse Event	Study Day of Start of Adverse Event	End Date/Tim Adverse Event
14050	C4591001 1120 11201050	11201050	1120	BNT162b2 Phase 2/3 (30 mcg)	58	YEARS	WHITE	F	USA	04AUG2020	27AUG2020	NEG	N	07NOV2020	Cardiac arrest	CARDIAC DISORDERS	2020-11-07	96	2020-11-07

The case report form containing all the data for this participant is available in the publicly released documents. **As of November 14, 2020, this death was indeed recorded in the laboratory's safety database** as occurring on November 7, 2020, <u>prior to the cutoff date set</u> for the interim analysis. However, the center recorded it on November 24, 2020; this date was corrected following a request for correction from the laboratory's pharmacovigilance team during the Serious Adverse Event Reconciliation Process, as indicated by the audit trail present in the observation notebook.

"*SAE RECON* (for SAE reconciliation) :*AER#2020477313, the date of death was reported as 07Nov2020 in Safety database but recorded as 24Nov2020 in AE CRF. Please confirm correct date of death. If safety update is required, please submit a follow-up form.*"

This error allowed for the non-disclosure of this death in December 2020. It would have been more than appropriate to investigate this death before releasing the results in order to avoid concealing a serious adverse effect with a fatal outcome.

Illustration 81 : Pfizer : Case Report Form made public on May 1, 2023 – Death due to cardiac arrest - Participant 11201050

Header Text: c4591001

Visit: Logs - Unscheduled	**Form:** ADVERSE EVENT REPORT
Form Version: 22-Apr-2020 21:02	**Form Status:** Data Complete, Frozen
Site No: 1120	**Site Name:** (1120) Meridian Clinical Research
Subject No: 11201050	**Subject Initials:** ---
Generated By: (b) (4)	**Generated Time (GMT):** 29-Mar-2021 11:09

Back to Form
eCRF Audit Trail History
Form Audit Trail

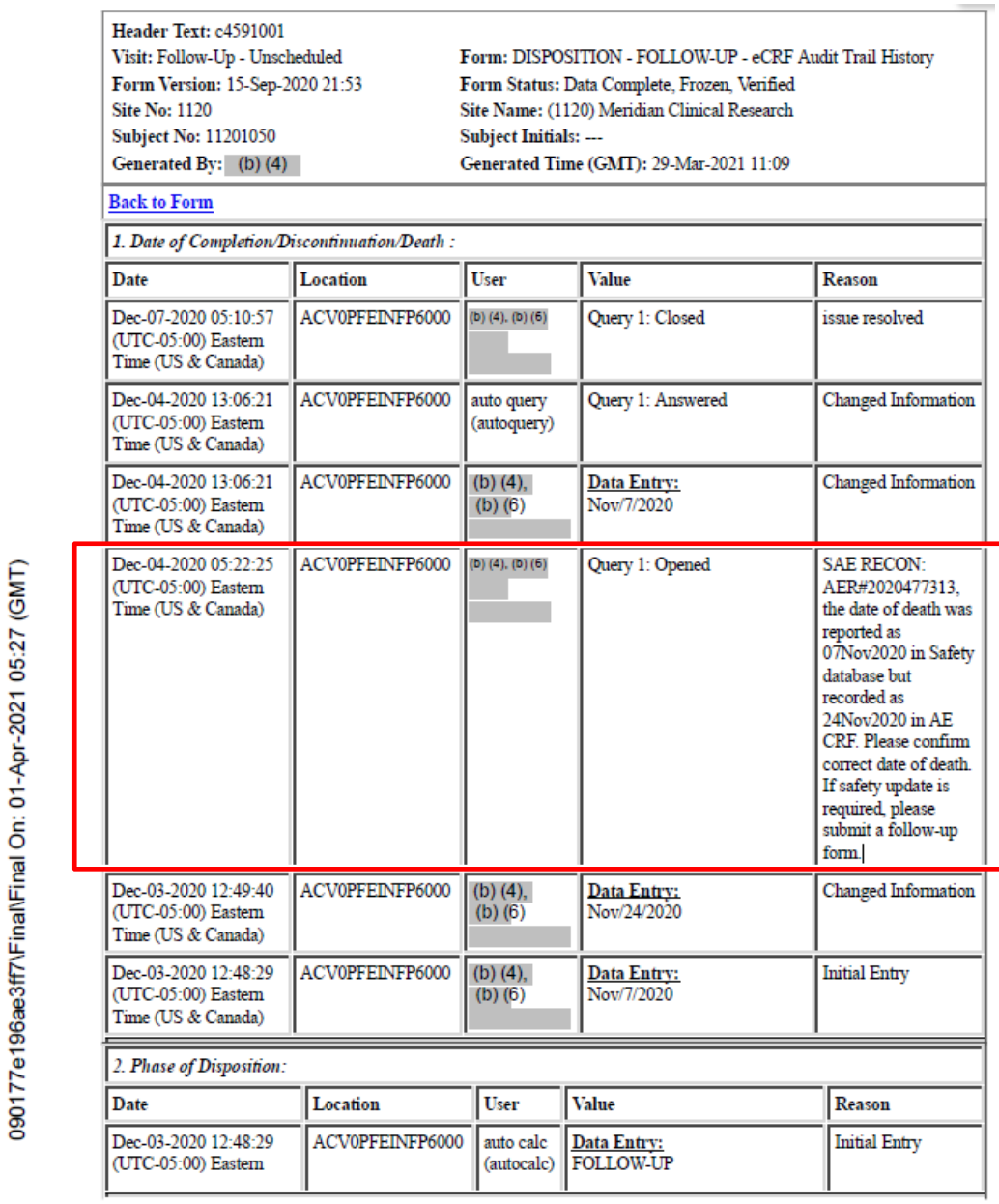
Adverse Event Report

1.	Category:	ADVERSE EVENT
2.	AE ID:	[1]
3.	Adverse Event: (If possible specify diagnosis, not individual symptoms)	[Cardiac arrest]
4.	Start Date Time:	Nov/7/2020 UNK:UNK
5.	Is the adverse event still ongoing?	NO End Date Time: Nov/7/2020 UNK:UNK
6.	Toxicity Grade:	4
7.	Is the adverse event serious? If Yes, NOTIFY PFIZER IMMEDIATELY. Fatal; Life-threatening; Inpatient hospitalization or prolongation of existing hospitalization; Persistent or significant disability/incapacity; Congenital anomaly/birth defect; Important medical event (i.e. may jeopardize subject and may require medical/surgical intervention to prevent above outcomes).	YES Is this serious event associated with congenital anomaly or birth defect? NO Did this serious event result in death? YES Did this serious event require or prolong hospitalization? NO Did this serious event result in persistent or significant disability/incapacity? NO Is this serious event life threatening? YES Other medically important serious event NO
8.	Is this adverse event the result of a study Medication Error? If Yes, record the type of medication error on the Medication Error Log.	NO

Source :

https://phmpt.org/wp-content/uploads/2023/05/125742_S1_M5_CRF_c4591001-1120-11201050.pdf

Illustration 82 : Pfizer : Case Report Form made public on May 1, 2023 – Death due to cardiac arrest - Participant 11201050 – Audit trail



Header Text: c4591001
Visit: Follow-Up - Unscheduled
Form: DISPOSITION - FOLLOW-UP - eCRF Audit Trail History
Form Version: 15-Sep-2020 21:53
Form Status: Data Complete, Frozen, Verified
Site No: 1120
Site Name: (1120) Meridian Clinical Research
Subject No: 11201050
Subject Initials: ---
Generated By: (b) (4)
Generated Time (GMT): 29-Mar-2021 11:09

Back to Form

1. Date of Completion/Discontinuation/Death :

Date	Location	User	Value	Reason
Dec-07-2020 05:10:57 (UTC-05:00) Eastern Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Query 1: Closed	issue resolved
Dec-04-2020 13:06:21 (UTC-05:00) Eastern Time (US & Canada)	ACV0PFEINFP6000	auto query (autoquery)	Query 1: Answered	Changed Information
Dec-04-2020 13:06:21 (UTC-05:00) Eastern Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Data Entry: Nov/7/2020	Changed Information
Dec-04-2020 05:22:25 (UTC-05:00) Eastern Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Query 1: Opened	SAE RECON: AER#2020477313, the date of death was reported as 07Nov2020 in Safety database but recorded as 24Nov2020 in AE CRF. Please confirm correct date of death. If safety update is required, please submit a follow-up form.
Dec-03-2020 12:49:40 (UTC-05:00) Eastern Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Data Entry: Nov/24/2020	Changed Information
Dec-03-2020 12:48:29 (UTC-05:00) Eastern Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Data Entry: Nov/7/2020	Initial Entry

2. Phase of Disposition:

Date	Location	User	Value	Reason
Dec-03-2020 12:48:29 (UTC-05:00) Eastern	ACV0PFEINFP6000	auto calc (autocalc)	Data Entry: FOLLOW-UP	Initial Entry

090177e196ae3ff7\Final\Final On: 01-Apr-2021 05:27 (GMT)

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Confidential

FDA-CBER-2021-5683-0798677

Source :

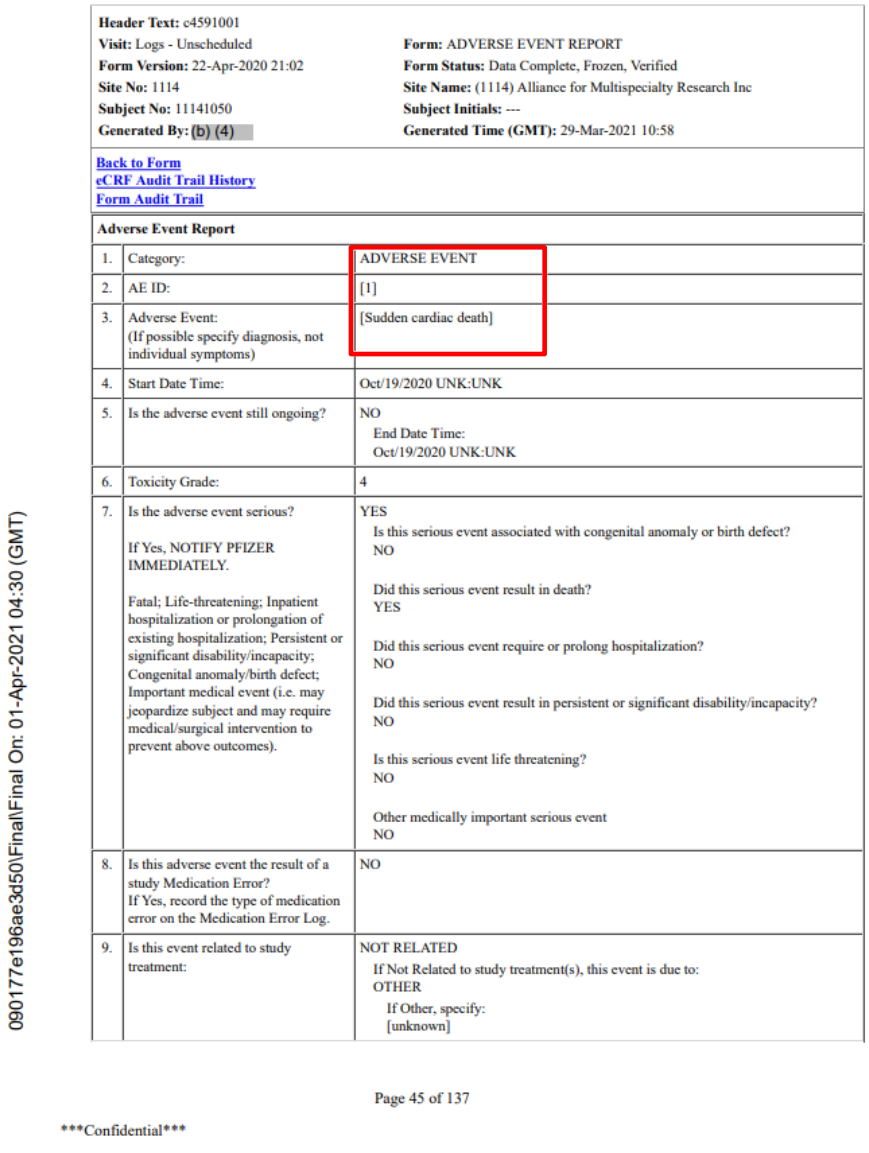
https://phmpt.org/wp-content/uploads/2023/05/125742_S1_M5_CRF_c4591001-1120-11201050.pdf

The case of patient **11141050** is quite similar: **aged 63**, she received the vaccine on August 18 and September 8, 2020, and died of **cardiac arrest** on October 19, 2020. **<u>This death does not appear in the report provided</u>** to the authorities in December 2020 **due to a data entry error** by the center. As a matter of fact, the centre staff recorded the death as November 25, 2020, as indicated by the audit trail present in the Case Report Form for this participant available in the public documents.

Illustration 83 : Pfizer : SAS® database – ADAE dataset – Death not reported into the Clinical Study Report of December 10, 2020 - Participant 11141050

Subject Identifier for the Study	Study Site Identifier	Description of Actual Arm	Age	Age Units	Race	Sex	Country	Vaccination Date 01	Vaccination Date 02	Baseline SARS-CoV-2 Status	HIV Positive Subjects Flag	Double Blinded Follow-up Censor Date	Reported Term for the Adverse Event	Body System or Organ Class	Start Date/Time of Adverse Event	Study Day of Start of Adverse Event	End Date/T Adverse Ev
11141050	1114	BNT162b2 Phase 2/3 (30 mcg)	63	YEARS	WHITE	F	USA	18AUG2020	08SEP2020	NEG	N	19OCT2020	Sudden cardiac death	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2020-10-19	63	2020-10-19

Illustration 84 : Pfizer : Case Report Form made public on May 1, 2023 – Death due to cardiac arrest - Participante 11141050



Header Text: c4591001
Visit: Logs - Unscheduled
Form: ADVERSE EVENT REPORT
Form Version: 22-Apr-2020 21:02
Form Status: Data Complete, Frozen, Verified
Site No: 1114
Site Name: (1114) Alliance for Multispecialty Research Inc
Subject No: 11141050
Subject Initials: ---
Generated By: (b) (4)
Generated Time (GMT): 29-Mar-2021 10:58

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eCRF Audit Trail History
Form Audit Trail

Adverse Event Report

1.	Category:	ADVERSE EVENT
2.	AE ID:	[1]
3.	Adverse Event: (If possible specify diagnosis, not individual symptoms)	[Sudden cardiac death]
4.	Start Date Time:	Oct/19/2020 UNK:UNK
5.	Is the adverse event still ongoing?	NO End Date Time: Oct/19/2020 UNK:UNK
6.	Toxicity Grade:	4
7.	Is the adverse event serious? If Yes, NOTIFY PFIZER IMMEDIATELY. Fatal; Life-threatening; Inpatient hospitalization or prolongation of existing hospitalization; Persistent or significant disability/incapacity; Congenital anomaly/birth defect; Important medical event (i.e. may jeopardize subject and may require medical/surgical intervention to prevent above outcomes).	YES Is this serious event associated with congenital anomaly or birth defect? NO Did this serious event result in death? YES Did this serious event require or prolong hospitalization? NO Did this serious event result in persistent or significant disability/incapacity? NO Is this serious event life threatening? NO Other medically important serious event NO
8.	Is this adverse event the result of a study Medication Error? If Yes, record the type of medication error on the Medication Error Log.	NO
9.	Is this event related to study treatment:	NOT RELATED If Not Related to study treatment(s), this event is due to: OTHER If Other, specify: [unknown]

090177e196ae3d50\Final\Final On: 01-Apr-2021 04:30 (GMT)

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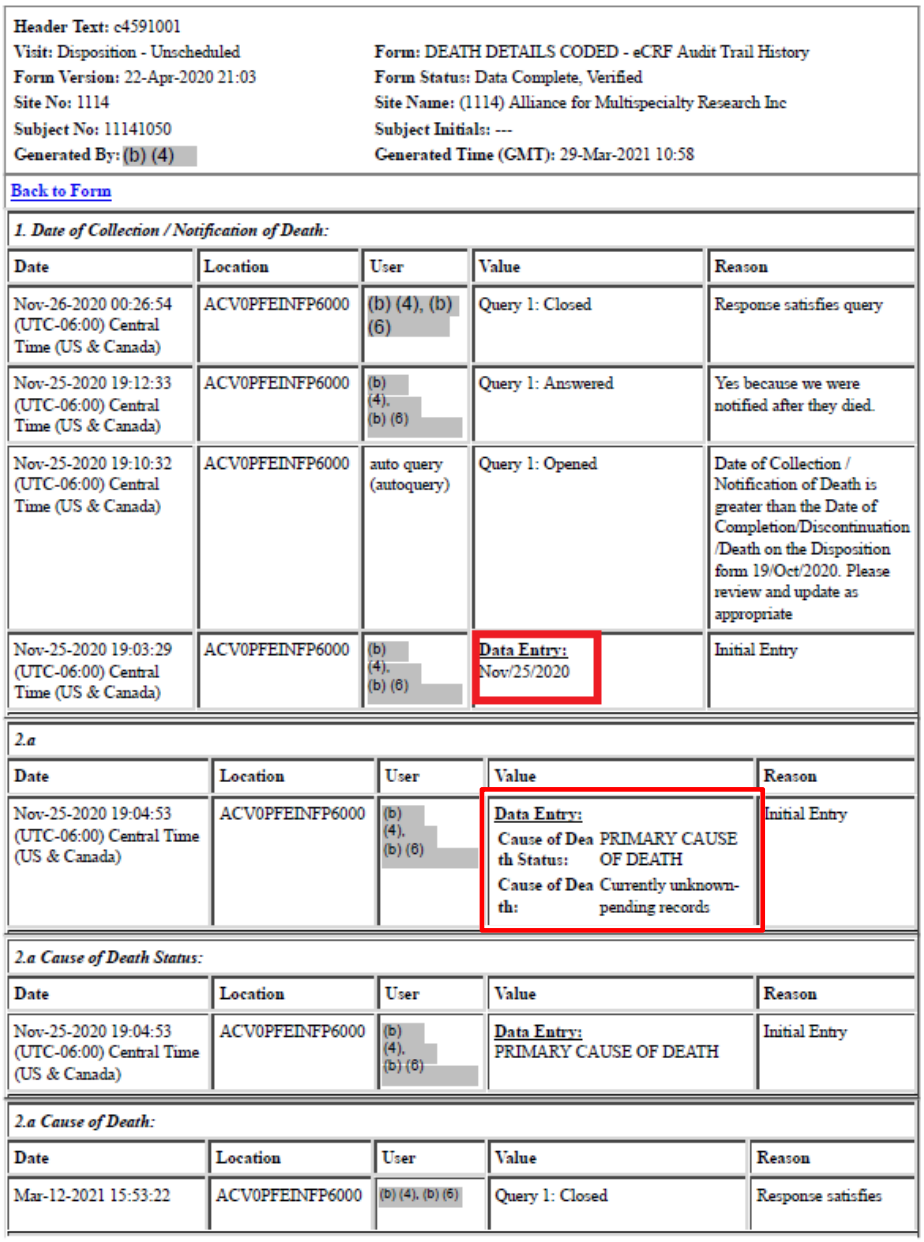
Source : https://phmpt.org/wp-content/uploads/2023/05/125742_S1_M5_CRF_c4591001-1114-11141050.pdf

Illustration 85 : Pfizer : Case Report Form made public on May 1, 2023 – Death due to cardiac arrest - Participant 11141050 – Audit trail



Header Text: c4591001
Visit: Disposition - Unscheduled
Form: DEATH DETAILS CODED - eCRF Audit Trail History
Form Version: 22-Apr-2020 21:03
Form Status: Data Complete, Verified
Site No: 1114
Site Name: (1114) Alliance for Multispecialty Research Inc
Subject No: 11141050
Subject Initials: ---
Generated By: (b) (4)
Generated Time (GMT): 29-Mar-2021 10:58

Back to Form

1. Date of Collection / Notification of Death:

Date	Location	User	Value	Reason
Nov-26-2020 00:26:54 (UTC-06:00) Central Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Query 1: Closed	Response satisfies query
Nov-25-2020 19:12:33 (UTC-06:00) Central Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Query 1: Answered	Yes because we were notified after they died.
Nov-25-2020 19:10:32 (UTC-06:00) Central Time (US & Canada)	ACV0PFEINFP6000	auto query (autoquery)	Query 1: Opened	Date of Collection / Notification of Death is greater than the Date of Completion/Discontinuation /Death on the Disposition form 19/Oct/2020. Please review and update as appropriate
Nov-25-2020 19:03:29 (UTC-06:00) Central Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Data Entry: Nov/25/2020	Initial Entry

2.a

Date	Location	User	Value	Reason
Nov-25-2020 19:04:53 (UTC-06:00) Central Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Data Entry: Cause of Death Status: PRIMARY CAUSE OF DEATH Cause of Death: Currently unknown-pending records	Initial Entry

2.a Cause of Death Status:

Date	Location	User	Value	Reason
Nov-25-2020 19:04:53 (UTC-06:00) Central Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Data Entry: PRIMARY CAUSE OF DEATH	Initial Entry

2.a Cause of Death:

Date	Location	User	Value	Reason
Mar-12-2021 15:53:22	ACV0PFEINFP6000	(b) (4), (b) (6)	Query 1: Closed	Response satisfies

090177e196ae3d50\Final\Final On: 01-Apr-2021 04:30 (GMT)

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FDA-CBER-2021-5683-0792408

Source : https://phmpt.org/wp-content/uploads/2023/05/125742_S1_M5_CRF_c4591001-1114-11141050.pdf

Patient **11521497**, **aged 72**, received the vaccine on October 7, 2020, and **died on November 11, 2020, from sepsis related to Shigella infection**. This death does not appear in the report provided to the authorities in December 2020. It seems that the pages detailing adverse effects were deleted by the center. Re-entry of adverse effects may have occurred on November 12, 2020. Correction requests were sent to the center but after the cutoff date

Illustration 86 : Pfizer : SAS® database – ADAE dataset – Death not reported into the Clinical Study Report of December 10, 2020 - Participant 11521497

Subject Identifier for the Study	Age	Sex (N)	Race	countryn	Description of Planned Arm	Vaccination Date 01	Vaccination Date 02	End Of Study Discontinuation Date	End Of Study Discontinuation Reason	End Of Treatment Discontinuation Date	Baseline SARS-CoV-2 Status	Category for Adverse Event	Reported Term for the Adverse Event	Body System or Organ Class
11521497	72	M	WHITE	USA	BNT162b2 Phase 2/3 (30 mcg)	07OCT2020	.	11NOV2020	DEATH	11NOV2020	NEG	ADVERSE EVENT	sepsis related to Shigella infection	INFECTIONS AND INFESTATIONS
11521497	72	M	WHITE	USA	BNT162b2 Phase 2/3 (30 mcg)	07OCT2020	.	11NOV2020	DEATH	11NOV2020	NEG	ADVERSE EVENT	vasovagal syncope	NERVOUS SYSTEM DISORDERS

Illustration 87 : Pfizer : Case Report Form made public on July 3, 2023 – Death due to sepsis - Participant 11521497

Header Text: c4591001
Visit: Disposition - Unscheduled
Form: DEATH DETAILS CODED
Form Version: 22-Apr-2020 21:03
Form Status: Data Complete, Frozen, Verified
Site No: 1152
Site Name: (1152) California Research Foundation
Subject No: 11521497
Subject Initials: ---
Generated By: (b) (4)
Generated Time (GMT): 29-Mar-2021 11:56

eCRF Audit Trail History

Death Details

1.	Date of Collection / Notification of Death:	Nov/11/2020

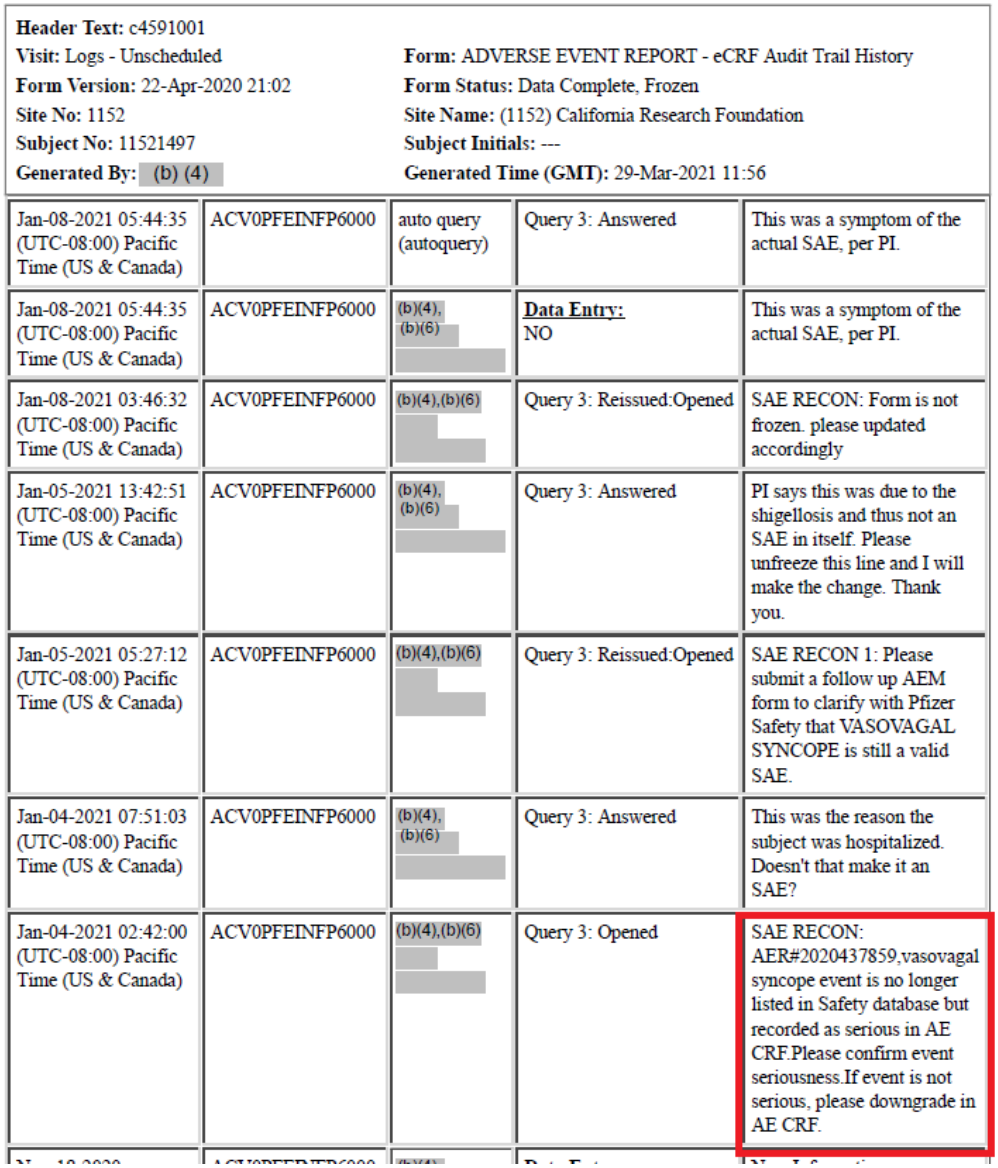
Cause of Death

2.a	Cause of Death Status:	PRIMARY CAUSE OF DEATH
	Cause of Death:	[SEPSIS RELATED TO SHIGELLA INFECTION]

Source :

https://phmpt.org/wp-content/uploads/2023/07/125742_S1_M5_CRF_c4591001-1152-11521497.pdf

Illustration 88 : Pfizer : Case Report Form made public on July 3, 2023 – Death due to septicemia - Participant 11521497 – Audit-trail



Header Text: c4591001
Visit: Logs - Unscheduled
Form: ADVERSE EVENT REPORT - eCRF Audit Trail History
Form Version: 22-Apr-2020 21:02
Form Status: Data Complete, Frozen
Site No: 1152
Site Name: (1152) California Research Foundation
Subject No: 11521497
Subject Initials: ---
Generated By: (b) (4)
Generated Time (GMT): 29-Mar-2021 11:56

Jan-08-2021 05:44:35 (UTC-08:00) Pacific Time (US & Canada)	ACV0PFEINFP6000	auto query (autoquery)	Query 3: Answered	This was a symptom of the actual SAE, per PI.
Jan-08-2021 05:44:35 (UTC-08:00) Pacific Time (US & Canada)	ACV0PFEINFP6000	(b)(4), (b)(6)	**Data Entry:** NO	This was a symptom of the actual SAE, per PI.
Jan-08-2021 03:46:32 (UTC-08:00) Pacific Time (US & Canada)	ACV0PFEINFP6000	(b)(4),(b)(6)	Query 3: Reissued:Opened	SAE RECON: Form is not frozen. please updated accordingly
Jan-05-2021 13:42:51 (UTC-08:00) Pacific Time (US & Canada)	ACV0PFEINFP6000	(b)(4), (b)(6)	Query 3: Answered	PI says this was due to the shigellosis and thus not an SAE in itself. Please unfreeze this line and I will make the change. Thank you.
Jan-05-2021 05:27:12 (UTC-08:00) Pacific Time (US & Canada)	ACV0PFEINFP6000	(b)(4),(b)(6)	Query 3: Reissued:Opened	SAE RECON 1: Please submit a follow up AEM form to clarify with Pfizer Safety that VASOVAGAL SYNCOPE is still a valid SAE.
Jan-04-2021 07:51:03 (UTC-08:00) Pacific Time (US & Canada)	ACV0PFEINFP6000	(b)(4), (b)(6)	Query 3: Answered	This was the reason the subject was hospitalized. Doesn't that make it an SAE?
Jan-04-2021 02:42:00 (UTC-08:00) Pacific Time (US & Canada)	ACV0PFEINFP6000	(b)(4),(b)(6)	Query 3: Opened	SAE RECON: AER#2020437859,vasovagal syncope event is no longer listed in Safety database but recorded as serious in AE CRF.Please confirm event seriousness.If event is not serious, please downgrade in AE CRF.

Source :

https://phmpt.org/wp-content/uploads/2023/07/125742_S1_M5_CRF_c4591001-1152-11521497.pdf

There are again, we face serious violations of Good Pharmacovigilance Practices, Good Clinical Practice, and Good Data Management Practice.

The patient **10891073**, **aged 63**, received the vaccine on August 6, 2020, and September 4, 2020. She died on November 12, 2020, from an **exacerbation of chronic obstructive bronchitis**. The death was reported by the participant's sister on November 12 but **was only entered into the system by the site on December 4**, constituting yet another serious violation of Good Clinical Practice.

Illustration 89 : Pfizer : SAS® database – ADAE dataset – Death not reported into the Clinical Study Report of December 10, 2020 - Participant 11521497

Subject Identifier for the Study	Age	Sex (N)	Race	countryn	Description of Planned Arm	Vaccination Date 01	Vaccination Date 02	End Of Study Discontinuation Date	End Of Study Discontinuation Reason	End Of Treatment Discontinuation Date	Baseline SARS-CoV-2 Status	Category for Adverse Event	Reported Term for the Adverse Event	Body System or Organ Class	Lowest Level Term
10891073	63	F	WHITE	USA	BNT162b2 Phase 2/3 (30 mcg)	06AUG2020	04SEP2020	12NOV2020	DEATH	.	NEG	ADVERSE EVENT	Worsening of COPD	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COPD exacerbation

Illustration 90 : Pfizer : Case Report Form made public on August 1, 2023 – Death - Participant 10891073

Header Text: c4591001
Visit: Follow-Up - Unscheduled
Form: DISPOSITION - FOLLOW-UP
Form Version: 15-Sep-2020 21:53
Form Status: Data Complete, Frozen, Verified
Site No: 1089
Site Name: (1089) PMG Research of Salisbury
Subject No: 10891073
Subject Initials: ---
Generated By: (b) (4)
Generated Time (GMT): 29-Mar-2021 10:22

eCRF Audit Trail History

Disposition - Follow-Up

1.	Date of Completion/Discontinuation/Death :	Nov/12/2020
2.	Phase of Disposition:	FOLLOW-UP
3.	Status:	DEATH
4.	Specify Status:	[ ]

Illustration 91 : Pfizer : Case Report Form made public on August 1, 2023 – Death - Participant 10891073 – Audit-trail

Header Text: c4591001
Visit: Follow-Up - Unscheduled
Form: DISPOSITION - FOLLOW-UP - eCRF Audit Trail History
Form Version: 15-Sep-2020 21:53
Form Status: Data Complete, Frozen, Verified
Site No: 1089
Site Name: (1089) PMG Research of Salisbury
Subject No: 10891073
Subject Initials: ---
Generated By: (b) (4)
Generated Time (GMT): 29-Mar-2021 10:22

4. Specify Status:

Date	Location	User	Value	Reason
Dec-04-2020 15:27:26 (UTC-05:00) Eastern Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Data Entry:	Transcription Error
Dec-04-2020 15:24:56 (UTC-05:00) Eastern Time (US & Canada)	ACV0PFEINFP6000	(b) (4), (b) (6)	Data Entry: Subjects sister-in-law notified s ite the patient deceased on 12N ov2020 due to chronic lung die sease	Initial Entry

Source : https://phmpt.org/wp-content/uploads/2023/08/125742_S1_M5_CRF_c4591001-1089-10891073.pdf

Such delays or errors in recording death dates persisting at the time of such an important interim analysis are entirely unusual, as data managers and pharmacovigilance personnel are particularly vigilant regarding deaths.

These constitute a serious violation that invalidates the safety results, as in December 2020, there were not 2 deaths in the vaccine group as stated in the report, but 6, including 3 cardiac arrests. This casts doubt on all the results provided.

It also highlights the risk taken by health agencies in evaluating such an innovative product based on an interim analysis with only 3 months of follow-up. Since the data are not fixed, the results presented are either false or significantly incomplete.

Indeed, if we refer to the deaths identified in the database as of 03/13/2021.

- **Patient 10391010**, an **84-year-old man** vaccinated with BNT162b2 on August 21 and September 9, 2020, reported pain at the injection site following each dose (classified under General Disorders and Administration Site Conditions). On the day of the first dose, he also suffered from bruising (classified under Injury, Poisoning, and Procedural Complications). The day after the second dose, he developed a fever (September 10, 2020). On August 21, 2020, he exhibited **cardiovascular adverse events**, including arteriosclerosis (classified under Vascular Disorders) and **hypertensive heart disease** (classified under Cardiac Disorders). **This patient passed away from these conditions on November 18, 2020, 4 days after the cutoff date**. These events were assessed as not related to the vaccine.

- **Patient 11271112, a 53-year-old man**, was vaccinated on August 20, 2020, and September 10, 2020. He died on December 4, 2020 (85 days after the second dose) from a **cardiac arrest**. This death is not included in the report dated December 10, 2020, as it occurred after the cutoff date. This death was assessed as not related to the vaccine.

- Patient **10211127**, **a 54-year-old man** vaccinated on August 31, 2020, and September 23, 2020, with BNT162b2 initially developed **acute left ventricular failure** (organ class, cardiac disorders) and **hypokalemia** (class, metabolic and nutritional disorders) on October 19, 2020, which corresponds to a delay of 50 days after his first injection. These adverse effects were noted as RECOVERED/RESOLVED. **However, on November 30, 2020, after the cutoff date, this patient died from congestive heart failure**. These effects were assessed as not related to the vaccine.

This analysis was confirmed by Australian Doctor Jeyanthi Kunadhasan, who also examined the database of the pivotal clinical trial.

Dr. Kunadhasan informed the Australian health authorities on March 21, 2024. Here is an excerpt from her 9-page substantiated and sourced letter:

"*Pfizer's clinical trial protocol required prompt reporting – immediately upon awareness and, under no circumstances, to exceed 24 hours – of serious adverse events (SAE), via the **Vaccine SAE Reporting Form, to Pfizer Safety**. Investigators were responsible for documenting all directly observed and spontaneously reported adverse events, including serious adverse events reported by participants, into the patient's Case Report Form (CRF). In the unfortunate event of a death, the next of kin or emergency contact had the responsibility to promptly inform the clinical trial site, distinguishing it from the self-reporting process for other adverse events. ...*

Examining the table below, which is adapted from the 'Forensic Analysis of the 38 Subject deaths in the 6-Month Interim Report of the Pfizer-BioNTech BNT162b2 mRNA Vaccine Clinical Trial' (Michels et al., 2023), ***reveals that as of the data cut-off date of November 14, 2020, a total of 11 deaths (six deaths in the vaccinated arm of the study and five in the placebo arm) were recorded****. This stands in contrast to the six deaths publicly disclosed at the VRBPAC meeting and in the Polack article. The capture rate seems to be 33% in the vaccinated arm (two reported deaths out of six) and 80% in the placebo arm (four reported deaths out of five).*"

Illustration 92 : Deaths reported with a delay –Dr Kunadhasan analysis

Days of delay in recording subject deaths

BNT162b2 arm

Period	Subject ID	Date of Death	Officially Recorded Date (from Case Report Form)	Delay Recording Death (Days)
*P-C	11621327	13Sept2020	24Sept2020	11
P-C	11141050	19Oct2020	25Nov2020	37
*P-C	10071101	21Oct2020	5Nov2020	15
P-C	11201050	07Nov2020	3Dec2020	26
P-C	11521497	11Nov2020	18Nov2020	7
P-C	10891073	12Nov2020	4Dec2020	22

Placebo arm

Period	Subject ID	Date of Death	Officially Recorded Date (from Case Report Form)	Delay Recording Death (Days)
#P-C	11521085	26Aug2020	27Aug2020	1
#P-C	12313972	28Sept2020	1Oct2020	3
P-C	11561124	02Nov2020	19Nov2020	17
#P-C	10661350	03Nov2020	10Nov2020	7
#P-C	10811194	04Nov2020	11Nov2020	7

SHADING — undisclosed at the Dec 10th VRPBAC meeting

"*To unravel the* ***discrepancies in reported deaths,*** *my co-authors and I initiated our investigation with the assumption that, as of November 14, 2020, Pfizer-BioNTech had no knowledge of any deaths during the trial. The only way to convincingly disprove this was to demonstrate, through publicly available records, that* ***Pfizer-BioNTech had knowledge of the deaths****.* ***By examination of these records, we were able to show Pfizer-BioNTech indeed did possess knowledge of them****. Scrutinizing each patient's notes accessible on the Public Health and Medical Professionals for Transparency (PHMPT) website, we identified the six deceased subjects, whose deaths were reported in the initial Polack publication and at the VRBPAC meeting on December 10, 2020.*

These subjects include vaccinated patients 11621327 and 10071101 along with the unvaccinated subjects 11521085, 12313972, 10661350, and 10811194. Their deaths occurred prior to November 14, 2020, and the documentation of their deaths was available in their respective Case Report Forms (CRFs) prior to November 14, 2020."

The letter can be downloaded at the following link.

https://openvaet.substack.com/p/pfizerbiontech-c4591001-trial-audit#footnote-93-144275433

Illustration 93 : Letter from Dr. Kunadhasan regarding concealed deaths submitted to the Australian health agency (TGA) – page 1

AMPS
Australian Medical Professionals' Society

21 March, 2024

Dr Tony Lawler, head of the TGA
Anthony.lawler@health.gov.au

Copied to:
Professor Paul Kelly
Paul.kelly@health.gov.au
Dr Blair Comley, Chair of the Department of Health
Blair.Comley@health.gov.au
Professor Nigel Crawford ATAGI
nigel.crawford@mcri.edu.au
Minister Mark Butler
minister.butler@health.gov.au

RE: Undisclosed Deaths in C4591001 Trial at the Vaccine and Related Biological Products Advisory Committee (VRBPAC) on December 10, 2020.

Dear Dr Tony Lawler

You will find at the end of this paper three specific questions which are being directed to you. This letter comes to you not only on my own behalf, but on behalf of The Australian Medical Professionals Society. Please treat it as being on the record.

I am Dr. Jeyanthi Kunadhasan, an anaesthetist and perioperative physician. I investigated the data, released on the Public Health and Medical Professionals for Transparency website,[1] which formed the basis of the Food and Drug Administration's emergency use authorization (EUA) of Pfizer-BioNTech's BNT162b2 mRNA COVID vaccine. Additionally, I serve as Treasurer of the Australian Medical Professionals Society.[2]

I co-authored Pfizer reports 42[3] and 76[4], available on dailyclout.io. Additionally, I contributed as a coauthor of "Forensic Analysis of the 38 Subject deaths in the 6-Month Interim Report of the Pfizer-BioNTech BNT162b2 mRNA Vaccine Clinical Trial."[5] This analysis of the Pfizer's COVID vaccine represents the inaugural examination of the original trial data by a group unaffiliated with clinical trial sponsorship.

I wish to highlight two undisclosed deaths of American trial participants in the BNT162b2-vaccinated arm of Pfizer's clinical trial. Pfizer's nondisclosure of these deaths occurred before Pfizer's data cut-off date for its EUA submission to the FDA (Michels et al., 2023).

The clinical trial data reportedly supporting the safety and efficacy of the BNT162b2 mRNA vaccine have been published twice. Polack et al. released their findings, 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine,' [6] on December 10, 2020, one day before the FDA issued Pfizer's EUA. Subsequently, on September 15, 2021, Stephen J. Thomas, MD, et al. published, 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months.'[7] The Polack publication in the *New England Journal of Medicine* stated, 'All the trial data were available to all the authors, who vouch for its accuracy and completeness and for adherence of the trial to the protocol,

Illustration 94 : Letter from Dr. Kunadhasan regarding concealed deaths submitted to the Australian health agency (TGA) – page 2

which is available with the full text of this article at NEJM.org. An independent data and safety monitoring board reviewed efficacy and unblinded safety data' (Polack et al., 2020).

The Polack paper disclosed six deaths — two in the BNT162b2 arm and four in the placebo arm. Both the journal article and the EUA approval documentation[8] showed the six deaths during the period of July 27, 2020, till November 14, 2020. This letter will demonstrate that Pfizer-BioNTech had records showing eight deaths, four in the BNT162b2 arm and four in the placebo arm, that Pfizer should have disclosed to the FDA. Additionally, the two undisclosed deaths indicated a cardiac event signal in the clinical trial's BNT162b2 recipients (Michels et al., 2023).

Pfizer's clinical trial protocol required prompt reporting – immediately upon awareness and, under no circumstances, to exceed 24 hours – of serious adverse events (SAE), via the Vaccine SAE Reporting Form, to Pfizer Safety.[9] Investigators were responsible for documenting all directly observed and spontaneously reported adverse events, including serious adverse events reported by participants, into the patient's Case Report Form (CRF). In the unfortunate event of a death, the next of kin or emergency contact had the responsibility to promptly inform the clinical trial site, distinguishing it from the self-reporting process for other adverse events. The clinical trial site's swift notification about an SAE to the trial sponsor, BioNTech in this instance, played a crucial role in meeting legal obligations and ethical responsibilities concerning participant safety and the study intervention under clinical investigation. BioNTech, as the sponsor, bore the legal duty to quickly notify both the local regulatory authority and other regulatory agencies about the safety of the study intervention under clinical investigation. Compliance with country-specific regulatory requirements for safety reporting to the regulatory authority, Independent Review Boards (IRBs)/Ethics Committees (ECs), and investigators was also obligatory.

Examining the table below, which is adapted from the 'Forensic Analysis of the 38 Subject deaths in the 6-Month Interim Report of the Pfizer-BioNTech BNT162b2 mRNA Vaccine Clinical Trial' (Michels et al., 2023), reveals that as of the data cut-off date of November 14, 2020, a total of 11 deaths (six deaths in the vaccinated arm of the study and five in the placebo arm) were recorded. This stands in contrast to the six deaths publicly disclosed at the VRBPAC meeting and in the Polack article. The capture rate seems to be 33% in the vaccinated arm (two reported deaths out of six) and 80% in the placebo arm (four reported deaths out of five).

Days of delay in recording subject deaths

BNT162b2 arm

Period	Subject ID	Date of Death	Officially Recorded Date (from Case Report Form)	Delay Recording Death (Days)
*P-C	11621327	13Sept2020	24Sept2020	11
P-C	11141050	19Oct2020	25Nov2020	37
*P-C	10071101	21Oct2020	5Nov2020	15
P-C	11201050	07Nov2020	3Dec2020	26
P-C	11521497	11Nov2020	18Nov2020	7
P-C	10891073	12Nov2020	4Dec2020	22

Placebo arm

Period	Subject ID	Date of Death	Officially Recorded Date (from Case Report Form)	Delay Recording Death (Days)
#P-C	11521085	26Aug2020	27Aug2020	1
#P-C	12313972	28Sept2020	1Oct2020	3
P-C	11561124	02Nov2020	19Nov2020	17
#P-C	10661350	03Nov2020	10Nov2020	7
#P-C	10811194	04Nov2020	11Nov2020	7

SHADING — undisclosed at the Dec 10th VRPBAC meeting

To unravel the discrepancies in reported deaths, my co-authors and I initiated our investigation with the assumption that, as of November 14, 2020, Pfizer-BioNTech had no knowledge of any deaths during the trial. The only way to convincingly disprove this was to demonstrate, through publicly available records, that Pfizer-BioNTech had knowledge of the deaths. By examination of these records, we were able to show Pfizer-BioNTech indeed did possess knowledge of them. Scrutinizing each patient's notes accessible on the Public Health and Medical Professionals for Transparency (PHMPT) website, we identified the six deceased subjects, whose deaths were reported in the initial Polack publication and at the VRBPAC meeting on December 10, 2020. These subjects include

In summary,

The research and data management within the database:

- Highlight the **disappearance of participants** between two versions of documents.

- Reveal the **troubling management of the Argentine center**, the largest recruiter of participants in the trial: the creation of a virtual center, failure to report serious adverse effects by the principal investigator, Fernando Polack, who authored the initial publication of results in the *New England Journal of Medicine*.

- **Confirm the biases mentioned in the methodological analysis** of the clinical trial protocol, Section 5.2, Characteristics of the Phase 1-2-3 Pfizer Trial (the main or pivotal trial), previously discussed in this document concerning the calculation of the primary efficacy endpoint.
  Participants who received the vaccine were tested less frequently than those in the placebo group, leading to an underestimation of cases for the vaccine and an overestimation of efficacy.
  The reported efficacy of 95%, as well as all subsequent results on this endpoint, are therefore fundamentally inaccurate.

- **Highlight the discrepancies in the counting of COVID-19 cases between the chosen primary efficacy endpoint and the anti-nucleocapsid serology**, which is a more objective criterion derived from blood tests that account for all symptomatic and asymptomatic COVID cases.
  The statistical analysis of this criterion indicated an efficacy result of approximately 54% based on the data frozen as of November 14, 2020.
  This result was not provided by Pfizer/BioNTech, which proved to be quite convenient since the actual efficacy for all COVID cases, symptomatic or otherwise, is barely above 50%.

- **Reveal delays, errors, and concealments of deaths**, even while the laboratory was aware of them. The analyses conducted by Dr. Kunadhasan confirm our findings within the database and the participant records made public throughout 2023.
  There are 4 missing deaths in the vaccinated group and 1 in the placebo group.
  Thus, the rates are 33% in the vaccinated group and 80% in the placebo group (4 reported deaths out of 5).
  These "errors" are inexcusable given the processes for reconciling serious adverse events between the pharmacovigilance department and data management.
  This represents yet another **violation of Good Clinical Practice**.
  The safety data reported in December 2020 is therefore also erroneous.

6.2 Interim analysis at 6 months from September 15, 2021

The results of the six-month follow-up of participants analysis were published in the *New England Journal of Medicine* by Thomas SJ, Moreira ED Jr, et al. on September 15, 2021.

https://pubmed.ncbi.nlm.nih.gov/34525277/

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110345

These results stem from an interim analysis **after six months of follow-up**, with the database having been "frozen" as of March 13, 2021 (the cutoff date).

We will not comment on the efficacy results, as this report has demonstrated the biases in their collection and calculation methods, rendering them, in fact, unreliable.

However, it is noteworthy to highlight the limitations identified by the authors:

« *This report has several limitations.* ***Duration of protection and safety data that could be collected in a blinded, placebo-controlled manner were limited by the ethical and practical need to immunize eligible initial placebo recipients*** *under emergency use authorization and according to the recommendations of public health authorities.*

The data presented here do not address whether vaccination prevents asymptomatic infection*; however, evaluation of that question is ongoing in this trial, and real-world data suggest that BNT162b2 prevents asymptomatic infection.*

Preliminary analyses of breakthrough cases ***have not yet identified a correlate of protection,*** *since vaccine protection rates remain high. This report* ***does not address vaccine efficacy and safety in pregnant women and in children younger than 12 years of age.*** *Studies evaluating BNT162b2 in these populations are ongoing.* »

Illustration 95 : Publication of 6-month results: NEJM article from September 15, 2021 – Limitations

including North America, Europe, South Africa, and Latin America. Although vaccine efficacy was slightly lower in Latin American countries, BNT162b2 had a high efficacy of approximately 86% in Argentina and Brazil. Circulation of SARS-CoV-2 variants — some of which are associated with more rapid transmission and potentially greater pathogenicity[27] — has raised concerns that such variants could evade vaccine-mediated protection. Our studies of in vitro neutralization of a variety of SARS-CoV-2 variants have, to date, showed that all tested BNT162b2-immune sera neutralize all tested variants.[14,28-32] The beta variant, which has shown the greatest reduction in neutralization and was the dominant strain in South Africa during the reported observation period, is still neutralized at serum titers higher than those observed at the onset of protection against Covid-19 after the first vaccine dose.[9,14,20] We found that BNT162b2 had an observed efficacy of 100% (95% CI, 53.5 to 100) against Covid-19 in South Africa (9 cases occurred in the placebo recipients and 0 cases in the BNT162b2 recipients), and 8 of 9 cases for which sequence information could be obtained involved the beta variant of SARS-CoV-2.

Safety data are now available for approximately 44,000 participants 16 years of age or older; 12,006 participants have at least 6 months

This report has several limitations. Duration of protection and safety data that could be collected in a blinded, placebo-controlled manner were limited by the ethical and practical need to immunize eligible initial placebo recipients under emergency use authorization and according to the recommendations of public health authorities. The data presented here do not address whether vaccination prevents asymptomatic infection; however, evaluation of that question is ongoing in this trial, and real-world data suggest that BNT162b2 prevents asymptomatic infection.[33,34] Preliminary analyses of breakthrough cases have not yet identified a correlate of protection, since vaccine protection rates remain high. This report does not address vaccine efficacy and safety in pregnant women and in children younger than 12 years of age. Studies evaluating BNT162b2 in these populations are ongoing.

The data in this report show that BNT162b2 prevents Covid-19 effectively for up to 6 months after the second dose across diverse populations, despite the emergence of SARS-CoV-2 variants, including the beta variant, and the vaccine continues to show a favorable safety profile.

Supported by BioNTech and Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Regarding the fatalities, the authors report that **15 participants died in the BNT162b2 group compared to 14 in the placebo group**. Three participants from the BNT162b2 group and two from the initial placebo group, who subsequently received BNT162b2 after unblinding, also died.

None of these deaths were deemed related to BNT162b2 by the investigators.

Illustration 96 : Publication of 6-month results: NEJM article from September 15, 2021 – Adverse events and deaths

Adverse Events

Analyses of adverse events during the blinded period included 43,847 participants 16 years of age or older (Table S3). Reactogenicity events among the participants who were not in the reactogenicity subgroup were reported as adverse events, which resulted in imbalances between the BNT162b2 group and the placebo group with respect to adverse events (30% vs. 14%), related adverse events (24% vs. 6%), and severe adverse events (1.2% vs. 0.7%). New adverse events attributable to BNT162b2 that were not previously identified in earlier reports included decreased appetite, lethargy, asthenia, malaise, night sweats, and hyperhidrosis. Few participants had serious adverse events or adverse events that led to trial withdrawal. No new serious adverse events were considered by the investigators to be related to BNT162b2 after the data cutoff date of the previous report.[9]

During the combined blinded and open-label periods, cumulative safety data during follow-up were available through 6 months after the second dose for 12,006 participants who were originally randomly assigned to the BNT162b2 group. No new safety signals relative to the previous report were observed during the longer follow-up period in the current report, which included open-label observation of the original BNT162b2 recipients and placebo recipients who received BNT162b2 after unblinding.[9]

The table indicating the fatalities in the appendices does not match the commentary, as it only mentions 3 deaths for the BNT162b2 group and 5 for the placebo group, which is completely impossible given that 11 deaths were identified in the database as early as December 2020, 6 in the vaccine group, 5 into the placebo group.

If you look at the note below the table, you will see that « This data only accounts for adverse effects occurring from **the first dose to one month after the second dose** during the blinded follow-up period, as indicated in the note below the table. »

Presenting only SAE or deaths <u>1 month after dose 2</u> is a mean to decrease the number of the safety issued

Again, a questionable method.

Illustration 97 : Publication of 6-month results: NEJM article from September 15, 2021 – Summary of participants with a least one AE, SAE or Death

Adverse Event	BNT162b2 (N[a]=21,926) n[b] (%)	Placebo (N[a]=21,921) n[b] (%)
Any event	6617 (30.2)	3048 (13.9)
Related[c]	5241 (23.9)	1311 (6.0)
Severe	262 (1.2)	150 (0.7)
Life-threatening	21 (0.1)	26 (0.1)
Any serious adverse event	127 (0.6)	116 (0.5)
Related[c,d]	3 (0.0)	0
Severe	71 (0.3)	66 (0.3)
Life-threatening	21 (0.1)	26 (0.1)
Any adverse event leading to withdrawal	32 (0.1)	36 (0.2)
Related[c]	13 (0.1)	11 (0.1)
Severe	10 (0.0)	10 (0.0)
Life-threatening	3 (0.0)	7 (0.0)
Death	3 (0.0)	5 (0.0)

Table S3 | Participants Reporting at Least 1 Adverse Event from Dose 1 to 1 Month After Dose 2 During the Blinded Follow-up Period. The population included all ≥16-year-old participants who received ≥1 dose of vaccine irrespective of follow-up time. a. N=number of participants in the specified group. This value is the denominator for the percentage calculations. b. n=Number of participants reporting ≥1 occurrence of the specified event category. For 'any event', n=number of participants reporting ≥1 occurrence of any event. c. Assessed by the investigator as related to investigational product. d. Shoulder injury related to vaccine administration, right axillary lymphadenopathy, and paroxysmal ventricular arrhythmia (as previously reported). Adverse events for 12–15-year-old participants were reported previously.[11]

It is noteworthy that at the 6-month follow-up of participants, **there were more than twice as many adverse effects reported: 30.2% for the vaccine group versus 13.9% for the placebo group.**

For severe adverse effects, the percentages were 1.2% for the vaccine group and 0.7% for the placebo group. Clearly, these % are not the exact reflect of the safety as they are only counted during a one-month period after dose 2.

It is unclear whether the adverse effects reported by Mr. Augusto Roux had been corrected by that time.

There were 4 cases of cardiac arrest among vaccinated participants compared to 1 in the placebo group.

The cardiovascular adverse effects included atherosclerosis (class: Vascular Disorders) and hypertensive heart disease from participant 10391010, the respiratory arrest of patient 11271112 (53 years old), and acute left ventricular failure in participant 10211127 (54 years old).

There was 1 death due to COVID-19 in the vaccinated group and 1 in the placebo group.

It was therefore clear that <u>no efficacy against COVID-19 mortality could be demonstrated</u>.

Illustration 98 : Publication of 6-month results: NEJM article from September 15, 2021 – Reported cause of death

Reported Cause of Death[a]	BNT162b2 (N=21,926) n	Placebo (N=21,921) n
Deaths	15	14
Acute respiratory failure	0	1
Aortic rupture	0	1
Arteriosclerosis	2	0
Biliary cancer metastatic	0	1
COVID-19	0	2
COVID-19 pneumonia	1	0
Cardiac arrest	4	1
Cardiac failure congestive	1	0
Cardiorespiratory arrest	1	1
Chronic obstructive pulmonary disease	1	0
Death	0	1
Dementia	0	1
Emphysematous cholecystitis	1	0
Hemorrhagic stroke	0	1
Hypertensive heart disease	1	0
Lung cancer metastatic	1	0
Metastases to liver	0	1
Missing	0	1
Multiple organ dysfunction syndrome	0	2
Myocardial infarction	0	2
Overdose	0	1
Pneumonia	0	2
Sepsis	1	0
Septic shock	1	0
Shigella sepsis	1	0
Unevaluable event	1	0

Table S4 | Causes of Death from Dose 1 to Unblinding (Safety Population, ≥16 Years Old). a. Multiple causes of death could be reported for each participant. There were no deaths among 12–15-year-old participants.

Source : https://www.nejm.org/doi/suppl/10.1056/NEJMoa2110345/suppl_file/nejmoa2110345_appendix.pdf

In Summary

In September 2021, the results of the 6-month follow-up analysis published in the *New England Journal of Medicine*

https://pubmed.ncbi.nlm.nih.gov/34525277/

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110345

indicate the following:

- The efficacy regarding COVID-19 cases and severe cases is invalid due to the method of data collection, as previously demonstrated.
- **No statistically significant efficacy against COVID-19 mortality** was demonstrated.
- As mentionned into the limitations hightlighted by the authors, **there is no established statistical correlation between the number of cases and the antibody levels**.

*Preliminary analyses of breakthrough cases **have not yet identified a correlate of protection**, since vaccine protection rates remain high.*

- **The numbers of adverse events, serious adverse events, deaths are incomplete as just counted from dose 1 to one month after dose 2**.
  In December 2020, 11 deaths were recorded into the database, only 8 are presented into the table.
  Despite, this serious « lack of rigor », the adverse event rate presented was twice as high among the vaccinated participants compared to those who received the placebo.

- The efficacy on asymptomatic COVID-19 cases is not statistically demonstrated as mentionned into the limitations hightlighted by the authors,

***The data presented here do not address whether vaccination prevents asymptomatic infection**; however, evaluation of that question is ongoing in this trial, and real-world data suggest that BNT162b2 prevents asymptomatic infection.33,34*

- The results on duration of protection and safety are **biased due to the vaccination** of the placebo group

***Duration of protection and safety data that could be collected in a blinded, placebo-controlled manner were limited by the ethical and practical need to immunize eligible initial placebo recipients** under emergency use authorization and according to the recommendations of public health authorities.*

- No data are available on pregnant women as they were excluded from the clinical trial

*This report **does not address vaccine efficacy and safety in <u>pregnant women</u> and in children younger than 12 years of age.** Studies evaluating BNT162b2 in these populations are ongoing.* »

- Doubts remain about the integrity and reliability of the data, and **the results cannot be considered accurate.**

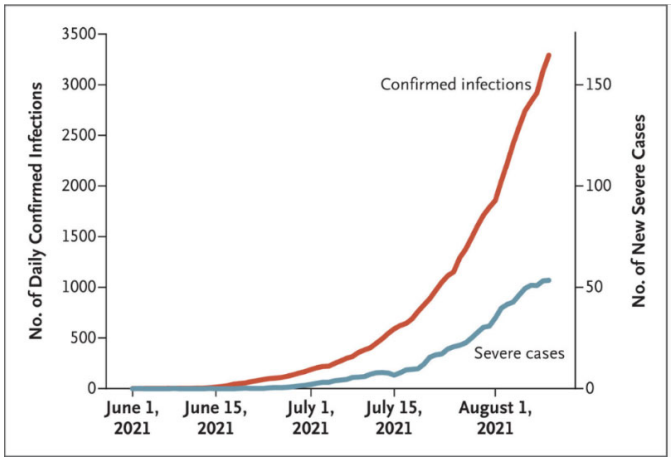
6.3 Clinical Trial Results on the Booster from September 17, 2021

On August 25, 2021, Pfizer submitted a supplement to its Biologics License Application (BLA) for COMIRNATY to seek approval for administering a booster dose (third dose) approximately six months after the initial two-dose primary series.

The clinical report on the third dose, or booster, was made available on the FDA website on September 17, 2021, at the following link: https://www.fda.gov/media/152161/download.

To justify the need for a booster dose, the application referenced several observational studies that indicated a **decrease in protection due to the emergence of variants,** particularly the Delta variant, in individuals who had already received the two-dose series. The publication "***Waning Immunity after the BNT162b2 Vaccine in Israel***" by Yair Goldberg et al. demonstrated an increase in COVID-19 cases, including severe cases.

Illustration 99 : Publication – Yair Goldberg et al - Confirmed infections and severe cases



Source : https://www.nejm.org/doi/full/10.1056/NEJMoa2114228

This report clearly demonstrates the decline in the efficacy of the initial two doses, with the previously announced 95% efficacy dropping to 53% against the Delta variant, according to the studies presented.

Illustration 100 : Pfizer - Clinical Report of September 17, 2021 – Adjusted Vaccine Efficacy in Individuals Over 12 Years Old

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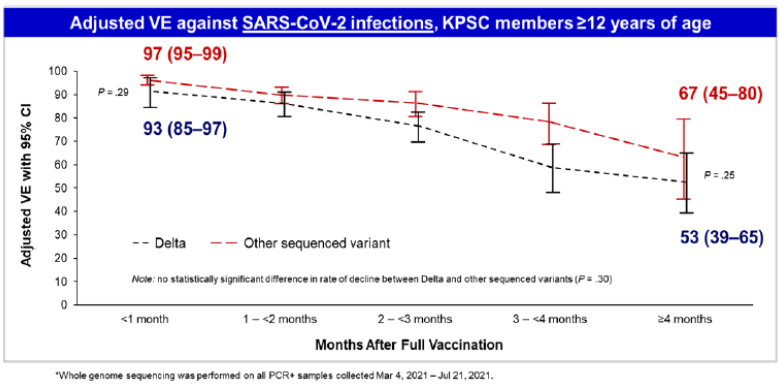
Figure 1. Adjusted VE Against SARS-CoV-2 Infections: KPSC Members ≥12 Years of Age



*Whole genome sequencing was performed on all PCR+ samples collected Mar 4, 2021 – Jul 21, 2021.

Regarding the results of the report, they were based on a subgroup of just over 300 participants from the pivotal trial, as indicated in section 2.2.2.1. Immunogenicity Evaluation Criteria and Analysis Methods - Phase 3 Booster Substudy:

« In the Phase 3 substudy of C4591001, the basis for demonstrating BNT162b2 booster (Dose 3) effectiveness ***is immunobridging: demonstration that the immune response to BNT162b2 30 µg at 1 month after Dose 3 is noninferior to that observed at 1 month after Dose 2*** *(when 95% efficacy was established in the primary analysis for this study), based on SARS-CoV-2 50% neutralizing titers to the reference strain in participants without prior evidence of SARS-CoV-2 infection up to 1 month following Dose 3.*

The immunobridging success criteria included prespecified margins for the geometric mean ratio (GMR) and seroresponse. Noninferiority was assessed based on the GMR of SARSCoV-2 neutralizing titers at 1 month after Dose 3 to 1 month after Dose 2 using a 1.5-fold margin and comparison of the point estimate of the GMR to 0.8. Noninferiority was declared if the lower bound of the 2-sided 97.5% CI for the GMR was >0.67 and the point estimate of the GMR was ≥0.8.

Noninferiority was also assessed based on the difference in percentages of participants with seroresponse at 1 month after Dose 3 and 1 month after Dose 2 using a 10% margin. Noninferiority was declared if the lower limit of the 97.5% CI for the difference in percentages of participants with seroresponse was greater than -10%.»

Note: The exact statistical term is non inferiority and not noninferiority.

Illustration 101 : Pfizer - Clinical Report of September 17, 2021 – Statistical methods

In the Phase 3 substudy of C4591001, the basis for demonstrating BNT162b2 booster (Dose 3) effectiveness is immunobridging: demonstration that the immune response to BNT162b2 30 µg at 1 month after Dose 3 is noninferior to that observed at 1 month after Dose 2 (when 95% efficacy was established in the primary analysis for this study), based on SARS-CoV-2 50% neutralizing titers to the reference strain in participants without prior evidence of SARS-CoV-2 infection up to 1 month following Dose 3.[a]

The immunobridging success criteria included prespecified margins for the geometric mean ratio (GMR) and seroresponse. Noninferiority was assessed based on the GMR of SARS-CoV-2 neutralizing titers at 1 month after Dose 3 to 1 month after Dose 2 using a 1.5-fold margin and comparison of the point estimate of the GMR to 0.8. Noninferiority was declared if the lower bound of the 2-sided 97.5% CI for the GMR was >0.67 and the point estimate of the GMR was ≥0.8.

Noninferiority was also assessed based on the difference in percentages of participants with seroresponse at 1 month after Dose 3 and 1 month after Dose 2 using a 10% margin. Noninferiority was declared if the lower limit of the 97.5% CI for the difference in percentages of participants with seroresponse was greater than -10%.

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations.

[a] Prior serological or virological evidence of SARS-CoV-2 infection was determined by N-binding antibody or nucleic acid amplification test (NAAT), respectively.

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This means that it is sufficient to demonstrate that the antibody levels after the third dose are statistically non-inferior to those after the second dose to establish efficacy. The focus here is no longer on counting the number of COVID-19 cases but solely on analyzing antibodies and inferring efficacy based on the number of cases.

As a reminder, neutralizing antibodies were used, **in the absence of better options**, to assess immunogenicity since no immune marker had been identified to establish protection against COVID-19, according to the document "Emergency Use Authorization for Vaccines to Prevent COVID-19" issued by the FDA»[3]

As previously mentioned in the last chapter, there is no established correlation between antibody levels and the likelihood of becoming ill due to the SARS-CoV-2 virus.

Therefore, this choice of efficacy criterion is highly questionable, as demonstrating an increase in antibodies does not allow for any conclusions about whether the vaccine prevents illness.

Consequently, this trial is not scientifically valid to prove the vaccine's efficacy.

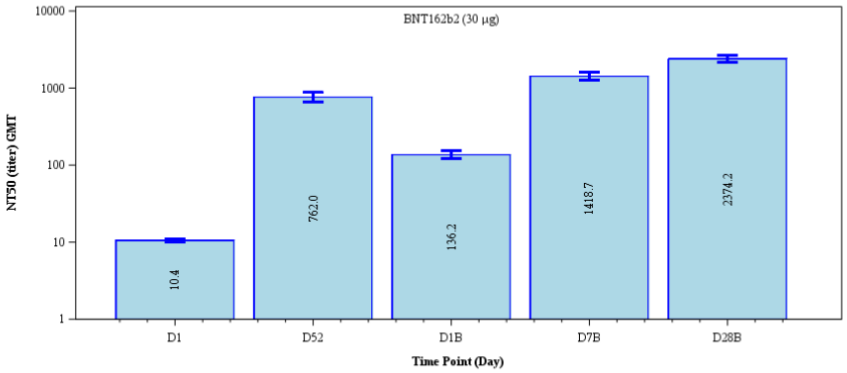
To return to the results of the measurements, they were presented on day 1, prior to the first dose, on day 52, following the two initial doses. They were then re-measured before the administration of the third dose and again 7 days and 28 days later, with a higher threshold indicating a greater antibody level.

A decline in antibodies is observed between day 52 and before the administration of the booster, clearly indicating a decrease in protection.

Illustration 102 : Pfizer - Clinical Report of September 17, 2021 – Neutralizing antibodies after 2 doses and post booster

BNT162b2
VRBPAC Briefing Document

Figure 4. Geometric Mean Titers and 95% Confidence Intervals, Reference Strain SARS-CoV-2 Neutralization Assay – NT50 – Phase 3 – BNT162b2-Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Dose 3 Booster Evaluable Immunogenicity Population



Abbreviations: B = booster vaccination; D = day; GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1, 3, 301, and 303 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1, 2, and 301) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
Note: Number within each bar denotes geometric mean titer.
PFIZER CONFIDENTIAL SDTM Creation: 16AUG2021 (09:19) Source Data: adva Table Generation: 18AUG2021 (22:21)
(Data Cutoff Date: 17JUN2021, Database Snapshot Date: 27JUL2021) Output File: /nda2_unblinded/C4591001_G1/adva_f002_nt50_p3_g1

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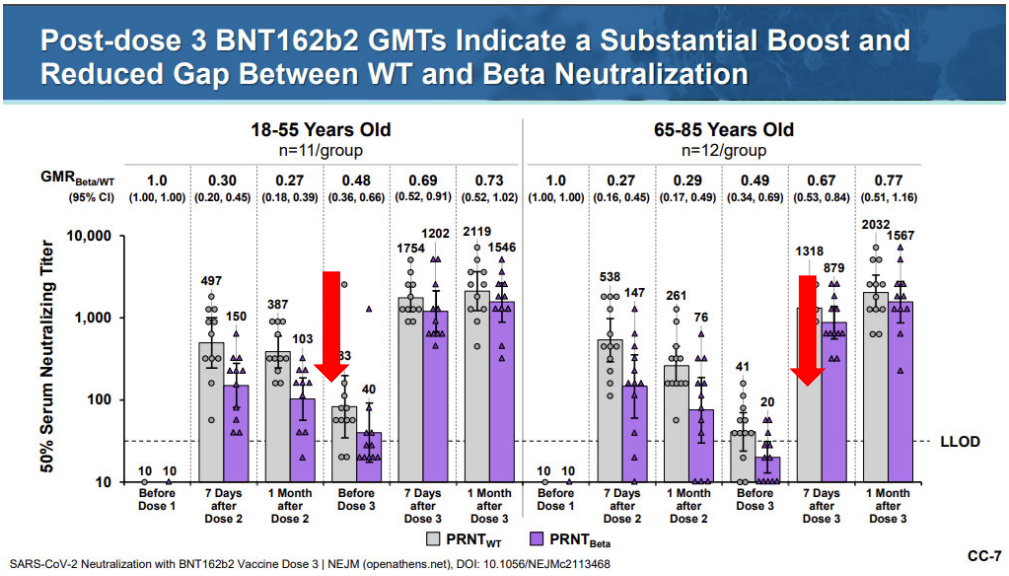
[3] *Emergency Use Authorization for Vaccines to Prevent COVID-19 - Guidance for Industry » , « Autorisation d'Urgence pour les vaccins contre la COVID-19 ».https://www.fda.gov/media/142749/download*

On September 22, 2021, Pfizer acknowledged before the CDC (page 20 of its presentation) that "data from Israel and the United States suggest that vaccine protection against COVID-19 diminishes approximately 6 to 8 months after the second dose." The graph presented below for the antibody measurement clearly indicates a decrease in antibody levels before the third dose (before booster), with the booster dose implemented to address the decline in vaccine protection.

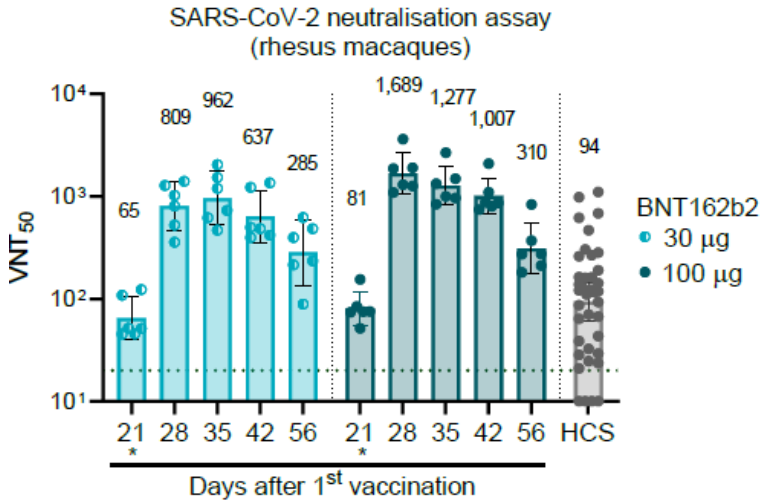
Illustration 103 : Pfizer - Clinical Report of September 17, 2021 – Evaluation of immunogenicity



Source: William C. Gruber, MD, FAAP, FIDSA, FPIDS September 22, 2021 -Senior Vice President -Vaccine Clinical Research and Development - Pfizer Inc
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/02-COVID-Gruber-508.pdf

This decline in immunity was, however, predictable, as it was observed two months after the second dose in the pre-publication study on monkeys from September 8, 2020.

Illustration 104 : Pfizer – Pre-publication from September 8, 2020 – Evaluation of neutralizing antibodies in monkeys



Source: preprint https://www.biorxiv.org/content/10.1101/2020.09.08.280818v1.full.pdf

Source: final https://www.nature.com/articles/s41586-021-03275-y

This graph is found only in the preprint article but not in the final version.

In summary,

The results of the sub-study on the booster demonstrate the decline in vaccine efficacy, which the laboratory attributes to the variants of SARS-CoV-2. **It also shows a decrease in antibodies 4 to 5 months after the second dose**.

This decline in antibodies—and thus in protection—could have been observed earlier:

- **If the interim analysis had been conducted at 6 months instead of the median 2 months**, as permitted by the FDA's Emergency Use Authorization.
- **If the trial had scheduled visits between 1 month and 6 months after the second dose**, which seems to be common sense for such an innovative product.

The design of the trial indeed contributed to obscuring this decline, which was, however, predictable:

- As soon as the results were obtained from the monkey studies.
- And from the first report in December 2020, where the antibody level measured at 2 months after the second dose (D52) was lower than the level measured 1 month after the second dose (D35).

Failing to plan for the measurement of antibodies over an extended period constitutes a serious oversight, if not methodological fraud, as no authorization would have been granted for a vaccine with a maximum protection duration of 6 months.

It is acknowledged in the 6-month publication that t**here is no established correlation between antibody levels and the likelihood of falling ill due to the SARS-CoV-2 virus**.

This choice of efficacy criterion is therefore highly questionable, as demonstrating an increase in antibodies does not allow for any conclusion that the vaccine prevents disease.

Consequently, this trial is not scientifically valid for proving the efficacy of the vaccine.

Despite the absence of an established correlate between antibody levels and the occurrence of the disease, the FDA authorized the booster on September 22, 2021, for:

- Individuals aged 65 years and older,
- Individuals aged 18 to 64 years at high risk of developing a severe form of COVID-19, and
- Individuals aged 18 to 64 years whose frequent exposure to SARS-CoV-2 in institutional or occupational settings places them at high risk of severe complications from COVID-19, including severe forms of the disease.

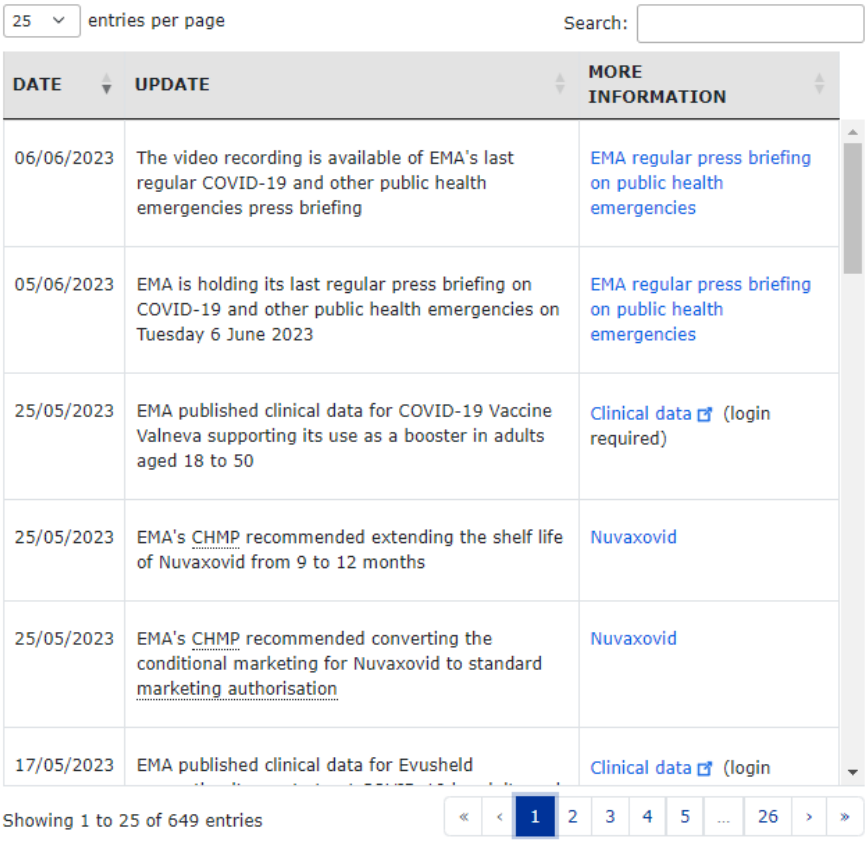
https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-covid-19-vaccine-certain-populations

6.4 July 28, 2023 Final Clinical Study Report

The final clinical report, along with numerous documents related to the clinical trial, can be downloaded from the EMA website at the following link after creating an account: https://clinicaldata.ema.europa.eu/web/cdp/login
Note: To create an account, visit https://register.ema.europa.eu/identityiq/help/selfregister.html

It should be noted that the reports are publicly accessible, but it is necessary to create an account to retrieve the documents concerning COVID vaccines.

Illustration 105 : EMA – Clinical Data Site – List of EMA Documents



25 entries per page Search:

DATE	UPDATE	MORE INFORMATION
06/06/2023	The video recording is available of EMA's last regular COVID-19 and other public health emergencies press briefing	EMA regular press briefing on public health emergencies
05/06/2023	EMA is holding its last regular press briefing on COVID-19 and other public health emergencies on Tuesday 6 June 2023	EMA regular press briefing on public health emergencies
25/05/2023	EMA published clinical data for COVID-19 Vaccine Valneva supporting its use as a booster in adults aged 18 to 50	Clinical data (login required)
25/05/2023	EMA's CHMP recommended extending the shelf life of Nuvaxovid from 9 to 12 months	Nuvaxovid
25/05/2023	EMA's CHMP recommended converting the conditional marketing for Nuvaxovid to standard marketing authorisation	Nuvaxovid
17/05/2023	EMA published clinical data for Evusheld	Clinical data (login

Showing 1 to 25 of 649 entries « ‹ 1 2 3 4 5 … 26 › »

Source : https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/coronavirus-disease-covid-19/covid-19-public-health-emergency-international-concern-2020-23/covid-19-latest-updates-archive

The report has been made available at the following link by individuals concerned with providing access to the documents without registration here.

https://mega.nz/file/XJ5mGTQY#6sGKu79MXyJXxhiWlEYOOrxeuea1wSTRMO01cppULOQ

Illustration 106 : EMA – Clinical Data Site – Extract from the research results for the COMIRNATY vaccine

Show 20 entries

	Name	Active substance	MAH Name	Product Status	Publication Date	Procedure Type	
☐	COMIRNATY	Tozinameran	BioNTech Manufacturing GmbH	Authorised	20/12/2023	Grouped Type II Variation	⌄
☐	COMIRNATY	Tozinameran	BioNTech Manufacturing GmbH	Authorised	19/12/2023	Type II variation	⌄
☐	COMIRNATY	Tozinameran	BioNTech Manufacturing GmbH	Authorised	19/09/2023	Line Extension	⌄
☐	COMIRNATY	COVID-19 mRNA vaccine (nucleoside-modified)	BioNTech Manufacturing GmbH	Authorised	19/09/2023	Extension of Indication	⌄
☐	COMIRNATY	COVID-19 mRNA vaccine (nucleoside-modified)	BioNTech Manufacturing GmbH	Authorised	17/05/2023	Type II variation	⌄

A total of 245 documents are available under the name BioNTech and not Pfizer, as indicated in the following table:

Illustration 107 : EMA – Clinical Data Site – Results from the research results for the COMIRNATY vaccine

Product Status	**Publication Date**	**Procedure Type**	**AtcCode**	**Procedure Number**	**Number Of Documents**
Authorised	20/12/2023	Grouped Type II Variation	J07BN01	EMEA/H/C/005735/II/0188/G	16
Authorised	19/12/2023	Type II variation	J07BN01	EMEA/H/C/005735/II/0187	11
Authorised	19/09/2023	Line Extension	J07BX03	EMEA/H/C/005735/X/0176	27
Authorised	19/09/2023	Extension of Indication	J07BN01	EMEA/H/C/005735/II/0177/G	2
Authorised	17/05/2023	Type II variation	J07BX03	EMEA/H/C/005735/II/0139	17
Authorised	17/05/2023	Type II variation	J07BX03	EMEA/H/C/005735/II/0160	10
Authorised	03/02/2023	Line Extension	J07BX03	EMEA/H/C/005735/X/0138	11
Authorised	23/01/2023	Line Extension	J07BX03	EMEA/H/C/005735/X/0147	6
Authorised	23/11/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0143	8
Authorised	09/11/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0141	2
Authorised	28/10/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0140	28
Authorised	25/10/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0129	10

Product Status	Publication Date	Procedure Type	AtcCode	Procedure Number	Number Of Documents
Authorised	01/08/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0102	10
Authorised	21/07/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0104	3
Authorised	06/07/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0093	8
Authorised	02/06/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0111	2
Authorised	13/04/2022	Line Extension	J07BX03	EMEA/H/C/005735/X/0077	15
Authorised	16/02/2022	Extension of Indication	J07BX03	EMEA/H/C/005735/II/0030	12
Authorised	02/02/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0067	11
Authorised	02/02/2022	Type II variation	J07BX03	EMEA/H/C/005735/II/0036	17
Authorised	10/09/2021	Initial Marketing Authorisation	J07BX03	EMEA/H/C/005735/0000	19

It should be noted that the ATC (Anatomical Therapeutic Classification) class was modified between the authorizations.

The class J07BN01, meaning "*COVID-19, RNA-based vaccine*," has been replaced by the class J07BX01, which refers to "*vaccines against smallpox and monkeypox*."

J ANTIINFECTIVES FOR SYSTEMIC USE
J07 VACCINES
J07B VIRAL VACCINES
J07BN Covid-19 vaccines
Source : https://atcddd.fhi.no/atc_ddd_index/?code=J07BN&showdescription=no

J07B VIRAL VACCINES
J07BX Other viral vaccines
Vaccines against smallpox and/or monkeypox infections are classified in J07BX01.

ATC code	Name	DDD	U	Adm.R	Note
J07BX01	smallpox and monkeypox vaccines				
J07BX02	ebola vaccines				
J07BX04	dengue virus vaccines				
J07BX05	respiratory syncytial virus vaccines				
J07BX06	enterovirus 71 vaccines				

Source : https://atcddd.fhi.no/atc_ddd_index/?code=J07BX&showdescription=yes

6.4.1 History of the Pivotal Clinical Trial Protocol (Phase 3 No. C459001)

The final clinical report of the Pfizer study details all the dates of clinical reports that led to submissions. The phase 3 clinical trial began in April 2020, with the first report submitted to the FDA on October 1, 2020. The report that led to market authorization was dated October 3, 2020, and subsequent reports span from April 2021 to July 2023.

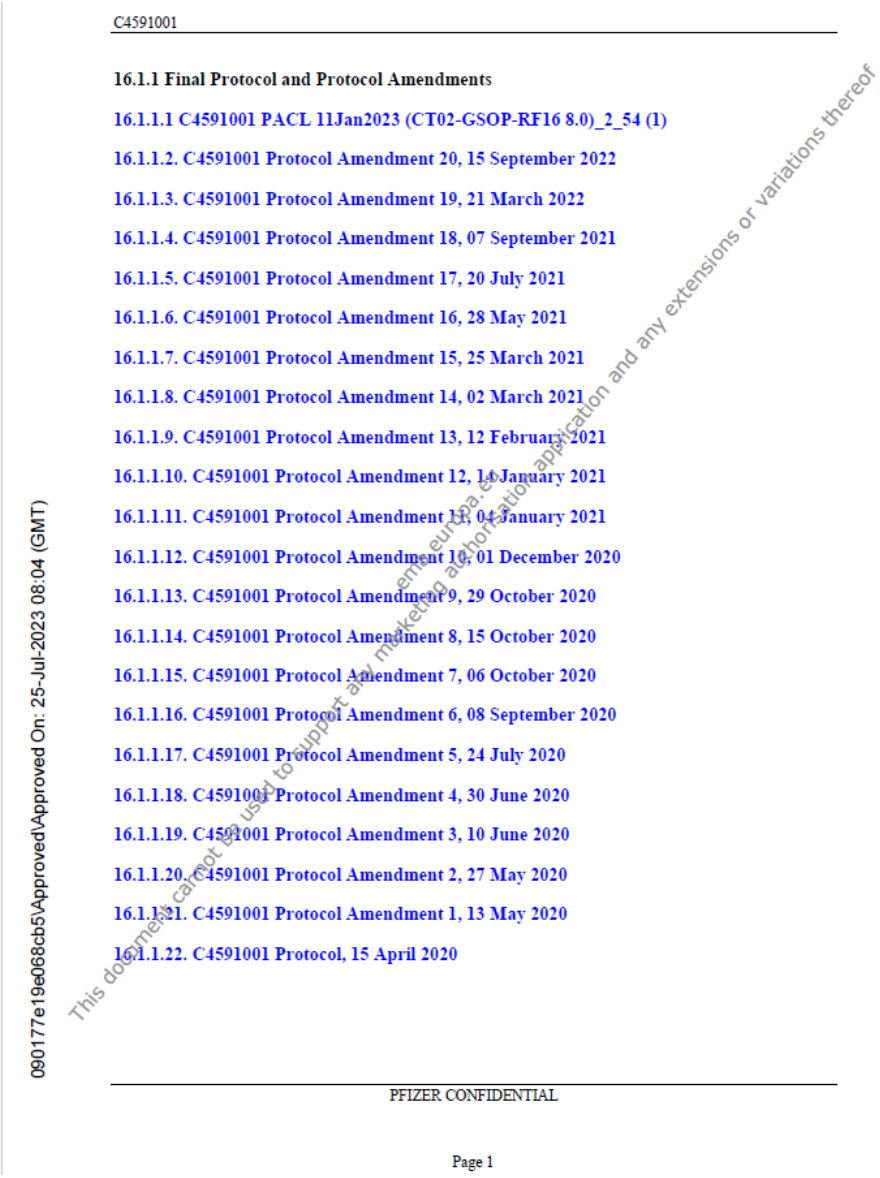
Illustration 108 : Pfizer – July 28, 2023 Final Clinical Study Report – History of the reports

Regulatory Agency or Public Disclosure Identifier Number:	EudraCT 2020-002641-42 (NCT04368728)	
CSR Version and Report Date:	**Document Version**	**Report Date**
	C4591001 Final Report Version 1.0	28 July 2023
	C4591001 Interim Report – 6-Month Analysis – BNT162b2 Booster (Dose 3) – Participants 12 Through 15 Years of Age Version 1.0	13 January 2023
	C4591001 Interim Report - BNT162b2$_{SA}$ VOC Booster Subset Version 1.0	20 May 2022
	C4591001 Interim Report - BNT162b2 (30 µg) Booster (Dose 3) – Phase 1 (4-Month Update) and Phase 3 (6-Month Update) Version 2.0	19 May 2022
	C4591001 Interim Report - Adolescent 6-Month Update Version 2.0	12 December 2021
	C4591001 Interim Report – BNT162b2 Booster (Dose 3) Version 1.0	23 August 2021
	C4591001 Interim Report - 6-Month Update Version 1.0	29 April 2021
	C4591001 Interim Report - Adolescent Version 1.0	14 April 2021
	C4591001 Final Analysis Interim Report Version 1.0	03 December 2020
	C4591001 Interim Report Version 1.0	12 November 2020
	C4591001 Interim Phase 1 Report Version 1.0	01 October 2020

The final protocol of study C4591001 was published on the website of the European Medicines Agency (EMA) on December 19 and 20, 2023.

The initial protocol was submitted on April 15, 2020, and the various amendments are summarized on page 1 of the protocol.

Illustration 109 : Pfizer – July 28, 2023 Final Clinical Study Report – History of protocol amendments



C4591001

16.1.1 Final Protocol and Protocol Amendments

16.1.1.1 C4591001 PACL 11Jan2023 (CT02-GSOP-RF16 8.0)_2_54 (1)

16.1.1.2. C4591001 Protocol Amendment 20, 15 September 2022

16.1.1.3. C4591001 Protocol Amendment 19, 21 March 2022

16.1.1.4. C4591001 Protocol Amendment 18, 07 September 2021

16.1.1.5. C4591001 Protocol Amendment 17, 20 July 2021

16.1.1.6. C4591001 Protocol Amendment 16, 28 May 2021

16.1.1.7. C4591001 Protocol Amendment 15, 25 March 2021

16.1.1.8. C4591001 Protocol Amendment 14, 02 March 2021

16.1.1.9. C4591001 Protocol Amendment 13, 12 February 2021

16.1.1.10. C4591001 Protocol Amendment 12, 14 January 2021

16.1.1.11. C4591001 Protocol Amendment 11, 04 January 2021

16.1.1.12. C4591001 Protocol Amendment 10, 01 December 2020

16.1.1.13. C4591001 Protocol Amendment 9, 29 October 2020

16.1.1.14. C4591001 Protocol Amendment 8, 15 October 2020

16.1.1.15. C4591001 Protocol Amendment 7, 06 October 2020

16.1.1.16. C4591001 Protocol Amendment 6, 08 September 2020

16.1.1.17. C4591001 Protocol Amendment 5, 24 July 2020

16.1.1.18. C4591001 Protocol Amendment 4, 30 June 2020

16.1.1.19. C4591001 Protocol Amendment 3, 10 June 2020

16.1.1.20. C4591001 Protocol Amendment 2, 27 May 2020

16.1.1.21. C4591001 Protocol Amendment 1, 13 May 2020

16.1.1.22. C4591001 Protocol, 15 April 2020

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Page 1

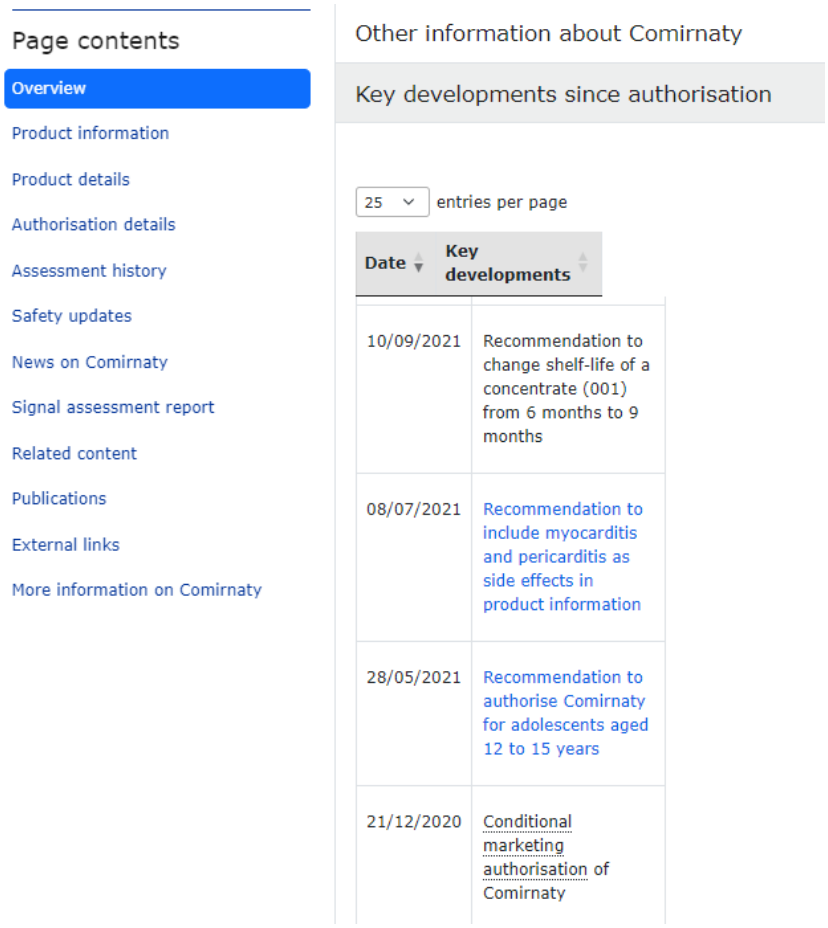
The history of changes on the ClinicalTrials.gov website indicates 43 updates. The study start date is listed as April 29, 2020, with the estimated study completion date set for January 23, 2023.

Source: https://classic.clinicaltrials.gov/ct2/show/record/NCT04368728?term=NCT04368728&draw=2&rank=1

The history of evaluations and authorizations by the EMA can be found here.

https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

Illustration 110 : EMA – Clinical Data Site – Overview of key developments since authorization



6.4.2 Vaccination of the placebo group

The regulations governing clinical trials allow for the administration of the investigational treatment once its efficacy has been demonstrated. This approach is understandable in the context of a trial testing a new anti-cancer drug, as it would be unethical not to provide the new, more effective treatment to patients in the other group if it has proven superior to existing treatments. Withholding it would represent a missed opportunity for their recovery and/or survival.

In the context of COVID-19 trials, however, the situation is different. The participants are not ill patients or terminal cancer patients, but mostly healthy volunteers. The risk of developing severe COVID-19, requiring hospitalization, or resulting in death was extensively discussed and deemed extremely low, particularly for younger individuals. Therefore, there was no apparent urgency to vaccinate participants who had received the placebo in the COVID-19 trials.

The publication « ***Ethical Considerations for Unblinding and Vaccinating COVID-19 Vaccine Trial Placebo Group Participants*** » [4] argues that participants in the placebo group, who believe they have been vaccinated, may change their behavior, either intentionally or unintentionally, and become less cautious following the release of results on vaccine efficacy. This behavioral shift could expose them to an **increased risk of contracting COVID-19.**

Thus, the process involves unblinding or lifting the study's blinding after several months of follow-up to reveal the type of product administered—whether the vaccine or placebo—and then administering vaccine doses to participants who received the placebo.

We can question this **partial reasoning**, as it applies equally to the group that received the vaccine. Once the product is identified, when people realize they have indeed been vaccinated, they are likely to adopt riskier behaviors than those who received the placebo, believing themselves protected by the vaccine. Since vaccine efficacy against transmission was never proven, vaccinating the placebo group did not protect them from contracting mild or moderate COVID-19, which poses no significant risk to their lives.

Despite the logical criticisms that can be made of this June 24, 2021 publication, this approach was adopted in Pfizer's clinical trial **without addressing the associated methodological issues**.

From a methodological perspective, vaccinating the placebo group introduces a significant bias in evaluating the vaccine, as it eliminates the control group, distorting not only efficacy results but also safety outcomes.

In the final trial protocol, Pfizer itself writes (Page 42) : « *As of protocol amendment 20, **because the study is now being fully unblinded with no control arm, making it observational in nature**, and with the active safety surveillance period for the majority of participants completed, following agreement with the FDA and EMA, the study will be concluded early. Following approval of protocol amendment 20, active study participants will be informed of the early completion of the study and further data collection will be ceased.* »

[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8264198/

Illustration 111 : Pfizer - September 15, 2022 Clinical Trial Protocol – Cover page

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Illustration 112 : Pfizer - September 15, 2022 Clinical Trial Protocol

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001
Final Protocol Amendment 20, 15 September 2022

As part of protocol amendment 19, the study may be terminated early for reasons including but not limited to the increased access and availability of BNT162b2 in the real world, reducing the value of participant involvement and observation in this clinical trial. Further to this, participants who are offered the possibility to participate in a future study within the Pfizer/BioNTech COVID-19 vaccine development program will be discontinued from this study.

As of protocol amendment 20, because the study is now being fully unblinded with no control arm, making it observational in nature, and with the active safety surveillance period for the majority of participants completed, following agreement with the FDA and EMA, the study will be concluded early. Following approval of protocol amendment 20, active study participants will be informed of the early completion of the study and further data collection will be ceased.

Pfizer itself acknowledges that the clinical trial is no longer a trial and thus loses all its methodological capacity to properly demonstrate efficacy and safety, as it has been converted into a simple observational study.

6.4.3 Main efficacy criterion

In the Clinical Report from July 2023, regarding the primary efficacy endpoint, there were 2,868 participants with COVID-19 as described in Section 4.2, Characteristics of the Pfizer Phase 1-2-3 Trial. Among the vaccinated participants, there were 2,868 cases of COVID-19, 1,135 cases for participants who received the placebo, and 4,144 participants who initially received the placebo and then the vaccine reported a diagnosis of COVID-19.

Vaccine efficacy is not calculated because the observation periods for the three groups of participants are not identical, making any comparison impossible.

This confirms the significant bias mentioned in the previous section.

Illustration 113 : Pfizer – July 28, 2023 Final Clinical Study Report – Main efficacy criterion

Final Full Clinical Study Report
Protocol C4591001

Table 37. Incidence Rates of First COVID-19 Occurrence After Vaccination – All-Available Efficacy Population

	Vaccine Group								
	Original BNT162b2 (30 µg)			Original Placebo Prior to Crossover			Placebo Crossover to BNT162b2 (30 µg)		
Efficacy Endpoint	n1[a]	Surveillance Time[b] (n2[c])	IR (/1000 PY)[d]	n1[a]	Surveillance Time[b] (n2[c])	IR (/1000 PY)[d]	n1[a]	Surveillance Time[b] (n2[c])	IR (/1000 PY)[d]
First COVID-19 occurrence after vaccination	2868	27.429 (21300)	104.562	1135	9.036 (22362)	125.722	4144	24.501 (19527)	169.138

a. n1 = Number of participants meeting the endpoint definition.
b. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. For the original BNT162b2 arm, time period for COVID-19 case accrual is from the dose 1 vaccination date to the earliest of confirmed case, death, withdrawn from the study, study completion date, or their first dose of BNT162b2SA vaccination. For original Placebo arm, the time period between vaccination in blinded period and the crossover date is considered. For the Placebo crossover to BNT162b2 (30 µg) arm, the time period from first BNT162b2 vaccination is considered as the starting point for surveillance.
c. n2 = Number of participants at risk for the endpoint.
d. Incidence rate (IR) is calculated as number of participants meeting the endpoint definition/total surveillance time across all participants at risk for the endpoint within the specific group.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19eu Table Generation: 17MAY2023 (00:35)
(Database Snapshot Date: 28APR2023) Output File: ./nda2_unblinded/C4591001_CSR/adc19ef_ve_overall_d1_aai

It is surprising to read in the correspondence between Pfizer and the FDA that, in June 2020, **the company initially anticipated an efficacy of 20%**.

« *Pfizer acknowledges CBER's position that the criterion of success for efficacy should be based on demonstrating vaccine efficacy (VE) >30%, and a statistical framework corresponding to this criterion is described below.* ***Pfizer's preference, however, is to retain a criterion based on demonstrating VE >20% in the protocol*** *because results from this study*

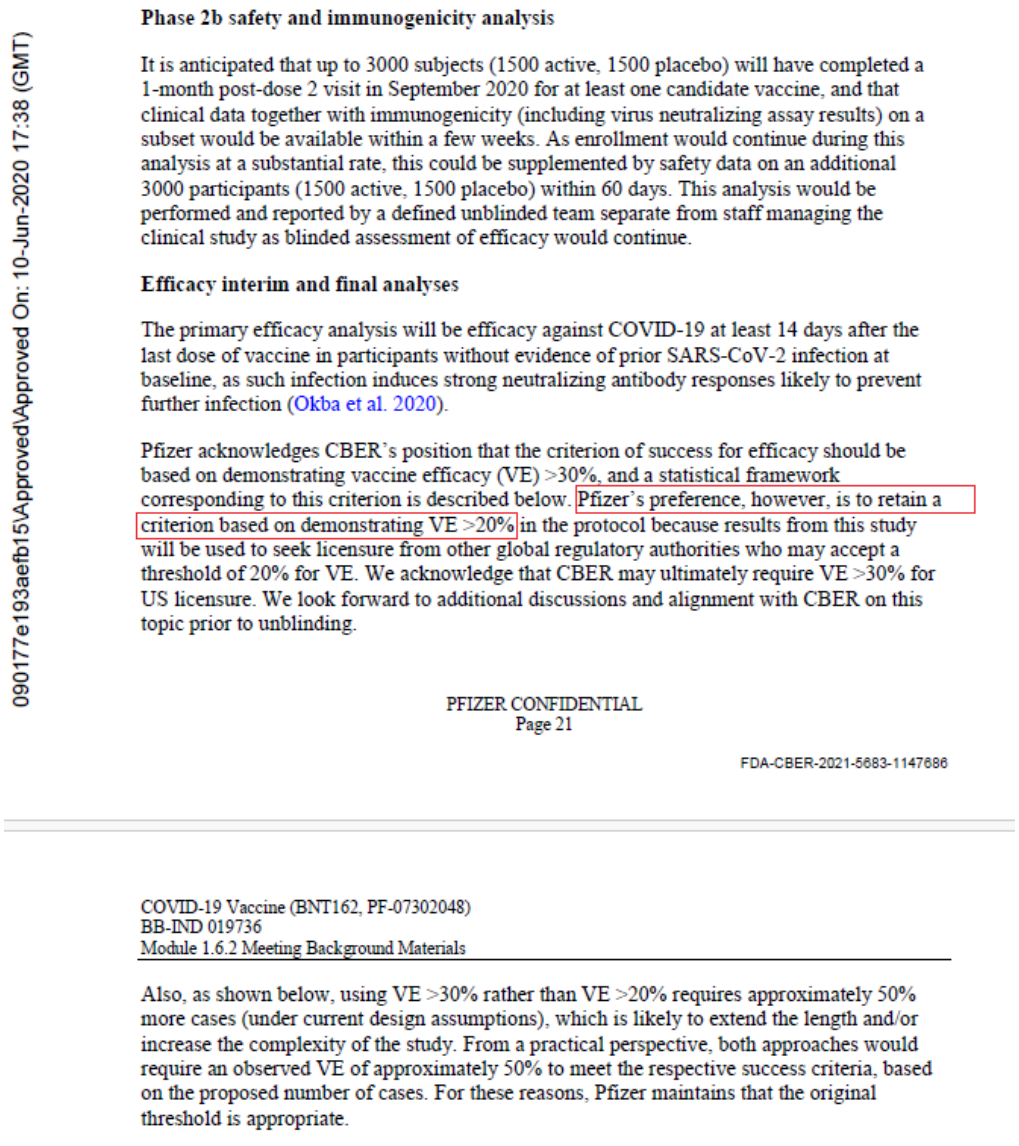
will be used to seek licensure from other global regulatory authorities who may accept a threshold of 20% for VE.

We acknowledge that CBER may ultimately require VE >30% for US licensure.

We look forward to additional discussions and alignment with CBER on this topic prior to unblinding.

*Also, as shown below, u**sing VE >30% rather than VE >20% requires approximately 50% more cases** (under current design assumptions), which is likely to extend the length and/or increase the complexity of the study. From a practical perspective, both approaches would require an observed VE of approximately 50% to meet the respective success criteria, based on the proposed number of cases. For these reasons, Pfizer maintains that the original threshold is appropriate.* »

Illustration 114 : Correspondance Pfizer-FDA- Vaccinal efficacy required by Pfizer



090177e193aefb15\Approved\Approved On: 10-Jun-2020 17:38 (GMT)

Phase 2b safety and immunogenicity analysis

It is anticipated that up to 3000 subjects (1500 active, 1500 placebo) will have completed a 1-month post-dose 2 visit in September 2020 for at least one candidate vaccine, and that clinical data together with immunogenicity (including virus neutralizing assay results) on a subset would be available within a few weeks. As enrollment would continue during this analysis at a substantial rate, this could be supplemented by safety data on an additional 3000 participants (1500 active, 1500 placebo) within 60 days. This analysis would be performed and reported by a defined unblinded team separate from staff managing the clinical study as blinded assessment of efficacy would continue.

Efficacy interim and final analyses

The primary efficacy analysis will be efficacy against COVID-19 at least 14 days after the last dose of vaccine in participants without evidence of prior SARS-CoV-2 infection at baseline, as such infection induces strong neutralizing antibody responses likely to prevent further infection (Okba et al. 2020).

Pfizer acknowledges CBER's position that the criterion of success for efficacy should be based on demonstrating vaccine efficacy (VE) >30%, and a statistical framework corresponding to this criterion is described below. Pfizer's preference, however, is to retain a criterion based on demonstrating VE >20% in the protocol because results from this study will be used to seek licensure from other global regulatory authorities who may accept a threshold of 20% for VE. We acknowledge that CBER may ultimately require VE >30% for US licensure. We look forward to additional discussions and alignment with CBER on this topic prior to unblinding.

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FDA-CBER-2021-5683-1147686

COVID-19 Vaccine (BNT162, PF-07302048)
BB-IND 019736
Module 1.6.2 Meeting Background Materials

Also, as shown below, using VE >30% rather than VE >20% requires approximately 50% more cases (under current design assumptions), which is likely to extend the length and/or increase the complexity of the study. From a practical perspective, both approaches would require an observed VE of approximately 50% to meet the respective success criteria, based on the proposed number of cases. For these reasons, Pfizer maintains that the original threshold is appropriate.

Source :https://phmpt.org/wp-content/uploads/2023/10/125742_S1_M1_meeting-correspondence.pdf

On July 8, 2020, the FDA requested that the laboratory establish a minimum efficacy threshold of 50% and a lower limit of the 95 % confidence of 30%.

« As communicated previously, **we do not agree with a success criterion defined as the lower limit of VE being >20%**. To ensure that a widely deployed vaccine is more than modestly effective, we request that the success criterion be defined equivalent to **a primary efficacy endpoint point estimate of at least 50%** and the lower limit of the alpha-adjusted 95% CI around that point estimate being >30%. In principle, the four interim analyses proposed in Table 6 of the briefing document, using a VE threshold of 30%, would be acceptable if the criteria were adjusted to preserve the type I error rate at 2.5%. »

Illustration 115 : Correspondance Pfizer-FDA- Vaccinal efficacy required by FDA

2.1.2.1. CBER Clinical Request 1b(i)

As communicated previously, we do not agree with a success criterion defined as the lower limit of VE being >20%. To ensure that a widely deployed vaccine is more than modestly effective, we request that the success criterion be defined equivalent to a primary efficacy

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FDA-CBER-2021-5683-1147706

COVID-19 Vaccine (BNT162, PF-07302048)
BB-IND 19736
M 1.6.3 – Correspondence Regarding Meetings

endpoint point estimate of at least 50% and the lower limit of the alpha-adjusted 95% CI around that point estimate being >30%. In principle, the four interim analyses proposed in Table 6 of the briefing document, using a VE threshold of 30%, would be acceptable if the criteria were adjusted to preserve the type I error rate at 2.5%. In addition, the proposed efficacy boundaries are based solely on case split, which presumes that the numbers of evaluable subjects and duration of follow-up in both groups are equivalent. Please clarify how you plan to adjust the boundaries for potential difference in numbers of evaluable subjects.

Source : https://phmpt.org/wp-content/uploads/2023/10/125742_S1_M1_meeting-correspondence.pdf

This document is part of the information released to the public by court order.

6.4.4 Efficacy on severe cases

The efficacy results on severe cases are no longer presented in the final report. Why?

6.4.5 Efficacy against asymptomatic infection

Efficacy against asymptomatic SARS-CoV-2 infection was one of the secondary efficacy endpoints.
The final clinical report also indicates that 44 cases were recorded among the population of 3,921 participants (2,092 in the BNT162b2 group and 1,829 in the placebo group) with no evidence of infection until the start of the asymptomatic surveillance period (January 2021).

The estimated vaccine efficacy (VE) was **37.2%** (95% two-sided **CI: -20.0%, 66.7%**) (Table 33). Since the confidence interval (CI) ranges from -20% to 66.7%, **no statistically significant efficacy is demonstrated for this endpoint**.

Efficacy against asymptomatic SARS-CoV-2 infection was 40.4% (95% two-sided CI: **-10.8%, 67.8%)** for dose 2 in the population for which complete efficacy data is available. Since the CI ranges from -10.8% to 67.8%, **no statistically significant efficacy is demonstrated for this endpoint**.

Illustration 116 : Pfizer – July 28, 2023 Final Clinical Study Report – Efficacy against Asymptomatic infection

5. EVALUATION OF RESPONSE TO STUDY INTERVENTION

5.1. Efficacy

5.1.1. Phase 2/3

5.1.1.1. Vaccine Efficacy Against Asymptomatic SARS-CoV-2 Infection

Vaccine Efficacy in Participants Without Evidence of SARS-CoV-2 Infection

For the secondary efficacy endpoint, VE for BNT162b2 30 µg (2-dose primary series) against asymptomatic SARS-CoV-2 infection was evaluated in participants without evidence of infection up to the start of the asymptomatic surveillance period (January 2021). Note that the median time between Dose 2 and the start of the asymptomatic surveillance period was 2.9 months for participants in the United States and 5.3 months for participants in Argentina. Cases were counted from the start of the asymptomatic surveillance period.

Among participants included in the evaluable efficacy (asymptomatic surveillance) population, 3921 participants (2092 in BNT162b2 group and 1829 in placebo group) did not have evidence of infection with SARS-CoV-2 prior to the start of the asymptomatic surveillance period (Table 25). There were 24 asymptomatic SARS-CoV-2 infections in the BNT162b2 (30 µg) group compared to 20 infections reported in the placebo group. The estimated VE was 37.2% (2-sided 95% CI: -20.0%, 66.7%) (Table 33). This descriptive analysis was limited by the accrual of only 44 cases total, resulting in a wide 2-sided 95% CI and limiting the precision of this estimate.

VE against asymptomatic SARS-CoV-2 infection was 40.4% (2-sided 95% CI: -10.8%, 67.8%) for Dose 2 all-available efficacy population (Supplemental Table 14.27 and Supplemental Table 14.28).

Illustration 117 : Pfizer – July 28, 2023 Final Clinical Study Report – Efficacy Against asymptomatic infection based on NAAT results

Table 33. Vaccine Efficacy – Asymptomatic SARS-CoV-2 Infection Based on Central Laboratory–Confirmed NAAT Result – Subjects Without Evidence of Infection Prior to the Start of the Asymptomatic Surveillance Period – Evaluable Efficacy (Asymptomatic Surveillance) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=2092)		Placebo (N[a]=1829)			
Efficacy Endpoint	n[b]	Surveillance Time[c]	n[b]	Surveillance Time[c]	VE (%)	(95% CI[d])
Asymptomatic SARS-CoV-2 infection based on central laboratory–confirmed NAAT result during asymptomatic surveillance period	24	0.383	20	0.200	37.2	(-20.0, 66.7)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence of past SARS-CoV-2 infection (i.e, negative N-binding antibody [serum] result at Visits 1 and 201, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visits) prior to the start of the asymptomatic surveillance period were included in the analysis.
a. N = number of subjects in the specified group.
b. n = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group. Time period for case accrual is from the start of the asymptomatic surveillance period to the end of the surveillance period.
d. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19nat Table Generation: 18JUL2023 (22:33)
(Snapshot Date: 28APR2023) Output File: nda2 unblinded/C4591001 ASYMP CSR/adc19nat ve as nat wo pd2 eval

6.4.6 Efficacy assessed by nucleocapcide serology

Efficacy against non-seroconversion is based on antibody measurement through **anti-nucleocapsid serology**, which we have mentioned several times in this document.

Among the participants included in the population determined to be evaluable for efficacy (seroconversion), 41,564 participants (20,872 in the BNT162b2 group and 20,692 in the placebo group) had no evidence of SARS-CoV-2 infection prior to their inclusion in the trial, as determined by the post-dose 2 binding assay. After two doses, there were **612 infections caused by SARS-CoV-2 in the BNT162b2 group (30 µg) and 608 in the placebo group.**

Despite this small difference of 4 participants, the estimated vaccine efficacy against asymptomatic diseases was **52.9% (95% two-sided CI: 47.2%, 57.9%).**

Illustration 118 : Pfizer – July 28, 2023 Final Clinical Study Report – Efficacy against asymptomatic infection based on antinucleocapcide serology

Table 35. Vaccine Efficacy – Asymptomatic Infection Based on N-Binding Antibody Seroconversion – Subjects Without Evidence of Infection Prior to the First Post–Dose 2 N-Binding Test – Evaluable Efficacy (Seroconversion) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=20872)		Placebo (N[a]=20692)			
Efficacy Endpoint	n[b]	Surveillance Time[c]	n[b]	Surveillance Time[c]	VE (%)	(95% CI[d])
Asymptomatic infection based on N-binding antibody seroconversion after Dose 2	612	13.840	608	6.481	52.9	(47.2, 57.9)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence of past SARS-CoV-2 infection before Dose 2 (ie, negative N-binding antibody [serum] result at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2) and had a negative NAAT (nasal swab) result at any unscheduled visit and without any important protocol deviation prior to the first post–Dose 2 N-binding test result were included in the analysis.
a. N = number of subjects in the specified group.
b. n = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group. Time period for case accrual is from Dose 2 to the end of the surveillance period.
d. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: adc19asm Table Generation: 18JUL2023 (22:31)
(Snapshot Date: 28APR2023) Output File: /sda2 unblinded/C4591001 ASYMP CSR/adc19asm ve as nig pd2 eval

It is worth noting that the duration of monitoring in the placebo group was shorter than in the BNT162b2 group.

The seroconversion results for all asymptomatic AND symptomatic infections are not provided.

This is quite convenient, as they would have allowed for a comparison of the efficacy obtained by counting cases according to the method chosen in the protocol with the objective cases determined by a blood test, meaning the actual number of COVID-19 cases regardless of symptomatology. This is yet another omission. Why is this result not provided?

6.4.7 Safety analysis – Deaths

The number of deaths is not clearly indicated in the clinical report; however, it has been possible to identify certain patient identifiers and reconstruct their history, knowing the nature of the products administered and the adverse events that occurred since the first injection based on the narratives. For reference, death narratives are a mandatory section in any clinical report.

On pages 556, 557, 558, and 559, there are 40, 46, 45, and 39 deaths, respectively, totaling 170 deaths.

Illustration 119 : Pfizer – July 28, 2023 Final Clinical Study Report – List of dead participants– page 1

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Protocol C4591001

PARTICIPANT NARRATIVES

Primary Reason for Narrative	**Subject Number**
Death	
	Subject PPD
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Illustration 120 : Pfizer – July 28, 2023 Final Clinical Study Report – List of dead participants – page 2

Subject PPD
Subject PPD
Subject PPD
Subject PPD
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Illustration 121 : Pfizer – July 28, 2023 Final Clinical Study Report – List of dead participants – page 3

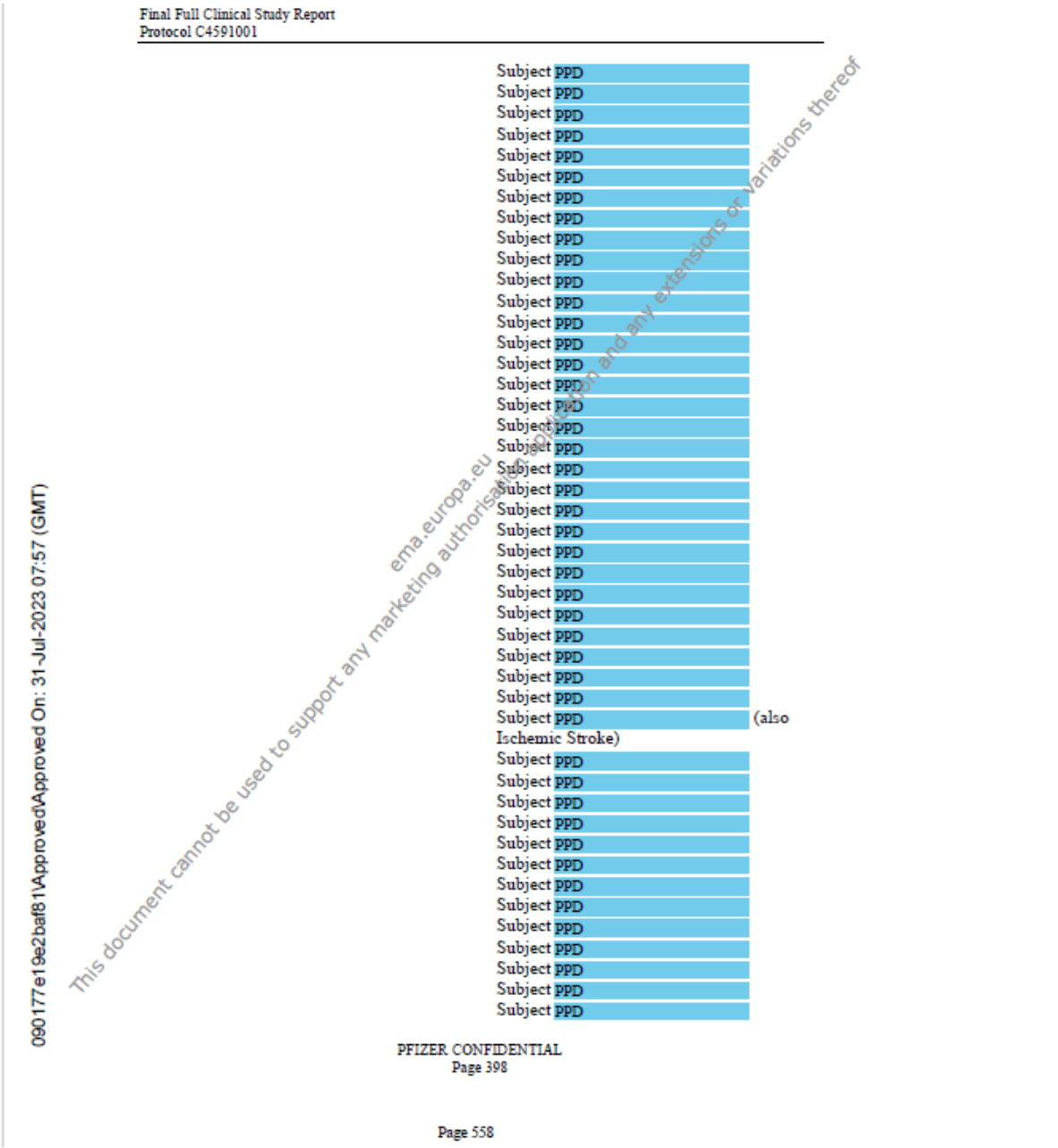

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Illustration 122 : Pfizer – July 28, 2023 Final Clinical Study Report – List of dead participants – page 4

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Related Serious Adverse Event

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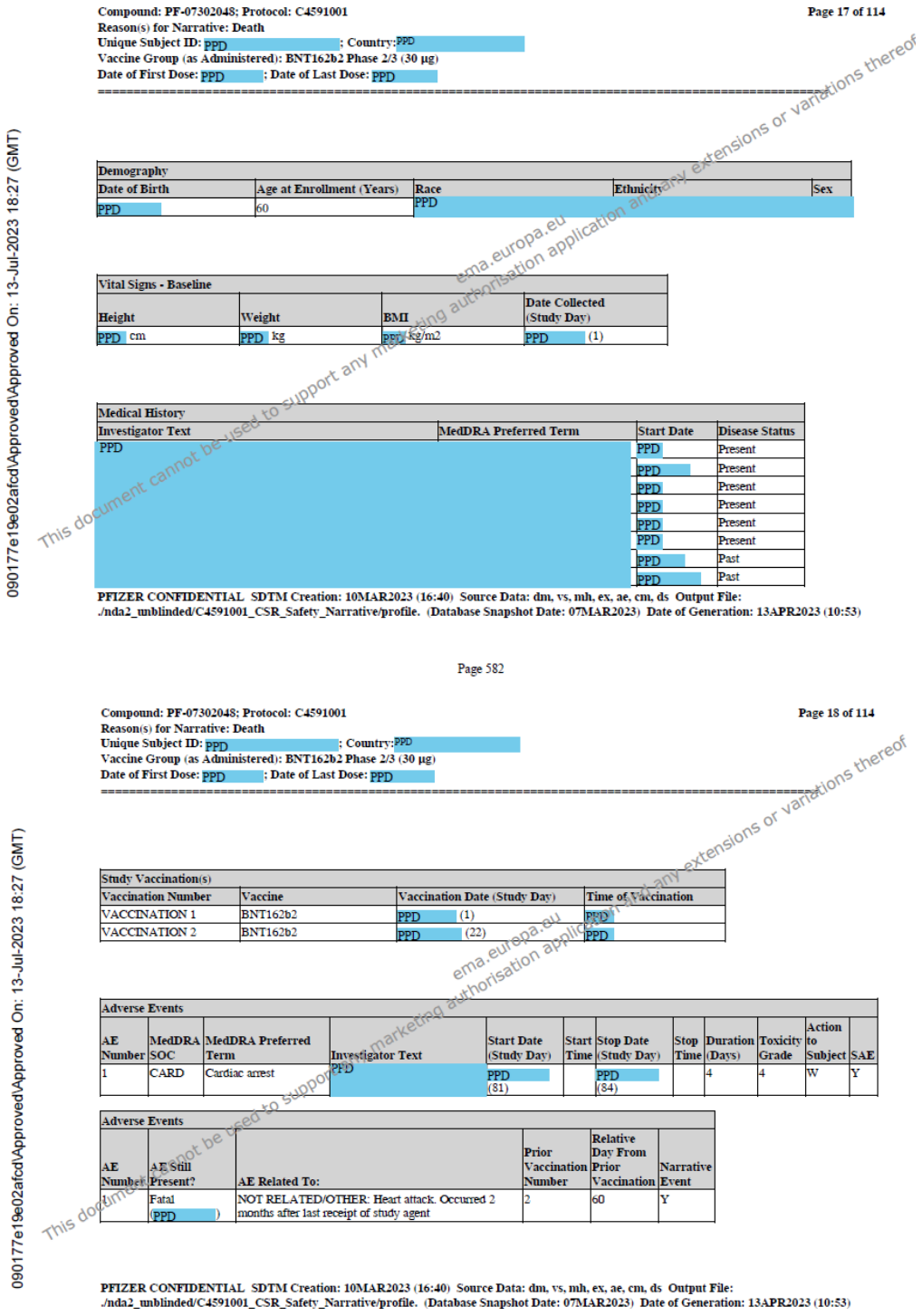
Illustration 123 : Pfizer – July 28, 2023 Final Clinical Study Report – Narrative examplef



Compound: PF-07302048; Protocol: C4591001 Page 17 of 114
Reason(s) for Narrative: Death
Unique Subject ID: PPD ; Country: PPD
Vaccine Group (as Administered): BNT162b2 Phase 2/3 (30 µg)
Date of First Dose: PPD ; Date of Last Dose: PPD

Demography				
Date of Birth	Age at Enrollment (Years)	Race	Ethnicity	Sex
PPD	60	PPD		

Vital Signs - Baseline			
Height	Weight	BMI	Date Collected (Study Day)
PPD cm	PPD kg	PPD kg/m2	PPD (1)

Medical History			
Investigator Text	MedDRA Preferred Term	Start Date	Disease Status
PPD		PPD	Present
		PPD	Present
		PPD	Present
		PPD	Present
		PPD	Present
		PPD	Present
		PPD	Past
		PPD	Past

PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: dm, vs, mh, ex, ae, cm, ds Output File:
./nda2_unblinded/C4591001_CSR_Safety_Narrative/profile. (Database Snapshot Date: 07MAR2023) Date of Generation: 13APR2023 (10:53)

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Compound: PF-07302048; Protocol: C4591001 Page 18 of 114
Reason(s) for Narrative: Death
Unique Subject ID: PPD ; Country: PPD
Vaccine Group (as Administered): BNT162b2 Phase 2/3 (30 µg)
Date of First Dose: PPD ; Date of Last Dose: PPD

Study Vaccination(s)			
Vaccination Number	Vaccine	Vaccination Date (Study Day)	Time of Vaccination
VACCINATION 1	BNT162b2	PPD (1)	PPD
VACCINATION 2	BNT162b2	PPD (22)	PPD

Adverse Events										
AE Number	MedDRA SOC	MedDRA Preferred Term	Investigator Text	Start Date (Study Day)	Start Time	Stop Date (Study Day)	Stop Time	Duration (Days)	Toxicity Grade	Action to Subject	SAE
1	CARD	Cardiac arrest	PPD	PPD (81)		PPD (84)		4	4	W	Y

Adverse Events					
AE Number	AE Still Present?	AE Related To:	Prior Vaccination Number	Relative Day From Prior Vaccination	Narrative Event
1	Fatal (PPD)	NOT RELATED/OTHER: Heart attack. Occurred 2 months after last receipt of study agent	2	60	Y

PFIZER CONFIDENTIAL SDTM Creation: 10MAR2023 (16:40) Source Data: dm, vs, mh, ex, ae, cm, ds Output File:
./nda2_unblinded/C4591001_CSR_Safety_Narrative/profile. (Database Snapshot Date: 07MAR2023) Date of Generation: 13APR2023 (10:53)

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Based on the narratives, we can nonetheless track the deaths by product and by adverse event.

There are **85 deaths in the vaccinated group from the start of the study, and 62 deaths among participants who received the placebo and the the vaccine**, totaling **147 deaths** post-administration of BNT162b2.

For those who received only BNT162b2, the cause of death is unknown for 10 participants. Fourteen deaths are attributed to cardiac arrest, congestive heart failure, cardiopulmonary

arrest, myocardial infarction, or acute myocardial infarction, with 3 of the participants having received 3 doses.

The average time to death is 345 days, ranging from 4 to 755 days.
Among the 240 reported adverse events, there are 34 cardiac events.
Among participants who received the placebo followed by BNT162b2, we count 16 deaths of unknown cause.

The average time to death is 428 days from the first placebo injection; when considering the first vaccination with BNT162b2, this duration decreases to 281 days.
Eight deaths are attributed to cardiac arrest, cardiopulmonary arrest, congestive heart failure, or other cardiac issues, with 4 participants having received only one dose of BNT162b2.

Regarding participants who received only the **placebo, we count 23 deaths**, most of which can be identified in the database, with only one being of unknown cause.

Out of a total of 148 deaths post-administration of BNT162b2, it is quite surprising that the **cause of death is undetermined for 16 of them, which is more than 10%!** This is uncommon in clinical trials and entirely inexcusable for a trial of this significance.

The most frequently reported adverse effects for participants who received BNT162b2 are of a cardiac nature (51), followed by general disorders and conditions at the administration site (58), infectious disorders (50), and cancers (32).

In the placebo group, there were 7 cases of COVID-19, representing 30.5%, with 2 cases in the BNT162b2 group and only 1 in the placebo-BNT162b2 group.

The laboratory took care to obtain the PCR test results for the placebo group, unlike the other groups.
There are 4 deaths due to COPD, pneumonia, or acute respiratory failure in the placebo-BNT162b2 group and 3 in the BNT162b2 group, without any tests conducted to exclude COVID-19.

This confirms the difference in the management of participants already highlighted in Section Analysis of the trial database.

Illustration 124 : - Number of adverse events per System Organ Class calculated according to the July 28, 2023 Final Clinical Study Report

	BNT162b2 **N=85 deaths**	**Placebo puis BNT162b2** **N=62 deaths**	**Placebo** **N=23 deaths**
CARD - Cardiac Disorders	34	17	9
GENRL General Disorders and Administration Site Conditions	27	31	5
INFEC Infections and Infestations	25	25	13
NEOPL Benign, Malignant, and Unspecified Tumors (including cysts and polyps)	25	7	3
INJ&P Injuries, Poisonings, and Procedural Complications	17	12	5
GASTR Gastrointestinal Disorders	16	13	3
VASC Vascular Disorders	15	4	2
RESP Respiratory, Thoracic, and Mediastinal Disorders	13	15	3
MUSC Musculoskeletal and Connective Tissue Disorders	12	7	2
HEPAT Hepatobiliary Disorders	11	1	0
NERV Nervous System Disorders	10	10	5
INV Investigations	9	1	0
PSYCH Psychiatric Disorders	6	4	1
RENAL Renal and Urinary Disorders	5	6	0
METAB Metabolism and Nutrition Disorders	4	2	1
SKIN Skin and Subcutaneous Tissue Disorders	4	2	0
BLOOD Blood and Lymphatic System Disorders	3	0	0
EAR Ear and Labyrinth Disorders	1	0	0
EYE Eye Disorders	1	1	0
REPRO Reproductive System and Breast Disorders	1	0	0
IMMUN Immune System Disorders	0	1	0
SOCCI Social Circumstances	0	1	0
TOTAL NUMBER OF AE	**240**	**160**	**52**

Note : several AE can be reported for 1 death

Illustration 125 : List of participants dead according to the July 28, 2023 Final Clinical Study Report –-BNT162b2

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
1		>75		1	22		1	GASTR	Abdominal rigidity	34	276	243	BLOOD	276	2
							2	GASTR	Constipation	39	276	238			
							3	GENRL	Death	276	276	1			
							4	BLOOD	Immune thrombocytopenia	243	-	-			
							5	MUSC	Muscle spasms	34	276	243			
2	10071101	56	F	1	22		1	CARD	**Cardiac arrest**	81	84	4	CARD	84	2
3		60		1	22	414	1	INJ&P	???	533	533	1	INJ&P	?	3
							2	INFEC	Skin infection	38	233	196			
4		50		1	22		1	GENRL	Death				**Unknown**	unknown	2
5		60		1	24		1	CARD	**Myocardial infarction**	226	226	1	CARD	226	2
6		30		1	21		1	RESP	Pulmonary embolism	277	277	1	RESP	277	2
7		70		1	21		1	CARD	Coronary artery disease	28	-	-	NERV	200	2
							2	NERV	Haemorrhagic stroke	197	200	4			
8		60		1	23		1	MUSC	Pain in extremity	28	29	2	**Unknown**	265	2
							2	GENRL	Chest pain	198	-				
							3	GENRL	death	265	265	1			
9	10211127	54	M	1	24		1	CARD	Acute left ventricular failure	50	52	3	CARD	111	2
							2	CARD	**Cardiac failure congestive**	92	111	20			
							3	METAB	Hypokalaemia	50	52	3			
10		70		1	23	377	1	NEOPL	Glioblastoma	512	554	43	NEOPL	554	3
11	10361140	64	M	1	22		1	INJ&P	Traumatic injury	112	112	1	INJ&P	112	2
							2	INJ&P	Motor vehicle accident	112	112	1			
12	10391010	84	M	1	20		1	VASC	Arteriosclerosis	90	90	1	CARD	90	2
							2	CARD	Hypertensive heart disease	90	90	1			
							3	GENRL	Injection site pain	1	3	3			
							4	GENRL	Injection site pain	20	22	3			

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
							5	GENRL	Pyrexia	21	21	1			
							6	INJ&P	Contusion	1	13	13			
13		70		1	21		1	CARD	**Acute myocardial infarction**	231	238	8	CARD	238	2
							2	RESP	Haemoptysis	231	238	8			
							3	GASTR	Melaena	231	238	8			
14		70		1	22		1	RESP	Chronic obstructive pulmonary disease	283	283	1	RESP	283	2
15		70		1	21		1	INFEC	Pneumonia aspiration	121	131	11	INFEC	131	2
16		70		1	20		1	INFEC	Peritonicis	461	461	1	INFEC	461	2
17		>75		1	22	399	1	INV	Blood lactic acid increased	310	523	214	NEOPL		3
							2	INV	**Fibrin D dimer increased**	309	523	215		523	
							3	NEOPL	Triple negative breast cancer	316	523	208			
18		70		1	21		1	INJ&P	???	371	371	1	INJ&P	371	
19		70		1	22		1	GASTR	Duodenal perforation	271	293	23	GASTR	293	2
							2	METAB	Hyperlipidaemia	185	-	-			
							3	VASC	Hypertension	183	-	-			
20	10841266	77	M	1	24		1	RENAL	Acute kidney injury	74	-	-	INFEC	144	2
							2	CARD	Atrial fibrillation	74	-	-			
							3	INFEC	Emphysematous cholecystitis	74	144	71			
							4	MUSC	Muscular weakness	68	-	-			
							5	MUSC	Rhabdomyolysis	73	84	12			
							6	INFEC	Sepsis	74	144	71			
21		>75		1	20	448	1	NEOPL	adenocarcinoma pancreas	469	517	49	NEOPL	517	3
							2	VASC	aneurysm	469	-	-			
							3	VASC	aortic aneurysm	469	-	-			
							4	VASC	arteriosclerosis	469	517	49			
							5	HEPAT	biliary obstruction	469	-	-			
							6	HEPAT	jaundice cholestatic	469	-	-			

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
							7	BLOOD	Splenic vein thrombosis	469	-	-			
22		>75					1	NEOPL	Acute myeloid leukemia	485	511	27	NEOPL	511	
23		70		1	22	428	1	CARD	**Acute myocardial infarction**	664	664	1	CARD	664	3
							2	METAB	Hypercholesterolaemia	410	-	-			
							3	INFEC	Prostate infection	13	20	8			
							4	INV	Prostatic specific antigen increased	13	20	8			
24	10881139	82	M	1	44		1	NEOPL	Metastases to lung	176	186	11	NEOPL	186	2
							2	NEOPL	Pancreatic carcinoma metastatic	176	186	11			
25	10891073	63	F	1	30		1	RESP	Chronic obstructive pulmonary disease	99	99	1	RESP	99	2
26		70		1	22	422	1	VASC	Aortic rupture	556	556	1	VASC	556	3
27		>75		1	23		1	NEOPL	Bladder cancer	247	408	162	NEOPL	408	2
28		60		1	24		1	VASC	Arteriosclerosis	217	217	1	VASC	217	2
							2	GASTR	Gastrointestinal haemorrhage	217	217	1			
							3	NERV	Restless legs syndrome	99	-	-			
29		50		1	20		1	NERV	**Cerebrovascular accident**	314	316	3	NERV	316	2
							2	GASTR	Gastritis	309	316	8			
30	10971023	86	F	1	23		1	SKIN	Actinic keratosis	65	65	1	INFEC	120	2
							2	EAR	Cerumen impaction	31	31	1			
							3	INFEC	**Septic shock**	115	120	6			
							4	SKIN	Skin lesion	65	71	7			
							5	NEOPL	Squamous cell carcinoma of skin	71	71	1			
31		>75		1	25		1	RENAL	Acute kidney injury	144	151	8	CARD	218	2
							2	CARD	Atrial fibrillation	127	129	3			
							3	CARD	Atrial fibrillation	144	218	75			
							4	CARD	**Cardiac failure congestive**	114	218	105			
							5	CARD	Mitral valve incompetence	144	218	75			

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
							6	INV	Troponine increased	144	151	8			
32		>75		1	23	409	1	INFEC	Bacterial sepsis	29	41	13	NEOPL	733	3
							2	NERV	Dizziness	166	-	-			
							3	INJ&P	Fall	166	166	166			
							4	NEOPL	Neoplasm malignant	733	733	1			
							5	INFEC	Urinary tract infection	29	41	13			
33		50		1	20		1	GENRL	Death	266	266	1	**unknown**	266	2
34		70		1	22	444	1	CARD	Acute myocardial infarction	593	593	1	CARD	593	3
							2	NERV	Haemorragic stroke	593	593	1			
							3	INFEC	septic endocarditis	593	593	1			
35		>75		1	29		1	CARD	**Cardio-respiratory arrest**	402	402	1	CARD	402	
36	11141050	63	F	1	22		1	VASC	Arteriosclerosis	63	63	1	VASC	63	
							2	CARD	Hypertensive heart disease	63	63	1			
37		>75		1	23	415	1	RESP	Acute respiratory failure	603	-	-	VASC	605	
							2	INV	biopsy skin	513	513	1			
							3	GENRL	Chills	38	39	2			
							4	HEPAT	Cholelithiasis	3	85	83			
							5	SKIN	Dermal cyst	46	46	1			
							6	INFEC	Diverticulitis	47	47	1			
							7	INJ&P	Fall	603	603	1			
							8	MUSC	Myalgia	38	39	2			
							9	GASTRO	Nausea	38	39	2			
							10	VASC	Neurogenic shock	603	605	3			
							11	RESP	Pulmonary embolism	603	-	-			
							12	MUSC	Rhabdomyolysis	603	605	3			
							13	INFEC	Sepsis	603	-	-			
							14	INJ&P	Spinal cord injury	603	605	3			

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
							15	MUSC	Spondylitis	3	435	433			
38	11201050	58	F	1	24		1	CARD	**Cardiac arrest**	96	96	1	CARD	96	
39	11201266	51	M	1	20		1	EYE	Blindness unilateral	86	-	-	NEOPL	132	
							2	NEOPL	Lung cancer metastatic	86	132	47			
40		>75		1	22		1	GENRL	Death	672	672	1	**unknown**	672	
							2	VASC	Hypertension	1	-	-			
41	11271112	53	M	1	22		1	CARD	**Cardio-respiratory arrest**	107	107	1	CARD	107	
42	11291166	78	F	1	21		1	CARD	**Myocardial infarction**	149	149	1	CARD	149	
43		40		1	21		1	GENRL	Death	579	579	1	**unknown**	579	
							2	INJ&P	Fall	-	-	-			
							3	MUSC	Rotator cuff syndrome	-	-	-			
44	11361102	76	M	1	22		1	CARD	**Cardiac arrest**	52	52	1	CARD	52	
							2	GENRL	Injection site pain	23	24	2			
							3	GENRL	Injection site pain	1	1	1			
45	11401117	58	M	1	22		1	CARD	**Cardiac arrest**	138	138	1	CARD	138	
46		70		1	22	414	1	GASTR	Abdominal pain upper	415	415	1	NEOPL	617	
							2	GENRL	Asthenia	415	415	1			
							3	GENRL	Chills	415	415	1			
							4	NEOPL	Colon cancer stage III	518	617	100			
							5	NERV	**Syncope**	415	415	1			
47	11521497	72	M	1			1	INFEC	Shigella sepsis	20	36	17	INFEC	36	1
							2	NERV	**Syncope**	20	20	1			
48	11561160	62	F	1	22		1	INJ&P	Motor vehicle accident	95	95	1	INJ&P	95	
49		60		1	21	363	1	GENRL	Sudden death	428	428	1	**Unknown**	428	
50		>75		1	23		1	CARD	**Cardio-respiratory arrest**	234	234	1	CARD	234	
51		70		1	23	475	1	NEOPL	Hepatic cancer	-	580	-	NEOPL	580	
52	11621327	60	M	1			1	VASC	Arteriosclerosis	4	4	1	VASC	4	

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
53		60		1	20		1	CARD	**Cardio-respiratory arrest**	345	350	6	CARD	350	
54		>75		1	22								**unknown**	unknown	
55		60		1	23		1	GENRL	Chills	24	25	2	RESP	306	
							2	GENRL	Injection site erythema	24	25	2			
							3	GENRL	injection site pain	2	4	3			
							4	GENRL	injection site pain	24	25	2			
							5	GENRL	injection site swelling	24	25	2			
							6	GASTR	Large intestine perforation	-	296	-			
							7	MUSC	Myalgia	24	25	2			
							8	RESP	Pulmonary embolism	306	306	1			
56		50		1	22								**unknown**	unknown	
57		60		1	20		1	INFEC	Staphylococcal sepsis	371	376	6	INFEC	376	
58		70		1	22		1	NERV	Basilar artery aneurysm	173	-	-	NERV	301	
							2	NERV	Ischaemic stroke	299	301	3			
59		70		1	20		1	NEOPL	Adenocarcinoma pancreas	58	459	402	NEOPL	459	
							2	SKIN	Decubitus ulcer	-	169	-			
							3	INFEC	Escherichia sepsis	85	87	3			
							4	HEPAT	hepatic cyst	83	459	377			
							5	GENRL	Impaired healing	120	125	6			
							6	GENRL	Oedema peripheral	-	117	-			
							7	CARD	Tachycardia	99	106	8			
60		30		1	29		1	PSYCH	???	258	258	1	PSYCH	258	
61		40		1	20	354							**unknown**	unknown	
62		30		1	22		1	PSYCH	???	114	114	1	PSYCH	114	
63		40		1	20		1	PSYCH	???	131	131	1	PSYCH	131	
64		70		1	22		1	NEOPL	???	43	-	-	NEOPL	319	
							2	NEOPL	???	318	319	2			

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
65		30		1	24		1	PSYCH	???	219	219	1	PSYCH	219	
66		60		1	21		1	NEOPL	Glioblastoma	219	321	103	NEOPL	321	2
							2	VASC	Hypertensive emergency	229	232	4			
							3	INFEC	Pneumonia aspiraton	222	236	5			
67		>24		1			1	PSYCH	???	415	415	1	PSYCH	415	1
							2	INJ&P	???	415	415	1			
68		70		1	23	450	1	CARD	**Cardiac arrest**	744	744	1	CARD	744	3
69		60		1	20		1	CARD	**Cardio-respiratory arrest**	383	383	1	CARD	383	2
70		>75		1	22	446	1	CARD	Aortic valve incompetence	582	582	1	INFEC	674	3
							2	HEPAT	hepatic cyst	516	516	1			
							3	GASTR	Hiatus hernia	516	516	1			
							4	CARD	Mitral valve incompetence	582	582	1			
							5	NEOPL	Mucincus breast carcinomia	447	-	-			
							6	INFEC	Pneumonia	663	674	12			
							7	CARD	Tricuspid valve incompetence	582	582	1			
71		60		1	20		1	NEOPL	Gastric cancer	155	461	307	NEOPL	461	2
							2	GASTR	Gastric ulcer	63	208	146			
							3	GASTR	Gastrooesophageal reflux disease	35	63	29			
							4	GASTR	Intestinal obstruction	416	461	46			
							5	RENAL	Oliguria	416	461	46			
72		70		1	20		1	CARD	Atrial fibrillation	211	284	74	NEOPL	407	2
							2	CARD	Atrial flutter	211	284	74			
							3	HEPAT	Bile duct stenosis	398	407	10			
							4	MUSC	Bursitis	209	243	35			
							5	NEOPL	Pancreatic neoplam	398	407	10			
							6	GASTR	Pancreatitis necrotising	401	407	7			
							7	RESP	Pulmonary emnolism	406	407	2			

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
							8	RENAL	Renal infact	404	-	-			
							9	INFEC	Sepsis	403	407	5			
73		60		1	20	545	1	NEOPL	Clear cell renal carcinoma	286	677	392	NEOPL	677	3
							2	INJ&P	Fall	427	427	1			
							3	GENRL	Injection site pain	546	546	1			
							4	INJ&P	Joint dislocation	427	509	83			
							5	INFEC	Mastoiditis	540	-	-			
							6	NEOPL	Meningioma	477	-	-			
							7	MUSC	Pathological fracture	427	614	188			
74		60		1	20		1	INFEC	Sepsis	282	330	49	INFEC	330	2
75		60		1	21	391	1	RESP	Chronic obstructive pulmonary disease	602	602	1	RESP	602	2
76	12521010	80	M	1	23		1	RENAL	Acute kidney injury	131	132	2	INFEC	132	2
							2	INFEC	COVID 19	131	132	2			
							3	INJ&P	Skin laceration	114	114	1			
77		>75		1	24	438	1	BLOOD	Anaemia	143	147	5	RESP		3
							2	RESP	Chronic obstructive pulmonary disease	143	147	5			
							3	RESP	Chronic obstructive pulmonary disease	631	664	34			
							4	METAB	Hyperkalaemia	143	147	5			
							5	INV	Lymphocyte count decreased	143	147	5			
							6	INV	Platelet count decreased	143	147	5			
							7	RESP	Respiratory failure	143	147	5			
							8	INFEC	Sepsis	143	147	5			
							9	INV	Troponin increased	143	147	5			
78		60		1	24		1	INFEC	COVID 19	351	355	5	INFEC	355	2
							2	MUSC	Intervertebral disc disorder	186	352	167			
79		70		1	22		1	GENRL	Death	382	382	1	**unknown**	382	2

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
							2	GASTR	Diarrhoea	1	3	3			
							3	GASTR	Diarrhoea	22	23	2			
80		70		1	22	386	1	CARD	**Cardiac arrest**	478	478	1	RESP	484	3
							2	VASC	Hypertension	41	83	43			
							3	NERV	Hypoxic-ischaemic encephalopathy	481	-	-			
							4	RESP	Pulmonary embolism	478	484	7			
81		60		1	23	431	1	CARD	**Acute myocardial infarction**	665	665	1	CARD	665	3
82		40		1	22	429	1	PSYCH	???	751	751	1	PSYCH	751	3
							2	GENRL	injection site pain	429	430	2			
							3	GENRL	Pyrexia	23	23	1			
83		60		1	22	419	1	CARD	**Cardiac arrest**	755	755	1	CARD	755	
84		>75		1	21		1	NEOPL	Benign gastrointestinal neoplasm	95	95	1	NEOPL	357	2
							2	HEPAT	Cholangitis	343	357	15			
							3	HEPAT	Cholelithiasis	80	105	26			
							4	INJ&P	Craniocerebral injury	343	357	15			
							5	VASC	**Deep vein thrombosis**	315	357	43			
							6	INJ&P	fall	343	343	1			
							7	NEOPL	**Pancreatic carcinoma metastatic**	137	357	221			
							8	GASTR	Pancreatitis acute	83	105	23			
							9	INFEC	Sepsis	343	357	15			
							10	INJ&P	Subdural haematoma	343	357	15			
85		>75		1	19	417	1	NEOPL	Adrenal adenoma	478	-	-	INFEC	513	3
							2	BLOOD	Anaemia	495	-	-			
							3	VASC	Aortic arteriosclerosis	478	-	-			
							4	REPRO	Benign prostatic hyperplasia	478	-	-			
							5	HEPAT	Bile duct stenosis	472	-	-			

N°	Unique subject ID	Age	Sex	Vacc. 01 BNT162b2	Vacc. 02 BNT162b2	Vacc. 03 BNT162b2	AE number	Med DRASOC	MedDRA Preferred term	Day since vaccination	Fin	Duration	Death	day of death	Doses
							6	HEPAT	Bile duct stone	472	-	-			
							7	HEPAT	Cholangitis	513	-	-			
							8	INV	Liver scan	478	-	-			
							9	NEOPL	Pancreatic carcinoma metastatic	486	-	-			
							10	INFEC	Septic shock	513	-	-			

Note :

MedDRA = Medical Dictionary for Regulatory Activities,
SOC = System Organ Class

Illustration 126 : – List of participants dead according to the July 28, 2023 Final Clinical Study Report – Placebo - BNT162b2

N°	Unique subject ID	Age	Sex	Vacc. 01 PLA	Vacc. 02 PLA	Vacc. 03 BNT162	Vacc. 04 BNT162	Vacc. 05 BNT162	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death	day of death from BNT162 injection
1		60		1	22	164	183		1	GASTR	Abdominal compartment symdrome	309	363	55	INFEC	412	248
									2	INFEC	Abdominal wall abscess	393	412	20			
									3	RENAL	Acute kidney injury	337	412	76			
									4	RESP	Acute respiratory distress syndrome	309	412	104			
									5	CARD	Atrial fibrillation	311	323	13			
									6	GENRL	Chills	3	7	5			
									7	MUSC	Flank pain	3	7	5			
									8	GASTR	Gastrointestinal necrosis	309	412	104			
									9	HEPAT	hepatic steatosis	307	319	13			
									10	NERV	Metabolic encephalopathiy	329	412	84			
									11	GASTR	Pancreatitis necrotising	307	412	106			
									12	INFEC	Sepsis	412	412	1			
									13	BLOOD	Thrombocytopenia	324	335	12			
									14	GASTR	Vomiting	3	9	7			
2		70		1	21	106	128	379	1	GENRL	Injection site pain	106	107	2	**Unknown**	**unknown**	
3		60		1	24	144	165								**Unknown**	**unknown**	
4		70		1	22	57	78		1	GENRL	Injection site pain	79	82	3	**Unknown**	**unknown**	
5		70		1	20	149	169		1	RESP	Respiratory failure	512	519	8	RESP	519	370
6		60		1	20	153	180	400	1	RESP	Acute respiratory failure	546	582	37	RESP	582	429
7		30		1	21	155	176		1	INJ&P	???	208	208	1	INJ&P	208	53
8		70		1	22	134	155	435	1	CARD	**Cardiac disorder**	543	-	-	CARD	543	409
									2	GENRL	???	543	-	-			
									3	GENRL	Injection site pain	156	156	1			
9		60		1	22	127	148		1	CARD	**Coronary artery disease**	402	406	5	CARD	406	279

N°	Unique subject ID	Age	Sex	Vacc. 01 PLA	Vacc. 02 PLA	Vacc. 03 BNT162	Vacc. 04 BNT162	Vacc. 05 BNT162	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death	day of death from BNT162 injection
									2	NERV	Headache	127	128	2			
									3	GENRL	Injection site pain	127	128	2			
									4	GENRL	Injection site pain	148	150	3			
10		70		1	20	162	187	416	1	NERV	Haemorrhage intracranial	737	751	15	NERV	751	589
11		60		1	21	144	164	437	1	INJ&P	???	582	582	1	INJ&P	582	438
12		30		1	22	161	180	414	1	GENRL	Chills	181	182	**2**	**Unknown**	**unknown**	
									2	GENRL	Fatigue	181	183	3			
									3	INFEC	Fungal skin infection	15	76	62			
									4	GENRL	Injection site pain	180	182	3			
									5	GENRL	Injection site pain	161	164	4			
									6	GENRL	Pyrexia	181	182	2			
13		60		1	19	151	172		1	CARD	Coronary artery disease	368	-	-	INFEC	435	284
									2	INFEC	postoperative wound infection	411	435	25			
14		70		1	23	155	176	425	1	INJ&P	Arthropod bite	325	362	38	CARD	777	622
									2	INJ&P	Arthropod bite	372	380	9			
									3	CARD	Cardiac failure congestive	712	777	66			
15		40		1	24	173	193		1	INJ&P	Toxicity to various agents	297	300	4	INJ&P	300	127
16		50		1	22	164	186	418	1	IMMUN	Haemophagocytic lymphohistiocytosis	692	-	-	IMMUN	???	
									2	MUSC	Musculoskeletal chest pain	419	430	12			
17		>75		1	22	153	176		1	NEOPL	Adenocarcinoma	-	461	-	NEOPL	461	308
									2	CARD	Cardiac failure congestive	214	220	7			
									3	INFEC	Cellulitis	198	461	264			
									4	RESP	Chronic obstructive pulmonary disease	141	461	321			
									5	INFEC	Urinary tract infection	139	153	15			
18		60		1	22	169	189		1	RESP	Pulmonary fibrosis	399	399	1	RESP	399	230

N°	Unique subject ID	Age	Sex	Vacc. 01 PLA	Vacc. 02 PLA	Vacc. 03 BNT162	Vacc. 04 BNT162	Vacc. 05 BNT162	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death	day of death from BNT162 injection
19		70		1	22	113	136	380	1	NEOPL	Pancreatic carcinoma	-	643	-	NEOPL	643	530
20		>75		1	21	109	130		1	RESP	Acute respiratory failure	332	332	1	RESP	332	223
									2	RESP	Chronic obstructive pulmonary disease	332	332	1			
21		50		1	23	202	225		1	INFEC	Diabetic foot infection	166	198	33	CARD	282	80
									2	VASC	Hypertension	194	282	89			
									3	CARD	Myocardial infaction	282	282	1			
22		40		1	22	135	154	463	1	SOCCI	???	598	598	1	SOCCI	598	463
23		60		1	24	176	198	425	1	GENRL	Death	-	-	-	**Unknown**	**Unknown**	
									2	INV	Hepatic enzyme increased	35	56	22			
24		>75		1	22	148	169		1	RENAL	Acute kidney injury	288	299	12	NERV	417	269
									2	NERV	**Cerebrovascular accident**	417	427	11			
									3	NERV	**Cerebrovascular accident**	185	207	23			
									4	NERV	**Cerebrovascular accident**	418	427	10			
									5	INJ&P	subdural haematoma	389	427	39			
									6	RENAL	Urinary retention	270	427	158			
									7	INFEC	Urinary tract infection	417	427	11			
25		40		1	23	111	132	457	1	PSYCH	???	557	557	1	PSYCH	557	446
									2	INJ&P	???	557	557	1			
									3	GENRL	Pain	132	133	2			
									4	GENRL	Pyrexia	132	133	2			
									5	GENRL	Injection site pain	132	133	2			
26		60		1	21	183	204		1	CARD	**Acute myocardial infarction**	267	267	1	CARD	267	84
27		60		1	24	212	231		1	GENRL	Death	316	-	-	**Unknown**	316	104
									2	METAB	Hyperkalaemia	191	204	14			

N°	Unique subject ID	Age	Sex	Vacc. 01 PLA	Vacc. 02 PLA	Vacc. 03 BNT162	Vacc. 04 BNT162	Vacc. 05 BNT162	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death	day of death from BNT162 injection
									3	METAB	Obesity	204	316	113			
									4	INFEC	Urinary tract infection	191	199	9			
28		30		1	22	204	225		1	INJ&P	Injury	573	573	1	INJ&P	573	369
									2	INJ&P	???	573	573	1			
29		70		1	22	165	186	473							**Unknown**	**Unknown**	
30		60		1	21	153	175		1	PSYCH	???	248	248	1	PSYCH	248	95
31	11311204	84	M	1	24	122			1	VASC	Aortic stenosis	137	145	9	VASC	147	25
									2	CARD	**Cardio-respiratory arrest**	147	147	1			
32		70		1	23	159	180	441	1	NEOPL	Adenocarcinoma pancreas	-	562	-	NEOPL	562	403
									2	CARD	**Cardiac failure congestive**	558	562	5			
									3	CARD	**Cardio-respiratory arrest**	562	562	1			
									4	INFEC	Pneumonia	558	562	5			
33	11351033	67	M	1	23	174			1	PSYCH	Suicide	178	178	1	PSYCH	178	4
									2	NERV	Hypoaesthesia	31	31	1			
34		70		1	21	195	216	512	1	MUSC	Back pain	6	6	1	NATURAL DEATH	552	357
									2	GENRL	Death	552	552	1			
									3	GASTR	Inguinal hernia	-	552	-			
									4	GENRL	Vaccination site pain	196	198	3			
									5	GASTR	Nausea	195	195	1			
35		70		1	22	174	195		1	RENAL	Acute kidney injury	366	-	-	CARD	388	214
									2	CARD	Aortic valve incompetence	44	-	-			
									3	CARD	**Cardiac arrest**	388	388	1			
									4	GENRL	Injection site pain	175	176	2			
									5	INFEC	Kidney infection	366	-	-			

N°	Unique subject ID	Age	Sex	Vacc. 01 PLA	Vacc. 02 PLA	Vacc. 03 BNT162	Vacc. 04 BNT162	Vacc. 05 BNT162	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death	day of death from BNT162 injection
									6	INFEC	Renal abscess	-	-	-			
									7	INFEC	Subcutaneous abscess	-	-	-			
36		>24		1	21	183	202		1	INJ&P	???	624	624	1	INJ&P	624	441
37		50		1	22	142	161		1	NERV	Amyotrophic lateral sclerosis	-	337	-	NERV	337	195
97		50		1	22	91	113		1	GENRL	Death	-	-	-	**Unknown**	**Unknown**	
				1	22	91	113		2	MUSC	Pain in extremity	113	114	2			
99		60		1	25	146	167		-						**Unknown**	**Unknown**	
107		70		1	23	177	198	407	1	GENRL	Death	764	764	1	**Unknown**	**764**	587
109		70		1	23	176	197		1	CARD	**Cardiac arrest**	256	256	1	CARD	256	80
116		>75		1	22	114	135		1	VASC	Shock haemorrhagic	351	351	1	VASC	351	237
121		50		1	22	80	99	447	1	RESP	Chronic obstructive pulmonary disease	337	339	3	**Unknown**	498	418
									2	GENRL	Death	498	498	1			
									3	GASTR	Gastritis	327	-	-			
									4	GENRL	Injection site pain	80	81	2			
126		50		1	22	194	214		1	INFEC	???	235	272	38	INFEC	272	78
									2	RESP	Acute respiratory failure	272	272	1			
									3	INFEC	???	255	272	18			
									4	GENRL	Injection site erythema	194	196	3			
									5	GENRL	Injection site pain	194	196	3			
									6	INFEC	Lower respiratory tract infection	272	272	1			
									7	INFEC	Pneumonia	235	264	30			
									8	SKIN	Pruritus	95	136	42			
									9	CARD	Supraventricular tachycardia	246	247	2			
127		>75		1	20	105	127		1	GENRL	Injection site pain	359	361	3	**Unknown**	**Unknown**	
130		60		1	22	140	161	445	1	GENRL	Death	783	783	1	**Unknown**	**Unknown**	

N°	Unique subject ID	Age	Sex	Vacc. 01 PLA	Vacc. 02 PLA	Vacc. 03 BNT162	Vacc. 04 BNT162	Vacc. 05 BNT162	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death	day of death from BNT162 injection
131		50		1	22	209	228	471	1	RENAL	Acute kidney injury	639	652	14	NEOPL	718	509
									2	NEOPL	Adenocarcinoma of colon	635	718	84			
									3	INFEC	Douglas abscess	698	718	21			
									4	GASTR	Duodenal stenosis	668	-	-			
									5	GASTR	Intestinal obstruction	639	652	14			
									6	GASTR	Intestinal obstruction	693	718	26			
									7	GENRL	Multi-organ disorder	693	718	26			
									8	INFEC	Septic shock	693	718	26			
132		60		1	22	187	207		1	CARD	**Cardiac arrest**	295	295	1	CARD	295	108
									2	MUSC	Tendonitis	228	232	5			
138		70		1	22	165	197		1	RESP	Pulmonary embolism	412	414	3	RESP	414	249
									2	NERV	Tension headache	52	57	6			
142		60		1	50	162	183		1	RESP	Bronchospasm	2	19	18	GASTR	336	174
									2	GASTR	Intestinal ischaemia	333	336	4			
									3	INFEC	Septic shock	334	336	3			
146		70		1	20	175	196		1	RESP	Acute respiratory distress syndrome	260	263	4	RESP	263	88
				1	20	175	196		2	INFEC	COVID 19 Pneumonia	260	263	4			
148		70		1	21	142	163		1	MUSC	Back pain	239	248	10	INFEC	248	106
									2	EYE	Optic ischaemic neuropathy	219	244	26			
									3	INFEC	Pneumonia	245	248	4			
150		60		1	21	141	162	471	1	GASTR	Abdominal hernia obstructive	609	610	2	GASTR	610	610
151		60		1	22	135	156		1	GASTR	Gastrointestinal haemorrhage	177	181	5	2	181	181
									2	VASC	Hypovolaemic shock	181	181	1			
152		>75		1	22	118	139	433	1	RENAL	Acute kidney injury	193	198	6	4	554	554

N°	Unique subject ID	Age	Sex	Vacc. 01 PLA	Vacc. 02 PLA	Vacc. 03 BNT162	Vacc. 04 BNT162	Vacc. 05 BNT162	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death	day of death from BNT162 injection
									2	NEOPL	Adenocarcinoma of colon	-	547	-			
									3	INFEC	Gastroenteritis	191	198	8			
									4	INFEC	Septic shock	552	554	3			
153		50		1	21	143	164		1	PSYCH	???	335	335	1	1	335	192
159		50		1	22	153	174	406							**Unknown**	**Unknown**	
160		70		1	22	148	169		1	NEOPL	Angiosarcoma	-	348	-	1	348	200
									2	CARD	**Cardio-respiratory arrest**	-	348	-			
									3	NEOPL	Vascular neoplasm	-	348	-			
161		40		1	22	140	161		1	INJ&P	???	215	215	1	1	215	75
163		60		1	22	165	186		1	NERV	Hypoaesthesia	435	-	-	**Unknown**	**Unknown**	
									2	MUSC	Muscular weakness	453	-	-			
									3	INJ&P	Wound dehiscence	418	-	-			
164		60		1	23	168	189	521	1	RESP	Brochopleural fistula	664	695	32	1	695	527
									2	INFEC	Infectious pleural effusion	690	695	6			
									3	GENRL	injection site pain	521	523	3			
									4	RESP	Pneumothorax spontaneous	661	695	35			
									5	RESP	**Pulmonary embolism**	677	695	19			
									6	SKIN	Subcutaneous emphysema	664	695	32			
168		60		1	22	150	170		1	GENRL	Sudden death	257	257	1	**Unknown**	257	107

Illustration 127 : List of participants dead according to the July 28, 2023 Final Clinical Study Report - Placebo

N°	Unique subject ID	Age	Sex (N)	Vaccination 01	Vaccination 02	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death
14	10191146	67	M	1	22	1	NEOPL	Biliary cancer metastatic	57	108	52	NEOPL	108
						2	NEOPL	metastases to liver	57	108	52		
16	10271191	68	F	1	22	1	RESP	Acute respiratory failure	124	156	33	INFEC	156
						2	INFEC	**COVID**	124	156	33		
24		50		1	22	1	NEOPL	Brest cancer metastatic	79	-	-	NEOPL	291
						2	GENRL	Death	291	291	1		
						3	GASTR	Mouth ulceration	27	29	3		
						4	GASTR	Stomatitis	27	29	3		
28		50		1	21	1	NERV	Basal ganglia haemorrhage	210	225	16	NERV	225
						2	PSYCH	???	210	225	16		
						3	VASC	Hypertensive urgency	210	-	-		
						4	NERV	Seizure	210	210	1		
35	10661350	58	M	1		1	CARD	Myocardial infaction	16	16	1	CARD	16
40	10811194	51	F	1	20	1	CARD	Myocardial infaction	56	56	1	CARD	56
42		>75		1	30	1	INFEC	Abdominal abscess	212	-	-	GASTR	225
						2	GASTR	Acute abdomen	212	-	-		
						3	CARD	Acute myocardial infarction	217	-	-		
						4	CARD	**Cardiac arrest**	225	225	1		
						5	GENRL	Complication associated with device	213	213	1		
						6	INJ&P	Contusion	57	-	-		
						7	INJ&P	Fall	28	28	1		
						8	INJ&P	Fall	57	57	1		
						9	GENRL	Multiple organ dysfunction syndrom	225	-	-		
						10	MUSC	Musculoskeletal stiffness	25	28	4		
						11	MUSC	Rotator cuff syndrome	28	-	-		
						12	INFEC	Sepsis	225	-	-		
						13	INJ&P	Skin abrasion	57	-	-		

N°	Unique subject ID	Age	Sex (N)	Vaccination 01	Vaccination 02	AE number	Med DRASOC	MedDRA Preferred term	debut	Fin	Duration	Death	day of death
43		40		1	22	1	GENRL	Death	702	702	1	**unknown**	702
46	10841470	65	M	1	22	1	INFEC	**COVID 19**	93	104	12	INFEC	104
						2	GENRL	Multiple organ dysfunction syndrome	93	104	12		
52	10881126	65	M	1	24	1	INFEC	**COVID 19**	91	-	-	INFEC	93
						2	CARD	Cadiac arrest	93	93	1		
						3	CARD	Coronary artery disease	93	93	1		
58	10891088	82	F	1	22	1	NERV	Dementia Alzeheimer's type	136	147	12	NERV	147
62	10941112	57	F	1	22	1	RESP	Acute respiratory failure	82	102	21	RESP	102
						2	INFEC	**COVID 19**	80	102	23		
						3	INFEC	Pneumonia	80	102	23		
76		>75		1	22	1	NERV	Dementia Alzeheimer's type	233	233	1	NERV	233
84	11281009	66	M	1	20	1	CARD	**Myocardial infarction**	89	90	2	INFEC	121
						2	INFEC	Pneumonia	90	121	32		
100	11521085	42	F	1		1	CARD	Cardiac failure	8	8	1	CARD	8
102	11561124	53	M	1	23	1	INJ&P	Multiple drug overdose	54	54	1	INJ&P	54
						2	RESP	Respiratory arrest	54	54	1		
12	11681083	64	M	1	22	1	VASC	Aortic dissection	86	-	-	CARD	86
						2	CARD	Pericardial haemorrhage	86	86	86		
113						1	INFEC	**COVID 19**	144	197	54	INFEC	197
120	12071055	65	M	1	22	1	INFEC	Pneumonia bacterial	93	97	5	INFEC	97
128	12291083	55	F	1	22	1	INFEC	**COVID 19**	93	97	5	INFEC	97
						2	METAB	Diabetes mellitus	93	-	-		
137	12313972	61	F	1	20	1	NERV	Haemorragic stroke	34	35	2	NERV	35
143	12314987	47	M	1	20	1	CARD	Cardio-respiratory arrest	100	101	2	CARD	101
147	12315324	58	F	1	21	1	INFEC	**COVID 19**	119	156	38	INFEC	156
						2	INFEC	Septic shock	119	156	38		

In summary,

- Vaccinating participants who initially received the placebo introduces a **major methodological bias in the evaluation of the vaccine, as it eliminates any possible comparison of efficacy results as well as safety**. Pfizer itself acknowledges that the clinical trial is no longer a trial, thereby losing its methodological capacity to properly demonstrate efficacy and safety, as it has been transformed into a simple observational study, which diminishes its initial level of evidence.

- The vaccine efficacy for the primary endpoint is not provided.

- Efficacy results for severe cases are no longer presented in the final report.

- The efficacy against asymptomatic SARS-CoV-2 infection was 40.4% (95% two-sided CI: -10.8%, 67.8%) for dose 2 in the population for which complete efficacy data is available. Thus, no statistically significant efficacy is demonstrated for this endpoint.
- The study of deaths shows a h**igher mortality rate among vaccinated participants** compared to those receiving the placebo, with **85 deaths** in the vaccinated group from the beginning of the study with BNT162b2, and **62 deaths among participants who received the placebo followed by the vaccine**, totaling 147 deaths post-administration of BNT162b2.
  Fourteen deaths occurred due to cardiac arrest, congestive heart failure, cardiopulmonary arrest, myocardial infarction, or acute myocardial infarction, with 3 participants having received 3 doses.

  For the placebo group, 23 deaths were reported.

  The number of deaths of unknown cause is 26 for vaccinated participants, which is more than suspicious in the context of such a trial aimed at evaluating the safety of an innovative product containing messenger RNA, a product that had never been used in real life until then.

- No efficacy has been demonstrated concerning COVID-19 mortality.

7 April 9, 2021 Clinical Study Report on the 12-15 year old population – Interim analysis at 3 months follow-up

In the April 9, 2021 report, the results of the analyses are presented for 2260 participants aged 12-15, 1,131 who received BNT162b2 injection, 1,129 who received placebo.
As for the population over 16 years of age, the follow-up time does not exceed 3 months with 42% being followed for less than 2 months, or 60 days as shown by the Illustration 128 (page 13 of the report).

Illustration 128 : Pfizer Clinical Study Report-April 9, 2021- Participants' follow-up

Table 3. Follow-up Duration After Dose 2, Participants 12 Through 15 Years of Age, Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1131)	Placebo (N[a]=1129)	Total (N[a]=2260)
Length of Follow-up[c]	n[b] (%)	n[b] (%)	n[b] (%)
<1 Month	13 (1.1)	25 (2.2)	38 (1.7)
≥1 Month to <2 months	458 (40.5)	456 (40.4)	914 (40.4)
≥2 Months to <3 months	612 (54.1)	599 (53.1)	1211 (53.6)
≥3 Months	48 (4.2)	49 (4.3)	97 (4.3)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 3, page 20.
[a] N=number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n=number of subjects with the specified characteristic.
[c] Length of follow-up is the total exposure from Dose 2 to cutoff date or the date of unblinding, whichever date was earlier.

Source : https://www.fda.gov/media/148542/download

On page 38 of this same report, the unknown benefits and data gaps associated with Pfizer's COVID-19 vaccine when used in adolescents aged 12 to 15 years are listed (see Illustration 129), they are the same as those detailed in the memorandum authorizing the vaccine for emergency use in persons aged 16 years and older.

Illustration 129 : Pfizer Clinical Study Report-April 9, 2021 – Unknown benefits and data gaps

5.2 Unknown Benefits/Data Gaps

The unknown benefits and data gaps associated with the Pfizer-BioNTech COVID-19 vaccine when used in adolescents 12-15 years of age are the same as those detailed in the memorandum authorizing the vaccine for emergency use in for the individuals 16 years of age and older.[1] They relate to:

- Duration of protection
- Effectiveness in certain populations at high risk of severe COVID-19
- Effectiveness in individuals previously infected with SARS-CoV-2
- Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections
- Vaccine effectiveness against asymptomatic infection
- Vaccine effectiveness against long-term effects of COVID-19 disease
- Vaccine effectiveness against mortality
- Vaccine effectiveness against transmission of SARS-CoV-2

This EUA Amendment provides additional insight for the following unknown benefit/data gap that was previously considered:

Effectiveness in pediatric populations

The study enrollment is limited to participants 12 years of age and older. No data are available at this time to evaluate the vaccine effectiveness in children under 12 years of age.

Source : https://www.fda.gov/media/148542/download

The long list of missing information on a product that has been used for nearly 6 months in real life on millions of people is more than worrisome.

Pfizer recognizes here, although in a roundabout way, the **impotence of its vaccine to act against asymptomatic infections** and thus to slow down the transmission of the virus, as already demonstrated earlier in this report, the main criterion chosen not being able to claim any effectiveness in this matter.

In summary,

In April 2021, regarding the results for adolescents aged 12 to 15 years, the following conclusions can be drawn:

- Follow-up duration for adolescents was 2 months.
- No statistically demonstrated efficacy on the **transmission** of SARS-CoV-2, as it was not studied.
- No statistically demonstrated efficacy on **severe cases**.
- No statistically demonstrated efficacy **in certain high-risk populations** for severe COVID-19.
- No statistically demonstrated efficacy **against asymptomatic infections**.
- No statistically demonstrated efficacy in individuals **already infected** with SARS-CoV-2.
- The primary endpoint was biased, leading to **erroneous results**.
- No statistically demonstrated efficacy **against COVID-19 mortality**.
- No efficacy of the vaccine **against the long-term effects of COVID-19**.
- No future efficacy of the vaccine, influenced by the characteristics of the pandemic.
- No demonstrated efficacy on the evolution of the virus and/or the potential effects of co-infections.
- No measurement of antibodies beyond 2 months after the second dose to avoid showing that they decline.
- Duration of protection is unknown.

Despite these uncertainties, the FDA authorized emergency use for individuals aged 12 to 15 on May 10, 2021, and the EMA granted conditional marketing authorization on May 28, 2021.

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use

https://www.ema.europa.eu/en/news/first-covid-19-vaccine-approved-children-aged-12-15-eu

8 October 26, 2021 Clinical Study Report on 5-11 year old – Interim analysis at 3 months follow-up

A second clinical trial was established to include children, and here is its title:

"***A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children***"

Source : https://clinicaltrials.gov/study/NCT04816643

From the title, it is evident that efficacy does not appear to be the primary concern of the laboratory, as the word "efficacy" is absent.

The October 26, 2021 clinical report present results based on the data extracted on the 08 October 2021 (cut-off date).

The randomization scheme was 2:1, with twice as many participants in the group BNT162b2 as in placebo group.

On this very young population of **2,238 children aged 5 to 11 years** (safety population), as in previous reports, the median follow-up time after Dose 2 was only 2 months, with 95.1% of participants being observed between 2 and 3 months with a maximum of 2.5 months (page 26 of the report). As with adults and adolescents, this is an interim analysis at three months.

Illustration 130 : Pfizer - October 26, 2021 Clinical Study Report on 5-11 year old – Participants' follow-up

BNT162b2
VRBPAC Briefing Document

Table 1. Follow-up Time After Dose 2 - Phase 2/3 - 5 to <12 Years of Age - Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)	Total (N[a]=2268) n[b] (%)
Time from Dose 2 to cutoff date			
<1 Month	7 (0.5)	4 (0.5)	11 (0.5)
≥1 Month to <2 months	67 (4.4)	32 (4.3)	99 (4.4)
≥2 Months to <3 months	1444 (95.1)	714 (95.2)	2158 (95.1)
≥3 Months	0	0	0
Mean (SD)	2.2 (0.19)	2.2 (0.22)	2.2 (0.20)
Median	2.3	2.3	2.3
Min, max	(0.0, 2.5)	(0.0, 2.5)	(0.0, 2.5)

Note: Follow-up time was calculated from Dose 2 to the cutoff date or withdrawal date or the date of unblinding (per protocol), whichever date was earlier. Follow-up time after Dose 2 for participants who did not receive Dose 2 was counted as 0.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

Source : https://www.fda.gov/media/153409/download

In the benefit/risk assessment section, it is clearly established that the sample size of this young population "***is too small to detect potential risks of myocarditis associated with vaccination***." *(see* Illustration 131 page 11 of the report).

As for other populations studied, the long-term safety of the COVID-19 vaccine could not be assessed without post-approval safety studies, *including a 5-year follow-up study to assess long-term sequelae of post-vaccination myocarditis/pericarditis*."

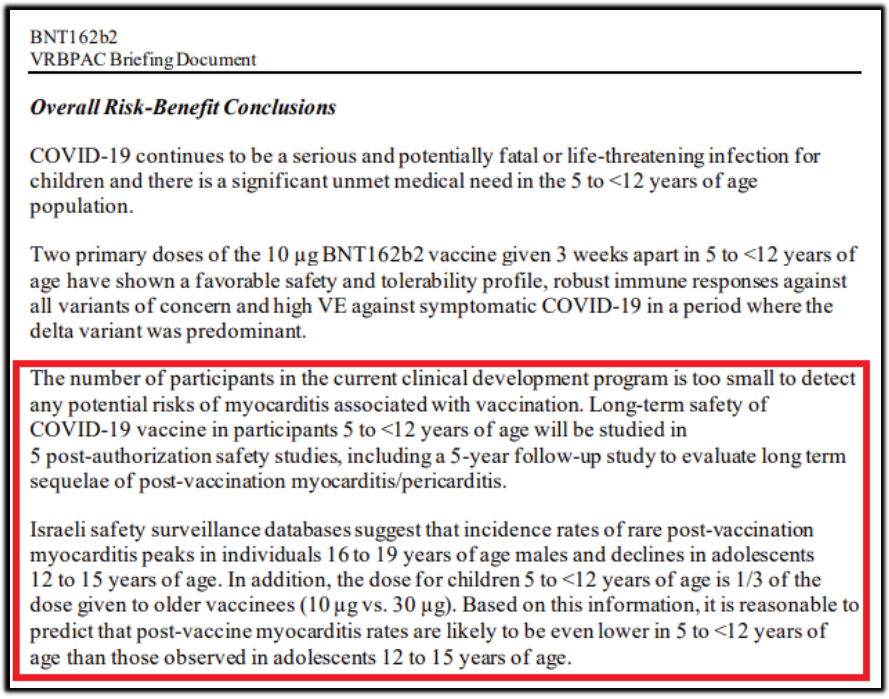
"The number of participants in the current clinical development program is too small to detect any potential risks of myocarditis associated with vaccination. Long-term safety of COVID-19 vaccine in participants 5 to <12 years of age will be studied in 5 post-authorization safety studies, including a 5-year follow-up study to evaluate long term sequelae of post-vaccination myocarditis/pericarditis."

It is evident that serious events, such as myocarditis and pericarditis, could not be detected in the safety results of the clinical trial because the calculated sample size was insufficient to identify rare serious adverse events. While this limitation is not uncommon in clinical research, it raises the question: why did the company not include a larger sample of children? The urgency to vaccinate young children was minimal, given their extremely low risk of developing severe COVID-19.

« *Israeli safety surveillance databases suggest that incidence rates of rare post-vaccination myocarditis* ***peaks in individuals 16 to 19 years*** *of age males and declines in adolescents 12 to 15 years of age. In addition, the dose for children 5 to <12 years of age is 1/3 of the dose given to older vaccineed (10 µg vs. 30 µg).*

Based in this information, ***it is reasonable to predict that post-vaccine myocarditis rates are likely to be even lower in 5 to <12 years of age*** *than those observed in adolescents 12 to 15 years of age.* »

Illustration 131 : Pfizer October 26, 2021 Clinical Study Report on 5-11 year old – Overall Risk/Benefit Conclusion



BNT162b2
VRBPAC Briefing Document

Overall Risk-Benefit Conclusions

COVID-19 continues to be a serious and potentially fatal or life-threatening infection for children and there is a significant unmet medical need in the 5 to <12 years of age population.

Two primary doses of the 10 µg BNT162b2 vaccine given 3 weeks apart in 5 to <12 years of age have shown a favorable safety and tolerability profile, robust immune responses against all variants of concern and high VE against symptomatic COVID-19 in a period where the delta variant was predominant.

The number of participants in the current clinical development program is too small to detect any potential risks of myocarditis associated with vaccination. Long-term safety of COVID-19 vaccine in participants 5 to <12 years of age will be studied in 5 post-authorization safety studies, including a 5-year follow-up study to evaluate long term sequelae of post-vaccination myocarditis/pericarditis.

Israeli safety surveillance databases suggest that incidence rates of rare post-vaccination myocarditis peaks in individuals 16 to 19 years of age males and declines in adolescents 12 to 15 years of age. In addition, the dose for children 5 to <12 years of age is 1/3 of the dose given to older vaccinees (10 µg vs. 30 µg). Based on this information, it is reasonable to predict that post-vaccine myocarditis rates are likely to be even lower in 5 to <12 years of age than those observed in adolescents 12 to 15 years of age.

Source : https://www.fda.gov/media/153409/download

Contrary to what has been publicly conveyed, myocarditis/pericarditis are far from benign, and thus it was essential to study their sequelae for a duration of 5 YEARS.

This report from October 2021 reiterated this safety signal identified several months prior as a "significant risk":

« *Myocarditis/pericarditis is considered an important identified risk of the vaccine in the Pharmacovigilance Plan; however, the very low incidence and favorable prognosis of these events compared to the known risks of COVID 19, including COVID-19 associated myocarditis, support a positive benefit/risk profile for this vaccine in the 5 to < 12 years of age group*. »

Illustration 132 : Pfizer - October 26, 2021 Clinical Study Report on 5-11 year old – Section 6. 5. POST-AUTHORIZATION SAFETY UPDATE

> Myocarditis/pericarditis is considered an important identified risk of the vaccine in the Pharmacovigilance Plan; however, the very low incidence and favorable prognosis of these events compared to the known risks of COVID 19, including COVID-19 associated myocarditis, support a positive benefit/risk profile for this vaccine in the 5 to <12 years of age group.

In summary,

In October 2021, the results regarding children aged 5 to 11 years allow for the following conclusions:

- Follow-up duration for children was 2 months median.
- No statistically demonstrated efficacy on the **transmission** of SARS-CoV-2, as it was not studied.
- No statistically demonstrated efficacy on **severe cases**.
- No statistically demonstrated efficacy in certain high-risk populations for severe COVID-19.
- No statistically demonstrated efficacy **against asymptomatic** infections.
- No statistically demonstrated efficacy **in individuals already infected with SARS-CoV-2**.
- The criterion for the number of COVID-19 cases is uncertain due to numerous potential biases.
- No statistically demonstrated efficacy against COVID-19 mortality.
- No demonstrated efficacy of the vaccine **against the long-term effects of COVID-19**.
- Duration of protection is unknown.
- Small sample size does not allow for the detection of rare severe adverse effects.
- Estimation of the risks of myocarditis/pericarditis is based on "**predictions**."

"*Based on this information, it is reasonable to predict that the rates of post-vaccination myocarditis will likely be even lower in children aged 5 to <12 years than those observed in adolescents aged 12 to 15 years*."

Risk assessment must rely on evidence, not predictions.

Despite all the persistent unknowns and the proven risk of serious pathologies such as myocarditis and pericarditis in young individuals, the FDA granted emergency use authorization for children aged 5 to 11 years on October 29, 2021, followed by the EMA on November 26, 2021.

https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age

https://www.ema.europa.eu/en/news/comirnaty-COVID-19-vaccine-ema-recommends-approval-children-aged-5-11

9 June 14-15, 2022 Clinical Study Report on 6 Months to < 5 Years old

The C4591007 study is an ongoing, randomized, placebo-controlled phase 1/2/3 pediatric trial conducted in healthy children aged 6 months to under 12 years.

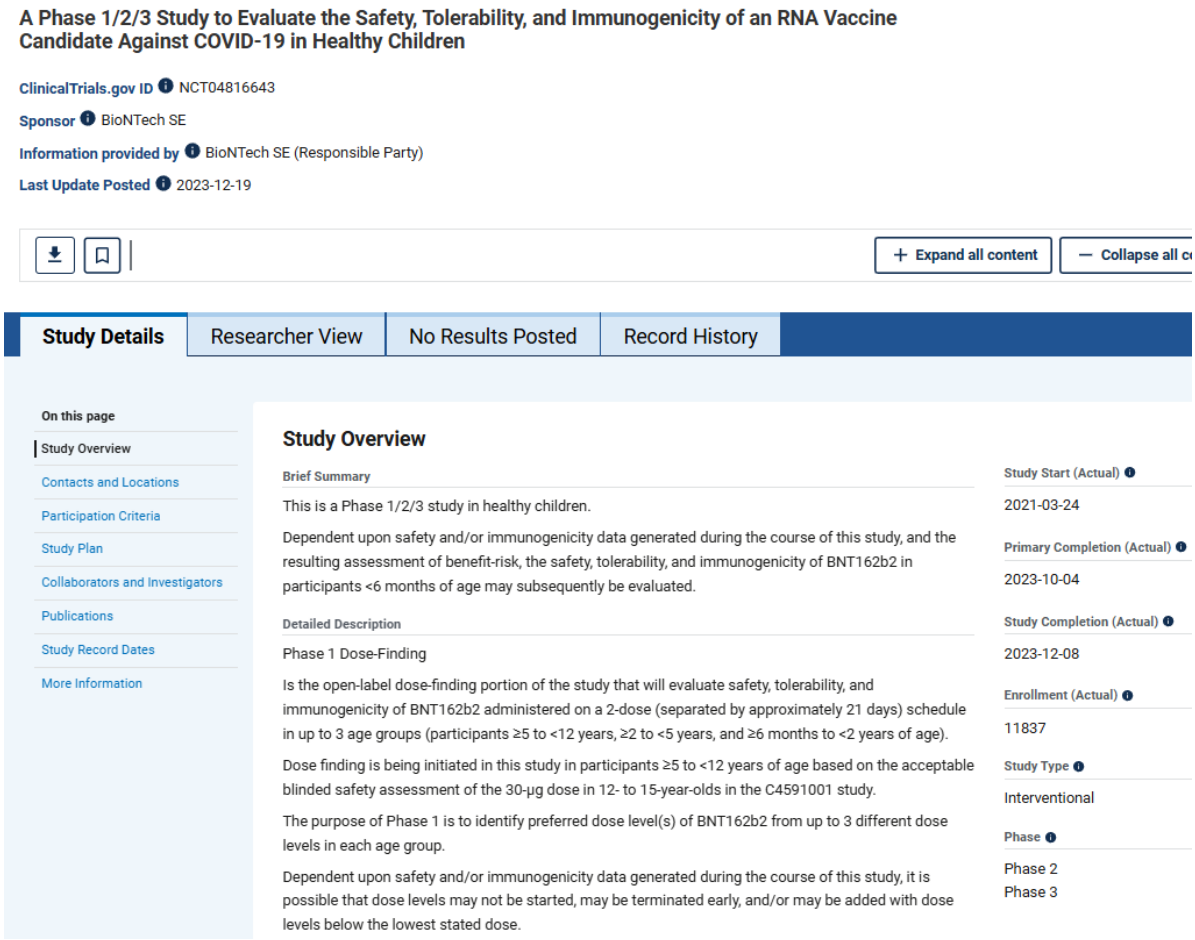
The primary objective of immunogenicity for phase 2/3 in children aged 6 months to under 5 years was to compare the immune responses against the wild-type SARS-CoV-2 strain between children aged 2 to under 5 years and those aged 6 months to under 2 years in the C4591007 study with those of young adults aged 16 to 25 years in the phase 3 efficacy study C4591001.

The administered dose was 3 µg.

https://clinicaltrials.gov/study/NCT04816643?term=C4591007&rank=1

The trial began on March 24, 2021, and concluded on December 8, 2023.

Illustration 133 : Clinicaltrial – Registration of the pediatric trial



A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children

ClinicalTrials.gov ID NCT04816643
Sponsor BioNTech SE
Information provided by BioNTech SE (Responsible Party)
Last Update Posted 2023-12-19

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Study Details | Researcher View | No Results Posted | Record History

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Study Overview

Brief Summary

This is a Phase 1/2/3 study in healthy children.

Dependent upon safety and/or immunogenicity data generated during the course of this study, and the resulting assessment of benefit-risk, the safety, tolerability, and immunogenicity of BNT162b2 in participants <6 months of age may subsequently be evaluated.

Detailed Description

Phase 1 Dose-Finding

Is the open-label dose-finding portion of the study that will evaluate safety, tolerability, and immunogenicity of BNT162b2 administered on a 2-dose (separated by approximately 21 days) schedule in up to 3 age groups (participants ≥5 to <12 years, ≥2 to <5 years, and ≥6 months to <2 years of age).

Dose finding is being initiated in this study in participants ≥5 to <12 years of age based on the acceptable blinded safety assessment of the 30-µg dose in 12- to 15-year-olds in the C4591001 study.

The purpose of Phase 1 is to identify preferred dose level(s) of BNT162b2 from up to 3 different dose levels in each age group.

Dependent upon safety and/or immunogenicity data generated during the course of this study, it is possible that dose levels may not be started, may be terminated early, and/or may be added with dose levels below the lowest stated dose.

Study Start (Actual) 2021-03-24

Primary Completion (Actual) 2023-10-04

Study Completion (Actual) 2023-12-08

Enrollment (Actual) 11837

Study Type Interventional

Phase Phase 2 Phase 3

The clinical report from June 14-15, 2022, distinguishes between two populations: children aged 2 to less than 5 years and children aged 6 months to less than 2 years.

Unlike other trials, **infants** and young children received **three** doses of BNT162b2 directly, as the first two doses were found to be ineffective, as previously demonstrated.

There are 2,750 participants aged 2 to <5 years, with 1,835 receiving BNT162b2 and 915 receiving the placebo. For the younger group, the phase 2/3 trial includes 1,776 participants, with 1,178 receiving BNT162b2 and 598 receiving the placebo. The randomization design is 2:1, meaning there are twice as many participants receiving the vaccine as those receiving the placebo, which is a common design in clinical trials.

As in previous reports, the results stem from an **interim analysis.**

The children were monitored for only a **median duration of 2 months**, with 95.1% being observed between 2 and 3 months, and a maximum observation period of 2 and a half months.

Illustration 134 : Pfizer - June 14-15, 2022 Clinical Study Report - Participants' follow-up for children 2 to < 5 years of age

3.5.1.1. Children 2 to <5 Years of Age

The safety population of 2750 Phase 2/3 participants 2 to <5 years of age reflected the 2:1 randomization in the BNT162b2 (N=1835) and placebo (N=915) groups. No participants in the safety population were excluded from the study.

Duration of Follow-up

The median duration of blinded follow-up for children 2 to <5 years of age after Dose 3 (N=886) was 1.4 months (range: 0.0 to 3.2 months). Combining the blinded and open-label periods, the median duration of follow-up after Dose 3 (N=1321) was 2.1 months (range: 0.0 to 3.2 months). The median duration of blinded follow-up after Dose 2 to Dose 3 (or data cutoff) was 4.0 months (range: 0.0 to 10.4 months), similar for both the BNT162b2 and placebo groups. The median duration of follow-up including both blinded and open-label follow-up (N=2727) was 4.3 months (range: 0.0 to 10.4 months), similar for both the BNT162b2 and placebo groups.

Illustration 135 : Pfizer - June 14-15, 2022 Clinical Study Report - Participants' follow-up for children 6 months to < 2 years of age

3.5.1.2. Children 6 Months to <2 Years of Age

The safety population of 1776 Phase 2/3 participants 6 months to <2 years of age reflected the 2:1 randomization in the BNT162b2 (N=1178) and placebo (N=598) groups. No participants in the safety population were excluded from the study.

Duration of Follow-up

The median duration of blinded follow-up for children 6 months to <2 years of age after Dose 3 (N=570) was 1.3 months (range: 0.0 to 3.2 months). Combining the blinded and open-label periods, the median duration of follow-up after Dose 3 (N=942) was 2.1 months (range: 0.0 to 3.2 months). The median duration of blinded follow-up after Dose 2 to Dose 3 (or data cutoff) was 6.3 months (range: 0.1 to 10.4 months), similar for both the BNT162b2 and placebo groups. The median duration of follow-up including both blinded and open-label follow-up (N=1763) was 6.3 months (range: 0.1 to 10.4 months).

Source : https://www.fda.gov/media/159193/download

Efficacy was evaluated at least 7 days after dose 2 and before dose 3 for the product administered to children aged 6 months to under 5 years without prior evidence of SARS-CoV-2 infection before or during the vaccination schedule (pages 51 to 56).

- For children aged 2 to under 5 years, there were 163 cases of COVID-19 in the BNT162b2 group and 113 cases in the placebo group, resulting in a vaccine efficacy of **28.3%.** The actual efficacy ranged between 8.0% and 43.9%, as indicated by the 95% confidence interval.
- For children aged 6 months to under 2 years, there were 73 cases in the BNT162b2 group and 44 cases in the placebo group, resulting in an efficacy of **16.1%,** with actual efficacy ranging from -24.9% to 43.1%. Therefore, no statistically significant efficacy was demonstrated for this age group.

Illustration 136 : Pfizer - June 14-15, 2022 Clinical Study Report – Efficacy results – Symptomatic COVID-cases

3.7.3.1. Total Population of Children 6 Months to <5 Years of Age

The observed VE from at least 7 days after Dose 2 to before Dose 3 for BNT162b2 3-µg administered to children 6 months to <5 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was 28.3% (2-sided 95% CI: 8.0%, 43.9%) based on 163 cases in the BNT162b2 group and 113 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo) (Table 4). In this population, observed VE against Delta and Omicron was 70.2% (2-sided 95% CI: 27.2%, 88.5%) and 21.8% (2-sided 95% CI: -1.7%, 39.7%), respectively (Table 4). Note that most of the cases across this age population that were confirmed post-Dose 2 to before Dose 3 were reported in January 2022.

Similar VE was observed from at least 7 days after Dose 2 to before Dose 3 for children 6 months to <5 years of age with or without prior evidence of SARS-CoV-2 infection (Table 4).

3.7.3.2. Children 2 Years to <5 Years of Age

The observed VE from at least 7 days after Dose 2 to before Dose 3 for BNT162b2 3-µg administered to children 2 to <5 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was 35.9% (2-sided 95% CI: 11.0%, 53.7%) based on 90 cases in the BNT162b2 group and 69 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization of vaccine:placebo) (Table 4). In this population, observed VE against Delta and Omicron was 56.3% (2-sided 95% CI: -27.5%, 85.3%) and 32.9% (2-sided 95% CI: 4.7%, 52.5%), respectively (Table 4). Note that most cases that were confirmed post-Dose 2 to before Dose 3 were reported in January 2022.

Source : https://www.fda.gov/media/159193/download

For children aged 2 to under 5 years, the observed vaccine efficacy against the Delta and Omicron variants was **70.2%** (95% bilateral CI: 27.2%, 88.5%) and **21.8%** (95% bilateral CI: -1.7%, 39.7%), meaning **no demonstrated efficacy against the Omicron variant**.

For children aged 6 months to under 2 years, the observed vaccine efficacy against the Delta and Omicron variants was **56.3%** (95% bilateral CI: -27.5%, 85.3%) and **32.9%** (95% bilateral CI: 4.7%, 52.5%), meaning no statistically significant efficacy was demonstrated against Delta.

Illustration 137 : Pfizer - June 14-15, 2022 Clinical Study Report – Efficacy results – Symptomatic COVID-cases on variants

Table 4. Vaccine Efficacy – First COVID-19 Occurrence from 7 Days After Dose 2 to Before Dose 3 – Blinded Follow-Up Period – Phase 2/3 – Dose 2 Evaluable Efficacy Population

	6 Months to <5 Years of Age		2 to <5 Years of Age		6 Months to <2 Years of Age	
Participants Without Prior Evidence of SARS-CoV-2 Infection						
	Case Split (BNT162b2:Placebo)	VE (2-sided 95% CI)	Case Split (BNT162b2:Placebo)	VE (2-sided 95% CI)	Case Split (BNT162b2:Placebo)	VE (2-sided 95% CI)
Overall VE	163:113	28.3% (8.0%, 43.9%)	90:69	35.9% (11.0%, 53.7%)	73:44	16.1% (-24.9%, 43.1%)
VE against Delta	9:15	70.2% (27.2%, 88.5%)	8:9	56.3% (-27.5%, 85.3%)	1:6	91.6% (30.6%, 99.8%)
VE against Omicron	154:98	21.8% (-1.7%, 39.7%)	82:60	32.9% (4.7%, 52.5%)	72:38	4.2% (-45.9%, 36.2%)
Participants With or Without Prior Evidence of SARS-CoV-2 Infection						
Overall VE	173:120	27.0% (7.1%, 42.5%)	97:73	34.3% (9.7%, 52.0%)	76:47	15.6% (-24.2%, 42.1%)
VE against Delta	10:15	66.3% (19.7%, 86.4%)	8:9	56.0% (-28.4%, 85.2%)	2:6	82.6% (2.7%, 98.3%)
VE against Omicron	163:105	21.4% (-1.4%, 38.9%)	89:64	31.2% (3.6%, 50.7%)	74:41	5.7% (-41.6%, 36.5%)

Source : https://www.fda.gov/media/159193/download

Regarding severe COVID-19 cases, 7 were reported: 6 in the group of children who received BNT162b2 and 1 in the placebo group. Considering the 2:1 randomization, this means there were three times as many children experiencing severe cases after being vaccinated with BNT162b2

Illustration 138 : Pfizer - June 14-15, 2022 Clinical Study Report – Efficacy results – Severe COVID-19 cases

Severe COVID-19 and MIS-C

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children to have very high sensitivity to alert for any potential severe illness) were fulfilled for 7 cases (6 BNT162b2 and 1 placebo [taking into account 2:1 randomization]) among children 2 to <5 years of age. Of these, 5/6 cases in the BNT162b2 group fulfilled a single criterion of increased heart rate or respiratory rate and 1 case in the placebo group fulfilled a single criterion of decreased SpO_2 (88% on room air); all occurred post-Dose 2 (Table 5). Note that in 2 such cases in the BNT162b2 group, the participants reported illness after they were unblinded, which could have introduced potential bias.

Table 5. Characterization of Cases Assigned as Severe That Met FDA Criteria: Children 2 to <5 Years of Age

Group	Age	Timing*	Severity Criteria Met	Severity Range	Meets CDC Criteria	Coinfection
BNT162b2	4 years	32 days	HR=132	>131	No	
BNT162b2	4 years	62 days	RR=32	>29	No	
BNT162b2	3 years	183 days	RR=32	>29	No	
BNT162b2	3 years	208 days	RR-32	>29	No	
BNT162b2	2 years	44 days	HR=150	>142	No	
BNT162b2	2 years	100 days	HR=150 RR=40 SpO2=91% Hospitalization	>142 >38 ≤92%	Yes (Hospitalization)	Parainfluenza virus type 3
Placebo	2 years	162 days	SpO2=88%	≤92%	No	

* All cases occurred post-Dose 2
Highlighted row (gray) presents case information for the only participant who fulfilled >1 severity criterion per protocol pediatric-modified FDA definition and including CDC criterion of hospitalization. This participant had coinfection with parainfluenza virus type 3, and clinical assessment included reported wheezing and salbutamol administration.
HR=heart rate, RR=respiratory rate, SpO_2=oxygen saturation

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Source : https://www.fda.gov/media/159193/download

The second document presented that day, titled "*FDA Briefing Document - Amendment Request for the EUA of the Pfizer-BioNTech COVID-19 Vaccine for Children 6 Months through 4 Years of Age*" is also available on the FDA website at the following link : https://www.fda.gov/media/159195/download

In section « ***6.2. Uncertainties Related to Benefits*** » (page 59), it is stated:

The uncertainties associated with benefits of the Pfizer-BioNTech COVID-19 vaccine when used in children 6 months through 4 years of age include the following:

- *Duration of vaccine effectiveness: the blinded, placebo-controlled evaluation period for descriptive efficacy analyses was **limited**, and **waning of protection** following a primary series has been observed in older age groups.*

- *Need for a booster dose: based on experience with adults, it is likely that a **booster dose will be needed in addition to the three-dose primary series to increase robustness**, breadth, and duration of protection against currently circulating and emerging SARS-CoV-2 variants in children 6 months through 4 years of age. A booster dose could be considered for authorization with submission of supportive data in a future amendment to the EUA.*

- *Effectiveness **in certain populations at high risk of severe COVID-19**, including immunocompromised individuals.*

- *Benefits in individuals previously infected with SARS-CoV-2: descriptive post-Dose 3 efficacy analyses do not include cases in previously infected participants. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred by natural immunity.53 Additionally, for individuals previously infected with the Omicron variant of SARS-CoV-2, a vaccine based on the ancestral strain S protein could provide a greater breadth of protection against SARS-CoV-2 variants.*

- *Effectiveness **in preventing post-acute sequelae of COVID-19**: available data are not conclusive on the effectiveness of COVID-19 vaccines currently in use against long-term sequelae of COVID-19 among individuals who are infected despite vaccination. Additional evaluation is needed to assess the effect of this vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.*

- ***Future vaccine effectiveness** as influenced by characteristics of the pandemic, including emergence of new variants: the continued evolution of the pandemic, including changes in the virus infectivity, antigenically significant mutations to the S protein, and changes in practice of nonpharmacologic interventions to mitigate against transmission, will likely influence vaccine effectiveness over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical.*

- ***Vaccine effectiveness <u>against asymptomatic infection and transmission</u> of SARS-CoV-2****: Available data for COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against symptomatic COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections*

Illustration 139 : Pfizer - June 14-15, 2022 Clinical Study Report – Résultats d'efficacité – Uncertainties Related to Benefits

VRBPAC Briefing Document: Pfizer-BioNTech COVID-19 Vaccine EUA Amendment for Use in Children 6 Months Through 4 Years of Age

6.2. Uncertainties related to benefits

The uncertainties associated with benefits of the Pfizer-BioNTech COVID-19 vaccine when used in children 6 months through 4 years of age include the following:

- Duration of vaccine effectiveness: the blinded, placebo-controlled evaluation period for descriptive efficacy analyses was limited, and waning of protection following a primary series has been observed in older age groups.
- Need for a booster dose: based on experience with adults, it is likely that a booster dose will be needed in addition to the three-dose primary series to increase robustness, breadth, and duration of protection against currently circulating and emerging SARS-CoV-2 variants in children 6 months through 4 years of age. A booster dose could be considered for authorization with submission of supportive data in a future amendment to the EUA.
- Effectiveness in certain populations at high risk of severe COVID-19, including immunocompromised individuals.
- Benefits in individuals previously infected with SARS-CoV-2: descriptive post-Dose 3 efficacy analyses do not include cases in previously infected participants. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred by natural immunity.[53] Additionally, for individuals previously infected with the Omicron variant of SARS-CoV-2, a vaccine based on the ancestral strain S protein could provide a greater breadth of protection against SARS-CoV-2 variants.
- Effectiveness in preventing post-acute sequelae of COVID-19: available data are not conclusive on the effectiveness of COVID-19 vaccines currently in use against long-term sequelae of COVID-19 among individuals who are infected despite vaccination. Additional evaluation is needed to assess the effect of this vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.
- Future vaccine effectiveness as influenced by characteristics of the pandemic, including emergence of new variants: the continued evolution of the pandemic, including changes in the virus infectivity, antigenically significant mutations to the S protein, and changes in practice of nonpharmacologic interventions to mitigate against transmission, will likely influence vaccine effectiveness over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical.
- Vaccine effectiveness against asymptomatic infection and transmission of SARS-CoV-2: Available data for COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against symptomatic COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections.

Here (section 6.3. Known and potential risks), we find a number of uncertainties previously mentioned in earlier reports, namely: no data on immunocompromised individuals, no demonstrated efficacy against asymptomatic infection, no demonstrated efficacy against transmission... yet, the plan now is **to administer a fourth dose** to infants and young children because protection wanes within a few months.

« *The uncertainties associated with risks of the Pfizer-BioNTech COVID-19 vaccine when used in children 6 months through 4 years of age include the following:*

- ***Risk of myocarditis/pericarditis**, as described in detail in Section 6.3 above, including:*
  - *Incidence of myocarditis/pericarditis in children 6 months through 4 years of age.*
  - *Short-term and potential long-term sequelae and outcomes in affected individuals*
  - *Whether the vaccine is associated with subclinical myocarditis, and if so, whether there are long-term sequelae.*
  - *Mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.*

- *Safety in certain subpopulations*
  - *Available data are insufficient to make conclusions about the safety of the vaccine in certain subpopulations such as immunocompromised children.*
  - *Safety data in children previously infected with SARS-CoV-2 are limited; however, available data do not suggest increased reactogenicity or other safety concerns among previously infected children.*
- *Adverse reactions that are very uncommon or that require longer follow-up to be detected. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals, Section 5, Pharmacovigilance Activities* »

Illustration 140 : Pfizer - June 14-15, 2022 Clinical Study Report - Participants' follow-up for children 2 to < 5 years of age

6.4. Uncertainties related to risks

The uncertainties associated with risks of the Pfizer-BioNTech COVID-19 vaccine when used in children 6 months through 4 years of age include the following:

- Risk of myocarditis/pericarditis, as described in detail in Section 6.3 above, including:
  - Incidence of myocarditis/pericarditis in children 6 months through 4 years of age.
  - Short-term and potential long-term sequelae and outcomes in affected individuals
  - Whether the vaccine is associated with subclinical myocarditis, and if so, whether there are long-term sequelae.
  - Mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.
- Safety in certain subpopulations
  - Available data are insufficient to make conclusions about the safety of the vaccine in certain subpopulations such as immunocompromised children.
  - Safety data in children previously infected with SARS-CoV-2 are limited; however, available data do not suggest increased reactogenicity or other safety concerns among previously infected children.
- Adverse reactions that are very uncommon or that require longer follow-up to be detected. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals, Section 5, Pharmacovigilance Activities.

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In summary,

As of June 2022, the results for children aged 2 to under 5 years and children aged 6 months to under 2 years can be summarized as follows:

- The follow-up duration for the children was only three months maximum, despite their immune system being different from that of adults.

- The efficacy results regarding the number of COVID-19 cases were very poor.
    - For children aged 2 to under 5 years, the reported efficacy was **28.3%**, but the actual efficacy ranged from **8.0% to 43.9%,** as indicated by the 95% confidence interval. The threshold set by the FDA for authorization is 50%.

    - For children aged 6 months to under 2 years, the efficacy was **16.1%**, with the actual efficacy ranging from **-24.9% to 43.1%.** Therefore, **no statistically significant efficacy was demonstrated** in this age group.
- No demonstrated efficacy against the Delta and Omicron variants overall.
- No statistically demonstrated efficacy on the **transmission** of SARS-CoV-2, as it was not studied.
- No statistically demonstrated efficacy **on severe cases**, with more severe cases observed in the vaccine group.
- No statistically demonstrated efficacy **against asymptomatic infections**.
- No statistically demonstrated efficacy **in individuals already infected with SARS-CoV-2**.
- No statistically demonstrated efficacy **against COVID-19 mortality**.
- No demonstrated efficacy **in certain high-risk populations** for severe COVID-19, including immunocompromised individuals.
- **Unknown duration of protection**.
- **Waning protection**, leading to the need for a fourth dose.
- **Small sample size, insufficient** to detect rare serious adverse events.

Despite these ongoing uncertainties and the emerging risk of myocarditis/pericarditis in young individuals, along with limited knowledge about the mechanism of occurrence and the potential short- and long-term consequences, the FDA approved the emergency use authorization for children aged 6 months to 5 years on October 29, 2022.

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-biontech-covid-19-vaccine-receives-fda-emergency-use

The fact sheet for healthcare providers is no longer available at the original link but can still be accessed via archived sites.

https://web.archive.org/web/20220622010134/https://www.fda.gov/media/159313/download

In the section "WHAT ARE THE RISKS OF THE VACCINE?" the manufacturer stated:

"There is a small risk that the vaccine may cause a severe allergic reaction. A severe allergic reaction typically occurs within minutes to an hour after receiving a dose of the vaccine. This is why the vaccinator may ask your child to stay at the vaccination site for monitoring after the vaccination.

Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the outer lining of the heart) have occurred in some people who have received the vaccine. In most of these individuals, symptoms appeared within a few days after receiving the second dose of the vaccine. The risk of this happening is very low. You should seek medical attention right away if your child experiences any of the following symptoms after receiving the vaccine."

The EMA approved the use of the vaccine for young children on October 19, 2022.

https://www.ema.europa.eu/en/news/ema-recommends-approval-comirnaty-and-spikevax-covid-19-vaccines-children-6-months-age

This raises serious questions about the methods used to evaluate the benefit-risk ratio.

10 Trials on bivalent vaccines

Regarding the bivalent vaccines, two new vaccines have been developed:

- The first contains the RNA sequence of the Spike protein from the Wuhan strain of SARS-CoV-2, to which the RNA sequence of the Omicron BA.1 variant has been added.
- The second is based on the Wuhan strains and the BA.4 and BA.5 variants.

The opinion of the HAS titled "Vaccination Strategy Against COVID-19 - Role of the Comirnaty Bivalent Vaccines Original/Omicron BA.1 and Original/Omicron BA.4-5" dated September 19, 2022, indicates in the section "**2.3.1. Overview of Studies Conducted in the Development of the Bivalent Vaccine (Original and BA.1)"**

"*The clinical development of the Comirnaty bivalent vaccine (Original/Omicron BA.1 15/15 µg) is primarily based on two randomized, double-blind clinical trials. These trials mainly aim to evaluate the immunogenicity and safety of the bivalent vaccine in subjects aged 55 years and older who have received three doses (primary vaccination with two doses and one booster dose) of Comirnaty (Wuhan strain).*"

Illustration 141 : HAS – Opinion of September 19, 2022 – Objectives of the Trials

2.3. Présentation des données disponibles

2.3.1. Panorama des études réalisées dans le cadre du développement du vaccin bivalent (Original et BA.1)

Le développement clinique du vaccin Comirnaty bivalent Original/Omicron BA.1 15/15 µg) repose essentiellement sur deux essais cliniques, randomisés en aveugle. Ces essais visent principalement à évaluer l'immunogénicité et la tolérance du vaccin bivalent chez les sujets de 55 ans et plus ayant été vaccinés avec trois doses (primovaccination à deux doses et une dose de rappel) de Comirnaty (souche Wuhan) (cf. Tableau 1).

Source : Avis de la HAS du 19 septembre 2022: Place des vaccins contre la Covid-19 Cominarty bivalents Original/Omicron BA.1 et Original/Omicron BA.4-5

https://www.has-sante.fr/upload/docs/application/pdf/2022-09/rapport_evaluation_place_des_vaccins_cominarty_bivalents_original.omicron_ba.1_et_origninal._omicron_ba.4-5.pdf

In the "Role of the Comirnaty Original/Omicron BA.1 and Original/Omicron BA.4-5 Vaccines in the COVID-19 Vaccination Strategy" section, the "*HAS concludes that the Comirnaty Original/Omicron BA.1 15/15 µg vaccine demonstrates* ***greater immunogenicity*** *against the SARS-CoV-2 virus (original strain and Delta, Omicron BA.1 variants) with similar reactogenicity compared to the monovalent Comirnaty vaccine when administered as a booster dose in adults who have received two doses and a booster of the Original Comirnaty vaccine.* ***However, in the absence of an established protection threshold for COVID-19, neutralizing antibody titers cannot be directly extrapolated to the level of protection conferred by vaccination.*****"**

Illustration 142 : HAS - Opinion of September 19, 2022 – – Vaccin Comirnaty Original / Omicron :Conclusion

Place des vaccins Comirnaty Original/Omicron BA.1 et Original/Omicron BA.4-5 dans la stratégie vaccinale contre la Covid-19

La HAS **conclut** à une immunogénicité plus importante du vaccin Comirnaty Original/Omicron BA.1 15/15 µg contre le virus SARS-CoV-2 (souche originale et variants Delta, Omicron BA.1) et une réactogénicité similaire par rapport au vaccin monovalent Comirnaty, lorsqu'il est administré en dose de rappel chez les adultes ayant reçu deux doses et un rappel du vaccin Comirnaty Original. En l'absence de seuil de protection établi à ce jour pour la Covid-19, les titres d'anticorps neutralisants ne peuvent toutefois pas être directement extrapolés à la protection conférée par la vaccination.

This opinion indicates that the increase in antibodies does not necessarily mean that vaccinated individuals will be protected. Regarding the bivalent Comirnaty Original/Omicron BA.4-5 vaccine, the opinion states, "*this evaluation procedure was based on more limited (preclinical) data and allows for the rapid availability of a vaccine, without the ability to quantify any potential gain in clinical efficacy*."

Conclusion, <u>no efficacy statistically proven</u> for bivalent Orignal/ Omicron BA.4-5 vaccine.

Illustration 143 : HAS – Opinion of September 19, 2022 – Vaccin Comirnaty Orignal / Omicron :Conclusion

- Il n'y a pas eu d'étude de *challenge* (infection expérimentale par le SARS-CoV-2) post-vaccination chez les souris pour mesurer l'efficacité vaccinale ;
- Il n'existe pas de données de comparaison directe de l'immunogénicité entre les vaccins adaptés BA.1 et BA.4-5 ;
- Cependant, les vaccins à ARNm bivalents ne sont pas des nouveaux vaccins, mais des vaccins adaptés aux souches circulantes, à l'instar des vaccins contre la grippe saisonnière. Ainsi, la plateforme vaccinale est la même, la quantité totale d'ARNm par dose également (la moitié codant pour la protéine spike de la souche ancestrale, la moitié contre la protéine spike correspondant aux différents sous-variants d'Omicron (BA.1 ou BA.4-5). **Il s'agit d'une variation du vaccin visant à développer des anticorps les plus adaptés aux variants circulants. Cette procédure d'évaluation, basée sur des données plus limitées que lors d'une évaluation initiale, permet d'assurer la mise à disposition très rapide des vaccins les plus adaptés au contexte épidémiologique et à la souche circulante.**
- Le laboratoire fournira des données cliniques complémentaires d'immunogénicité et de tolérance du vaccin bivalent BA.4-5 post AMMc.

Source :

https://www.has-sante.fr/upload/docs/application/pdf/2022-09/rapport_evaluation_place_des_vaccins_cominarty_bivalents_original.omicron_ba.1_et_origninal._omicron_ba.4-5.pdf

Regarding pregnant women, there is no additional data beyond what is available for the original vaccine.

*« **No data is yet available regarding the use of Comirnaty Original/Omicron BA.1 during pregnancy**. However, a large body of observational data on pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimesters of pregnancy has not shown any harmful effects on pregnancy. Although data on pregnancy outcomes following vaccination during the first trimester is limited, no increased risk of miscarriage has been observed. Animal studies have not shown direct or indirect harmful effects on gestation, embryo-fetal development, delivery, or postnatal development. Given that the differences between the products are limited to the Spike protein sequence and that no clinically significant differences in terms of reactogenicity have been identified, Comirnaty Original/Omicron BA.1 can be used during pregnancy.*

I would like to remind that clinical research **regulations require products to be tested in the context of clinical trials, not in real-world settings !**

Illustration 144 : HAS – Opinion of September 19, 2022 - Bivalents - Pregancy

2.2.4. Précautions d'emploi

2.2.4.1. Grossesse

Aucune donnée n'est encore disponible concernant l'utilisation de Comirnaty Original/Omicron BA.1 pendant la grossesse.

Cependant, un grand nombre de données observationnelles chez les femmes enceintes vaccinées par le vaccin Comirnaty initialement approuvé au cours du deuxième et du troisième trimestre de grossesse n'a pas mis en évidence de conséquences néfastes pour la grossesse. Bien que les données sur l'issue des grossesses après une vaccination au cours du premier trimestre de grossesse soient limitées, aucune augmentation du risque de fausse couche n'a été observée. Les études effectuées chez l'animal n'ont pas mis en évidence d'effets délétères directs ou indirects sur la gestation, le développement embryo-fœtal, la mise-bas ou le développement postnatal. Étant donné que les différences entre les produits se limitent à la séquence de la protéine Spike et qu'il n'existe aucune différence cliniquement significative en termes de réactogénicité, Comirnaty Original/Omicron BA.1 peut être utilisé pendant la grossesse.

2.2.4.2. Allaitement

Aucune donnée n'est encore disponible concernant l'utilisation de Comirnaty Original/Omicron BA.1 pendant l'allaitement.

Source : https://www.has-sante.fr/upload/docs/application/pdf/2022-09/rapport_evaluation_place_des_vaccins_cominarty_bivalents_original.omicron_ba.1_et_origninal._omicron_ba.4-5.pdf

On October 11, 2022, the Strategic Advisory Group of Experts (SAGE), a group of experts advising the WHO on global vaccination policies and strategies, noted that the **available data was insufficient**.

Here is part of their statement, which can be found in its entirety in the attached document, specifically on page 17.

«Four bivalent variant-containing mRNA vaccines developed by Pfizer-BioNTech and Moderna are currently authorized for use as booster doses in several countries. They contain mRNA of the ancestral virus strain in combination with mRNA of either the BA.1 or BA.4/5 sub-lineages of the Omicron variant. Immunogenicity studies showed that variant-containing bivalent vaccines induced a superior antibody response against the Omicron BA.1 sub-lineage

compared with the original vaccines and non-inferior immunogenicity against the pre-Omicron variants and the ancestral virus. »

In this document, the Strategic Advisory Group of Experts (SAGE) noted the absence of results on the usual efficacy criteria (number of COVID-19 cases, number of severe cases, etc.) and reiterated the lack of proven correlation between the level of neutralizing antibodies and the occurrence of infections.

*« SAGE noted the absence of data on the effect of the variant-containing COVID-19 vaccines on **infection or disease outcomes**. While neutralization antibody levels have been shown to be predictive of immune protection, it is **unknown** whether the modestly superior immunogenicity results of the variant-containing products will translate into improved clinical effectiveness compared with products containing only the ancestral strain, and whether this will differ by disease outcome (severe versus non-severe COVID-19) or among the 4 currently available variant-containing vaccines. »*

In clear terms, since the occurrence of the disease was not studied in the trials, it has not been demonstrated that the bivalent vaccines are superior to the vaccines developed based on the original strain, which have been shown to have no effect on the variants.

Illustration 145 : Strategic Advisory Group of Experts (SAGE) of October 11, 2022

duration of protection following a second booster dose, but a similar waning pattern is observed.

Four bivalent variant-containing mRNA vaccines developed by Pfizer-BioNTech and Moderna are currently authorized for use as booster doses in several countries. They contain mRNA of the ancestral virus strain in combination with mRNA of either the BA.1 or BA.4/5 sub-lineages of the Omicron variant. Immunogenicity studies showed that variant-containing bivalent vaccines induced a superior antibody response against the Omicron BA.1 sub-lineage compared with the original vaccines and non-inferior immunogenicity against the pre-Omicron variants and the ancestral virus. Data indicate that the immune responses induced by such Omicron variant-containing vaccine boosters induce cross-neutralizing antibody activity against the Omicron sub-lineages not included in the vaccine, although the effect varies between the vaccines.

SAGE noted the absence of data on the effect of the variant-containing COVID-19 vaccines on infection or disease outcomes. While neutralization antibody levels have been shown to be predictive of immune protection, it is unknown whether the modestly superior immunogenicity results of the variant-containing products will translate into improved clinical effectiveness compared with products containing only the ancestral strain, and whether this will differ by disease outcome (severe versus non-severe COVID-19) or among the 4 currently available variant-containing vaccines.

SAGE noted that no studies have been conducted using variant-containing vaccines for the primary vaccination series. Until supportive evidence or regulatory approval becomes available, variant-containing vaccines should not be used for the primary series; rather, any of the WHO EUL COVID-19 vaccines should be used. SAGE reiterated the priority to achieve high and equitable rates of primary series vaccination with ancestral strain vaccines.

Following completion of the primary series, booster doses should be offered in accordance with WHO's prioritization roadmap.[13] Currently available data are not sufficient to support a preferential recommendation for selecting a bivalent variant-containing vaccine booster over ancestral-virus-only vaccine boosters.

de la protection après une deuxième dose de rappel sont moins nombreuses, mais on observe une tendance à la baisse similaire.

Quatre vaccins bivalents contenant également l'ARNm d'un variant, mis au point par Pfizer-BioNTech et Moderna, sont actuellement autorisés dans le cadre de la vaccination de rappel dans plusieurs pays. Ils contiennent l'ARNm de la souche virale ancestrale et celui de la sous-lignée BA.1 ou BA.4/5 du variant Omicron. Les études d'immunogénicité ont montré que ces vaccins bivalents induisaient une réponse en anticorps supérieure contre la sous-lignée BA.1 d'Omicron par rapport aux vaccins d'origine et une immunogénicité non inférieure contre les variants antérieurs à Omicron et le virus ancestral. Les données indiquent que les réponses immunitaires induites par les doses de rappel de vaccins contenant l'ARNm de ces sous-lignées du variant Omicron donnent lieu à une activité croisée des anticorps neutralisants contre des sous-lignées d'Omicron non ciblées par le vaccin, bien que cet effet varie d'un vaccin à l'autre.

Le SAGE a remarqué l'absence de données relatives à l'effet des vaccins anti-COVID-19 ciblant des variants sur l'infection ou l'issue de la maladie. Bien qu'il ait été démontré que les taux d'anticorps neutralisants permettent de prédire une protection immunitaire, on ne sait pas si les résultats d'immunogénicité légèrement supérieurs des vaccins ciblant des variants se traduiront par une meilleure efficacité clinique par rapport aux vaccins basés uniquement sur la souche ancestrale, et si cette efficacité différera selon la gravité de la maladie (COVID-19 sévère ou non sévère) ou parmi les 4 vaccins ciblant des variants actuellement disponibles.

Le SAGE a relevé qu'aucune étude n'a été menée sur l'utilisation des vaccins ciblant des variants dans le cadre de la primovaccination. Dans l'attente de données probantes ou d'une approbation réglementaire favorables, ces vaccins ne devraient pas être utilisés en primovaccination; tous les vaccins anti-COVID-19 autorisés au titre du protocole EUL de l'OMS peuvent en revanche être utilisés pour la primovaccination. Le SAGE a réitéré que la priorité était de parvenir à des taux élevés et équitables de primovaccination avec les vaccins basés sur la souche ancestrale.

Après l'achèvement de la primovaccination, des doses de rappel doivent être proposées conformément à la feuille de route de l'OMS pour l'établissement des priorités.[13] Les données actuellement disponibles ne sont pas suffisantes pour étayer une recommandation préférentielle en faveur d'un vaccin bivalent par rapport à un vaccin basé sur la souche ancestrale dans le cadre de la vaccination de rappel.

Source : https://iris.who.int/bitstream/handle/10665/365498/WER9801-eng-fre.pdf

The over eight hours of deliberations can be found on the FDA's YouTube channel: https://www.youtube.com/watch?v=BFdzNUus_CE

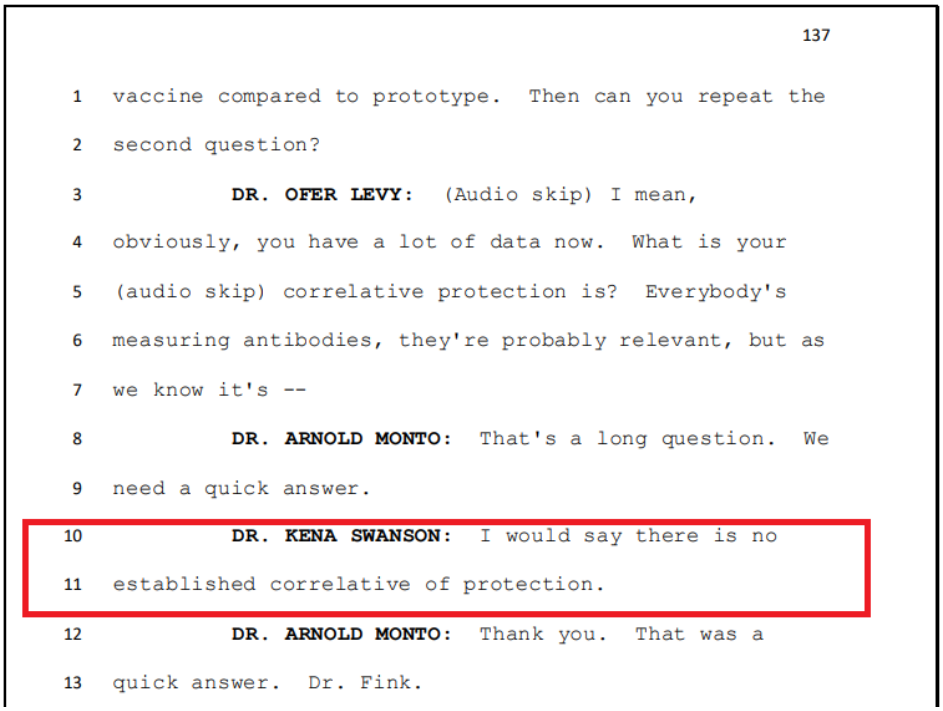
Whether concerning adults or children, the trials for the bivalent vaccines assume that an increase in antibodies is sufficient to prove efficacy. However, it has been established in several documents that demonstrating an increase in antibodies is not enough to prove the vaccine's effectiveness against the disease. This lack of correlation between the SARS-CoV-2 disease and antibody levels was formally acknowledged by Kena Swanson, Vice President of Pfizer, during the same meeting: " I would say there is no established correlative of protection."

Illustration 146 : FDA – Center for Biologics Evaluation and Research (CBER) - 175th Vaccines and Related Biological Products Advisory Committee (VRBPAC) du 28 juin 2022 – Transcription

In the second discussion topic, the Committee was asked to discuss the evidence

supporting 1) the selection of a particular Omicron sub-lineage in the vaccine, 2) the choice of a monovalent versus a bivalent vaccine formulation, and 3) the extrapolation of the available clinical data for modified vaccines to different age ranges. This was a complex set of issues and most committee members chose to try to address most of the three points at the same time during their remarks. The discussion elicited a wide range of opinions, but of the committee members who expressed a firm preference, a bivalent booster vaccine containing an Omicron BA.4/BA.5 seemed to be the preferred option. Several committee members expressed a concern about the limited amount of pediatric data available for modified vaccines and the need to obtain additional safety data in these populations, and some committee members noted the need for additional data related to the clinical meaningfulness of the improved antibody responses and the need for more information on correlates of protection. The extensive deliberations elicited by this 3-part second topic precluded discussion of the planned third discussion question related to the possible updating of the COVID-19 primary series vaccine.

Illustration 147 : FDA – Center for Biologics Evaluation and Research (CBER)- 175th Vaccines and Related Biological Products Advisory Committee (VRBPAC) du 28 juin 2022 – Transcription – Réponse de Kena Swanson



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vaccine compared to prototype. Then can you repeat the second question?

DR. OFER LEVY: (Audio skip) I mean, obviously, you have a lot of data now. What is your (audio skip) correlative protection is? Everybody's measuring antibodies, they're probably relevant, but as we know it's --

DR. ARNOLD MONTO: That's a long question. We need a quick answer.

DR. KENA SWANSON: I would say there is no established correlative of protection.

DR. ARNOLD MONTO: Thank you. That was a quick answer. Dr. Fink.

Source ; https://www.fda.gov/media/160778/download

It has therefore been acknowledged from the outset that merely increasing antibody levels is insufficient to prevent individuals from becoming ill.

Consequently, all trials that measure only antibody levels do not constitute evidence of the vaccines' efficacy against SARS-CoV-2 disease.

In fact, all products authorized on this erroneous methodological basis should be withdrawn from the market. Any future authorization cannot be based on scientific principles.

In summary,

Regarding bivalent vaccines, the trials study antibodies and safety without any proven correlation between antibody levels and the occurrence of COVID-19 disease.

This absence of a link between SARS-CoV-2 disease and antibody levels was formally acknowledged by Kena Swanson, Vice President of Pfizer, during a CBER meeting:

"*I would say there is no established correlate of protection*."

Thus, merely increasing antibody levels is insufficient to prevent individuals from becoming ill.

Consequently, no trials (past of future) measuring only antibody levels provide statistical evidence of the vaccines' efficacy against COVID-19 caused by SARS-CoV-2.

All products authorized on this erroneous methodological basis should be withdrawn from the market. Any future authorization cannot be based on scientific principles.

11 Identified Risks and Missing informations

Since the start of the vaccination campaign, the Risk Management Plan has been available at the following link:

https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty.

Each version replaces the previous one, and the plan is updated based on new findings and newly identified risks.

The Risk Management Plan from December 20, 2020, identifies several safety concerns:

- **Pregnant or breastfeeding women**, as they were excluded from the Phase 3 study.
- **Immunocompromised** patients.
- Vulnerable **patients with comorbidities** (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) (see Table 44 of the RMP).
- Patients with **autoimmune diseases or inflammatory disorders**.

The **interaction with other vaccines** and **long-term safety** were unknown.

Illustration 148 : Pfizer – December 20, 2020 Risk Management Plan- Summary of safety concerns

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns of COVID-19 mRNA vaccine in the initial RMP are listed in Table 17.

Table 17. Summary of Safety Concerns

Important Identified Risks	Anaphylaxis
Important Potential Risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

CONFIDENTIAL
Page 62

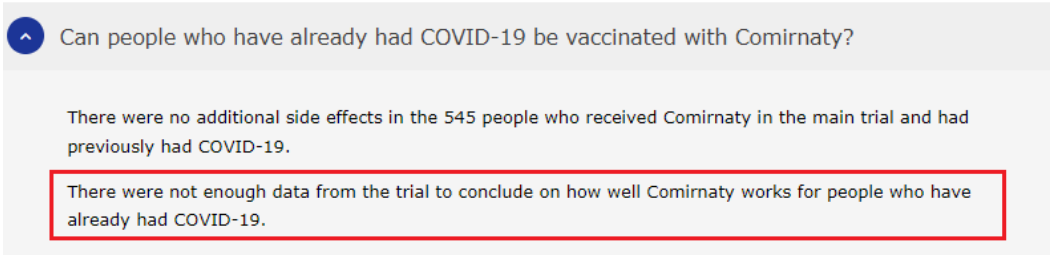
Source: https://web.archive.org/web/20210214040948/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pd

The European Medicines Agency (EMA) website provides a summary of the vaccine's characteristics highlighting key points from the Risk Management Plan.
https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

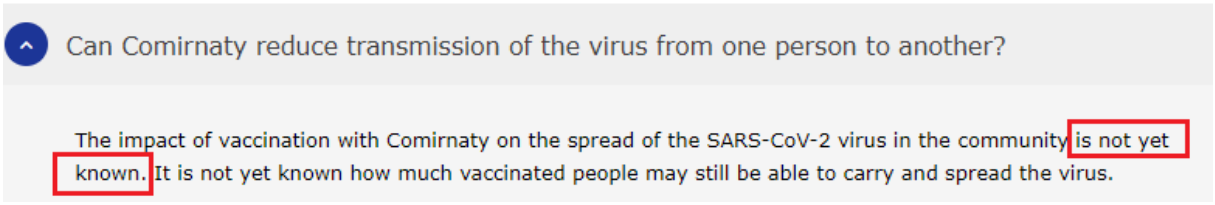
In december 2020, the limited knowledge regarding the vaccine was obvious.

https://web.archive.org/web/20201224012625/https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

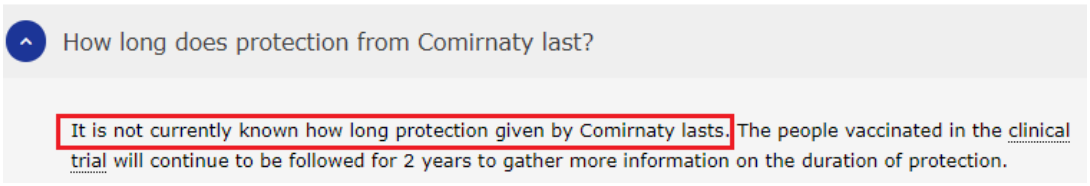
- Not enough information to conclude on side effects of vaccine action in people who have had a COVID-19 infection



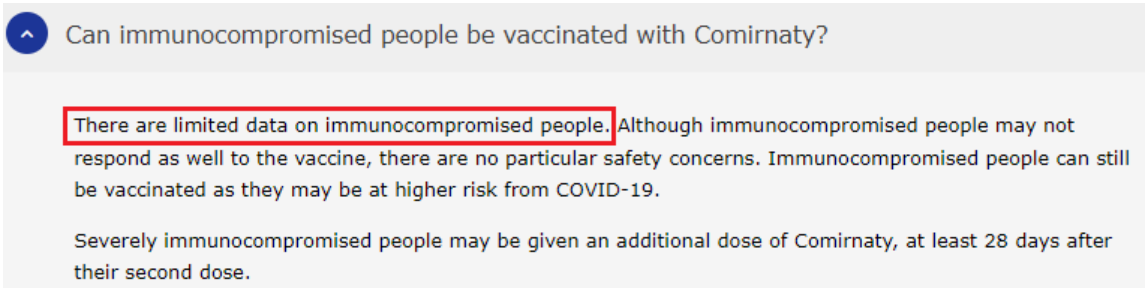
- Impact on transmission not yet known



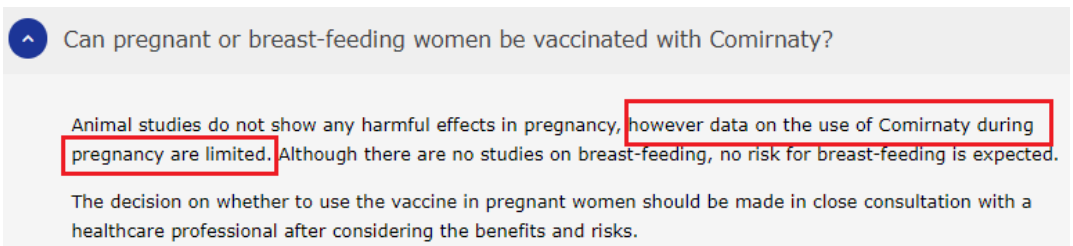
- Duration of protection not yet known



- Limited data on immunocompromised people



- Limited data on pregnant women



Despite the lack of information clearly documented by the laboratory itself and the EMA for months, these populations are undergoing real-life vaccination.

On the April 29th, 2021, The Risk Management Plan still mentioned in chapter SVII.3.2:

- Use in pregnancy and while breast feeding
- Use in immunocompromised patients
- Use in frail patients with co-morbidities (i.e. chronic obstructive
- Pulmonary disease [COPD], diabetes, chronic neurological disease,
- Cardiovascular disorders)
- Use in patients with autoimmune or inflammatory disorders
- Interaction with other vaccines
- Long term safety data

Illustration 149 : Pfizer – April 29, 2021 Risk Management Plan- List of important Risks and Missing information

BNT162b2
Risk Management Plan 29 April 2021

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Comirnaty is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Comirnaty are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Comirnaty. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 44. List of Important Risks and Missing Information

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

Source : https://web.archive.org/web/20210614094739/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf

In response to identified real-life adverse events, based on the emerging signal of myocarditis and pericarditis following COVID-19 mRNA vaccines discussed at the June 10, 2021, FDA and CDC Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings, the Comirnaty Vaccine Emergency Authorization Fact Sheet **was revised on June 25, 2021, to add a warning for myocarditis and pericarditis.** The Pharmacovigilance Plan was also amended to include myocarditis and pericarditis as significant risks identified.

All of this is clearly explained in the Clinical Review Memorandum written by Drs. Susan Wollersheim and Ann Schwartz on August 23, 2021 (page 14).

Source: https://www.fda.gov/media/152256/download

Doctors Wollersheim and Schwartz conclude in section "4.7 Risk and Benefit Assessment" that *« The benefit-risk estimates **are limited by uncertainties** associated with the dynamics of pandemics. The major uncertainties in benefits are related to potential changes in COVID-19 incidence over time and vaccine efficacy and duration of protection in the face of emerging virus variants. **The major risk uncertainty is the data on vaccine-related myocarditis cases and deaths**. »*

Illustration 150 : August 23, 2021 Memorandum by Drs. Wollersheim and Schwartz

respectively. The excess myocarditis/pericarditis cases and associated hospitalizations and deaths attributable to the vaccine are 196, 196, and 0 per million vaccinated individuals in this age group, respectively. Even with the conservative assumption on the myocarditis/pericarditis death rate, the model predicted 0 deaths associated with myocarditis/pericarditis. The model predicts a higher number of myocarditis/pericarditis-related hospitalizations compared to prevented COVID-19 hospitalizations. However, considering the differential clinical outcomes of the hospitalization from two difference causes, FDA considers the benefits of the vaccine still outweigh the risks for the highest risk group, males 16-17 years old, under this worst-case scenario.

The benefit-risk estimates are limited by uncertainties associated with the dynamics of pandemics. The major uncertainties in benefits are related to potential changes in COVID-19 incidence over time and vaccine efficacy and duration of protection in the face of emerging virus variants. The major risk uncertainty is the data on vaccine-related myocarditis cases and deaths.

For further details, please refer to the review memorandum from the Analytics and Benefit-Risk Assessment Team, Office of Biostatistics and Epidemiology, CBER.

Source: https://www.fda.gov/media/152256/download

The Risk Management Plan of September 24, 2021 therefore includes **myocarditis/pericarditis in the significant risks identified** (page 82). The other risks mentioned have been present since the first version of the Risk Management Plan.

Illustration 151 : – September 24, 2021 Risk Management Plan- Important Risks

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Anaphylaxis

Risk-benefit impact

Anaphylaxis is a serious adverse reaction that, although very rare, can be life-threatening.

Important Identified Risk: Myocarditis and Pericarditis

Risk-benefit impact

Myocarditis and pericarditis are serious conditions that may occur concomitantly and that may range in clinical importance from mild to life-threatening.

Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Source : https://web.archive.org/web/20211114215356/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf

These same risks and the same information were still mentioned in the Risk Management Plan dated November 25, 2021

Illustration 152 : Pfizer — November 25, 2021 Risk Management Plan – Missing information

BNT162b2
Risk Management Plan November 2021

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Comirnaty is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Comirnaty are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Comirnaty. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 64. List of Important Risks and Missing Information

Important identified risks	Anaphylaxis Myocarditis and Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

Source : https://web.archive.org/web/20211228225313/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf

Several clinical trials are therefore planned or on going to address these many persistent uncertainties about the subpopulations involved.

Regarding menstrual disorders, ONLY heavy bleeding was added as a side effect for Comirnaty and Spikevax by the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA, as indicated in its press release dated October 28, 2022.

https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022

« *Heavy menstrual bleeding (heavy periods) may be defined as bleeding characterised by an increased volume and/or duration which interferes with the person's physical, social, emotional and material quality of life.* ***Cases of heavy menstrual bleeding have been reported after the first, second and booster doses of Comirnaty and Spikevax.***

The PRAC ***finalised the assessment of this safety signal*** *after reviewing the available data, including cases reported during clinical trials, cases spontaneously reported in Eudravigilance and findings from the medical literature.* »

Illustration 153 : EMA - October 28, 2022 Pharmacovigilance Risk Assessment Committee (PRAC) Meeting highlights

Comirnaty and Spikevax: heavy menstrual bleeding added as a side effect

The PRAC has recommended that heavy menstrual bleeding should be added to the product information as a side effect of unknown frequency of the mRNA COVID-19 vaccines Comirnaty and Spikevax.

Heavy menstrual bleeding (heavy periods) may be defined as bleeding characterised by an increased volume and/or duration which interferes with the person's physical, social, emotional and material quality of life. Cases of heavy menstrual bleeding have been reported after the first, second and booster doses of Comirnaty and Spikevax.

The PRAC finalised the assessment of this safety signal after reviewing the available data, including cases reported during clinical trials, cases spontaneously reported in Eudravigilance and findings from the medical literature.

After reviewing the data, the Committee concluded that there is at least a reasonable possibility that the occurrence of heavy menstrual bleeding is causally associated with these vaccines and therefore recommended the update of the product information.

The 13th and final ongoing Risk Management Plan was signed on May 31, 2024. It still addresses the risks of myocarditis/pericarditis and the same uncertainties.

Module SVIII. Summary of the Safety Concerns

Table 64. Summary of Safety Concerns

Important Identified Risks	Myocarditis and Pericarditis
Important Potential Risks	None
Missing Information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Long term safety data

Source : https://web.archive.org/web/20240926190710/https://www.ema.europa.eu/en/documents/rmp/comirnaty-epar-risk-management-plan_en.pdf

In summary,

The successive Risk Management Plans have allowed for the i**dentification of safety issues over time since December 2020.**

Anaphylaxis and Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD), have been removed from the identified risks, while myocarditis and pericarditis have been added.

Menstrual disorders, specifically heavy bleeding, were added as a side effect for Comirnaty and Spikevax by the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA, as indicated in its press release dated October 28, 2022, without being mentioned in the safety issues of the risk management plans.

A preliminary signal of a potential ischemic stroke has also been identified by the CDC for the bivalent BNT162b2 - Omicron BA.4/BA.5 vaccine in older adults.

Regarding missing information, it has not changed since the beginning, as no results have been provided on:

- Pregnant or breastfeeding women due to their exclusion from the phase 3 study.
- Immunocompromised patients.
- Frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological diseases, cardiovascular disorders) (see Table 44 of the Risk Management Plan).
- Patients with autoimmune diseases or inflammatory issues.

12 Pregnant and breastfeeding women

As previously mentioned in this report, **pregnant women were excluded from the clinical trials that led to the approval of the vaccines by regulatory authorities,** as stipulated by the drug manufacturers' protocols. This exclusion is fairly common, as pregnant women are part of populations protected by patient protection laws.

In Europe, the Clinical Trials Regulation (Regulation (EU) No 536/2014) also highlight the specific case of pregnant women several articles. Article 10 - Specific considerations for vulnerable populations. **Pregnant women are then considered as a vulnerable population.**

Illustration 154 : European Union: Clinical Trials Regulation (Regulation (EU) No 536/2014)

Article 10

Specific considerations for vulnerable populations

1. Where the subjects are minors, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of paediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of paediatrics.

2. Where the subjects are incapacitated subjects, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant disease and the patient population concerned or after taking advice on clinical, ethical and psychosocial questions in the field of the relevant disease and the patient population concerned.

3. Where the subjects are pregnant or breastfeeding women, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant condition and the population represented by the subject concerned.

4. If according to the protocol a clinical trial provides for the participation of specific groups or subgroups of subjects, where appropriate, specific consideration shall be given to the assessment of the application for authorisation of that clinical trial on the basis of expertise in the population represented by the subjects concerned.

5. In any application for authorisation of a clinical trial referred to in Article 35, specific consideration shall be given to the circumstances of the conduct of the clinical trial.

Source : https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R0536

In the U.S. Federal Regulations, the 21 CFR 50 Subpart B — Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research - §46.204 Research involving pregnant women or fetuses, the text mentions that "*Pregnant women or fetuses **may be involved** in research if all of the following conditions are met:*

*a) **Where scientifically appropriate, preclinical studies**, including studies on pregnant animals, and **clinical studies**, including studies on nonpregnant women, **have been conducted and provide data for assessing potential risks to pregnant women and fetuses** »*

Illustration 155 : U.S. Federal Regulations (21 CFR 50 Subpart B)

§46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

Source : https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-b/index.html

As no data were on any population were available at the start of the COVID-19 clinical trials in 2020, this point was not filled to be able to include any pregnant woman.

In January 2021, the UK government's website was very clear about the state of knowledge regarding this population in Chapter 3.4 Toxicology - Toxicity conclusions.

« *The **absence of reproductive toxicity data is a reflection of the speed of development** to first identify and select COVID-19 mRNA Vaccine BNT162b2 for clinical testing and its rapid development to meet the ongoing urgent health need.*

In principle, a decision on licensing a vaccine could be taken in these circumstances without data from reproductive toxicity studies animals, but there are studies ongoing and these will be provided when available.

***In the context of supply under Regulation 174, it is considered that sufficient reassurance of safe use of the vaccine in pregnant women cannot be provided at the present time**: however, use in women of childbearing potential could be supported provided healthcare professionals are advised to rule out known or suspected pregnancy prior to vaccination.*

Women who are breastfeeding should also not be vaccinated.

*These judgements **reflect the absence of data at the present time** and do not reflect a specific finding of concern. Adequate advice with regard to women of childbearing potential, pregnant women and breastfeeding women has been provided in both the Information for UK Healthcare Professionals and the Information for UK recipients*. »

Illustration 156 : UK government - 3.4 Toxicology

Toxicity conclusions

The absence of reproductive toxicity data is a reflection of the speed of development to first identify and select COVID-19 mRNA Vaccine BNT162b2 for clinical testing and its rapid development to meet the ongoing urgent health need. In principle, a decision on licensing a vaccine could be taken in these circumstances without data from reproductive toxicity studies animals, but there are studies ongoing and these will be provided when available. In the context of supply under Regulation 174, it is considered that sufficient reassurance of safe use of the vaccine in pregnant women cannot be provided at the present time: however, use in women of childbearing potential could be supported provided healthcare professionals are advised to rule out known or suspected pregnancy prior to vaccination. Women who are breastfeeding should also not be vaccinated. These judgements reflect the absence of data at the present time and do not reflect a specific finding of concern. Adequate advice with regard to women of childbearing potential, pregnant women and breastfeeding women has been provided in both the Information for UK Healthcare Professionals and the Information for UK recipients.

Source : https://web.archive.org/web/20210104140536/https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-COVID-19/summary-public-assessment-report-for-pfizerbiontech-COVID-19-vaccine

The same text was present in November 2022 and in January 2024,

https://web.archive.org/web/20221122120626/https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-COVID-19/summary-public-assessment-report-for-pfizerbiontech-COVID-19-vaccine

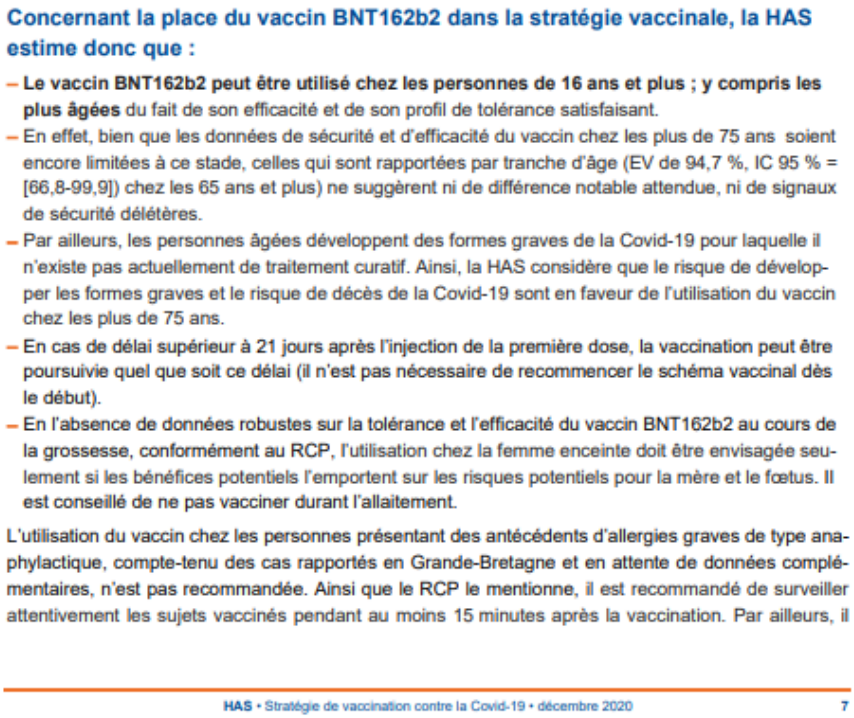
https://web.archive.org/web/20240120213736/https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-COVID-19/summary-public-assessment-report-for-pfizerbiontech-COVID-19-vaccine

The page was removed from the UK government website for an unknown reason.

For pregnant women, the December 2020 opinion from the French National Authority for Health (HAS) states, « ***in the absence of robust data on the safety and efficacy of the BNT162b2 vaccine during pregnancy**, in accordance with the product's summary of characteristics, its use in pregnant women **should only be considered if the potential benefits outweigh the potential risks to both the mother and the fetus**. It is recommended **not** to administer the vaccine during breastfeeding* ».

This is therefore a vaccination prescribed based **on an individual (or case-by-case) assessment of benefits and risks,** rather than a mass vaccination for this category.

Illustration 157 : December 2020 French National Authority for Health (HAS) opinion – Pregnant women



Concernant la place du vaccin BNT162b2 dans la stratégie vaccinale, la HAS estime donc que :

- **Le vaccin BNT162b2 peut être utilisé chez les personnes de 16 ans et plus ; y compris les plus âgées** du fait de son efficacité et de son profil de tolérance satisfaisant.
- En effet, bien que les données de sécurité et d'efficacité du vaccin chez les plus de 75 ans soient encore limitées à ce stade, celles qui sont rapportées par tranche d'âge (EV de 94,7 %, IC 95 % = [66,8-99,9]) chez les 65 ans et plus) ne suggèrent ni de différence notable attendue, ni de signaux de sécurité délétères.
- Par ailleurs, les personnes âgées développent des formes graves de la Covid-19 pour laquelle il n'existe pas actuellement de traitement curatif. Ainsi, la HAS considère que le risque de développer les formes graves et le risque de décès de la Covid-19 sont en faveur de l'utilisation du vaccin chez les plus de 75 ans.
- En cas de délai supérieur à 21 jours après l'injection de la première dose, la vaccination peut être poursuivie quel que soit ce délai (il n'est pas nécessaire de recommencer le schéma vaccinal dès le début).
- En l'absence de données robustes sur la tolérance et l'efficacité du vaccin BNT162b2 au cours de la grossesse, conformément au RCP, l'utilisation chez la femme enceinte doit être envisagée seulement si les bénéfices potentiels l'emportent sur les risques potentiels pour la mère et le fœtus. Il est conseillé de ne pas vacciner durant l'allaitement.

L'utilisation du vaccin chez les personnes présentant des antécédents d'allergies graves de type anaphylactique, compte-tenu des cas rapportés en Grande-Bretagne et en attente de données complémentaires, n'est pas recommandée. Ainsi que le RCP le mentionne, il est recommandé de surveiller attentivement les sujets vaccinés pendant au moins 15 minutes après la vaccination. Par ailleurs, il

HAS • Stratégie de vaccination contre la Covid-19 • décembre 2020 7

Source : https://web.archive.org/web/20201225223409/https://www.has-sante.fr/upload/docs/application/pdf/2020-12/strategie_vaccination_covid_19_place_vaccin_a_arnm_comirnaty_bnt162b2.pdf

The document « 1.6.3 meeting-correspondence », made available by legal decision, mentions in the 6.4 Pregnancy Paragraph

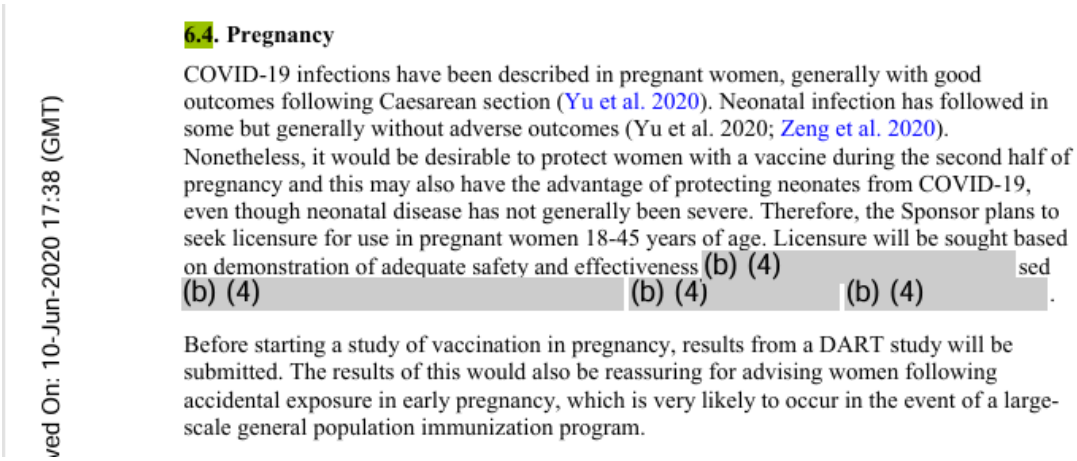
« COVID-19 infections have been described in pregnant women, generally with good outcomes following Caesarean section (Yu et al. 2020). Neonatal infection has followed in some but generally without adverse outcomes (Yu et al. 2020; Zeng et al. 2020).

Nonetheless, it would be desirable to protect women with a vaccine during the second half of pregnancy and this may also have the advantage of protecting neonates from COVID-19, even though neonatal disease has not generally been severe.

***Therefore, the Sponsor plans to seek licensure for use in pregnant women 18-45 years of age**. Licensure will be sought based on demonstration of adequate safety and effectiveness (b) (4) (b) (4) (b) (4) (b) (4) sed . **Before starting a study of vaccination in pregnancy, results from a DART study will be submitted. The results of this would also be reassuring for advising women following accidental exposure in early pregnancy**, which is very likely to occur in the event of a large scale general population immunization program. »*

It was therefore planned to vaccinate pregnant women after the first trimester of pregnancy, based on solid evidence that the vaccine is safe and effective, which would come from clinical trial results.

Illustration 158 : FDA – Pfizer - Correspondance regarding meetings – Pregnancy



ved On: 10-Jun-2020 17:38 (GMT)

6.4. Pregnancy

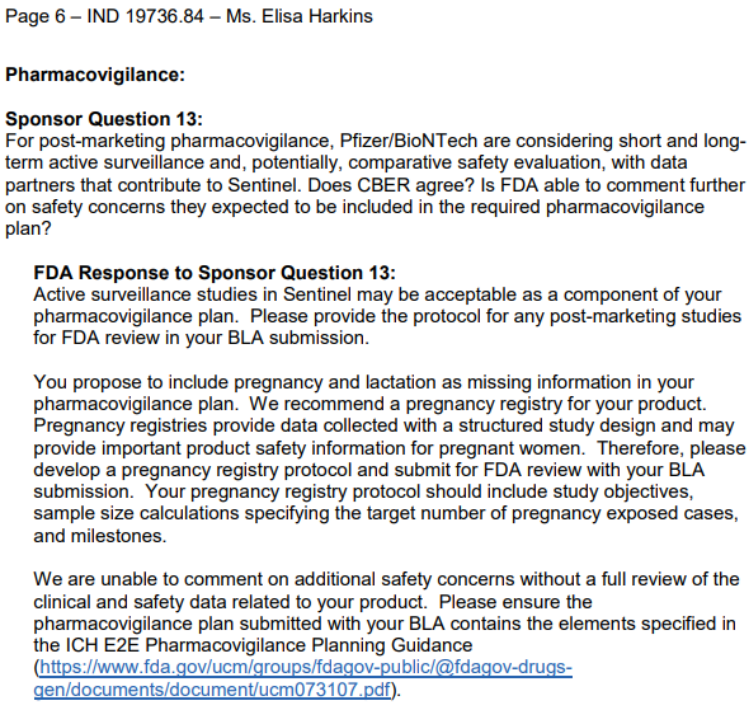
COVID-19 infections have been described in pregnant women, generally with good outcomes following Caesarean section (Yu et al. 2020). Neonatal infection has followed in some but generally without adverse outcomes (Yu et al. 2020; Zeng et al. 2020). Nonetheless, it would be desirable to protect women with a vaccine during the second half of pregnancy and this may also have the advantage of protecting neonates from COVID-19, even though neonatal disease has not generally been severe. Therefore, the Sponsor plans to seek licensure for use in pregnant women 18-45 years of age. Licensure will be sought based on demonstration of adequate safety and effectiveness (b) (4) sed (b) (4) (b) (4) (b) (4) .

Before starting a study of vaccination in pregnancy, results from a DART study will be submitted. The results of this would also be reassuring for advising women following accidental exposure in early pregnancy, which is very likely to occur in the event of a large-scale general population immunization program.

Source : https://phmpt.org/wp-content/uploads/2023/10/125742_S1_M1_meeting-correspondence.pdf

The FDA requested in a letter identified as INS19736, dated September 28, 2020, that Pfizer include pregnancy and breastfeeding as missing information in [the] pharmacovigilance plan. This has already been highlighted several times in this report. U.S. health authorities also requested that Pfizer provide a **pregnancy registry protocol and submit it to the FDA for review** with the biologics license application (BLA). Pregnancy registries collect data through a structured study plan and can provide important information on the safety of the product for pregnant women.

Illustration 159 : FDA – Pfizer - Correspondance regarding meetings – Pharmacovigilance on Pregnant women



Page 6 – IND 19736.84 – Ms. Elisa Harkins

Pharmacovigilance:

Sponsor Question 13:
For post-marketing pharmacovigilance, Pfizer/BioNTech are considering short and long-term active surveillance and, potentially, comparative safety evaluation, with data partners that contribute to Sentinel. Does CBER agree? Is FDA able to comment further on safety concerns they expected to be included in the required pharmacovigilance plan?

FDA Response to Sponsor Question 13:
Active surveillance studies in Sentinel may be acceptable as a component of your pharmacovigilance plan. Please provide the protocol for any post-marketing studies for FDA review in your BLA submission.

You propose to include pregnancy and lactation as missing information in your pharmacovigilance plan. We recommend a pregnancy registry for your product. Pregnancy registries provide data collected with a structured study design and may provide important product safety information for pregnant women. Therefore, please develop a pregnancy registry protocol and submit for FDA review with your BLA submission. Your pregnancy registry protocol should include study objectives, sample size calculations specifying the target number of pregnancy exposed cases, and milestones.

We are unable to comment on additional safety concerns without a full review of the clinical and safety data related to your product. Please ensure the pharmacovigilance plan submitted with your BLA contains the elements specified in the ICH E2E Pharmacovigilance Planning Guidance (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073107.pdf).

Source : https://phmpt.org/wp-content/uploads/2023/10/125742_S1_M1_meeting-correspondence.pdf

The company therefore evaluated the efficacy and safety in this population in another clinical trial, which was registered on the website www.clinicaltrial.com on February 16, 2021. The goal was to recruit 4,000 healthy women, aged 18 years or older, who were between 24 and 34 weeks of gestation on the day of the scheduled vaccination, having an uncomplicated singleton pregnancy and presenting no known increased risk of complications.

This trial was conducted not only in the United States but also in South Africa, Brazil, Spain, and England.

Illustration 160 : Clinicaltrial – Trial Registration on Pregnant women

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	683 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Prevention
Official Title:	A PHASE 2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SARS-COV-2 RNA VACCINE CANDIDATE (BNT162b2) AGAINST COVID-19 IN HEALTHY PREGNANT WOMEN 18 YEARS OF AGE AND OLDER
Actual Study Start Date :	February 16, 2021
Actual Primary Completion Date :	July 15, 2022
Actual Study Completion Date :	July 15, 2022

Source : https://classic.clinicaltrials.gov/ct2/show/study/NCT04754594

The protocol defined the study as an "*interventional study* *is designated as a* PASS [5] (Post-Authorization Safety Study)*, identified as Category 3 in the EU RMP, and is conducted as a* ***conditional marketing approval commitment to the EMA and Swissmedic* *and an emergency use authorization commitment to the US FDA and numerous other health authorities under respective national emergency use legislation. »*

Illustration 161 : Pfizer- Final Protocol Amendment 5, 08 March on pregnant women – Study type

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591015
Final Protocol Amendment 5, 08 March 2022

- the potential of the BioNTech platform of RNA-based vaccines to deliver high numbers of vaccine doses rapidly in a single production campaign.
- the threat posed by the SARS-CoV-2 variants emerging worldwide.
- the potential need for enhancing immunoresponses to overcome waning immunity.

These data suggest a favorable risk/benefit profile in pregnant women. Anticipated AEs after vaccination in maternal participants are expected to be manageable using routine symptom-driven standard of care as determined by the investigators. As a result, the profile of these vaccine candidates supported initiation of this PASS clinical study. This interventional study is designated as a PASS, identified as Category 3 in the EU RMP, and is conducted as a conditional marketing approval commitment to the EMA and Swissmedic and an emergency use authorization commitment to the US FDA and numerous other health authorities under respective national emergency use legislation.

Source : https://classic.clinicaltrials.gov/ProvidedDocs/94/NCT04754594/Prot_000.pdf

[5] https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/post-authorisation-safety-studies-pass

The initial version of the protocol dates back to December 20, 2020, and it has been **amended five times.** The final version of the protocol dated March 5, 2022, clearly states: « ***There are no ongoing randomized controlled COVID-19 vaccine studies including pregnant women.*** *Vaccination of pregnant women has been used globally to protect both women and their infants against influenza and as a mechanism to protect infants against pertussis. Several studies have demonstrated that maternal immunization is safe for both mother and infant and an important strategy to protect pregnant women and their infants against infectious diseases. Currently maternal immunization studies are being conducted as part of the development of* ***novel RSV and GBS vaccines***. »

The laboratory explicitly notes that in April 2022, despite vaccination being recommended for all pregnant women for a year, the risks to their health and that of their babies remained unknown.

Illustration 162 : Pfizer- Final Protocol Amendment 5, 08 March on pregnant women - Background

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591015
Final Protocol Amendment 5, 08 March 2022

Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.[14,15] The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.[14,15]

There are no ongoing randomized controlled COVID-19 vaccine studies including pregnant women. Vaccination of pregnant women has been used globally to protect both women and their infants against influenza and as a mechanism to protect infants against pertussis. Several studies have demonstrated that maternal immunization is safe for both mother and infant and an important strategy to protect pregnant women and their infants against infectious diseases. Currently maternal immunization studies are being conducted as part of the development of novel RSV and GBS vaccines.[16,17]

BNT162b2 is a SARS-CoV-2–RNA-LNP vaccine based on a platform of modRNA with blunted innate immune sensor–activating capacity and augmented expression encoding the P2 S.

Given the recruitment challenges and despite the number of centers established, the sample size was reduced by an amendment to the protocol on May 14, 2021 (Amendment 3), one of the arguments being the availability of vaccines in real life for everyone. Why enroll in a clinical trial when women could easily get vaccinated anywhere? It is noteworthy that this amendment removed the efficacy objectives, as confirmed by the title of the clinical trial.

It should be noted that this amendment **removed the efficacy objectives**, as confirmed by the title of the clinical trial.

« A PHASE 2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO **EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY** OF A SARS-COV-2 RNA VACCINE CANDIDATE (BNT162b2) AGAINST COVID-19 IN HEALTHY PREGNANT WOMEN 18 YEARS OF AGE AND OLDER »

It is abundantly clear that the efficacy against the disease was not the primary concern of the laboratory.

Illustration 163 : Pfizer- Final Protocol Amendment 5, 08 March on pregnant women – May 14, 2021 Amendement 3

Protocol amendment 3	14 May 2021	• Reduced the study sample size based on regulatory feedback and evolving global availability of COVID-19 vaccines for pregnant women. • Modified the study objectives to align with the reduced sample size. • Removed the hypothesis-based efficacy objective, estimands, and endpoints. • Modified the statistical analysis timing to align with the reduced sample size and changes in the objectives.

PFIZER CONFIDENTIAL

[redacted]

Page 3

Illustration 164 : Pfizer- Final Protocol Amendment 5, 08 March on pregnant women – Cover page

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591015
Final Protocol Amendment 5, 08 March 2022

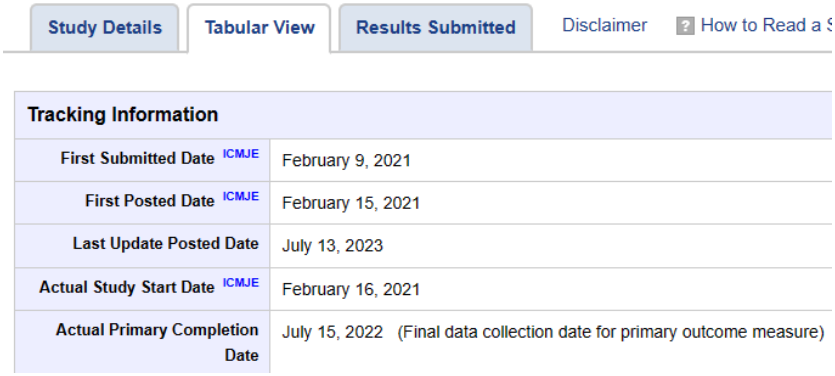
A PHASE 2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SARS-COV-2 RNA VACCINE CANDIDATE (BNT162b2) AGAINST COVID-19 IN HEALTHY PREGNANT WOMEN 18 YEARS OF AGE AND OLDER

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-005444-35
Protocol Number:	C4591015
Phase:	Phase 2/3

Short Title: A Phase 2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS-CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older

The study concluded on **July 15, 2022**, with 683 women enrolled. It took until **July 13, 2023**, for Pfizer to release the results.

Illustration 165 : Trial Registration on Pregnant women – Dates



Study Details | Tabular View | Results Submitted | Disclaimer | How to Read a S

Tracking Information	
First Submitted Date ICMJE	February 9, 2021
First Posted Date ICMJE	February 15, 2021
Last Update Posted Date	July 13, 2023
Actual Study Start Date ICMJE	February 16, 2021
Actual Primary Completion Date	July 15, 2022 (Final data collection date for primary outcome measure)

Source : https://clinicaltrials.gov/study/NCT04754594?tab=history&a=1#version-content-panel

Despite the one-year delay between the end of the trial and the publication of results on the clinicaltrial website, the results posted in July 2023 were very **incomplete**, with the number of COVID cases and the results of neutralizing antibody assays missing. Pfizer took a full year to publish results that did not demonstrate any conclusive efficacy of the vaccine in pregnant women.

The missing results were finally published on June 24, 2024, nearly two years after the trial concluded, which is highly unusual, as biostatisticians typically provide results within a month of study completion. Among evaluable maternal participants without evidence of prior SARS-CoV-2 infection prior to 7 days after receipt of Dose 2, **the data showed 2 cases of COVID among vaccinated women (2.3%) compared to 2 in the placebo group (2.2%), with the reported VACCINE EFFICACY being only 3.8%.** The cases were counted from 7 days after Dose 2 up to 1 month after delivery.

There is no published paper on these disastrous results, which are only visible on the clinicaltrial.com website, and the company has not promoted this information.

In calculating vaccine efficacy using the standard formula, we find:

$$\text{Relative Risk (RR)} = \frac{2 / 86}{2 / 89} = \frac{0{,}02326}{0{,}02247} = 1{,}034883721$$

Vaccine efficacy = 100 x (1- RR) = 100 x (1-1,034883721) = --3,48 %.

The placebo would therefore appear to be even more effective than the vaccine.

Illustration 166 : Trial efficacy results on Pregnant women - Maternal participants without evidence of prior SARS-CoV-2 infection – June 24, 2024

9. Number of Participants With COVID-19 Occurrence Per 100 Person-Years of Blinded Follow-Up in Evaluable Maternal Participants Without Evidence of Prior SARS-CoV-2 Infection Type: Secondary | Time Frame: From 7 days after Dose 2 up to 1 month after delivery (Surveillance time [100 person-year]: BNT162b2- 0.155, Placebo- 0.149)		
Description	Number of participants with COVID-19 occurrence per 100 person-years of blinded follow-up in evaluable maternal participants without evidence of prior SARS-CoV-2 infection prior to 7 days after receipt of Dose 2 was reported in this outcome measure.	
Time Frame	From 7 days after Dose 2 up to 1 month after delivery (Surveillance time [100 person-year]: BNT162b2- 0.155, Placebo- 0.149)	
Analysis Population Description	Evaluable efficacy population included all eligible randomized participants who received all vaccinations as randomized, with Dose 2 received within predefined window (within 19-42 days after Dose 1) and had no other important protocol deviations as determined by clinician on or before 7 days after Dose 2. Here, "Overall Number of Participants Analyzed" signifies participants evaluable for this outcome measure. HIV positive participants were excluded from analysis as pre-specified in SAP.	
Arm/Group Title	Maternal Participants: BNT162b2 30 mcg	Maternal Participants: Placebo
Arm/Group Description	Maternal participants received two doses of BNT162b2 30 micrograms (mcg) as an intramuscular injection separated by 21 days during their 24 to 34 weeks gestation in the blinded phase.	Maternal participants received two doses of placebo as an intramuscular injection separated by 21 days during their 24 to 34 weeks gestation in the blinded phase.
Overall Number of Participants Analyzed	86	89
Measure Type: Count of Participants | Unit of Measure: Participants	2 2.3%	2 2.2%

Statistical Analysis 1	
Statistical Analysis Overview	
Comparison Group Selection	Maternal Participants: BNT162b2 30 mcg, Maternal Participants: Placebo
Comments	[Not Specified]
Type of Statistical Test	Other
Comments	Vaccine efficacy was estimated by 100*(1 - illness rate ratio [IRR]), where IRR=calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine group to the corresponding illness rate in the placebo group.
Method of Estimation	
Estimation Parameter	Vaccine efficacy
Estimated Value	3.8
Confidence Interval	(2-Sided) 95% -1227.8 to 93.0
Estimation Comments	[Not Specified]

Source: https://clinicaltrials.gov/study/NCT04754594?tab=history&a=24#version-content-panel

Among evaluable maternal participants **with or without evidence of prior SARS-CoV-2 infection**, the efficacy is 35.1% but as the 95% Confidence Interval is (-466.5,94.6), no statistical significance is shown between BNT162b2 and Placebo.

Illustration 167 : Trial efficacy results on Pregnant women - Maternal participants with or without evidence of prior SARS-CoV-2 infection – June 24, 2024

10. Number of Participants With COVID-19 Occurrence Per 100 Person-Years of Blinded Follow-Up in Evaluable Maternal Participants With or Without Evidence of Prior SARS-CoV-2 Infection

Type: Secondary | Time Frame: From 7 days after Dose 2 up to 1 month after delivery (Surveillance time [100 person-year]: BNT162b2- 0.270, Placebo- 0.263)

Description	Number of participants with COVID-19 occurrence per 100 person-years of blinded follow-up in evaluable maternal participants with or without evidence of prior SARS-CoV-2 infection was reported in this outcome measure.	
Time Frame	From 7 days after Dose 2 up to 1 month after delivery (Surveillance time [100 person-year]: BNT162b2- 0.270, Placebo- 0.263)	
Analysis Population Description	Evaluable efficacy population included all eligible randomized participants who received all vaccinations as randomized, with Dose 2 received within predefined window (within 19-42 days after Dose 1) and had no other important protocol deviations as determined by clinician on or before 7 days after Dose 2. Here, "Overall Number of Participants Analyzed" signifies participants evaluable for this outcome measure. HIV positive participants were excluded from analysis as pre-specified in SAP.	
Arm/Group Title	Maternal Participants: BNT162b2 30 mcg	Maternal Participants: Placebo
Arm/Group Description	Maternal participants received two doses of BNT162b2 30 micrograms (mcg) as an intramuscular injection separated by 21 days during their 24 to 34 weeks gestation in the blinded phase. Participants were followed-up until 6 months post-delivery.	Maternal participants received two doses of placebo as an intramuscular injection separated by 21 days during their 24 to 34 weeks gestation in the blinded phase.
Overall Number of Participants Analyzed	145	149
Measure Type: Count of Participants | Unit of Measure: Participants	2 1.4%	3 2.0%

Statistical Analysis 1

Statistical Analysis Overview

Comparison Group Selection	Maternal Participants: BNT162b2 30 mcg, Maternal Participants: Placebo
Comments	[Not Specified]
Type of Statistical Test	Other
Comments	Vaccine efficacy was estimated by 100*(1 - IRR), where IRR=calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine group to the corresponding illness rate in the placebo group.

Method of Estimation

Estimation Parameter	Vaccine efficacy
Estimated Value	35.1
Confidence Interval	(2-Sided) 95% -466.5 to 94.6
Estimation Comments	[Not Specified]

<u>Conclusions: NO statistically demonstrated efficacy in pregnant women.</u>

In summary,

Pregnant women have been included in the successive Risk Management Plans since December 2020, indicating that **no data were available regarding them**, either in terms of efficacy, antibody levels, or tolerance.

In February 2021, the French High Authority for Health (HAS) recommended vaccination for pregnant women "*only if the potential benefits outweighed the potential risks to the mother and fetus*." Therefore, each case needed to be evaluated individually before proceeding with vaccination. It was even advised not to administer the vaccine during breastfeeding.

The opinion of the British government was aligned with this view (Chapter 3.4 Toxicology[6]).

« *The **absence** **of reproductive toxicity data is a reflection of the speed of development** to first identify and select COVID-19 mRNA Vaccine BNT162b2 for clinical testing and its rapid development to meet the ongoing urgent health need.*

In principle, a decision on licensing a vaccine could be taken in these circumstances without data from reproductive toxicity studies animals, but there are studies ongoing and these will be provided when available.

***In the context of supply under Regulation 174, it is considered that sufficient reassurance of safe use of the vaccine in pregnant women cannot be provided at the present time**: however, use in women of childbearing potential could be supported provided healthcare professionals are advised to rule out known or suspected pregnancy prior to vaccination.*

Women who are breastfeeding should also not be vaccinated.

*These judgements **reflect the absence of data at the present time** and do not reflect a specific finding of concern. Adequate advice with regard to women of childbearing potential, pregnant women and breastfeeding women has been provided in both the Information for UK Healthcare Professionals and the Information for UK recipients*. »

The laboratory was asked to test the efficacy and safety of its vaccine in a clinical trial in order to meet the conditions for renewing the MA (Marketing Authorization) and the EUA (Emergency Use Authorization).

The protocol for this trial, dated March 5, 2022, confirms the absence of data as of that date regarding the risk of obstetric and/or neonatal adverse events following vaccination during pregnancy.

https://classic.clinicaltrials.gov/ProvidedDocs/94/NCT04754594/Prot_000.pdf

The company therefore states explicitly that, as of April 2022, while vaccination had been recommended for pregnant women by everyone for a year, the risks to their health and that of their baby were still unknown.

[6] https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-COVID-19/summary-public-assessment-report-for-pfizerbiontech-COVID-19-vaccine

The study ended on July 15, 2022, with 683 women included. It wasn't until July 13, 2023, that Pfizer published the results. The missing results were finally released on June 24, 2024, nearly two years after the conclusion of the trial, which is highly unusual, as biostatisticians typically provide results within a month of study completion. The displayed vaccine efficacy was 3.8% with a non significant difference between placebo and vaccine groups.

Therefore, the efficacy of the Pfizer/BioNTech vaccine has never been demonstrated in pregnant women.

13 Real-life adverse events and Security Reports

As required by the Pharmacovigilance regulations, the sponsor remains responsible for the management of post-marketing safety data.

The reported effects come from multiple sources

- The laboratory's own database of spontaneously reported cases
- Cases reported to health authorities
    - EudraVigilance in Europe, https://dap.ema.europa.eu/analytics/saw.dll?PortalPages
    - VAERS (Vaccine Adverse Event Reporting System) in the US, www.vaers.hhs.gov
- Cases published in the medical literature,
- Cases from marketing programs sponsored by the laboratory,
- Identified cases of non-interventional studies
- Cases of serious adverse events reported in clinical trials,

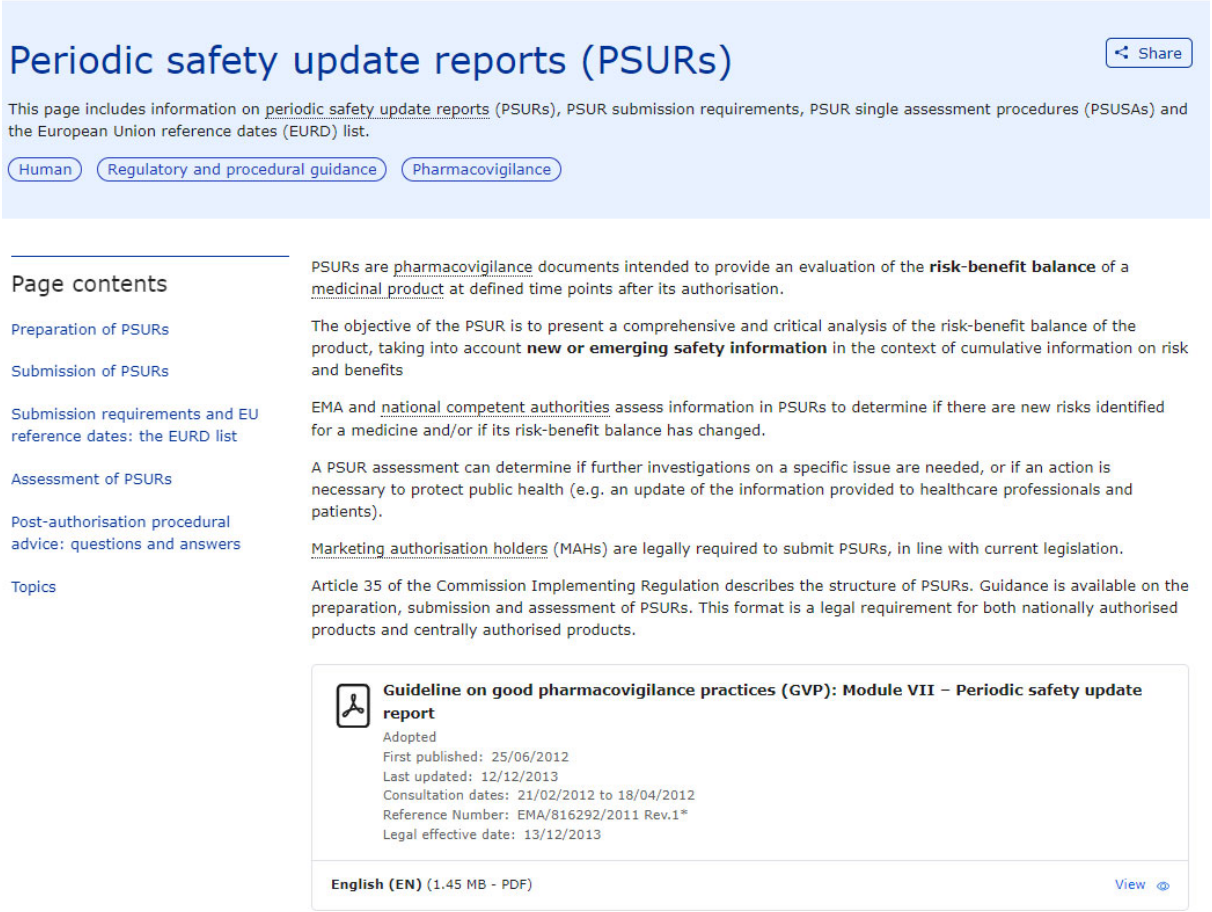
All cases must be reported; independently of the evaluation of causality, it is the analysis of cases that will allow the calculation of **safety signals** for the **detection of adverse drug reactions not highlighted in clinical trials** and to evaluate potential causal associations between an event and the product and to update the list of risks identified when people take the product.

13.1 Periodic Safety Update Report (PSUR) - Definition

The European Medicines Agency (EMA) defines Periodic Safety Update Reports (PSURs) as « *pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points after its authorisation.*

The objective of the PSUR is to ***present a comprehensive and critical analysis of the risk-benefit balance of the product****, taking into account new or emerging safety information in the context of cumulative information on risk and benefits.* »

Illustration 168 : EMA –PSUR - Definition



Periodic safety update reports (PSURs)

Share

This page includes information on periodic safety update reports (PSURs), PSUR submission requirements, PSUR single assessment procedures (PSUSAs) and the European Union reference dates (EURD) list.

Human | Regulatory and procedural guidance | Pharmacovigilance

Page contents

- Preparation of PSURs
- Submission of PSURs
- Submission requirements and EU reference dates: the EURD list
- Assessment of PSURs
- Post-authorisation procedural advice: questions and answers
- Topics

PSURs are pharmacovigilance documents intended to provide an evaluation of the **risk-benefit balance** of a medicinal product at defined time points after its authorisation.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account **new or emerging safety information** in the context of cumulative information on risk and benefits

EMA and national competent authorities assess information in PSURs to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed.

A PSUR assessment can determine if further investigations on a specific issue are needed, or if an action is necessary to protect public health (e.g. an update of the information provided to healthcare professionals and patients).

Marketing authorisation holders (MAHs) are legally required to submit PSURs, in line with current legislation.

Article 35 of the Commission Implementing Regulation describes the structure of PSURs. Guidance is available on the preparation, submission and assessment of PSURs. This format is a legal requirement for both nationally authorised products and centrally authorised products.

Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report

Adopted
First published: 25/06/2012
Last updated: 12/12/2013
Consultation dates: 21/02/2012 to 18/04/2012
Reference Number: EMA/816292/2011 Rev.1*
Legal effective date: 13/12/2013

English (EN) (1.45 MB - PDF) View

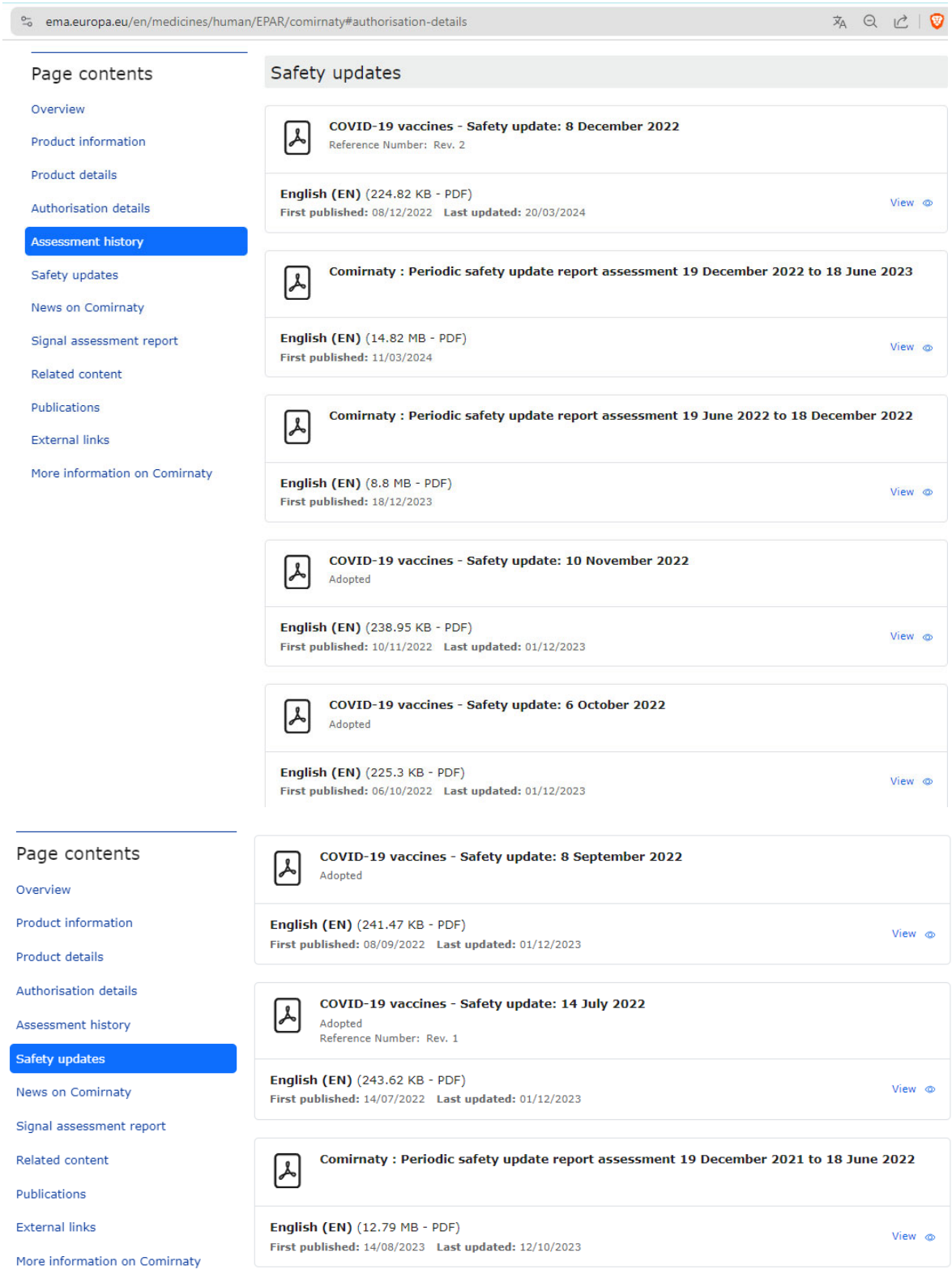
Source :

https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/periodic-safety-update-reports-psurs

The PSURs from the manufacturer are available on the EMA website at https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty#authorisation-details under the safety updates section.

Below is an excerpt from the available documents.

Illustration 169 : EMA – Liste des PSUR pour le vaccin Comirnaty® de Pfizer – extrait



13.2 October 22, 2020 Presentation of Adverse Events of Special Interest (AESI)

As of October 22, 2020, Tom Shimakuburo, former Deputy Director of the H1N1 Vaccine Task Force at the Centers for Disease Control and Prevention (CDC), member of the COVID-19 Vaccine Task Force Vaccine Safety Team at CDC and Steeve Anderson, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research (CBER), presented an impressive list of adverse events of particular interest to the FDA's CBER meeting.

They were :

- COVID-19 disease
- Death
- Vaccination during pregnancy and adverse pregnancy outcomes
- Guillain-Barré syndrome (GBS)
- Other clinically serious neurologic AEs (group AE)
- Acute disseminated encephalomyelitis (ADEM)
- Transverse myelitis (TM)
- Multiple sclerosis (MS)
- Optic neuritis (ON)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Encephalitis
- Myelitis
- Encephalomyelitis
- Meningoencephalitis
- Meningitis
- Encephalopathy
- Ataxia
- Seizures / convulsions
- Stroke
- Narcolepsy / cataplexy
- Autoimmune disease
- Anaphylaxis
- Non-anaphylactic allergic reactions
- Acute myocardial infarction
- Myocarditis / pericarditis
- Thrombocytopenia
- Disseminated intravascular coagulation (DIC)
- Venous thromboembolism (VTE)
- Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)
- Kawasaki disease
- Multisystem Inflammatory Syndrome (MIS-C, MIS-A)

Illustration 170 : FDA – CBER – October 22, 2020 – Tom Shimabukuro – COVID-19 Vaccine Surveillance – List of Adverse Events of Special Interest

Preliminary list of VAERS AEs of special interest

- COVID-19 disease
- Death
- Vaccination during pregnancy and adverse pregnancy outcomes
- Guillain-Barré syndrome (GBS)
- Other clinically serious neurologic AEs (group AE)
  - Acute disseminated encephalomyelitis (ADEM)
  - Transverse myelitis (TM)
  - Multiple sclerosis (MS)
  - Optic neuritis (ON)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Encephalitis
  - Myelitis
  - Encephalomyelitis
  - Meningoencephalitis
  - Meningitis
  - Encephalopathy
  - Ataxia
- Seizures / convulsions
- Stroke
- Narcolepsy / cataplexy
- Autoimmune disease
- Anaphylaxis
- Non-anaphylactic allergic reactions
- Acute myocardial infarction
- Myocarditis / pericarditis
- Thrombocytopenia
- Disseminated intravascular coagulation (DIC)
- Venous thromboembolism (VTE)
- Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)
- Kawasaki disease
- Multisystem Inflammatory Syndrome (MIS-C, MIS-A)

Source : https://www.fda.gov/media/143530/download

Illustration 171 : FDA – CBER – October 22, 2020 – Steve Anderson – COVID-19 Vaccine Surveillance – List of Adverse Events of Special Interest

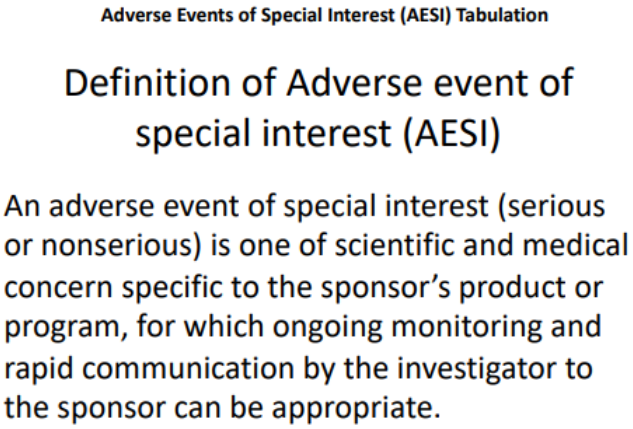
FDA Safety Surveillance of COVID-19 Vaccines : DRAFT Working list of possible adverse event outcomes ***Subject to change***

- Guillain-Barré syndrome
- Acute disseminated encephalomyelitis
- Transverse myelitis
- Encephalitis/myelitis/encephalomyelitis/ meningoencephalitis/meningitis/ encepholapathy
- Convulsions/seizures
- Stroke
- Narcolepsy and cataplexy
- Anaphylaxis
- Acute myocardial infarction
- Myocarditis/pericarditis
- Autoimmune disease
- Deaths
- Pregnancy and birth outcomes
- Other acute demyelinating diseases
- Non-anaphylactic allergic reactions
- Thrombocytopenia
- Disseminated intravascular coagulation
- Venous thromboembolism
- Arthritis and arthralgia/joint pain
- Kawasaki disease
- Multisystem Inflammatory Syndrome in Children
- Vaccine enhanced disease

Source: https://www.fda.gov/media/143557/download

Yet adverse events of particular interest (AEIS) are mentioned in all clinical trial protocols since, according to the presentation by ChuanFeng Shih from GlaxoSmithKline, an AEIS "is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate.

Illustration 172 : GlaxoSmithKline – AESI definition



Source : https://lexjansen.com/phuse-us/2019/dh/DH02_ppt.pdf

This involved keeping a close eye on all the events identified by Tom Shimakuburo from October 2020 onwards.

13.3 Analysis of adverse events by Pfizer from December 01, 2020 to February 28, 2021

« 5.3.6 Cumulative Analysis of Post-authorization Adverse Event Reports » provides an analysis of cumulative U.S. and international post-authorization safety data and a cumulative analysis of identified significant risks, significant potential risks, and Missing Information.

From December 01, 2020 to February 28, 2021, 42,086 case reports are in the database, 25,379 medically confirmed and 16,707 non-medically confirmed, containing 158,893 events 34,762 in the United States, 13,739 in the United Kingdom, 13,404 in Italy 7,324 were distributed in 56 other countries.

Among the 42,086 reports, 1,223 deaths were reported, or nearly 3% (see below).

Illustration 173 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – General Analysis

BNT162b2
5.3.6 Cumulative Analysis of Post-authorization Adverse Event Reports

Table 1 below presents the main characteristics of the overall cases.

Table 1. General Overview: Selected Characteristics of All Cases Received During the Reporting Interval

Characteristics		Relevant cases (N=42086)
Gender:	Female	29914
	Male	9182
	No Data	2990
Age range (years): 0.01 -107 years Mean = 50.9 years n = 34952	≤ 17 18-30 31-50 51-64 65-74 ≥ 75 Unknown	175[a] 4953 13886 7884 3098 5214 6876
Case outcome:	Recovered/Recovering	19582
	Recovered with sequelae	520
	Not recovered at the time of report	11361
	Fatal	1223
	Unknown	9400

a. in 46 cases reported age was <16-year-old and in 34 cases <12-year-old.

Source : https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf

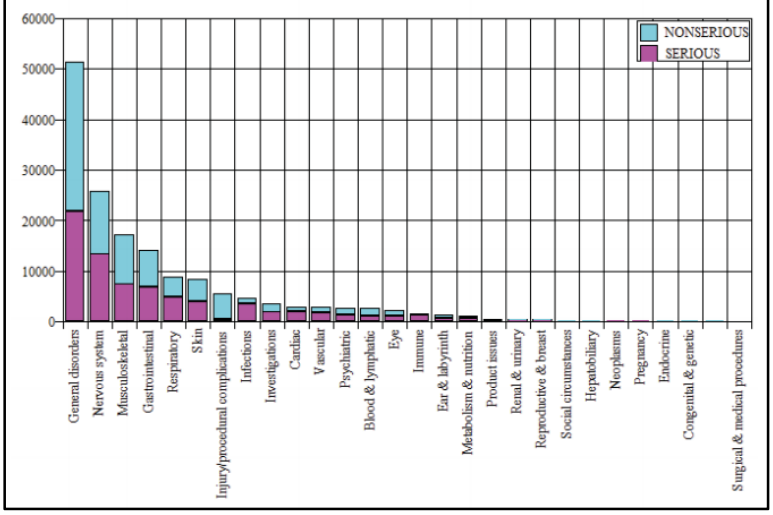
The most reported adverse events (AEs) were general disorders and administration site conditions (51,335 AEs), nervous system disorders (25,957), musculoskeletal and connective tissue disorders (17,283) gastrointestinal disorders (14,096), skin and subcutaneous tissue disorders (8,476), respiratory, thoracic, and mediastinal disorders (8,848), infections and infestations (4,610), injuries, poisonings, and procedural complications (5,590), and investigations (3,693).

Illustration 174 shows a **high proportion of serious events** (indicated in purple), more than 50% of the reported effects were serious for almost all categories, and more particularly among cardiac diseases, infections, autoimmune diseases.

Illustration 174 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 - Total Number of Adverse Events by Organ Class and Seriousness

BNT162b2
5.3.6 Cumulative Analysis of Post-authorization Adverse Event Reports

Figure 1. Total Number of BNT162b2 AEs by System Organ Classes and Event Seriousness



Source : https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf

It is interesting to note that **1,927 COVID-19 out of 42,086 were reported (**4.6%) in the Infections and infestations class (System Organ Class of the MedDRA dictionary) as mentioned into the table below.

Illustration 175 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 - Events reported ≥ 2% Cases

Table 2. Events Reported in ≥2% Cases

		Cumulatively Through 28 February 2021
MedDRA SOC	**MedDRA PT**	**AEs (AERP%) N = 42086**
	Pain	3691 (8.8%)
	Malaise	2897 (6.9%)
	Asthenia	2285 (5.4%)
	Drug ineffective	2201 (5.2%)
	Vaccination site erythema	930 (2.2%)
	Vaccination site swelling	913 (2.2%)
	Influenza like illness	835 (2%)
Infections and infestations		
	COVID-19	1927 (4.6%)
Injury, poisoning and procedural complications		
	Off label use	880 (2.1%)
	Product use issue	828 (2.0%)
Musculoskeletal and connective tissue disorders		
	Myalgia	4915 (11.7%)
	Pain in extremity	3959 (9.4%)
	Arthralgia	3525 (8.4%)
Nervous system disorders		
	Headache	10131 (24.1%)
	Dizziness	3720 (8.8%)
	Paraesthesia	1500 (3.6%)
	Hypoaesthesia	999 (2.4%)
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	2057 (4.9%)
	Cough	1146 (2.7%)
	Oropharyngeal pain	948 (2.3%)
Skin and subcutaneous tissue disorders		
	Pruritus	1447 (3.4%)
	Rash	1404 (3.3%)
	Erythema	1044 (2.5%)
	Hyperhidrosis	900 (2.1%)
	Urticaria	862 (2.1%)
Total number of events		**93473**

The report also highlighted the occurrence of

- Cardiac adverse events myocardial infarction, arrhythmia, heart failure, cardiogenic shock; coronary heart disease, myocardial infarction, tachycardia, cardiomyopathy
- Hematological adverse events: leukopenia, neutropenia, thrombocytopenia, hemorrhage
- Facial paralysis or paresis ...

Although pregnant women were excluded from the clinical trials, they were also vaccinated in real life, and the report mentions 270 pregnant women among whom 26 spontaneous abortions or neonatal deaths were reported.

Illustration 176 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 - Pregnant women

Pregnancy cases: 274 cases including:

- 270 mother cases and 4 foetus/baby cases representing 270 unique pregnancies (the 4 foetus/baby cases were linked to 3 mother cases; 1 mother case involved twins).
- Pregnancy outcomes for the 270 pregnancies were reported as spontaneous abortion (23), outcome pending (5), premature birth with neonatal death, spontaneous abortion with intrauterine death (2 each), spontaneous abortion with neonatal death, and normal outcome (1 each). No outcome was provided for 238 pregnancies (note that 2 different outcomes were reported for each twin, and both were counted).

This document also mentions adverse events of particular interest.

Illustration 177: Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 - AESI

BNT162b2
5.3.6 Cumulative Analysis of Post-authorization Adverse Event Reports

3.1.3. Review of Adverse Events of Special Interest (AESIs)

Please refer to Appendix 1 for the list of the company's AESIs for BNT162b2.

The company's AESI list takes into consideration the lists of AESIs from the following expert groups and regulatory authorities: Brighton Collaboration (SPEAC), ACCESS protocol, US CDC (preliminary list of AESI for VAERS surveillance), MHRA (unpublished guideline).

The AESI terms are incorporated into a TME list and include events of interest due to their association with severe COVID-19 and events of interest for vaccines in general.

The AESI list is comprised of MedDRA PTs, HLTs, HLGTs or MedDRA SMQs and can be changed as appropriate based on the evolving safety profile of the vaccine.

APPENDIX 1: LIST OF ADVERSE EVENTS OF PARTICULAR INTEREST contains a nine-page list of over a thousand pathologies.

Illustration 178 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 1

APPENDIX 1. LIST OF ADVERSE EVENTS OF SPECIAL INTEREST

1p36 deletion syndrome;2-Hydroxyglutaric aciduria;5'nucleotidase increased;Acoustic neuritis;Acquired C1 inhibitor deficiency;Acquired epidermolysis bullosa;Acquired epileptic aphasia;Acute cutaneous lupus erythematosus;Acute disseminated encephalomyelitis;Acute encephalitis with refractory, repetitive partial seizures;Acute febrile neutrophilic dermatosis;Acute flaccid myelitis;Acute haemorrhagic leukoencephalitis;Acute haemorrhagic oedema of infancy;Acute kidney injury;Acute macular outer retinopathy;Acute motor axonal neuropathy;Acute motor-sensory axonal neuropathy;Acute myocardial infarction;Acute respiratory distress syndrome;Acute respiratory failure;Addison's disease;Administration site thrombosis;Administration site vasculitis;Adrenal thrombosis;Adverse event following immunisation;Ageusia;Agranulocytosis;Air embolism;Alanine aminotransferase abnormal;Alanine aminotransferase increased;Alcoholic seizure;Allergic bronchopulmonary mycosis;Allergic oedema;Alloimmune hepatitis;Alopecia areata;Alpers disease;Alveolar proteinosis;Ammonia abnormal;Ammonia increased;Amniotic cavity infection;Amygdalohippocampectomy;Amyloid arthropathy;Amyloidosis;Amyloidosis senile;Anaphylactic reaction;Anaphylactic shock;Anaphylactic transfusion reaction;Anaphylactoid reaction;Anaphylactoid shock;Anaphylactoid syndrome of pregnancy;Angioedema;Angiopathic neuropathy;Ankylosing spondylitis;Anosmia;Antiacetylcholine receptor antibody positive;Anti-actin antibody positive;Anti-aquaporin-4 antibody positive;Anti-basal ganglia antibody positive;Anti-cyclic citrullinated peptide antibody positive;Anti-epithelial antibody positive;Anti-erythrocyte antibody positive;Anti-exosome complex antibody positive;Anti-GAD antibody negative;Anti-GAD antibody positive;Anti-ganglioside antibody positive;Antigliadin antibody positive;Anti-glomerular basement membrane antibody positive;Anti-glomerular basement membrane disease;Anti-glycyl-tRNA synthetase antibody positive;Anti-HLA antibody test positive;Anti-IA2 antibody positive;Anti-insulin antibody increased;Anti-insulin antibody positive;Anti-insulin receptor antibody increased;Anti-insulin receptor antibody positive;Anti-interferon antibody negative;Anti-interferon antibody positive;Anti-islet cell antibody positive;Antimitochondrial antibody positive;Anti-muscle specific kinase antibody positive;Anti-myelin-associated glycoprotein antibodies positive;Anti-myelin-associated glycoprotein associated polyneuropathy;Antimyocardial antibody positive;Anti-neuronal antibody positive;Antineutrophil cytoplasmic antibody increased;Antineutrophil cytoplasmic antibody positive;Anti-neutrophil cytoplasmic antibody positive vasculitis;Anti-NMDA antibody positive;Antinuclear antibody increased;Antinuclear antibody positive;Antiphospholipid antibodies positive;Antiphospholipid syndrome;Anti-platelet antibody positive;Anti-prothrombin antibody positive;Antiribosomal P antibody positive;Anti-RNA polymerase III antibody positive;Anti-saccharomyces cerevisiae antibody test positive;Anti-sperm antibody positive;Anti-SRP antibody positive;Antisynthetase syndrome;Anti-thyroid antibody positive;Anti-transglutaminase antibody increased;Anti-VGCC antibody positive;Anti-VGKC antibody positive;Anti-vimentin antibody positive;Antiviral prophylaxis;Antiviral treatment;Anti-zinc transporter 8 antibody positive;Aortic embolus;Aortic thrombosis;Aortitis;Aplasia pure red cell;Aplastic anaemia;Application site thrombosis;Application site vasculitis;Arrhythmia;Arterial bypass occlusion;Arterial bypass thrombosis;Arterial thrombosis;Arteriovenous fistula thrombosis;Arteriovenous graft site stenosis;Arteriovenous graft thrombosis;Arteritis;Arteritis

Illustration 179 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 2

coronary;Arthralgia;Arthritis;Arthritis enteropathic;Ascites;Aseptic cavernous sinus thrombosis;Aspartate aminotransferase abnormal;Aspartate aminotransferase increased;Aspartate-glutamate-transporter deficiency;AST to platelet ratio index increased;AST/ALT ratio abnormal;Asthma;Asymptomatic COVID-19;Ataxia;Atheroembolism;Atonic seizures;Atrial thrombosis;Atrophic thyroiditis;Atypical benign partial epilepsy;Atypical pneumonia;Aura;Autoantibody positive;Autoimmune anaemia;Autoimmune aplastic anaemia;Autoimmune arthritis;Autoimmune blistering disease;Autoimmune cholangitis;Autoimmune colitis;Autoimmune demyelinating disease;Autoimmune dermatitis;Autoimmune disorder;Autoimmune encephalopathy;Autoimmune endocrine disorder;Autoimmune enteropathy;Autoimmune eye disorder;Autoimmune haemolytic anaemia;Autoimmune heparin-induced thrombocytopenia;Autoimmune hepatitis;Autoimmune hyperlipidaemia;Autoimmune hypothyroidism;Autoimmune inner ear disease;Autoimmune lung disease;Autoimmune lymphoproliferative syndrome;Autoimmune myocarditis;Autoimmune myositis;Autoimmune nephritis;Autoimmune neuropathy;Autoimmune neutropenia;Autoimmune pancreatitis;Autoimmune pancytopenia;Autoimmune pericarditis;Autoimmune retinopathy;Autoimmune thyroid disorder;Autoimmune thyroiditis;Autoimmune uveitis;Autoinflammation with infantile enterocolitis;Autoinflammatory disease;Automatism epileptic;Autonomic nervous system imbalance;Autonomic seizure;Axial spondyloarthritis;Axillary vein thrombosis;Axonal and demyelinating polyneuropathy;Axonal neuropathy;Bacterascites;Baltic myoclonic epilepsy;Band sensation;Basedow's disease;Basilar artery thrombosis;Basophilopenia;B-cell aplasia;Behcet's syndrome;Benign ethnic neutropenia;Benign familial neonatal convulsions;Benign familial pemphigus;Benign rolandic epilepsy;Beta-2 glycoprotein antibody positive;Bickerstaff's encephalitis;Bile output abnormal;Bile output decreased;Biliary ascites;Bilirubin conjugated abnormal;Bilirubin conjugated increased;Bilirubin urine present;Biopsy liver abnormal;Biotinidase deficiency;Birdshot chorioretinopathy;Blood alkaline phosphatase abnormal;Blood alkaline phosphatase increased;Blood bilirubin abnormal;Blood bilirubin increased;Blood bilirubin unconjugated increased;Blood cholinesterase abnormal;Blood cholinesterase decreased;Blood pressure decreased;Blood pressure diastolic decreased;Blood pressure systolic decreased;Blue toe syndrome;Brachiocephalic vein thrombosis;Brain stem embolism;Brain stem thrombosis;Bromosulphthalein test abnormal;Bronchial oedema;Bronchitis;Bronchitis mycoplasmal;Bronchitis viral;Bronchopulmonary aspergillosis allergic;Bronchospasm;Budd-Chiari syndrome;Bulbar palsy;Butterfly rash;C1q nephropathy;Caesarean section;Calcium embolism;Capillaritis;Caplan's syndrome;Cardiac amyloidosis;Cardiac arrest;Cardiac failure;Cardiac failure acute;Cardiac sarcoidosis;Cardiac ventricular thrombosis;Cardiogenic shock;Cardiolipin antibody positive;Cardiopulmonary failure;Cardio-respiratory arrest;Cardio-respiratory distress;Cardiovascular insufficiency;Carotid arterial embolus;Carotid artery thrombosis;Cataplexy;Catheter site thrombosis;Catheter site vasculitis;Cavernous sinus thrombosis;CDKL5 deficiency disorder;CEC syndrome;Cement embolism;Central nervous system lupus;Central nervous system vasculitis;Cerebellar artery thrombosis;Cerebellar embolism;Cerebral amyloid angiopathy;Cerebral arteritis;Cerebral artery embolism;Cerebral artery thrombosis;Cerebral gas embolism;Cerebral microembolism;Cerebral septic infarct;Cerebral thrombosis;Cerebral venous sinus thrombosis;Cerebral venous thrombosis;Cerebrospinal thrombotic

Illustration 180 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 3

tamponade;Cerebrovascular accident;Change in seizure presentation;Chest discomfort;Child-Pugh-Turcotte score abnormal;Child-Pugh-Turcotte score increased;Chillblains;Choking;Choking sensation;Cholangitis sclerosing;Chronic autoimmune glomerulonephritis;Chronic cutaneous lupus erythematosus;Chronic fatigue syndrome;Chronic gastritis;Chronic inflammatory demyelinating polyradiculoneuropathy;Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids;Chronic recurrent multifocal osteomyelitis;Chronic respiratory failure;Chronic spontaneous urticaria;Circulatory collapse;Circumoral oedema;Circumoral swelling;Clinically isolated syndrome;Clonic convulsion;Coeliac disease;Cogan's syndrome;Cold agglutinins positive;Cold type haemolytic anaemia;Colitis;Colitis erosive;Colitis herpes;Colitis microscopic;Colitis ulcerative;Collagen disorder;Collagen-vascular disease;Complement factor abnormal;Complement factor C1 decreased;Complement factor C2 decreased;Complement factor C3 decreased;Complement factor C4 decreased;Complement factor decreased;Computerised tomogram liver abnormal;Concentric sclerosis;Congenital anomaly;Congenital bilateral perisylvian syndrome;Congenital herpes simplex infection;Congenital myasthenic syndrome;Congenital varicella infection;Congestive hepatopathy;Convulsion in childhood;Convulsions local;Convulsive threshold lowered;Coombs positive haemolytic anaemia;Coronary artery disease;Coronary artery embolism;Coronary artery thrombosis;Coronary bypass thrombosis;Coronavirus infection;Coronavirus test;Coronavirus test negative;Coronavirus test positive;Corpus callosotomy;Cough;Cough variant asthma;COVID-19;COVID-19 immunisation;COVID-19 pneumonia;COVID-19 prophylaxis;COVID-19 treatment;Cranial nerve disorder;Cranial nerve palsies multiple;Cranial nerve paralysis;CREST syndrome;Crohn's disease;Cryofibrinogenaemia;Cryoglobulinaemia;CSF oligoclonal band present;CSWS syndrome;Cutaneous amyloidosis;Cutaneous lupus erythematosus;Cutaneous sarcoidosis;Cutaneous vasculitis;Cyanosis;Cyclic neutropenia;Cystitis interstitial;Cytokine release syndrome;Cytokine storm;De novo purine synthesis inhibitors associated acute inflammatory syndrome;Death neonatal;Deep vein thrombosis;Deep vein thrombosis postoperative;Deficiency of bile secretion;Deja vu;Demyelinating polyneuropathy;Demyelination;Dermatitis;Dermatitis bullous;Dermatitis herpetiformis;Dermatomyositis;Device embolisation;Device related thrombosis;Diabetes mellitus;Diabetic ketoacidosis;Diabetic mastopathy;Dialysis amyloidosis;Dialysis membrane reaction;Diastolic hypotension;Diffuse vasculitis;Digital pitting scar;Disseminated intravascular coagulation;Disseminated intravascular coagulation in newborn;Disseminated neonatal herpes simplex;Disseminated varicella;Disseminated varicella zoster vaccine virus infection;Disseminated varicella zoster virus infection;DNA antibody positive;Double cortex syndrome;Double stranded DNA antibody positive;Dreamy state;Dressler's syndrome;Drop attacks;Drug withdrawal convulsions;Dyspnoea;Early infantile epileptic encephalopathy with burst-suppression;Eclampsia;Eczema herpeticum;Embolia cutis medicamentosa;Embolic cerebellar infarction;Embolic cerebral infarction;Embolic pneumonia;Embolic stroke;Embolism;Embolism arterial;Embolism venous;Encephalitis;Encephalitis allergic;Encephalitis autoimmune;Encephalitis brain stem;Encephalitis haemorrhagic;Encephalitis periaxialis diffusa;Encephalitis post immunisation;Encephalomyelitis;Encephalopathy;Endocrine disorder;Endocrine ophthalmopathy;Endotracheal intubation;Enteritis;Enteritis leukopenic;Enterobacter pneumonia;Enterocolitis;Enteropathic spondylitis;Eosinopenia;Eosinophilic

Illustration 181 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 4

fasciitis;Eosinophilic granulomatosis with polyangiitis;Eosinophilic oesophagitis;Epidermolysis;Epilepsy;Epilepsy surgery;Epilepsy with myoclonic-atonic seizures;Epileptic aura;Epileptic psychosis;Erythema;Erythema induratum;Erythema multiforme;Erythema nodosum;Evans syndrome;Exanthema subitum;Expanded disability status scale score decreased;Expanded disability status scale score increased;Exposure to communicable disease;Exposure to SARS-CoV-2;Eye oedema;Eye pruritus;Eye swelling;Eyelid oedema;Face oedema;Facial paralysis;Facial paresis;Faciobrachial dystonic seizure;Fat embolism;Febrile convulsion;Febrile infection-related epilepsy syndrome;Febrile neutropenia;Felty's syndrome;Femoral artery embolism;Fibrillary glomerulonephritis;Fibromyalgia;Flushing;Foaming at mouth;Focal cortical resection;Focal dyscognitive seizures;Foetal distress syndrome;Foetal placental thrombosis;Foetor hepaticus;Foreign body embolism;Frontal lobe epilepsy;Fulminant type 1 diabetes mellitus;Galactose elimination capacity test abnormal;Galactose elimination capacity test decreased;Gamma-glutamyltransferase abnormal;Gamma-glutamyltransferase increased;Gastritis herpes;Gastrointestinal amyloidosis;Gelastic seizure;Generalised onset non-motor seizure;Generalised tonic-clonic seizure;Genital herpes;Genital herpes simplex;Genital herpes zoster;Giant cell arteritis;Glomerulonephritis;Glomerulonephritis membranoproliferative;Glomerulonephritis membranous;Glomerulonephritis rapidly progressive;Glossopharyngeal nerve paralysis;Glucose transporter type 1 deficiency syndrome;Glutamate dehydrogenase increased;Glycocholic acid increased;GM2 gangliosidosis;Goodpasture's syndrome;Graft thrombosis;Granulocytopenia;Granulocytopenia neonatal;Granulomatosis with polyangiitis;Granulomatous dermatitis;Grey matter heterotopia;Guanase increased;Guillain-Barre syndrome;Haemolytic anaemia;Haemophagocytic lymphohistiocytosis;Haemorrhage;Haemorrhagic ascites;Haemorrhagic disorder;Haemorrhagic pneumonia;Haemorrhagic varicella syndrome;Haemorrhagic vasculitis;Hantavirus pulmonary infection;Hashimoto's encephalopathy;Hashitoxicosis;Hemimegalencephaly;Henoch-Schonlein purpura;Henoch-Schonlein purpura nephritis;Hepaplastin abnormal;Hepaplastin decreased;Heparin-induced thrombocytopenia;Hepatic amyloidosis;Hepatic artery embolism;Hepatic artery flow decreased;Hepatic artery thrombosis;Hepatic enzyme abnormal;Hepatic enzyme decreased;Hepatic enzyme increased;Hepatic fibrosis marker abnormal;Hepatic fibrosis marker increased;Hepatic function abnormal;Hepatic hydrothorax;Hepatic hypertrophy;Hepatic hypoperfusion;Hepatic lymphocytic infiltration;Hepatic mass;Hepatic pain;Hepatic sequestration;Hepatic vascular resistance increased;Hepatic vascular thrombosis;Hepatic vein embolism;Hepatic vein thrombosis;Hepatic venous pressure gradient abnormal;Hepatic venous pressure gradient increased;Hepatitis;Hepatobiliary scan abnormal;Hepatomegaly;Hepatosplenomegaly;Hereditary angioedema with C1 esterase inhibitor deficiency;Herpes dermatitis;Herpes gestationis;Herpes oesophagitis;Herpes ophthalmic;Herpes pharyngitis;Herpes sepsis;Herpes simplex;Herpes simplex cervicitis;Herpes simplex colitis;Herpes simplex encephalitis;Herpes simplex gastritis;Herpes simplex hepatitis;Herpes simplex meningitis;Herpes simplex meningoencephalitis;Herpes simplex meningomyelitis;Herpes simplex necrotising retinopathy;Herpes simplex oesophagitis;Herpes simplex otitis externa;Herpes simplex pharyngitis;Herpes simplex pneumonia;Herpes simplex reactivation;Herpes simplex sepsis;Herpes simplex viraemia;Herpes simplex virus conjunctivitis neonatal;Herpes simplex visceral;Herpes virus

Illustration 182 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 5

infection;Herpes zoster;Herpes zoster cutaneous disseminated;Herpes zoster infection neurological;Herpes zoster meningitis;Herpes zoster meningoencephalitis;Herpes zoster meningomyelitis;Herpes zoster meningoradiculitis;Herpes zoster necrotising retinopathy;Herpes zoster oticus;Herpes zoster pharyngitis;Herpes zoster reactivation;Herpetic radiculopathy;Histone antibody positive;Hoigne's syndrome;Human herpesvirus 6 encephalitis;Human herpesvirus 6 infection;Human herpesvirus 6 infection reactivation;Human herpesvirus 7 infection;Human herpesvirus 8 infection;Hyperammonaemia;Hyperbilirubinaemia;Hypercholia;Hypergammaglobulinaemia benign monoclonal;Hyperglycaemic seizure;Hypersensitivity;Hypersensitivity vasculitis;Hyperthyroidism;Hypertransaminasaemia;Hyperventilation;Hypoalbuminaemia;Hypocalcaemic seizure;Hypogammaglobulinaemia;Hypoglossal nerve paralysis;Hypoglossal nerve paresis;Hypoglycaemic seizure;Hyponatraemic seizure;Hypotension;Hypotensive crisis;Hypothenar hammer syndrome;Hypothyroidism;Hypoxia;Idiopathic CD4 lymphocytopenia;Idiopathic generalised epilepsy;Idiopathic interstitial pneumonia;Idiopathic neutropenia;Idiopathic pulmonary fibrosis;IgA nephropathy;IgM nephropathy;IIIrd nerve paralysis;IIIrd nerve paresis;Iliac artery embolism;Immune thrombocytopenia;Immune-mediated adverse reaction;Immune-mediated cholangitis;Immune-mediated cholestasis;Immune-mediated cytopenia;Immune-mediated encephalitis;Immune-mediated encephalopathy;Immune-mediated endocrinopathy;Immune-mediated enterocolitis;Immune-mediated gastritis;Immune-mediated hepatic disorder;Immune-mediated hepatitis;Immune-mediated hyperthyroidism;Immune-mediated hypothyroidism;Immune-mediated myocarditis;Immune-mediated myositis;Immune-mediated nephritis;Immune-mediated neuropathy;Immune-mediated pancreatitis;Immune-mediated pneumonitis;Immune-mediated renal disorder;Immune-mediated thyroiditis;Immune-mediated uveitis;Immunoglobulin G4 related disease;Immunoglobulins abnormal;Implant site thrombosis;Inclusion body myositis;Infantile genetic agranulocytosis;Infantile spasms;Infected vasculitis;Infective thrombosis;Inflammation;Inflammatory bowel disease;Infusion site thrombosis;Infusion site vasculitis;Injection site thrombosis;Injection site urticaria;Injection site vasculitis;Instillation site thrombosis;Insulin autoimmune syndrome;Interstitial granulomatous dermatitis;Interstitial lung disease;Intracardiac mass;Intracardiac thrombus;Intracranial pressure increased;Intrapericardial thrombosis;Intrinsic factor antibody abnormal;Intrinsic factor antibody positive;IPEX syndrome;Irregular breathing;IRVAN syndrome;IVth nerve paralysis;IVth nerve paresis;JC polyomavirus test positive;JC virus CSF test positive;Jeavons syndrome;Jugular vein embolism;Jugular vein thrombosis;Juvenile idiopathic arthritis;Juvenile myoclonic epilepsy;Juvenile polymyositis;Juvenile psoriatic arthritis;Juvenile spondyloarthritis;Kaposi sarcoma inflammatory cytokine syndrome;Kawasaki's disease;Kayser-Fleischer ring;Keratoderma blenorrhagica;Ketosis-prone diabetes mellitus;Kounis syndrome;Lafora's myoclonic epilepsy;Lambl's excrescences;Laryngeal dyspnoea;Laryngeal oedema;Laryngeal rheumatoid arthritis;Laryngospasm;Laryngotracheal oedema;Latent autoimmune diabetes in adults;LE cells present;Lemierre syndrome;Lennox-Gastaut syndrome;Leucine aminopeptidase increased;Leukoencephalomyelitis;Leukoencephalopathy;Leukopenia;Leukopenia neonatal;Lewis-Sumner syndrome;Lhermitte's sign;Lichen planopilaris;Lichen planus;Lichen sclerosus;Limbic encephalitis;Linear IgA disease;Lip oedema;Lip swelling;Liver function test abnormal;Liver function test decreased;Liver function test increased;Liver induration;Liver injury;Liver iron concentration abnormal;Liver iron concentration

Illustration 183 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 6

increased;Liver opacity;Liver palpable;Liver sarcoidosis;Liver scan abnormal;Liver tenderness;Low birth weight baby;Lower respiratory tract herpes infection;Lower respiratory tract infection;Lower respiratory tract infection viral;Lung abscess;Lupoid hepatic cirrhosis;Lupus cystitis;Lupus encephalitis;Lupus endocarditis;Lupus enteritis;Lupus hepatitis;Lupus myocarditis;Lupus myositis;Lupus nephritis;Lupus pancreatitis;Lupus pleurisy;Lupus pneumonitis;Lupus vasculitis;Lupus-like syndrome;Lymphocytic hypophysitis;Lymphocytopenia neonatal;Lymphopenia;MAGIC syndrome;Magnetic resonance imaging liver abnormal;Magnetic resonance proton density fat fraction measurement;Mahler sign;Manufacturing laboratory analytical testing issue;Manufacturing materials issue;Manufacturing production issue;Marburg's variant multiple sclerosis;Marchiafava-Bignami disease;Marine Lenhart syndrome;Mastocytic enterocolitis;Maternal exposure during pregnancy;Medical device site thrombosis;Medical device site vasculitis;MELAS syndrome;Meningitis;Meningitis aseptic;Meningitis herpes;Meningoencephalitis herpes simplex neonatal;Meningoencephalitis herpetic;Meningomyelitis herpes;MERS-CoV test;MERS-CoV test negative;MERS-CoV test positive;Mesangioproliferative glomerulonephritis;Mesenteric artery embolism;Mesenteric artery thrombosis;Mesenteric vein thrombosis;Metapneumovirus infection;Metastatic cutaneous Crohn's disease;Metastatic pulmonary embolism;Microangiopathy;Microembolism;Microscopic polyangiitis;Middle East respiratory syndrome;Migraine-triggered seizure;Miliary pneumonia;Miller Fisher syndrome;Mitochondrial aspartate aminotransferase increased;Mixed connective tissue disease;Model for end stage liver disease score abnormal;Model for end stage liver disease score increased;Molar ratio of total branched-chain amino acid to tyrosine;Molybdenum cofactor deficiency;Monocytopenia;Mononeuritis;Mononeuropathy multiplex;Morphoea;Morvan syndrome;Mouth swelling;Moyamoya disease;Multifocal motor neuropathy;Multiple organ dysfunction syndrome;Multiple sclerosis;Multiple sclerosis relapse;Multiple sclerosis relapse prophylaxis;Multiple subpial transection;Multisystem inflammatory syndrome in children;Muscular sarcoidosis;Myasthenia gravis;Myasthenia gravis crisis;Myasthenia gravis neonatal;Myasthenic syndrome;Myelitis;Myelitis transverse;Myocardial infarction;Myocarditis;Myocarditis post infection;Myoclonic epilepsy;Myoclonic epilepsy and ragged-red fibres;Myokymia;Myositis;Narcolepsy;Nasal herpes;Nasal obstruction;Necrotising herpetic retinopathy;Neonatal Crohn's disease;Neonatal epileptic seizure;Neonatal lupus erythematosus;Neonatal mucocutaneous herpes simplex;Neonatal pneumonia;Neonatal seizure;Nephritis;Nephrogenic systemic fibrosis;Neuralgic amyotrophy;Neuritis;Neuritis cranial;Neuromyelitis optica pseudo relapse;Neuromyelitis optica spectrum disorder;Neuromyotonia;Neuronal neuropathy;Neuropathy peripheral;Neuropathy, ataxia, retinitis pigmentosa syndrome;Neuropsychiatric lupus;Neurosarcoidosis;Neutropenia;Neutropenia neonatal;Neutropenic colitis;Neutropenic infection;Neutropenic sepsis;Nodular rash;Nodular vasculitis;Noninfectious myelitis;Noninfective encephalitis;Noninfective encephalomyelitis;Noninfective oophoritis;Obstetrical pulmonary embolism;Occupational exposure to communicable disease;Occupational exposure to SARS-CoV-2;Ocular hyperaemia;Ocular myasthenia;Ocular pemphigoid;Ocular sarcoidosis;Ocular vasculitis;Oculofacial paralysis;Oedema;Oedema blister;Oedema due to hepatic disease;Oedema mouth;Oesophageal achalasia;Ophthalmic artery thrombosis;Ophthalmic herpes simplex;Ophthalmic herpes zoster;Ophthalmic vein thrombosis;Optic neuritis;Optic

Illustration 184 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 7

neuropathy;Optic perineuritis;Oral herpes;Oral lichen planus;Oropharyngeal oedema;Oropharyngeal spasm;Oropharyngeal swelling;Osmotic demyelination syndrome;Ovarian vein thrombosis;Overlap syndrome;Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection;Paget-Schroetter syndrome;Palindromic rheumatism;Palisaded neutrophilic granulomatous dermatitis;Palmoplantar keratoderma;Palpable purpura;Pancreatitis;Panencephalitis;Papillophlebitis;Paracancerous pneumonia;Paradoxical embolism;Parainfluenzae viral laryngotracheobronchitis;Paraneoplastic dermatomyositis;Paraneoplastic pemphigus;Paraneoplastic thrombosis;Paresis cranial nerve;Parietal cell antibody positive;Paroxysmal nocturnal haemoglobinuria;Partial seizures;Partial seizures with secondary generalisation;Patient isolation;Pelvic venous thrombosis;Pemphigoid;Pemphigus;Penile vein thrombosis;Pericarditis;Pericarditis lupus;Perihepatic discomfort;Periorbital oedema;Periorbital swelling;Peripheral artery thrombosis;Peripheral embolism;Peripheral ischaemia;Peripheral vein thrombus extension;Periportal oedema;Peritoneal fluid protein abnormal;Peritoneal fluid protein decreased;Peritoneal fluid protein increased;Peritonitis lupus;Pernicious anaemia;Petit mal epilepsy;Pharyngeal oedema;Pharyngeal swelling;Pityriasis lichenoides et varioliformis acuta;Placenta praevia;Pleuroparenchymal fibroelastosis;Pneumobilia;Pneumonia;Pneumonia adenoviral;Pneumonia cytomegaloviral;Pneumonia herpes viral;Pneumonia influenzal;Pneumonia measles;Pneumonia mycoplasmal;Pneumonia necrotising;Pneumonia parainfluenzae viral;Pneumonia respiratory syncytial viral;Pneumonia viral;POEMS syndrome;Polyarteritis nodosa;Polyarthritis;Polychondritis;Polyglandular autoimmune syndrome type I;Polyglandular autoimmune syndrome type II;Polyglandular autoimmune syndrome type III;Polyglandular disorder;Polymicrogyria;Polymyalgia rheumatica;Polymyositis;Polyneuropathy;Polyneuropathy idiopathic progressive;Portal pyaemia;Portal vein embolism;Portal vein flow decreased;Portal vein pressure increased;Portal vein thrombosis;Portosplenomesenteric venous thrombosis;Post procedural hypotension;Post procedural pneumonia;Post procedural pulmonary embolism;Post stroke epilepsy;Post stroke seizure;Post thrombotic retinopathy;Post thrombotic syndrome;Post viral fatigue syndrome;Postictal headache;Postictal paralysis;Postictal psychosis;Postictal state;Postoperative respiratory distress;Postoperative respiratory failure;Postoperative thrombosis;Postpartum thrombosis;Postpartum venous thrombosis;Postpericardiotomy syndrome;Post-traumatic epilepsy;Postural orthostatic tachycardia syndrome;Precerebral artery thrombosis;Pre-eclampsia;Preictal state;Premature labour;Premature menopause;Primary amyloidosis;Primary biliary cholangitis;Primary progressive multiple sclerosis;Procedural shock;Proctitis herpes;Proctitis ulcerative;Product availability issue;Product distribution issue;Product supply issue;Progressive facial hemiatrophy;Progressive multifocal leukoencephalopathy;Progressive multiple sclerosis;Progressive relapsing multiple sclerosis;Prosthetic cardiac valve thrombosis;Pruritus;Pruritus allergic;Pseudovasculitis;Psoriasis;Psoriatic arthropathy;Pulmonary amyloidosis;Pulmonary artery thrombosis;Pulmonary embolism;Pulmonary fibrosis;Pulmonary haemorrhage;Pulmonary microemboli;Pulmonary oil microembolism;Pulmonary renal syndrome;Pulmonary sarcoidosis;Pulmonary sepsis;Pulmonary thrombosis;Pulmonary tumour thrombotic microangiopathy;Pulmonary vasculitis;Pulmonary veno-occlusive disease;Pulmonary venous thrombosis;Pyoderma gangrenosum;Pyostomatitis vegetans;Pyrexia;Quarantine;Radiation leukopenia;Radiculitis

Illustration 185 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 8

brachial;Radiologically isolated syndrome;Rash;Rash erythematous;Rash pruritic;Rasmussen encephalitis;Raynaud's phenomenon;Reactive capillary endothelial proliferation;Relapsing multiple sclerosis;Relapsing-remitting multiple sclerosis;Renal amyloidosis;Renal arteritis;Renal artery thrombosis;Renal embolism;Renal failure;Renal vascular thrombosis;Renal vasculitis;Renal vein embolism;Renal vein thrombosis;Respiratory arrest;Respiratory disorder;Respiratory distress;Respiratory failure;Respiratory paralysis;Respiratory syncytial virus bronchiolitis;Respiratory syncytial virus bronchitis;Retinal artery embolism;Retinal artery occlusion;Retinal artery thrombosis;Retinal vascular thrombosis;Retinal vasculitis;Retinal vein occlusion;Retinal vein thrombosis;Retinol binding protein decreased;Retinopathy;Retrograde portal vein flow;Retroperitoneal fibrosis;Reversible airways obstruction;Reynold's syndrome;Rheumatic brain disease;Rheumatic disorder;Rheumatoid arthritis;Rheumatoid factor increased;Rheumatoid factor positive;Rheumatoid factor quantitative increased;Rheumatoid lung;Rheumatoid neutrophilic dermatosis;Rheumatoid nodule;Rheumatoid nodule removal;Rheumatoid scleritis;Rheumatoid vasculitis;Saccadic eye movement;SAPHO syndrome;Sarcoidosis;SARS-CoV-1 test;SARS-CoV-1 test negative;SARS-CoV-1 test positive;SARS-CoV-2 antibody test;SARS-CoV-2 antibody test negative;SARS-CoV-2 antibody test positive;SARS-CoV-2 carrier;SARS-CoV-2 sepsis;SARS-CoV-2 test;SARS-CoV-2 test false negative;SARS-CoV-2 test false positive;SARS-CoV-2 test negative;SARS-CoV-2 test positive;SARS-CoV-2 viraemia;Satoyoshi syndrome;Schizencephaly;Scleritis;Sclerodactylia;Scleroderma;Scleroderma associated digital ulcer;Scleroderma renal crisis;Scleroderma-like reaction;Secondary amyloidosis;Secondary cerebellar degeneration;Secondary progressive multiple sclerosis;Segmented hyalinising vasculitis;Seizure;Seizure anoxic;Seizure cluster;Seizure like phenomena;Seizure prophylaxis;Sensation of foreign body;Septic embolus;Septic pulmonary embolism;Severe acute respiratory syndrome;Severe myoclonic epilepsy of infancy;Shock;Shock symptom;Shrinking lung syndrome;Shunt thrombosis;Silent thyroiditis;Simple partial seizures;Sjogren's syndrome;Skin swelling;SLE arthritis;Smooth muscle antibody positive;Sneezing;Spinal artery embolism;Spinal artery thrombosis;Splenic artery thrombosis;Splenic embolism;Splenic thrombosis;Splenic vein thrombosis;Spondylitis;Spondyloarthropathy;Spontaneous heparin-induced thrombocytopenia syndrome;Status epilepticus;Stevens-Johnson syndrome;Stiff leg syndrome;Stiff person syndrome;Stillbirth;Still's disease;Stoma site thrombosis;Stoma site vasculitis;Stress cardiomyopathy;Stridor;Subacute cutaneous lupus erythematosus;Subacute endocarditis;Subacute inflammatory demyelinating polyneuropathy;Subclavian artery embolism;Subclavian artery thrombosis;Subclavian vein thrombosis;Sudden unexplained death in epilepsy;Superior sagittal sinus thrombosis;Susac's syndrome;Suspected COVID-19;Swelling;Swelling face;Swelling of eyelid;Swollen tongue;Sympathetic ophthalmia;Systemic lupus erythematosus;Systemic lupus erythematosus disease activity index abnormal;Systemic lupus erythematosus disease activity index decreased;Systemic lupus erythematosus disease activity index increased;Systemic lupus erythematosus rash;Systemic scleroderma;Systemic sclerosis pulmonary;Tachycardia;Tachypnoea;Takayasu's arteritis;Temporal lobe epilepsy;Terminal ileitis;Testicular autoimmunity;Throat tightness;Thromboangiitis obliterans;Thrombocytopenia;Thrombocytopenic purpura;Thrombophlebitis;Thrombophlebitis migrans;Thrombophlebitis

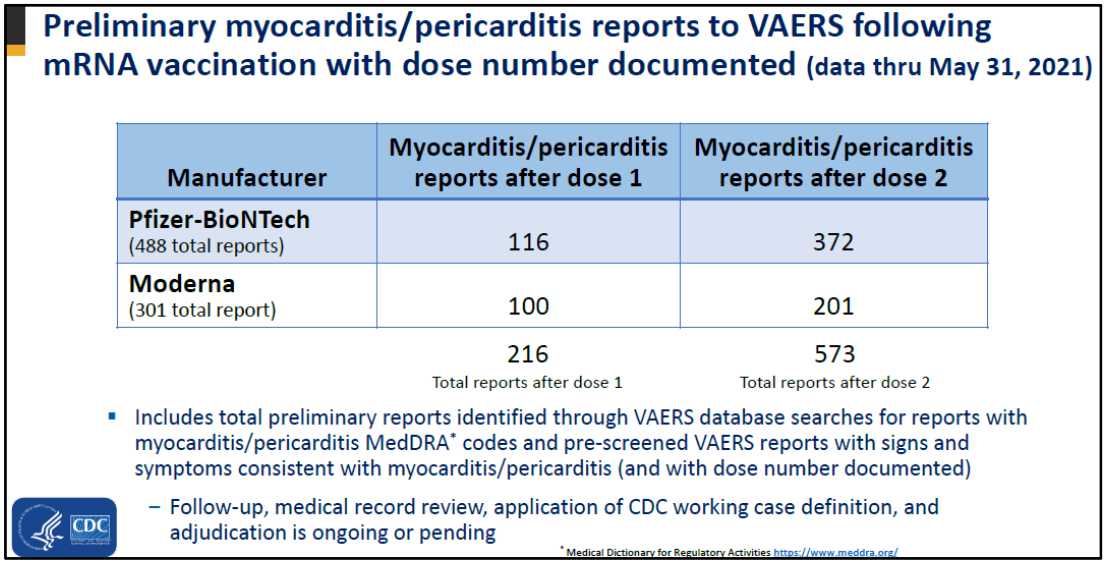
Illustration 186 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – December 2020 to February 2021 – AESI page 9

neonatal;Thrombophlebitis septic;Thrombophlebitis superficial;Thromboplastin antibody positive;Thrombosis;Thrombosis corpora cavernosa;Thrombosis in device;Thrombosis mesenteric vessel;Thrombotic cerebral infarction;Thrombotic microangiopathy;Thrombotic stroke;Thrombotic thrombocytopenic purpura;Thyroid disorder;Thyroid stimulating immunoglobulin increased;Thyroiditis;Tongue amyloidosis;Tongue biting;Tongue oedema;Tonic clonic movements;Tonic convulsion;Tonic posturing;Topectomy;Total bile acids increased;Toxic epidermal necrolysis;Toxic leukoencephalopathy;Toxic oil syndrome;Tracheal obstruction;Tracheal oedema;Tracheobronchitis;Tracheobronchitis mycoplasmal;Tracheobronchitis viral;Transaminases abnormal;Transaminases increased;Transfusion-related alloimmune neutropenia;Transient epileptic amnesia;Transverse sinus thrombosis;Trigeminal nerve paresis;Trigeminal neuralgia;Trigeminal palsy;Truncus coeliacus thrombosis;Tuberous sclerosis complex;Tubulointerstitial nephritis and uveitis syndrome;Tumefactive multiple sclerosis;Tumour embolism;Tumour thrombosis;Type 1 diabetes mellitus;Type I hypersensitivity;Type III immune complex mediated reaction;Uhthoff's phenomenon;Ulcerative keratitis;Ultrasound liver abnormal;Umbilical cord thrombosis;Uncinate fits;Undifferentiated connective tissue disease;Upper airway obstruction;Urine bilirubin increased;Urobilinogen urine decreased;Urobilinogen urine increased;Urticaria;Urticaria papular;Urticarial vasculitis;Uterine rupture;Uveitis;Vaccination site thrombosis;Vaccination site vasculitis;Vagus nerve paralysis;Varicella;Varicella keratitis;Varicella post vaccine;Varicella zoster gastritis;Varicella zoster oesophagitis;Varicella zoster pneumonia;Varicella zoster sepsis;Varicella zoster virus infection;Vasa praevia;Vascular graft thrombosis;Vascular pseudoaneurysm thrombosis;Vascular purpura;Vascular stent thrombosis;Vasculitic rash;Vasculitic ulcer;Vasculitis;Vasculitis gastrointestinal;Vasculitis necrotising;Vena cava embolism;Vena cava thrombosis;Venous intravasation;Venous recanalisation;Venous thrombosis;Venous thrombosis in pregnancy;Venous thrombosis limb;Venous thrombosis neonatal;Vertebral artery thrombosis;Vessel puncture site thrombosis;Visceral venous thrombosis;VIth nerve paralysis;VIth nerve paresis;Vitiligo;Vocal cord paralysis;Vocal cord paresis;Vogt-Koyanagi-Harada disease;Warm type haemolytic anaemia;Wheezing;White nipple sign;XIth nerve paralysis;X-ray hepatobiliary abnormal;Young's syndrome;Zika virus associated Guillain Barre syndrome.

13.4 June 10, 2021 Centers for Disease Control and Prevention (CDC) evaluation of safety signals

At its June 10, 2021, CDC safety Updates safety meeting, CDC counted **216 myocarditis/pericarditis after Pfizer and Moderna doses 1, 573 after dose 2, for a total of 789 identified from the VAERS site**.

Illustration 187 : June 10, 2021 CDC safety Updates – Number of myocarditis/pericarditis



Preliminary myocarditis/pericarditis reports to VAERS following mRNA vaccination with dose number documented (data thru May 31, 2021)

Manufacturer	Myocarditis/pericarditis reports after dose 1	Myocarditis/pericarditis reports after dose 2
Pfizer-BioNTech (488 total reports)	116	372
Moderna (301 total report)	100	201
	216 Total reports after dose 1	573 Total reports after dose 2

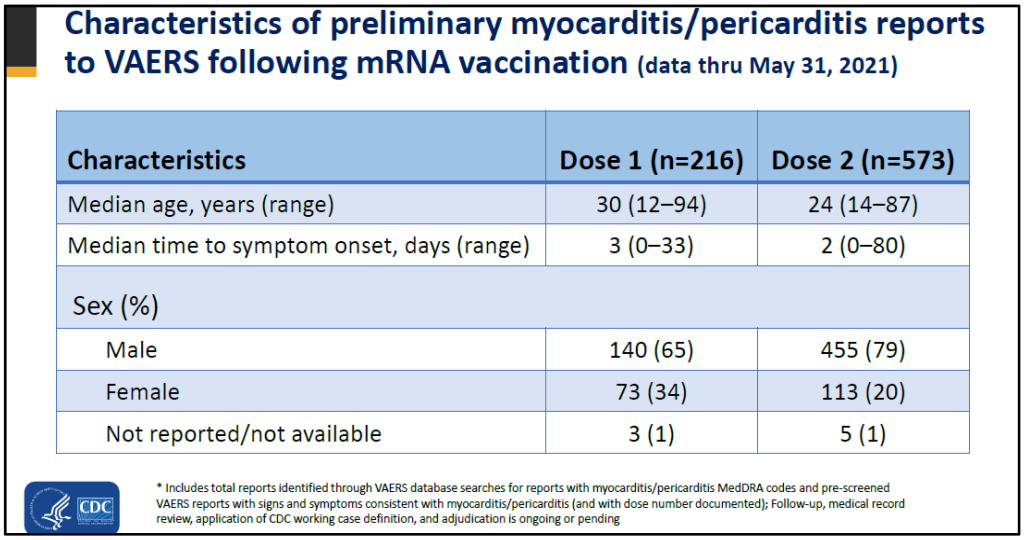
- Includes total preliminary reports identified through VAERS database searches for reports with myocarditis/pericarditis MedDRA* codes and pre-screened VAERS reports with signs and symptoms consistent with myocarditis/pericarditis (and with dose number documented)
  - Follow-up, medical record review, application of CDC working case definition, and adjudication is ongoing or pending

* Medical Dictionary for Regulatory Activities https://www.meddra.org/

Source : CDC safety Updates Vaccines and Related Biological Products Advisory Committee (VRBPAC), Tom Shimabukuro - https://www.fda.gov/media/150054/download

50% of the events were observed in subjects under 30 years of age after dose 1 and in subjects under 24 years of age after dose 2 (see median age line Illustration 188) with events occurring on the same day after injection up to 80 days (Illustration 188 line Median time to symptom).

Illustration 188 : June 10, 2021 CDC safety Updates - Age of patients with myocarditis/ pericarditis



Characteristics of preliminary myocarditis/pericarditis reports to VAERS following mRNA vaccination (data thru May 31, 2021)

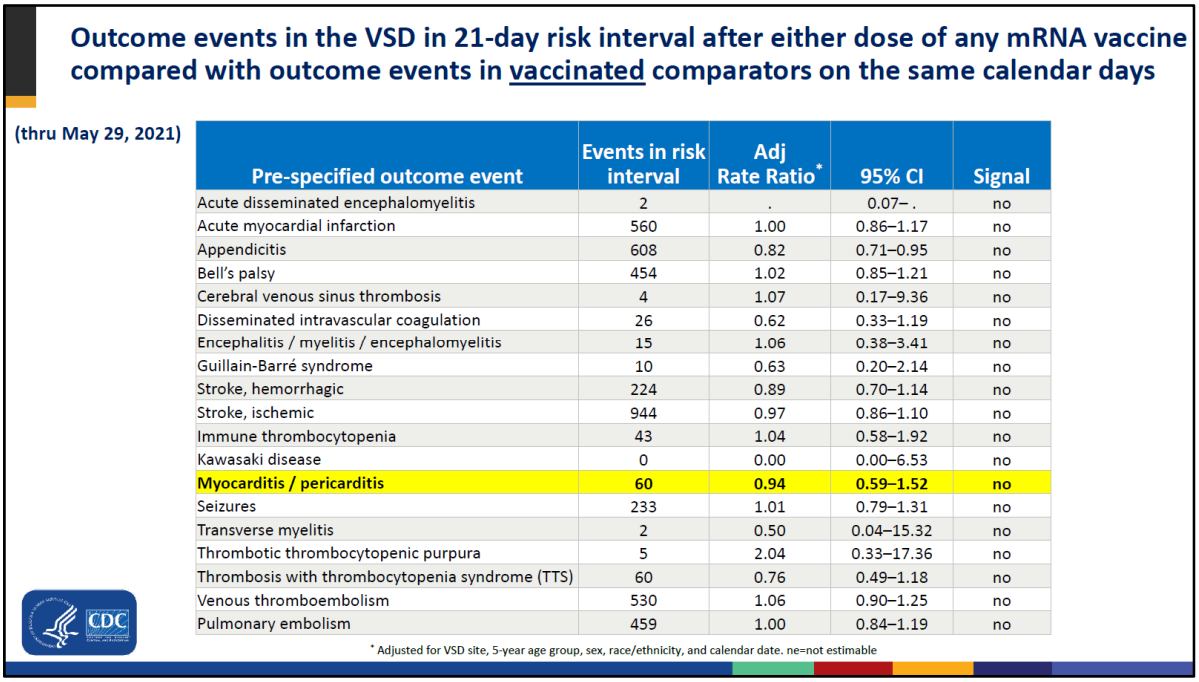
Characteristics	Dose 1 (n=216)	Dose 2 (n=573)
Median age, years (range)	30 (12–94)	24 (14–87)
Median time to symptom onset, days (range)	3 (0–33)	2 (0–80)
Sex (%)		
Male	140 (65)	455 (79)
Female	73 (34)	113 (20)
Not reported/not available	3 (1)	5 (1)

* Includes total reports identified through VAERS database searches for reports with myocarditis/pericarditis MedDRA codes and pre-screened VAERS reports with signs and symptoms consistent with myocarditis/pericarditis (and with dose number documented); Follow-up, medical record review, application of CDC working case definition, and adjudication is ongoing or pending

Source : CDC safety Updates Vaccines and Related Biological Products Advisory Committee (VRBPAC), Tom Shimabukuro - https://www.fda.gov/media/150054/download

Of the 789 myocarditis/pericarditis events, **only 60** were considered, i.e., only 7.6% in the calculation of the signals supposed to warn of an adverse effect in real life. Indeed, due to the calculation method, only events occurring within **21 days after injection** were counted.

Illustration 189 : June 10, 2021 CDC safety Updates – Myocarditis/Pericarditis Risk Assessment



Outcome events in the VSD in 21-day risk interval after either dose of any mRNA vaccine compared with outcome events in vaccinated comparators on the same calendar days

(thru May 29, 2021)

Pre-specified outcome event	Events in risk interval	Adj Rate Ratio*	95% CI	Signal
Acute disseminated encephalomyelitis	2	.	0.07– .	no
Acute myocardial infarction	560	1.00	0.86–1.17	no
Appendicitis	608	0.82	0.71–0.95	no
Bell's palsy	454	1.02	0.85–1.21	no
Cerebral venous sinus thrombosis	4	1.07	0.17–9.36	no
Disseminated intravascular coagulation	26	0.62	0.33–1.19	no
Encephalitis / myelitis / encephalomyelitis	15	1.06	0.38–3.41	no
Guillain-Barré syndrome	10	0.63	0.20–2.14	no
Stroke, hemorrhagic	224	0.89	0.70–1.14	no
Stroke, ischemic	944	0.97	0.86–1.10	no
Immune thrombocytopenia	43	1.04	0.58–1.92	no
Kawasaki disease	0	0.00	0.00–6.53	no
Myocarditis / pericarditis	**60**	**0.94**	**0.59–1.52**	**no**
Seizures	233	1.01	0.79–1.31	no
Transverse myelitis	2	0.50	0.04–15.32	no
Thrombotic thrombocytopenic purpura	5	2.04	0.33–17.36	no
Thrombosis with thrombocytopenia syndrome (TTS)	60	0.76	0.49–1.18	no
Venous thromboembolism	530	1.06	0.90–1.25	no
Pulmonary embolism	459	1.00	0.84–1.19	no

* Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable

Source : CDC safety Updates Vaccines and Related Biological Products Advisory Committee (VRBPAC), Tom Shimabukuro - https://www.fda.gov/media/150054/download

As a result, the safety signal for the occurrence of this serious effect, which could lead to the death of the patient, was minimized. One could have expected, on the contrary, a calculation rather unfavourable to the product, as it is usually done in the pharmaceutical industry, in order not to miss severe risks, especially for a product developed in such a short time and to be distributed worldwide.

In contrast to all the emergency measures taken for COVID-19, no specific steps have been taken to further monitor real-life vaccine adverse events.

In the previous illustration, it should be noted that a significant number of vascular accidents (1168 cases), whether haemorrhagic (Stroke, haemorrhagic) or ischemic (Stroke, ischemic), the same for thrombotic events (5+ 60 +530 + 459 = 1054).

Assuming that, as with myocarditis/pericarditis, the CDC did not count even 10% of reported cases, there would have been more than 12,000 cases of vascular events and more than 12,000 thrombotic events for all COVID-19 vaccines as of June 11.

13.5 Periodic Safety Report 1 (PSUR1) – 19 December 2020 through 18 June 2021

The Safety Report 1, covering the period from December 19, 2020, to June 18, 2021, authored by Pfizer, is curiously unavailable on the EMA website.

https://tkp.at/wp-content/uploads/2023/10/OCR_R-Comirnaty-19-Dec-2020-To-18-June-2021-PSUR-1_body.pdf

Section 15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED (pages 85 to 87)

Regarding the detected safety signals, they included: anaphylaxis, hyperhidrosis, night sweats, asthenia, lethargy, decreased appetite, vaccine-related stress reactions (including dizziness, paresthesia, and tachycardia), diarrhea, extremity pain (arm), vomiting, hypersensitivity other than anaphylaxis, thromboembolic events, delayed skin reactions, delayed syncope, eye pain and swelling, herpes zoster, including ophthalmic shingles, appendicitis, hearing loss and tinnitus, significant limb swelling, dermal filler-associated reactions, injection site pruritus, insomnia, overdose, death (including in elderly or frail individuals), facial nerve paralysis, immune thrombocytopenia, **myocarditis and pericar**ditis, hypertensive crisis with intracranial hemorrhage, and dizziness.

All signals were closed by health authorities except for the last four conditions, for which the signal had not yet been determined.

Illustration 190 : Pfizer – Periodic Safety Report 1 (PSUR1) – 19 December 2020 through 18 June 2021 - Detected safety signals

Table 15. Overview of Signals

Signal	Signal Type	Source	Category	Regulatory Procedure
Anaphylaxis	Closed	Inquiry from a competent authority	Important Identified risk	EMEA/H/C/005735/LEG/022, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Hyperhidrosis	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Night sweats	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Asthenia	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Lethargy	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Decreased appetite	Closed	Clinical study data	Identified risk	EMEA/H/C/005735/II/0036
Vaccine stress-related responses (including Dizziness, Paraesthesia and Tachycardia)[a]	Closed	Routine Pharmacovigilance, Inquiry from a competent authority	Identified risk[b]	EMEA/H/C/005735/II/0038/G, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Diarrhea	Closed	Clinical study data, Inquiry from a competent authority	Identified risk	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Pain in extremity (arm)	Closed	Inquiry from a competent authority	Identified risk	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Vomiting	Closed	Clinical study data, Inquiry from a competent authority	Identified risk	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Hypersensitivity, other than anaphylaxis	Closed	Inquiry from a competent authority	Identified risk	EMEA/H/C/005735/LEG/022, EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Seizure	Closed, Refuted	Inquiry from a competent authority	No risk	-
Thromboembolic events	Closed, Refuted	Inquiry from a competent authority	No risk	-
Delayed skin reaction	Closed, Refuted	Scientific Literature, Inquiry from a competent authority	No risk	-

Table 15. Overview of Signals

Signal	Signal Type	Source	Category	Regulatory Procedure
Delayed syncope	Closed, Refuted	Inquiry from a competent authority	No risk	-
Eye pain and eye swelling	Closed, Refuted	Inquiry from a competent authority	No risk	-
Herpes zoster, including ophthalmic herpes zoster	Closed, Refuted	Routine Pharmacovigilance, Inquiry from a competent authority	No risk	-
Appendicitis	Closed, Refuted	Routine Pharmacovigilance, Inquiry from a competent authority	No risk	-
Hearing loss and Tinnitus	Closed, Refuted	Routine Pharmacovigilance, Inquiry from a competent authority	No risk	-
Extensive swelling of the limbs	Closed, Refuted	Inquiry from a competent authority	No risk[c]	EMEA/H/C/005735/MEA/002.3
Reaction associated with dermal fillers	Closed, Refuted	Routine Pharmacovigilance, Inquiry from a competent authority	No risk[c]	EMEA/H/C/005735/SDA/023 (EPITT ref. 19674), EMEA/H/C/005735/MEA/002.2
Injection site pruritus	Closed, Refuted	Inquiry from a competent authority	No risk[c]	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1
Insomnia	Closed, Refuted	Inquiry from a competent authority	No risk[c]	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Overdose[d]	Closed, Refuted	Routine Pharmacovigilance	No risk	-
Deaths (including elderly or frail individuals)[e]	Closed, Refuted	Inquiry from a competent authority	No risk	-
Facial nerve palsy	Closed, Refuted	Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002, EMEA/H/C/005735/MEA/002.1, EMEA/H/C/005735/MEA/002.2
Immune thrombocytopenia[f]	Ongoing	Inquiry from a competent authority	Not yet determined	PAM-SDA-034 (EPITT No.: 19680).

Table 15. Overview of Signals

Signal	Signal Type	Source	Category	Regulatory Procedure
Trigeminal neuralgia[g]	Ongoing	Inquiry from a competent authority	Not yet determined	-
Myocarditis and pericarditis[h]	Ongoing	Inquiry from a competent authority	Not yet determined	EMA/PRAC/325882/2021 PAM-SDA-032 (EPITT No. 19712)
Hypertensive crisis with intracranial haemorrhage[i]	Ongoing	Inquiry from a competent authority	Not yet determined	-

a. In Appendix 3, Dizziness, Tachycardia and Paraesthesia appear as individual signals determined to be risk.
b. Added to CDS and local labels as potential symptom of Vaccination stress-related response in the Warnings and Precautions section (not ADR section). Identified risk for the process of vaccination rather than the vaccine substrate. CDS, Section 4.4 updated to enhance the providers understanding to take precautions and to differentiate stress/anxiety related reactions versus anaphylaxis reactions.
c. No risk in the CDS; identified risk in the EU-SmPC.
d. Interval reporting period data are summarized in Section 16.3.4.2 *Overdose*.
e. Interval reporting period and cumulative data are summarized in Section 16.3.4.1 *Death* and in Section 16.3.4.1.1 *Death Review by Age Group*.
f. Closed after the PSUR DLP on 04 August 2021 as no risk.
g. Closed after the PSUR DLP on 02 July 2021 as non-validated signal.
h. Closed after the PSUR DLP on 30 June 2021 as Important identified risk.
i. Closed after the PSUR DLP on 30 June 2021 as non-validated signal.

The occurrence of **menstrual disorders** following vaccination was discussed as early as April 2021, with the signal being reassessed in June 2021. It was requested that data be provided to better evaluate this signal in August 2021.

The PSUR states: « *In the final AR of the 5th SMSR (01 April 2021 - 29 April 2021), it was stated that* ***a number of queries have been received about menstrual disorders, especially menorrhagia****. This issue merits further investigation in the upcoming PSUR which, may be a matter of concern for young women, a review is expected in the upcoming PSUR. In the preliminary AR of the 7th SMSR (01 June 2021 - 30 June 2021) this additional request is reported.*"

Despite the risk faced by all women, particularly young women, the report concluded that it was not possible to establish a cause-and-effect relationship between vaccination and menstrual irregularities. These are likely to be associated with **psychological distress** and **stress related to the pandemic**, **weight gain**, **longer working hours**, and **dietary changes**.

Illustration 191 : Pfizer – Periodic Safety Report 1 (PSUR1) – 19 December 2020 through 18 June 2021 – Menstrual disorders

15.10. Menstrual Disorders

In the final AR of the 5th SMSR (01 April 2021 – 29 April 2021), it was stated that a number of queries have been received about menstrual disorders, especially menorrhagia. This issue merits further investigation in the upcoming PSUR which, may be a matter of concern for young women, a review is expected in the upcoming PSUR.

In the preliminary AR of the 7th SMSR (01 June 2021 – 30 June 2021) this additional request is reported.
In accordance with the LoQ of the 5th MSSR, the MAH will provide a review on Menstrual disorders in the PSUR to be submitted in August 2021. The MAH is requested to include in this PSUR review a separate 'post-marketing cases evaluation' of the cases reporting a menstrual disorder, which should also include a sub-analysis of cases divided between post-menopausal cases and menstrual disorder cases. Causality assessment should be provided per case for at least the serious cases. SmPC and/or RMP changes with regards to menstrual disorders should also be discussed, supported with clinical data and data from literature. In addition, an O/E analysis, with sensitivity analysis to compensate for backlog cases, for Menstrual disorders, including an age-stratified analysis which separates females of childbearing age from post-menopausal aged women, should also be performed by the MAH. The MAH should use a cut-off date after the DLP of the PSUR, as accurate as possible, in order to provide properly above requested data in the PSUR.

- Search criteria: HLGT of Menstrual cycle and uterine bleeding disorders (Primary path).

See Appendix 6B.6 for details.

Conclusion

Recent studies have demonstrated that a sizable proportion of women have experienced menstrual cycle disturbances because of the COVID-19 pandemic. In one study, almost half of the women reported periods that were heavier and painful compared to before the pandemic. These are likely to be associated with psychological distress and stress related to

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Between December 19, 2020, and June 18, 2021, **327,827 cases were reported** (page 31); 702 came from clinical trials (CT), all of which were serious, and 327,125 were reported by healthcare professionals or patients who received the vaccine after authorization. These cases accounted for 1,172,887 adverse events.

The cases predominantly involved women, with an average age of 50 years, ranging from a 6-day-old infant to a 121-year-old. Of these cases, 100,808 were classified as serious, representing 30%.

There were <u>5,115 deaths</u>, including 46 during the clinical trials.

Illustration 192 : Pfizer – Periodic Safety Report 1 (PSUR1) – 19 December 2020 through 18 June 2021 – All cases

6.3.1. General Overview – All Cases

A total of 327,827 case reports (702 from CT[20] and 327,125 from PM[21]) containing 1,172,887 events fulfilled criteria for inclusion in this PSUR. Refer to Appendix 2.1 and Appendix 2.2 for the summary tabulations of all cases received during the current reporting period. Selected characteristics of all cases received during the reporting interval are shown in Table 5 and Table 6.

Table 5. Selected Case Characteristics - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases	CT [a,b] No. of Cases	PM No. of Cases
No. of Cases		327,827	702	327,125
Gender	Female	233,948	329	233,619
	Male	75,340	371	74,969
	Unknown/No Data	18539	2	18,537
Age (years)	N	280,285	695	279,590
	Min-Max[c]	6 days – 121 years	12 – 87 years	6 days – 121 years
	Mean	50.3	55.4	50.3
	Median	49	58	49
Age group	≤ 17	2076	33[d]	2043[e]
	18-30	41,247	39	41,208
	31-50	107,416	182	107,234
	51-64	68,685	191	68,494
	65-74	26,991	175	26,816
	≥ 75	35,097	80	35,017
	Unknown	46,315	2[f]	46,313[g]
Country of occurrence (≥2% of all cases)	United States (US)	68,331	494	67,837
	United Kingdom (UK)	67,305	0	67,305
	Italy	45,791	0	45,791
	France	21,858	0	21,858
	Mexico	15,712	0	15,712
	Netherlands	14,840	0	14,840
	Spain	13,076	0	13,076
	Germany	11,796	20	11,776
	Japan	9766	2	9764
Case Seriousness	Serious	100,808	702	100,106
	Non-serious	227,019	0	227,019

Table 5. Selected Case Characteristics - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases	CT [a,b] No. of Cases	PM No. of Cases
Case Outcome	Resolved/Resolving	172,162	540	171,622
	Resolved with sequelae	3319	41	3278
	Not resolved	76,960	72	76,888
	Fatal	5115	46	5069
	Unknown	70,271	3	70,268

13.6 October 25, 2021 Centers for Disease Control and Prevention (CDC) evaluation of Safety Signals

As of October 25, 2021, the same Tom Shimabukuro presented an update on the risks for myocarditis and pericarditis. Of 1640 reported cases, 877 were retained in the assessment, **which concluded, as expected, that Pfizer/BioNTech and Moderna vaccines increased the risk of both conditions in 12-39 year olds**.

Illustration 193 : CDC Safety Updates – October 25th, 2021 - Number of Myocarditis/

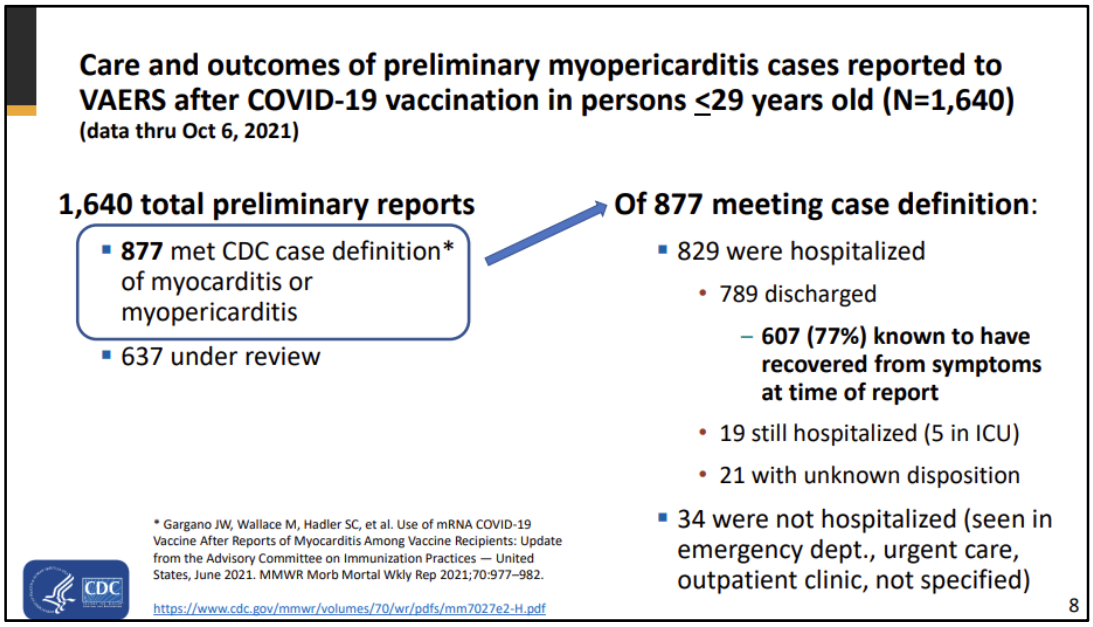
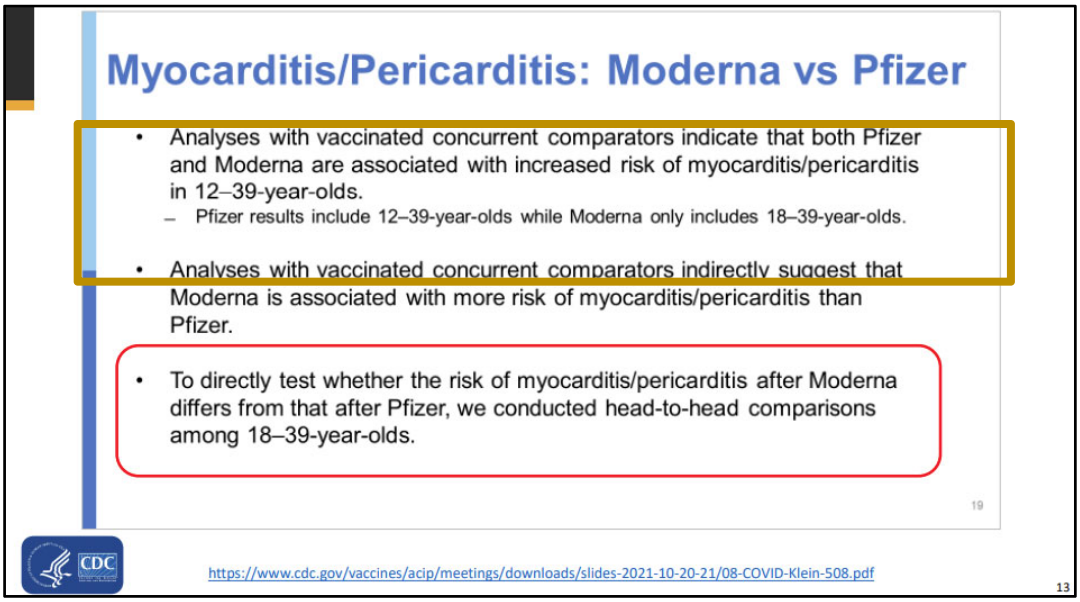


Illustration 194 : CDC Safety Updates – October 25th, 2021 – Myocarditis/Pericarditis Risk Assessment



Source : **https://cdn.who.int/media/docs/default-source/blue-print/shimabukuro_who-blueprint_myocarditis_who-vr-call_25oct2021.pdf?sfvrsn=40e99d51_7**

13.7 Periodic Safety Report 2 (PSUR2) –18 June 2021 through 18 December 2021

Pfizer's Safety Report 2, reviewed by the EMA, is available here:

https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-june-2021-18-december-2021_en.pdf

The signals are summarized in Section 15: OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED.

- **Signals considered to pose no risk:** Appendicitis, herpes zoster, including ophthalmic herpes zoster, immune thrombocytopenia, myasthenia gravis, thrombocytopenia and thrombosis syndrome (TTS), erythema multiforme, glomerulonephritis and nephrotic syndrome, hypoesthesia/paresthesia, rhabdomyolysis, uveitis, multisystem inflammatory syndrome in adults (MIS-A) and children (MIS-C), liver injury/autoimmune hepatitis.

- **Important risks identified:** Myocarditis and pericarditis.

- **Ongoing signals:** Vasculitis, cerebral venous sinus thrombosis (CVST).

Illustration 195 : EMA-Pfizer Periodic Safety Report 2 (PSUR2) – 18 June 2021 through 18 December 2021 - Detected safety signals

COVID-19 mRNA vaccine (nucleoside modified) — Reporting Period
Periodic Safety Update Report (PSUR) 2 — 19 June 2021 through 18 December 2021

Table 24. Overview of Signals

Signal	Signal Type	Source	Category*	Regulatory Procedure
Liver Injury/ Autoimmune Hepatitis**	Closed	Inquiry from a competent authority	No risk	EMA/PRAC/632042/2021 EMA/720589/2021 EPITT no: 19749
Multisystem Inflammatory Syndrome (MIS) in adults (MIS-A) and children (MIS-C)	Closed	Inquiry from a competent authority	No risk	EMA/PRAC/473788/2021 EPITT no: 19732 Procedure no: SDA 038
Uveitis	Closed	Scientific literature	No risk	EMEA/H/C/005735/MEA/002.9
Rhabdomyolysis	Closed	Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002.7 EMEA/H/C/005735/MEA/002.8 EMEA/H/C/005735/MEA/002.9 EMEA/H/C/005735/MEA/002.10 EMEA/H/C/005735/MEA/002.11
Hypoaesthesia/ Paraesthesia	Closed	Inquiry from a competent authority	No risk	EMEA/H/C/005735/II/0080
Glomerulonephritis and Nephrotic Syndrome	Closed	Inquiry from a competent authority	No risk	EMA/PRAC/416198/2021 EPITT no: 19722 Procedure no: SDA 035
Erythema Multiforme	Closed	Inquiry from a competent authority	No risk	EMA/PRAC/398391/2021 EPITT no: 19721 Procedure no: SDA 034
Thrombocytopenia Thrombosis Syndrome (TTS)	Closed	Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002.6

Table 24. Overview of Signals

Signal	Signal Type	Source	Category*	Regulatory Procedure
Myasthenia gravis	Closed	Epidemiology O/E Analysis Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002.8
Myocarditis and Pericarditis	Closed	Inquiry from a competent authority	Important identified risk (EU-RMP, US-PVP)	EMA/PRAC/575791/2021 EPITT no: 19712 SDA 032.2
Immune Thrombocytopenia	Closed	Inquiry from a competent authority. Evaluation for PSUR.	No risk	EMEA/H/C/PSUSA/00010898/202106
Herpes Zoster including Ophthalmic herpes zoster	Closed	Spontaneous report: non-statistical line listing	No risk	EMEA/H/C/005735/MEA/002.7

COVID-19 mRNA vaccine (nucleoside modified)
Periodic Safety Update Report (PSUR) 2

Reporting Period
19 June 2021 through 18 December 2021

Table 24. Overview of Signals

Signal	Signal Type	Source	Category*	Regulatory Procedure
Appendicitis	Closed	Clinical Trial Data Inquiry from a competent authority	No risk	EMEA/H/C/005735/MEA/002.9
Vasculitis	Ongoing	Inquiry from a competent authority	Not yet determined	-
Cerebral venous sinus thrombosis	Ongoing	Inquiry from a competent authority	Not yet determined	-

* Reflects MAH position and entry into signal log following signal evaluation. This may not be the same as the position of the competent authority.
** On 09 November 2021, TGA (Australia) requested an analysis of Comirnaty and 'acute liver injury adverse events of special interest' and 'autoimmune hepatitis;' MAH provided a response on 14 December 2021. On 03 December 2021, EMA PRAC requested supplemental information from the MAH on the signal Autoimmune hepatitis; MAH provided a response on 31 January 2022.

Regarding **myocarditis/pericarditis**, PSUR 2 explained that the safety signal was closed on February 15, 2021, reopened on April 19, 2021, and was regularly reevaluated until it was classified as Important Identified Risks. It was then added to the risk management plan in October 2021 (page 325 of the PDF).

« *During the reporting period, on 05 August 2021 ,* ***the MAH submitted the 2.3 version of the EU-RMP including myocarditis/pericarditis as important identified risk****; this version received a positive CHMP opinion on 30 September 202 1 . In the PSUR #1, the MAH had proposed to include myocarditis/pericarditis in the list of safety concerns for the next reporting period, subject to the PRAC approval of the EU-RMP version 2.3, therefore interval data for this risk are presented in Section 1 6.3. 1 .2. »*

Illustration 196 : EMA - Periodic Safety Report 2 (PSUR2) – 18 June 2021 through 18 December 2021– Summary of safety concerns

2. Signal and risk evaluation

2.1. Summary of safety concerns

The important risks and missing information for BNT162b2 at the beginning of the reporting interval, as per EU RMP v 2.0 adopted 31 May 2021:

Table 1. Ongoing Safety Concerns

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data

During the reporting period, on 05 August 2021, the MAH submitted the 2.3 version of the EU-RMP including myocarditis/ pericarditis as important identified risk; this version received a positive CHMP opinion on 30 September 2021. In the first PSUR, the MAH had proposed to include myocarditis/ pericarditis in the list of safety concerns for the next reporting period, subject to the PRAC approval of the EU RMP version 2.3.

There are no further changes to propose with regard to the safety concerns.

It took <u>eight months</u> for myocarditis/pericarditis, serious disorders that can lead to death, especially in young individuals, to be integrated into the Risk Management Plan as important risks, under the pretext that establishing causality was difficult.

In the signal table, it is surprising to read « *These limitations of the postmarketing data are important factors that preclude proper medical assessment of causality between the event occurrence and vaccine administration*. »

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) acknowledges the limitations of the data, as it is derived from reports by healthcare professionals and patients.

Ms. Jonville Bera, head of the Regional Pharmacovigilance Centers in France (CRPV), noted a reporting rate of only 1 to 10% for vaccines in 2006[7].

This means that all figures should be multiplied by 10, or even by 100 depending on the type of adverse event.

Illustration 197 : EMA - Pfizer – Periodic Safety Report 2 (PSUR2) – 18 June 2021 through 18 December 2021 – Summary of myocarditis / péricarditis signal

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
				Signals Determined Important Risks			
Myocarditis and pericarditis	15 Feb 2021 Re-opened 19 Apr 2021 Re-opened 24 May 2021 Re-opened 24 Jun 2021 Re-opened 30 Jun 2021 Re-opened 14 Oct 2021	Closed	10 Nov 2021	Enquiry from a competent authority	Signal previously reviewed in the context of ongoing discussions with a health authority (Israel MoH) and in response to a PRAC signal assessment report and several requests from other Health Authorities. The MAH has continuously monitor the emerging evidence on the association between COVID-19 mRNA vaccine Comirnaty and myocarditis and pericarditis arising from all available of sources. In October 2021, PRAC Signal procedure prompted by new data on the known risk of myocarditis, pericarditis in a preliminary report of a meta-analysis of data from Denmark, Finland, Norway and Sweden. The signal re-evaluation found that in large, controlled, pivotal study C4591001, myocarditis and pericarditis cases have been reported infrequently, and no imbalance was seen between placebo and active arm for events of myocarditis and pericarditis. The comprehensive evaluation of potential mechanisms for myocarditis or pericarditis found, to date, there is nothing of substance from the nonclinical perspective to identify a potential root cause to consider an established mechanism. In aggregate, the epidemiology studies reported higher risk after Dose 2 compared to Dose 1, and among younger males compared to older males or females of any age post-vaccination. Risk was lower for individuals 12-15 years, higher for 16-19 years, and generally declining thereafter with age. Reported risk for myocarditis after COVID-19 infections was higher when compared with reported rates for individuals without COVID-19 infection or after vaccination. The review of the post-marketing cases of myocarditis found that although the number of cases increases as the vaccine exposure increases, the profile of cases remains largely unchanged. Even in these cases where myocarditis or pericarditis diagnosis is confirmed, the review of data to assess causality reveals that cases lack proper accounting of case duration, severity, outcome, concomitant medication and/or investigative measures to exclude alternate aetiologies such as viral infections or cardiovascular disorders. These limitations of the post-marketing data are important factors that preclude proper medical assessment of causality between the event occurrence and vaccine administration.	Safety and Clinical database review Literature review O/E analysis	A causal association between the vaccine and this event has not been confirmed. Continuous monitoring of the emerging data continues. At the request of several HAs, the events were included as adverse reactions in local product labelling and as Important Identified risk in risk management and pharmacovigilance plans. Most recently, in response to the Nordic observational study data, the PRAC requested that the frequency be changed from "Not known" to "very rare" in the SmPC.

[7] https://www.sciencedirect.com/science/article/abs/pii/S0929693X05005956?via%3Dihub

During the period covered by the report, there were **657,528 cases (2,173,477 reported adverse event**s), with 542,562 classified as serious and 1,631,402 as non-serious (page 278 of the PDF).

Women were affected 2.6 times more than men (68.4% compared to 26.7%).

Illustration 198 : EMA-Pfizer – Periodic Safety Report 2 (PSUR2) – 18 June 2021 through 18 December 2021 - Cases

Adverse Event Data

A total of 2,173,417 AEs (of which 542,562 were serious and 1,631,402 non-serious[20]) were reported in 657,528 PM cases.

The MedDRA SOCs containing the greatest number of events (≥2%) were General disorders and administration site conditions (738,521), Nervous system disorders (308,965), Musculoskeletal and connective tissue disorders (242,863), Gastrointestinal disorders (140,894), Skin and subcutaneous tissue disorders (96,458), Injury, poisoning and procedural complications (82,952), Reproductive system and breast disorders (93,828), Respiratory, thoracic and mediastinal disorders (80,334), Infections and infestations (59,737), and Cardiac disorders (52,788).

The overall safety evaluation includes a review of the most frequently reported events by SOC and by the PT for events reported in ≥2% of all post-marketing cases during the interval period as compared to the cumulative period through 18 December 2021.

Table 16. Post-Authorisation Data: Events Reported in ≥2% Cases

MedDRA SOC MedDRA PT	Reporting Period 19 Jun 2021 – 18 Dec 2021		Cumulatively through 18 Dec 2021
	All Cases (N=657,528) AEs (n=2,173,417)	Serious Cases (N=173,179) Serious AEs[a] (n=542,562)	All Cases (N=982,006) AEs (n=3,365,224)
	n (AERP,[b] %)	n (AERP, %)	n (AERP, %)
Blood and lymphatic system disorders			
Lymphadenopathy[b]	29,431 (4.5)	4187 (2.4)	48,081 (4.9)
Gastrointestinal disorders			
Nausea[b]	55,741 (8.5)	9083 (5.2)	93,727 (9.5)
Diarrhoea[b]	20,881 (3.2)	3562 (2.1)	34,169 (3.5)
Vomiting[b]	15,923 (2.4)	4432 (2.6)	27,477 (2.8)
General disorders and administration site conditions			
Fatigue[b]	109,479 (16.7)	14,173 (8.2)	166,902 (17.0)
Pyrexia[b]	106,127 (16.1)	12,153 (7.0)	170,558 (17.4)
Vaccination site pain[b]	95,981 (14.6)	3422 (2.0)	139,567 (14.2)
Malaise[b]	81,598 (12.4)	6391 (3.7)	109,616 (11.2)

[20] Multiple episodes of the same event were reported with a different seriousness in some cases hence the sum of the events seriousness exceeds the total number of events.

Table 16. Post-Authorisation Data: Events Reported in ≥2% Cases

MedDRA SOC MedDRA PT	Reporting Period 19 Jun 2021 – 18 Dec 2021		Cumulatively through 18 Dec 2021
	All Cases (N=657,528) AEs (n=2,173,417)	Serious Cases (N=173,179) Serious AEs[a] (n=542,562)	All Cases (N=982,006) AEs (n=3,365,224)
	n (AERP,[b] %)	n (AERP, %)	n (AERP, %)
Chills[b]	53,523 (8.1)	5452 (3.1)	94,925 (9.7)
Pain[c]	37,943 (5.8)	6245 (3.6)	63,924 (6.5)
Vaccination site swelling[b]	22,115 (3.4)	670 (0.4)	29,275 (3.0)
Asthenia[b]	21,198 (3.2)	4773 (2.8)	45,807 (4.7)
Chest pain[c]	17,528 (2.7)	7437 (4.3)	22,706 (2.3)
Influenza like illness[c]	12,656 (1.9)	1831 (1.1)	21,409 (2.2)
Vaccination site erythema[b]	13,101 (2.0)	569 (0.3)	19,852 (2.0)
Infections and infestations			
COVID-19[d]	19,691 (3.0)	18,857 (10.9)	27,943 (2.8)
Injury, poisoning and procedural complications			
Off label use[e]	22,049 (3.4)	5764 (3.3)	25,873 (2.6)
Inappropriate schedule of product administration[e]	18,827 (2.9)	467 (0.3)	23.218 (2.4)
Musculoskeletal and connective tissue disorders			
Myalgia[b]	84,891 (12.9)	7203 (4.2)	134,432 (13.7)
Arthralgia[b]	56,611 (8.6)	7251 (4.2)	92,100 (9.4)
Pain in extremity[b]	39,010 (5.9)	8030 (4.6)	67,970 (6.9)
Nervous system disorders			
Headache[b]	135,039 (20.5)	16,738 (9.7)	219,030 (22.3)
Dizziness[c]	37,982 (5.8)	8760 (5.1)	62,240 (6.3)
Paraesthesia[f]	19,809 (3.0)	4766 (2.8)	29,497 (3.0)
Hypoaesthesia[f]	13,597 (2.1)	3980 (2.3)	19,995 (2.0)
Reproductive system and breast disorders			
Heavy menstrual bleeding[c]	16,613 (2.5)	4150 (2.4)	17,535 (1.8)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea[b]	23,757 (3.6)	9714 (5.6)	35,024 (3.6)
Skin and subcutaneous tissue disorders			
Rash[b]	17,591 (2.7)	3095 (1.8)	28,255 (2.9)
Pruritus[b]	16,653 (2.5)	2980 (1.7)	27,923 (2.8)
Surgical and medical procedures			
Immunisation[g]	21,712 (3.3)	8339 (4.8)	21,737 (2.21)

a. Non-serious events are not included.
b. Listed or consistent with listed AEs in current RSI.
c. Unlisted in the current RSI.
d. Listed per case processing conventions, except for fatal cases.
e. Listed per case processing conventions.
f. Paresthesia / Hypoesthesia are going to be included as ADRs in the EU-SmPC Section 4.8 as per PRAC recommendation (Procedure number EMEA/H/C/005735/II/0080).
g. PTs selected per case processing conventions to indicate cases reporting third/booster doses.
h. Reporting proportion calculated as n/N (% of all incremental cases, incremental serious cases and all cumulative cases).
N: Number of cases; n: Number of events.

There were 5,413 deaths, including 46 during the clinical trials.

Illustration 199 : EMA-Pfizer – Periodic Safety Report 2 (PSUR2) – 18 June 2021 through 18 December 2021 – Caracteristics of cases

Table 12. Demographic Information - All Cases Received during the Reporting Interval

Characteristics		All No. of Cases (%[a]) N=658,249	CT No. of Cases (%[a]) N=721	PM No. of Cases (%[a]) N=657,528[b]
Case Outcome	Fatal	5413 (0.8)	46 (6.4)	5367 (0.8)
	Not recovered	213,015 (32.4)	116 (16.1)	212,899 (32.4)
	Recovered/ Recovering	300,809 (45.7)	526 (73.0)	300,283 (45.7)
	Recovered with sequelae	7512 (1.1)	29 (4.0)	7483 (1.1)
	Unknown	131,499 (20.0)	4 (0.6)	131,495 (20.0)

13.8 Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022

The Safety Report 3, authored by Pfizer and reviewed by the EMA, is available at the following link:
https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-december-2021-18-june-2022_en.pdf-0.

The report authored by Pfizer begins on page 274 of the PDF.

Regarding the evaluation of safety signals, they are summarized in Section 15: **OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED** (pages 374 and 375 of the PDF document).

During the reporting interval, the following signals were evaluated, with risks yet to be determined, and no new significant safety issues were identified based on the data provided in the PSUR: Appendicitis, hemolytic anemia, uveitis, exacerbation and/or flare-up of underlying autoimmune disease or inflammatory disorders, capillary leak syndrome, corneal graft rejection, vasculitis, cerebral venous sinus thrombosis, lymphocytic colitis, chronic urticaria, polymyalgia rheumatica, subacute thyroiditis, stroke/cerebrovascular accident, amenorrhea, loss/alteration of taste and smell, and irritability.

Heavy menstrual bleeding and **hearing loss with tinnitus** were under evaluation during the period covered by the report.

Illustration 200 : Pfizer - Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022 – Summary of signals

Table 32. Overview of Signals (at DLP 18 June 2022)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Myocarditis and Pericarditis	Closed	Other: Routine safety surveillance	Important identified risk	-
Irritability	New and closed	Clinical Trial C4591007 unblinded review of data in 6 months to <5-year-old (Pfizer)	Identified risk (not "important")	-
Appendicitis	Re-opened and closed	Inquiry from a competent authority (Singapore BoH)	No risk	-
Hemolytic anemia	New and closed	Inquiry from a competent authority (Saudi Arabia SFDA)	No risk	-
Uveitis	New and closed	Inquiry from a competent authority (Health Canada)	No risk	-
Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	-
Capillary Leak Syndrome (CLS)	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	PAM-SDA-051 EPITT 19743

Table 32. Overview of Signals (at DLP 18 June 2022)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Corneal Graft Rejection	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	PAM-SDA-055 EPITT 19789
Vasculitis	Ongoing and closed	Notification from a competent authority (Netherlands Lareb)	No risk	-
Cerebral venous sinus thrombosis (CVST)	Ongoing and closed	Inquiry from a competent authority (Switzerland Swissmedic)	No risk	-
Lymphocytic colitis	New and closed	Scientific literature[72]	No risk	-
Chronic Urticaria	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	-
Polymyalgia Rheumatica (PMR)	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	-
Subacute Thyroiditis (SAT)	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	-
Cerebrovascular Accident (CVA)/Stroke	New and closed	Inquiry from a competent authority (Australia TGA)	No risk	-
Amenorrhea	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	PAM-SDA-052 EPITT 19784
Heavy Menstrual Bleeding	New and closed	Inquiry from a competent authority (EMA PRAC)	No risk	PAM-SDA-053 EPITT 19783
Loss of/Altered Taste and Smell	New and closed	Inquiry from a competent authority (Australia TGA)	No risk	-
Hearing Loss	Re-opened and Ongoing	Inquiry from a competent authority	Not yet determined	-

* Reflects the MAH position and entry into MAH signal log following evaluation. This may not be the same as the position of the competent authority.

The number of adverse effects has reached 4.9 million for 1.3 million reported cases since the start of vaccination (pages 336 and 337 of the PDF).

In addition to pain at the vaccination site, headaches, dizziness, paresthesia, fatigue, fever, malaise, and asthenia, reports included nausea, vomiting, diarrhea, as well as dyspnea, palpitations, tachycardia, menstrual disorders, and **heavy menstrual bleeding**.

A total of 37,926 vaccine failures were reported. Additionally, nearly 31,000 cases of "**poor-quality product**" were noted.

Illustration 201 : Pfizer – Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022 – Cases

Table 18. Post-Authorisation Data: Events Reported in ≥2% Cases

MedDRA SOC MedDRA PT	Reporting Period 19 Dec 2021 – 18 Jun 2022		Cumulatively through 18 Jun 2022	
	All Cases (N=507,683) AEs (n=1,596,793)	Serious Cases (N=151,420) Serious AEs [a] (n=439,443)	All Cases (N=1,484,945) AEs (n=4,974,391)	Serious Cases (N=425,314) Serious AEs [a] (n=1,326,116)
	n (AERP, [f]%)	n (AERP, [f] %)	n (AERP, [f]%)	n (AERP, [f] %)
Nervous system disorders				
Headache [b]	77,974 (15.4)	9451 (6.2)	297,293 (20.0)	41,338 (9.7)
Dizziness [b]	30,880 (6.1)	5418 (3.6)	93,304 (6.3)	20,903 (4.9)
Paraesthesia [g]	14,993 (3.0)	3018 (2.0)	44,666 (3.0)	10,640 (2.5)
General disorders and administration site conditions				
Fatigue [b]	67,879 (13.4)	8675 (5.7)	235,562 (15.9)	34,742 (8.2)
Pyrexia [b]	57,746 (11.4)	6642 (4.4)	228,574 (15.4)	29,973 (7.0)
Vaccination site pain [b]	49,263 (9.7)	2199 (1.5)	190,875 (12.9)	9,703 (2.3)
Chills [b]	33,542 (6.6)	2895 (1.9)	128,602 (8.7)	14,687 (3.5)
Malaise [b]	32,701 (6.4)	3337 (2.2)	142,545 (9.6)	15,085 (3.5)
Drug ineffective [h]	26,688 (5.3)	26,664 (17.6)	41,566 (2.8)	41,515 (9.8)
Vaccination failure [d]	24,419 (4.8)	24,415 (16.1)	37,933 (2.6)	37,926 (8.9)
Chest pain [i]	17,945 (3.5)	5694 (3.8)	40,839 (2.8)	15,623 (3.7)
Pain [b]	16,529 (3.3)	3618 (2.4)	80,302 (5.4)	14,660 (3.4)
Asthenia [b]	13,703 (2.7)	2793 (1.8)	59,692 (4.0)	11,424 (2.7)
Vaccination site swelling [b]	10,670 (2.1)	446 (0.3)	40,218 (2.7)	1,954 (0.5)
Infections and infestations				
COVID-19 [c]	47,988 (9.5)	47,449 (31.3)	76,044 (5.1)	72,718 (17.1)
Musculoskeletal and connective tissue disorders				
Myalgia [b]	43,916 (8.7)	4451 (2.9)	178,198 (12.0)	18,937 (4.5)
Arthralgia [b]	29,430 (5.8)	4702 (3.1)	121,898 (8.2)	18,152 (4.3)
Pain in extremity [b]	25,090 (4.9)	4584 (3.0)	93,467 (6.3)	18,828 (4.4)
Limb discomfort [b]	11,578 (2.3)	670 (0.4)	23,939 (1.6)	2,558 (0.6)
Injury, poisoning and procedural complications				
Inappropriate schedule of product administration [d]	35,318 (7.0)	466 (0.3)	57,719 (3.9)	1,020 (0.2)
Off label use [d]	29,927 (5.9)	10,293 (6.8)	54,754 (3.7)	16,400 (3.9)
Poor quality product administered [j]	17,859 (3.5)	4 (0.003)	30,830 (2.1)	14 (0.004)

Table 18. Post-Authorisation Data: Events Reported in ≥2% Cases

MedDRA SOC MedDRA PT	Reporting Period 19 Dec 2021 – 18 Jun 2022		Cumulatively through 18 Jun 2022	
	All Cases (N=507,683) AEs (n=1,596,793)	Serious Cases (N=151,420) Serious AEs [a] (n=439,443)	All Cases (N=1,484,945) AEs (n=4,974,391)	Serious Cases (N=425,314) Serious AEs [a] (n=1,326,116)
	n (AERP, [f]%)	n (AERP, [f] %)	n (AERP, [f]%)	n (AERP, [f] %)
Blood and lymphatic system disorders				
Lymphadenopathy [b]	31,132 (6.1)	2794 (1.9)	79,285 (5.3)	10,712 (2.5)
Gastrointestinal disorders				
Nausea [b]	30,670 (6.0)	4338 (2.9)	124,557 (8.4)	22,152 (5.2)
Vomiting [b]	11,424 (2.3)	2454 (1.6)	38,996 (2.6)	10,498 (2.5)
Diarrhoea [b]	10,211 (2.0)	1644 (1.1)	44,491 (3.0)	8,409 (2.0)
Surgical and medical procedures				
Immunisation [e]	25776 (5.1)	11,063 (7.3)	46,775 (9.6)	19,305 (4.5)
Interchange of vaccine products [e]	25,233 (5.0)	9397 (6.2)	38,522 (2.6)	14,276 (3.4)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea [b]	21,736 (4.3)	6947 (4.6)	56,998 (3.8)	22,516 (5.3)
Skin and subcutaneous tissue disorders				
Rash [b]	13,640 (2.7)	1802 (1.2)	41,937 (2.8)	7,742 (1.8)
Cardiac disorders				
Palpitations [b]	13,071 (2.6)	4231 (2.8)	30,535 (2.1)	10,716 (2.5)
Tachycardia [i]	10,914 (2.2)	3028 (2.0)	25,602 (1.7)	7,887 (1.9)
Reproductive system and breast disorders				
Heavy menstrual bleeding [i]	12,905 (2.5)	1711 (1.1)	30,498 (2.1)	6,381 (1.5)
Menstrual disorder [i]	12,579 (2.5)	871 (0.6)	24,442 (1.6)	2,370 (0.6)

a. Non-serious events are not included.
b. Listed or consistent with listed AEs in current RSI.
c. Listed per case processing conventions, except for fatal cases.
d. Listed per case processing conventions.
e. PTs selected per case processing conventions to indicate cases reporting third/booster doses.
f. Reporting proportion calculated as n/N (% of all incremental cases, incremental serious cases and all cumulative cases).
g. Paresthesia / Hypoesthesia were included as ADRs in the EU-SmPC Section 4.8 as per PRAC recommendation (Procedure number EMEA/H/C/005735/11/0080).
h. Drug ineffective represents efficacy-related conditions.
i. Unlisted in the current RSI.
j. Follow the listedness of the associated AE.
N=Number of cases; n=Number of events; MedDRA=Medical Dictionary for Regulatory Activities; SOC=System Organ Class; PT=Preferred Term;
AE=Adverse Event; AERP=Adverse Event Reporting Proportion; RSI=Reference Safety Information

The report indicated that there were 13,659 deceased individuals (page 564 of the PDF).

The most frequently reported causes of death (more than 500 occurrences) were: death without further details (3,145), COVID-19 (1,296), **cardiac arrest (892)**, dyspnea (725), **sudden death (618), myocardial infarction (610)**, vaccine failure (574), cardiorespiratory arrest (557), pyrexia (541), ineffective medication (517), and pulmonary embolism (514).

Illustration 202 : Pfizer – Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022 – Number of deaths until 18 june 2022

Cumulative Reporting Period

This is a high-level overview of the 13,659 relevant cumulative cases with a fatal outcome. According to the corePSUR19 guidance,[75] summary tabulation of fatal reports by age groups and SOCs is provided in Appendix 6C.2[150].

Clinical Trial Data

- Number of cases: 150[151] (6.2% of 2426 cases, the total CT dataset; 143 cases involved blinded therapy [67]/BNT162b2 [76]). In the remaining 7 cases subjects received placebo.
- Causes of death most frequently reported (>7 occurrences): Disease progression (29), Cardiac arrest (15), Death (14), Completed suicide (10), Cardio-respiratory arrest, Myocardial infarction (8 each).
- Autopsy results were provided in 10 cases and the most commonly (≥2 occurrences) reported were: Arteriosclerosis, Hypertensive heart disease, Pulmonary embolism (2 each).
- Events with a fatal outcome (n = 198): The most frequently reported PTs (≥5 occurrences) were: Death (14), Completed suicide (10), Cardio-respiratory arrest (9), Cardiac arrest, Myocardial infarction (8 each), Pulmonary embolism (6), Acute respiratory failure, COVID-19, COVID-19 pneumonia, and Septic shock (5 each). None of these events are considered related to blinded therapy/BNT162b2.

Post-Authorisation Data

- Number of cases: 13,509[152] (0.9 % of 1,484,945 cases, the total cumulative PM dataset).
- MC cases (9582), NMC cases (3927).
- Causes of death most frequently reported (>500 occurrences): Death (3145), COVID-19 (1296), Cardiac arrest (892), Dyspnoea (725), Sudden death (618), Myocardial infarction (610), Vaccination failure (574), Cardio-respiratory arrest (557), Pyrexia (541), Drug ineffective (517), and Pulmonary embolism (514).

he analysis by the number of adverse events (and not by cases) showed that all age groups were affected, with 70% occurring in the group aged over 70 years (page 566).

Illustration 203 : Pfizer – Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022 – Number of deaths by System Organ Class and age

Table 66. Post-Authorisation Data: Total Number of AEs with a Fatal Outcome by SOCs and by Age Group - Cumulative Reporting Interval

SOC	Total number of events	≤ 17 years	18-24 years	25-49 years	50-59 years	60-69 years	70+ years	Unk
General disorders and administration site conditions	8735	115	65	612	534	956	5720	733
Cardiac disorders	5014	78	59	539	433	700	3075	130
Nervous system disorders	3818	56	63	336	311	516	2433	103
Respiratory, thoracic and mediastinal disorders	3535	62	32	282	251	444	2395	69
Infections and infestations	3473	28	21	108	118	355	2596	247

Of note, multiple AEs may be reported in a single case.

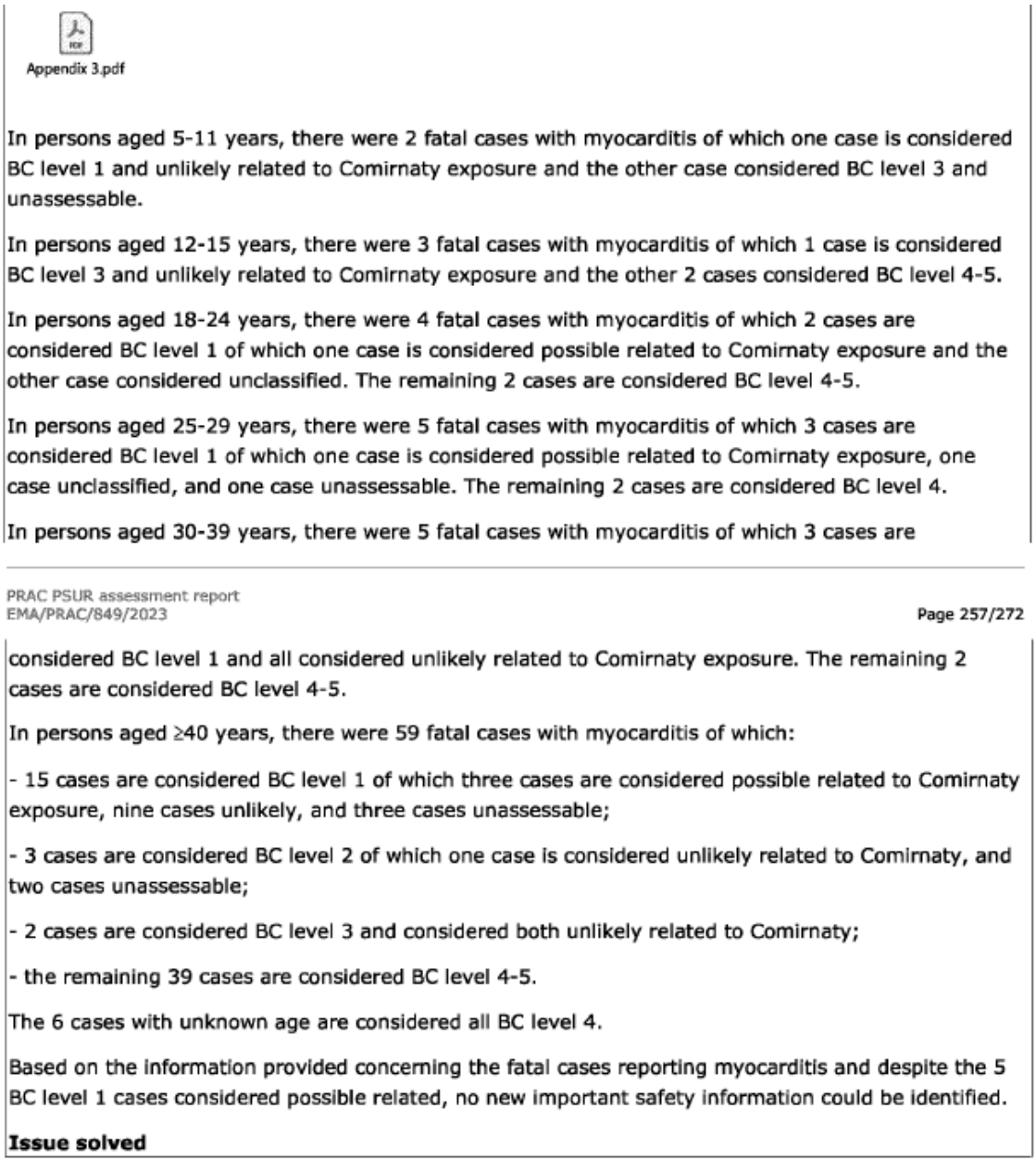
Myocarditis / pericarditis

Regarding myocarditis and pericarditis, the EMA requested that the marketing authorization holder "provide detailed information regarding fatal cases of myocarditis in individuals aged 5 to 11 years, 12 to 15 years, 18 to 24 years, 25 to 29 years, 30 to 39 years, and ≥40 years."

The laboratory's response indicated the following fatalities due to myocarditis:

- **2 deaths in children aged 5 to 11 years**
- 3 deaths in adolescents aged 12 to 15 years
- 4 deaths in individuals aged 18 to 24 years
- 5 deaths in individuals aged 25 to 29 years
- 5 deaths in individuals aged 30 to 39 years
- 59 deaths in individuals aged over 40 years.

Illustration 204 : Pfizer – Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022 – Deaths due to myocarditis



Appendix 3.pdf

In persons aged 5-11 years, there were 2 fatal cases with myocarditis of which one case is considered BC level 1 and unlikely related to Comirnaty exposure and the other case considered BC level 3 and unassessable.

In persons aged 12-15 years, there were 3 fatal cases with myocarditis of which 1 case is considered BC level 3 and unlikely related to Comirnaty exposure and the other 2 cases considered BC level 4-5.

In persons aged 18-24 years, there were 4 fatal cases with myocarditis of which 2 cases are considered BC level 1 of which one case is considered possible related to Comirnaty exposure and the other case considered unclassified. The remaining 2 cases are considered BC level 4-5.

In persons aged 25-29 years, there were 5 fatal cases with myocarditis of which 3 cases are considered BC level 1 of which one case is considered possible related to Comirnaty exposure, one case unclassified, and one case unassessable. The remaining 2 cases are considered BC level 4.

In persons aged 30-39 years, there were 5 fatal cases with myocarditis of which 3 cases are

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considered BC level 1 and all considered unlikely related to Comirnaty exposure. The remaining 2 cases are considered BC level 4-5.

In persons aged ≥40 years, there were 59 fatal cases with myocarditis of which:

- 15 cases are considered BC level 1 of which three cases are considered possible related to Comirnaty exposure, nine cases unlikely, and three cases unassessable;

- 3 cases are considered BC level 2 of which one case is considered unlikely related to Comirnaty, and two cases unassessable;

- 2 cases are considered BC level 3 and considered both unlikely related to Comirnaty;

- the remaining 39 cases are considered BC level 4-5.

The 6 cases with unknown age are considered all BC level 4.

Based on the information provided concerning the fatal cases reporting myocarditis and despite the 5 BC level 1 cases considered possible related, no new important safety information could be identified.

Issue solved

Regarding pericarditis, there were 2 deaths in individuals aged 25 to 29 years and 9 deaths in individuals aged 40 years or older.

Illustration 205 : Pfizer – Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022 – Deaths dus to pericarditis

Rapporteur assessment comment:

Please refer regarding the assessment of the 11 fatal cases to the PRAC Rapporteur's comments in:

Appendix 4.pdf

In persons aged 25-29 years, there were 2 fatal cases with pericarditis of which both cases are considered BC level 1 and unlikely related to Comirnaty exposure.

In persons aged ≥40 years, there were 9 fatal cases with pericarditis of which two cases are considered BC level 1 and both unlikely related to Comirnaty exposure. The remaining 7 cases are considered BC level 4-5.

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Reported Fatal Cases in Children:

The laboratory's response cited 81 fatal cases in individuals aged 5 to 11 years and 12 to 17 years. The information has been redacted, preventing any commentary on this section.

Illustration 206 : Pfizer – Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022 – Infants dead

6. *Regarding **fatal cases reported in paediatric persons**, the MAH is requested to provide detailed information concerning the fatal cases in persons aged 5-11 years and 12-17 years, perform per case a WHO causality assessment, and an assessment according to Brighton Collaboration case definition and Level of certainty classification, if applicable.*

MAH response

There were 81 fatal cases in persons aged 5-11 years and 12-17 years, one case ([redacted] was a 19-year-old subject. A listing of the 82 cases, including narratives, is provided in Appendix 2 (not reproduced here).

Of note, there were 3 reports [redacted] originating from EMA EudraVigilance-WEB that described non-fatal cases of pyrexia and pyrexia with somnolence; these cases were downgraded to non-serious cases.

Of the remaining 79 cases, 56 cases [redacted] were classified as unassessable because the information provided is either insufficient to assess or contradictory and could not be verified.

This report, released on January 12, 2023, mentions in Section 5: Request for Additional Information from the Rapporteur (page 252).

*« Regarding **multiple repeated booster doses**, during the reporting period the number of persons receiving multiple booster doses (i.e., homologous, heterologous, different strains) is increasing whereas the impact on safety and efficacy remains uncertain. In addition **the impact (including long-term) of repeatedly (e.g., yearly) receiving booster doses (with or without strain updates) also remains unknown.** The MAH is requested to discuss whether **'safety following multiple repeated booster doses** (i.e., homologous, heterologous, different strains)' **should be considered as Missing** information in the Risk Management Plan, and proposals should be provided how to address this knowledge gap in ongoing or newly proposed PASSs, as applicable.*

This confirms the risks associated with regularly administering doses of the product, as the safety remains unknown.

Illustration 207 : Pfizer – Periodic Safety Report 3 (PSUR3) – 19 December 2021 through 18 june 2022 – Rapporteur request for supplementary information

5. Rapporteur request for supplementary information

1. Regarding **multiple repeated booster doses**, during the reporting period the number of persons receiving multiple booster doses (i.e., homologous, heterologous, different strains) is increasing whereas the impact on safety and efficacy remains uncertain. In addition the impact (including long-term) of repeatedly (e.g., yearly) receiving booster doses (with or without strain updates) also remains unknown. The MAH is requested to discuss whether 'safety following multiple repeated booster doses (i.e., homologous, heterologous, different strains)' should be considered as *Missing information* in the RMP, and proposals should be provided how to address this knowledge gap in ongoing or newly proposed PASSs, as applicable.

13.9 Periodic Safety Report 4 (PSUR4) –19 june 2022 through 18 December 2022

The fourth safety report, authored by Pfizer and reviewed by the EMA, is available at the following link:
https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-june-2022-18-december-2022_en.pdf.

The report authored by Pfizer begins on page 172 of the PDF.

Regarding the evaluation of safety signals, they are summarized in Section 15: **OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED** (page 299 of the PDF document) and discussed by the EMA on pages 5 and 6.

« *During the reporting interval, **the following signals were evaluated**, not to be determined risks, and no new important safety issue was identified based on the data provided in the PSUR:*

• *Haemophagocytic lymphohistiocytosis (HLH); Dermatomyositis; Histiocytic necrotizing lymphadenitis (HNL); Genital (e.g., vulvovaginal) ulceration.*

*The following were **ongoing signals** during the reporting interval:*

• *Pemphigus and Pemphigoid (EPITT 19859).*

During the reporting interval, there were post-approval regulatory requests for the following topics for which no safety signal was identified based on the information provided in the PSUR:

• *Multisystem inflammatory syndrome children/-adults (MIS-C/-A); Dyspnoea; Palpitations; Tachycardia/Heart Rate Increase; Subacute thyroiditis; Amenorrhea*. »

The EMA revisited the issue of myocarditis/pericarditis, indicating that it may no longer be as benign as previously stated.

« *There was a new aspect of a previously recognised important safety issue identified, which included the clinical course (including intensive care support) and outcome (including fatal outcome) of Comirnaty associated myocarditis/pericarditis at short term follow-up (:::;;3 months). Therefore, the wording of the warning concerning myocarditis and pericarditis in the Comirnaty PI should be amended accordingly (please refer to section 3 Recommendations below)*.»

The EMA has removed the important potential risk of VAED/VAERD (Vaccine-Associated Enhanced Disease/Vaccine-Associated Enhanced Respiratory Disease) from the list of safety concerns « *as the available cumulative data (clinical trial and post-marketing data) showed no safety information that substantiates retaining VAED/VAERD as an important potential risk. VAED/VAERD should continue to monitor through routine pharmacovigilance*. »

Illustration 208 : EMA – Periodic Safety Report 4 (PSUR4) –19 june 2022 through 18 December 2022 – Overview of signals

During the reporting interval, Dizziness (with frequency Uncommon) and Heavy menstrual bleeding (with frequency Unknown) were added as ADRs to the Comirnaty product information.

During the reporting interval, the following signals were evaluated, not to be determined risks, and no new important safety issue was identified based on the data provided in the PSUR:

- Haemophagocytic lymphohistiocytosis (HLH); Dermatomyositis; Histiocytic necrotizing lymphadenitis (HNL); Genital (e.g., vulvovaginal) ulceration.

The following were ongoing signals during the reporting interval:

- Pemphigus and Pemphigoid (EPITT 19859).

During the reporting interval, there were post-approval regulatory requests for the following topics for which no safety signal was identified based on the information provided in the PSUR:

- Multisystem inflammatory syndrome children/-adults (MIS-C/-A); Dyspnoea; Palpitations; Tachycardia/Heart Rate Increase; Subacute thyroiditis; Amenorrhea.

There was a new aspect of a previously recognised important safety issue identified, which included the clinical course (including intensive care support) and outcome (including fatal outcome) of Comirnaty associated myocarditis/pericarditis at short term follow-up (≤3 months). Therefore, the wording of the warning concerning myocarditis and pericarditis in the Comirnaty PI should be amended accordingly (please refer to section 3 Recommendations below).

During the reporting interval, the important identified risk Anaphylaxis was removed from the list of safety concerns in the Comirnaty RMP.

The important potential risk VAED/VAERD can be removed from the list of safety concerns in both RMP and PSUR, as the available cumulative data (clinical trial and post-marketing data) showed no safety information that substantiates retaining VAED/VAERD as an important potential risk. VAED/VAERD should continue to monitor through routine pharmacovigilance.

Taking into account the extensive use of the vaccine and the relatively well-established safety profile, the PRAC endorses the proposal to move the PSUR cycle to 1 year. As the MAH has expressed a wish to keep the cycle aligned with the EURD, two additional 6-monthly PSURs will be submitted, followed by the yearly PSUR.

The benefit-risk balance for the use of Comirnaty (tozinameran), Comirnaty Original/Omicron BA.1 (tozinameran and riltozinameran), and Comirnaty Original/Omicron BA.4-5 (tozinameran and famtozinameran) in its authorised indications remains unchanged.

Illustration 209 : Pfizer – Periodic Safety Report 4 (PSUR4) –19 june 2022 through 18 December 2022 – Overview of signals

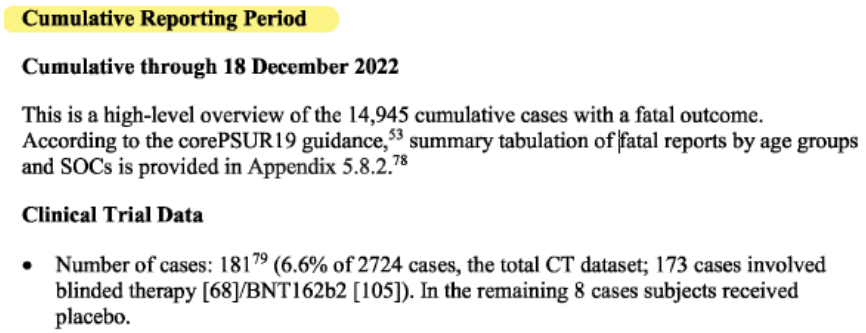
Table 51. Overview of Signals (at DLP 18 December 2022)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Pemphigus and Pemphigoid	New and ongoing	Enquiry from a competent authority (EMA PRAC)	Not applicable	EPITT No. 19859
Dizziness	New and closed	Enquiry from a competent authority (EMA PRAC)	Adverse reaction (i.e., identified risk)	EMEA/H/C/PSUSA/00010898/202112
Haemophagocytic lymphohistiocytosis (HLH)	New and closed	Other: Routine safety surveillance	No risk	-
Dermatomyositis	New and closed	Other: Routine safety surveillance	No risk	-
Histiocytic necrotizing lymphadenitis (HNL)	New and closed	Enquiry from a competent authority (EMA PRAC)	No risk	EMA/PRAC/689208/2022 EPITT: no: 19835
Genital (vulvovaginal) ulceration	New and closed	Enquiry from a competent authority (Australia TGA and EMA PRAC)	No risk	EPITT No. 19840
IgA nephropathy	New and closed	Enquiry from a competent authority (EMA PRAC)	No risk	-
Acquired haemophilia	New and closed	Enquiry from a competent authority (EMA PRAC)	No risk	-
Hearing loss	New and closed	Enquiry from a competent authority (Health Canada and EMA PRAC)	No risk	-

* Reflects the MAH position in the MAH signal log. This may differ from the position of the competent authority.

The report indicated 1.7 million cases reported to pharmacovigilance as of December 18, 2022, including 14,945 deaths (pages 412 and 413 of the PDF).

Illustration 210 : Pfizer – Periodic Safety Report 4 (PSUR4) –19 june 2022 through 18 December 2022 – Deaths



Cumulative Reporting Period

Cumulative through 18 December 2022

This is a high-level overview of the 14,945 cumulative cases with a fatal outcome. According to the corePSUR19 guidance,[53] summary tabulation of fatal reports by age groups and SOCs is provided in Appendix 5.8.2.[78]

Clinical Trial Data

- Number of cases: 181[79] (6.6% of 2724 cases, the total CT dataset; 173 cases involved blinded therapy [68]/BNT162b2 [105]). In the remaining 8 cases subjects received placebo.

The results and causes of death are consistent with those outlined in the section 5.4.7 Safety analysis – Deaths of the final clinical study report.

The most frequent causes of death were:

- Unknown causes: 3,446
- COVID-19: 1,361
- Cardiac arrest: 971
- Dyspnea: 787
- Myocardial infarction: 672
- Sudden death: 655
- Cardio-respiratory arrest: 612
- Vaccination failure: 603
- Pyrexia: 596
- Ineffective medication: 555
- Pulmonary embolism: 555
- Heart failure: 536.

The 14,764 people who died suffered 36,585 adverse events.

Illustration 211 : Pfizer – Periodic Safety Report 4 (PSUR4) –19 june 2022 through 18 December 2022 - Deaths post authorization

- Events with a fatal outcome (n = 242); the most frequently reported PTs (≥5) included Death (19), Cardiac arrest, Completed suicide (11 each), Cardio-respiratory arrest, Myocardial infarction (9 each), Pulmonary embolism, Septic shock (7 each), Acute myocardial infarction, Acute respiratory failure, Condition aggravated, COVID-19 pneumonia, Pneumonia, Road traffic accident (5 each).

Post-Authorisation Data

- Number of cases: 14,764[80] (0.9 % of 1,689,088 cases, the total cumulative PM dataset).
- MC cases (10,357), NMC cases (4407).
- Causes of death most frequently reported (>500): Death (3446), COVID-19 (1361), Cardiac arrest (971), Dyspnoea (787), Myocardial infarction (672), Sudden death (655), Cardio-respiratory arrest (612), Vaccination failure (603), Pyrexia (596), Drug ineffective, Pulmonary embolism (555 each), and Cardiac failure (536).
- Autopsy results were provided in 795 cases and the most commonly (> 30) results described: Pulmonary embolism (87), Pulmonary oedema (68), Arteriosclerosis (62), Myocardial infarction (54), Arteriosclerosis coronary artery (51), Myocarditis (50), Acute myocardial infarction (48), Cardiac hypertrophy (34), Cardiomegaly (33), Pulmonary congestion (31).
- Events with a fatal outcome (n = 36,586): The most frequently reported (>500) events included Death (3300), COVID-19 (1457), Cardiac arrest (990), Dyspnoea (895), Drug ineffective (777), Vaccination failure (773), Sudden death (749), Pyrexia (685), Myocardial infarction (681), Cardio-respiratory arrest (625), Pulmonary embolism (583), Cardiac failure (538), Immunisation (537).

Regarding **cerebral venous thromboses** (section on strokes, page 136), a study comparing observed versus expected cases (O/E) included in the PSUR confirms the **increased risk of stroke for women aged 18 to 49** within a 21-day window after vaccination in Europe and the United States, with a risk 4.764 times higher for the age group of 25 to 49 years.

Illustration 212 : EMA – Periodic Safety Report 4 (PSUR4) –19 june 2022 through 18 December 2022 – Analysis of Cerebral Venous Thrombosis

Table 12. Observed to Expected (O/E) Analysis of Cerebral Venous Sinous Thrombosis in European Economic Area Countries and in the United States, Cumulative Period, Low Background Rate

Stratification	Low Bkgd rate[a,16]	21-Day Risk Window					42-Day Risk Window				
		Obs Cases	PY	Exp Cases	O/E Ratio	95%CI[c]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males <5 years	0.45	0	43691.043	0.2	0.000	-	0	58749.912	0.3	0.000	-
Males 5-11 years	0.45	0	893,455	4.0	0.000	-	0	1,318,570	5.9	0.000	-
Males 12-17 years	0.45	4	1,601,261	7.2	0.555	0.151, 1.421	5	2,449,692	11.0	0.454	0.147, 1.058
Males 18-24 years	0.42	11	2,270,238	9.5	**1.154**	**0.576, 2.064**	13	3,555,446	14.9	0.871	0.464, 1.489
Males 25-49 years	0.40	56	9,551,716	38.2	**1.466**	**1.107, 1.903**	75	15,120,116	60.5	**1.240**	**0.975, 1.554**
Males 50-59 years	1.24	29	4,742,810	58.8	0.493	0.330, 0.708	40	7,685,823	95.3	0.420	0.300, 0.572
Males 60-69 years	1.25	21	4,458,018	55.7	0.377	0.233, 0.576	31	7,401,897	92.5	0.335	0.228, 0.476
Males 70+ years	1.51	27	6,427,256	97.1	0.278	0.183, 0.405	39	10,778,587	162.8	0.240	0.170, 0.328
Females <5 years	0.97	0	47,884	0.5	0.000	-	0	64,480	0.6	0.000	-
Females 5-11 years	0.97	0	1,000,124	9.7	0.000	-	0	1,478,826	14.3	0.000	-
Females 12-17 years	0.97	5	1,795,974	17.4	0.287	0.093, 0.670	7	2,753,762	26.7	0.262	0.105, 0.540
Females 18-24 years	0.97[b]	42	2,547,315	24.7	**1.700**	**1.225, 2.298**	47	3,998,625	38.8	**1.212**	**0.890, 1.611**
Females 25-49 years	0.26	133	10,737,666	27.9	**4.764**	**3.989, 5.646**	164	17,036,815	44.3	**3.702**	**3.157, 4.314**
Females 50-59 years	1.55	56	5,354,817	83.0	0.675	0.510, 0.876	69	8,701,996	134.9	0.512	0.398, 0.647
Females 60-69 years	0.75	37	5,042,541	37.8	0.978	0.689, 1.349	42	8,397,235	63.0	0.667	0.481, 0.901
Females 70+ years	1.07	55	7,280,453	77.9	0.706	0.532, 0.919	63	12,240,037	131.0	0.481	0.370, 0.615
Overall, monovalent dose 1	0.76	160	23,679,349	180.0	0.889	**0.757, 1.038**	183	23,679,349	180.0	**1.017**	**0.875, 1.175**
Overall, monovalent dose 2	0.76	259	21,041,667	159.9	**1.620**	**1.428, 1.829**	317	42,062,666	319.7	0.992	0.885, 1.107
Overall, monovalent dose 3+	0.76	54	16,270,622	123.7	0.437	0.328, 0.570	91	32,233,484	245.0	0.371	0.299, 0.456
Overall, bivalent BA.1	0.76	2	527,065	4.0	0.499	0.060, 1.804	2	1,001,576	7.6	0.263	0.032, 0.949
Overall, bivalent BA.4/5	0.76	1	2,276,515	17.3	0.058	0.001, 0.322	2	4,063,581	30.9	0.065	0.008, 0.234

a. Background rate per 100,000 person years (PY). Source: Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, Narrow Algorithm ES SIDIAP PCHOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

b. Background rate from ACCESS 0-19 years used since 20-29 years rate is 0 and O/E would not be able to be calculated.

c. All occurrences of "-" in the table indicate not estimable because of 0 observed cases

This risk has also been identified after the second booster, not only in women aged 18 to 49 but also in men aged 25 to 49.

Rapporteur assessment comment:

It is noted that for cerebral venous sinus thrombosis the O/E analysis results (O/E ratios >1) for the 18-24 and 25-49 year age groups (in both males and females) using the low background rate for both the 21-day and 42-day risk windows are consistent with the previous 3rd PSUR:

Table 11. Observed to Expected (O/E) Analysis of Cerebral Venous Sinous Thrombosis in European Economic Area Countries and in the United States, Cumulative Period, Low Background Rate

		21-Day Risk Window					42-Day Risk Window				
Stratification	Low Bkgd rate[a,35]	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males ≤11 years	0.45	0	901,382	4.1	0.000	NE[c]	0	1,306,591	5.9	0.000	NE
Males 12-17 years	0.45	4	1,562,311	7.0	0.569	0.155, 1.457	5	2,409,778	10.8	0.461	0.150, 1.076
Males 18-24 years	0.42	11	2,224,929	9.3	1.177	0.588, 2.106	12	3,514,277	14.8	0.813	0.420, 1.420
Males 25-49 years	0.40	53	9,186,672	36.7	1.442	1.080, 1.887	74	14,565,823	58.3	1.270	0.997, 1.594
Males 50-59 years	1.24	26	4,241,876	52.6	0.494	0.323, 0.724	33	6,796,938	84.3	0.392	0.270, 0.550
Males 60-69 years	1.25	20	3,713,614	46.4	0.431	0.263, 0.665	30	6,042,722	75.5	0.397	0.268, 0.567
Males 70+ years	1.51	26	5,152,276	77.8	0.334	0.218, 0.490	37	8,411,485	127.0	0.291	0.205, 0.402
Females ≤11 years	0.97	1	1,016,452	9.9	0.101	0.003, 0.565	1	1,473,390	14.3	0.070	0.002, 0.390
Females 12-17 years	0.97	6	1,761,755	17.1	0.351	0.129, 0.764	9	2,717,409	26.4	0.341	0.156, 0.648
Females 18-24 years	0.97[b]	35	2,508,963	24.3	1.438	1.002, 2.000	40	3,962,908	38.4	1.041	0.743, 1.417
Females 25-49 years	0.26	122	10,359,439	26.9	4.529	3.761, 5.408	150	16,425,290	42.7	3.512	2.973, 4.122
Females 50-59 years	1.55	50	4,783,392	74.1	0.674	0.501, 0.889	62	7,664,632	118.8	0.522	0.400, 0.669
Females 60-69 years	0.75	35	4,187,692	31.4	1.114	0.776, 1.550	39	6,814,133	51.1	0.763	0.543, 1.043
Females 70+ years	1.07	50	5,810,014	62.2	0.804	0.597, 1.060	58	9,485,291	101.5	0.571	0.434, 0.739
Overall, dose 1	0.76	150	22,917,286	174.2	0.861	0.729, 1.011	173	22,917,286	174.2	0.993	0.851, 1.153
Overall, dose 2	0.76	240	21,280,003	161.7	1.484	1.302, 1.684	302	42,494,750	323.0	0.935	0.833, 1.047
Overall, dose 3	0.76	48	13,213,476	100.4	0.478	0.352, 0.634	74	26,178,631	199.0	0.372	0.292, 0.467

a. Background rate per 100,000 person years (PY). Source: Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, Narrow Algorithm ES SIDIAP PCHOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.
b. Background rate from ACCESS 0-19 years used since 20-29 years rate is 0 and O/E would not be able to be calculated.
c. Not estimable (NE) because of 0 observed cases

These tables were commented on in the EMA report.

« *In the age-stratified and overall analysis, some of the 0/E ratios (including 95% Cl) were > 1 (not in paediatric persons), this was only seen when applying the low background rates. Using the mid-range background rate all 0/E ratios were below 1.*

The 0/E result using the low background rate and the 42-day risk window (0/E ratio 1.017 [95%CI 0.875; 1.175]) for the overall monovalent dose 1 of which the 95% Cl included 1 that indicate lack of statistical significance, is new in current 4th PSUR.

0/E ratios for ischemic stroke and hemorrhagic stroke were well below 1.

No new important safety concern could be identified for stroke. »

In summary, <u>there is indeed a statistically significant signal identified</u>, but it is deemed not to be a safety issue despite the severity of the problem and the lack of consideration for the underreporting of adverse effects.

13.10 Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023

The fifth safety report, covering the period from December 18, 2022, to June 18, 2023, and reviewed by the EMA, is available at the following link:
https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-december-2022-18-june-2023_en.pdf
The Pfizer report starts on page 144.

Regarding the evaluation of **safety signals**, they are summarized in Section 15, "OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED" (page 207 of the PDF) and discussed by the EMA on pages 5 and 6.

« *During the interval period,* ***the following signals were evaluated, not to be determined risks****, and no new important safety issue was identified based on the data provided in the PSUR:*

• *Myositis (EPITT 19883); Pemphigus and Pemphigoid (EPITT 19859).*

The following were ongoing signals during the interval period:

• ***Menstrual irregularities*** *(closed after DLP, no causal association with Comirnaty and continue to monitor through routine pharmacovigilance);*

• ***Sensorineural hearing loss*** *(closed after DLP, no causal association with Comirnaty and continue to monitor through routine pharmacovigilance);*

• ***Retinal vascular occlusion*** *(ongoing, MAH's evaluation is awaited).*

During the interval period, there were ***post-approval regulatory requests*** *for the following topics for which no safety signal was identified based on the information provided in the PSUR:*

• ***Multisystem inflammatory syndrome children/-adults*** *(MIS-C/-A)*

During the interval period, the important potential risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) was removed from the list of safety concerns in the Comirnaty RMP and PSUR, and will continue to monitor through routine pharmacovigilance. »

Illustration 213 : EMA – Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 – Overview of signals

During the interval period, the following signals were evaluated, not to be determined risks, and no new important safety issue was identified based on the data provided in the PSUR:

- Myositis (EPITT 19883); Pemphigus and Pemphigoid (EPITT 19859).

The following were ongoing signals during the interval period:

- Menstrual irregularities (closed after DLP, no causal association with Comirnaty and continue to monitor through routine pharmacovigilance);
- Sensorineural hearing loss (closed after DLP, no causal association with Comirnaty and continue to monitor through routine pharmacovigilance);
- Retinal vascular occlusion (ongoing, MAH's evaluation is awaited).

During the interval period, there were post-approval regulatory requests for the following topics for which no safety signal was identified based on the information provided in the PSUR:

- Multisystem inflammatory syndrome children/-adults (MIS-C/-A); Dyspnoea; Palpitations; Tachycardia/Heart Rate Increase; Haemophagocytic lymphohistiocytosis (HLH); Pemphigus and Pemphigoid (new cases/data through 18 Jun 2023).

During the interval period, the important potential risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) was removed from the list of

safety concerns in the Comirnaty RMP and PSUR, and will continue to monitor through routine pharmacovigilance.

Illustration 214 : Pfizer – Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 – Overview of signals

Table 32. Overview of Signals (at DLP 18 June 2023)

Signal	Signal Status*	Source	Category*	EMA Regulatory Procedure
Sensorineural Hearing Loss	New and ongoing	Enquiry from a competent authority (TGA, Australia)	Not applicable	
Retinal Vascular Occlusion	New and ongoing	Medical Literature	Not applicable	
Menstrual Irregularities	New and ongoing	This expanded focus topic (menstrual irregularities) is undergoing internal review following closure of the PRAC signal for Amenorrhea and Heavy Menstrual Bleeding	Not applicable	
Pemphigus and Pemphigoid[a]	Closed	Enquiry from a competent authority (EMA PRAC)	No Risk	EPITT No. 19859
Myositis	New and closed	Enquiry from a competent authority (EMA PRAC)	No Risk	EPITT No. 19883

a. Pemphigus and Pemphigoid is discussed in the subsection Other Safety Topic not Considered Signals as per PRAC indication [Signal procedure assessment report (EMEA/H/C/005735/SDA/061 - EPITT 19859)].
* Reflects the MAH position in the MAH signal log. This may differ from the position of the competent authority.

In Section 1.3.5.8, "***Late-breaking Information***," it is revealed that a new signal (**mastitis/breast swelling**) was opened following a request from the Australian regulatory authority (TGA). The ongoing signals (menstrual irregularities and sensorineural hearing loss) were closed due to the absence of risk on July 26, 2023, and July 19, 2023, respectively.

Illustration 215 : Pfizer – Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 – Signaux de dernière minute

1.3.5.8. Late-breaking information

After the DLP,

- An updated CDS (version 22.0) was made effective on 24 July 2023; this updated version includes the addition of vaccine presentations anticipated for the 2023-2024 new variant (Omicron XBB.1.5), several sections of the CDS have been reformatted to simplify and consolidate the existing information where possible to remove redundancy and repetition. No new information related to the indication, dosing, safety or efficacy/immunogenicity has been added or revised as a result of the consolidation or formatting changes.
- Signals:
  - A new signal (Mastitis/Breast swelling) was opened based upon an enquiry from the Australian regulatory authority (TGA). The signal is ongoing.
  - The ongoing signals (Menstrual irregularities and Sensorineural Hearing Loss) were closed as no risk on 26 July 2023 and on 19 July 2023, respectively.

The data analysis report dated March 7, 2023, titled "**Incidence Rate of Pemphigus and Pemphigoid After Administration of COVID-19 Vaccines**", reported an **increased incidence rate** of pemphigoid and pemphigus 90 and 180 days after the second dose of Comirnaty in the UK database (IMRD UK).

Illustration 216 : Pfizer – Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 – Incidence Rate of Pemphigus and Pemphigoid

*Table 5. Standardised incidence rates of new onset pemphigoid or pemphigus **[using narrow endpoint definition]** per 100,000 years of follow-up following exposure to COVID-19 vaccines*

Database	Vaccine	Vaccine window	After receiving first dose			After receiving second dose			After receiving third dose		
			Events*	Follow-up time (person years)	Rate per 100,000 (95% CI)	Events*	Follow-up time (person years)	Rate per 100,000 (95% CI)	Events	Follow-up time (person years)	Rate per 100,000 (95% CI)
IMRD UK	Comirnaty	90-day	6	113,244	5.32 (1.82-11.18)	16	118,999	**12.93 (7.05-20.97)**	<6	-	1.69 (0.33-4.54)
	Spikevax		0	9,259	0.00 (.-.)	0	7,563	0.00 (.-.)	0	2,232	0.00 (.-.)
	Vaxzevria		<6	-	5.75 (1.38-13.48)	12	121,122	11.41 (5.44-19.98)	0	354	0.00 (.-.)
	Comirnaty	180-day	9	133,042	7.37 (3.12-13.84)	29	215,862	**10.84 (7.00-15.68)**	12	122,654	4.41 (2.01-7.85)
	Spikevax		<6	-	3.66 (0.09-17.12)	0	12,939	0.00 (.-.)	0	3,717	0.00 (.-.)
	Vaxzevria		7	109,241	6.94 (2.28-14.44)	25	238,267	**12.11 (7.43-18.10)**	0	643	0.00 (.-.)
THIN® Spain	Comirnaty	90-day	<10	-	20.28 (9.18-37.14)	16	113,759	10.65 (5.93-17.09)	<10	-	3.76 (1.35-7.82)
	Spikevax		<10	-	23.37 (0.00-85.88)	<10	-	8.98 (1.08-28.83)	<10	-	20.45 (4.21-54.59)
	Vaxzevria		<10	-	8.90 (0.00-34.76)	<10	-	1.28 (0.14-4.13)	0	7	0.00 (.-.)
	Comirnaty	180-day	<10	-	18.01 (8.10-33.08)	36	218,673	12.81 (8.79-17.75)	20	48,432	7.19 (4.34-10.94)
	Spikevax		<10	-	25.18 (0.00-81.75)	<10	-	18.99 (7.11-38.14)	<10	-	17.14 (5.54-37.62)
	Vaxzevria		<10	-	7.98 (0.00-31.04)	<10	-	1.14 (0.22-3.06)	0	13	0.00 (.-.)

* **N.B.**: Events that occur within both the first and second vaccine windows were included only in the second vaccine window and the denominator (follow-up time) was also truncated at the second vaccination. Thus, the incidence rate is the rate from 1st vaccination date to the earliest of: 90 days, end of follow-up or next vaccination date.

95% CI: 95% Confidence intervals

PSUR 5 did include this pathology but did not classify it as a signal. The second signal that emerged relates to myositis, which was also closed.

The signal for postmenopausal hemorrhage was initiated, confirmed, and remains ongoing.

The report also demonstrates **an increased risk of myocarditis/pericarditis starting <u>from the age of 5</u>**.

Illustration 217 : Pfizer – Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 – Risk of myocarditis

Literature

During the reporting interval, there were no new significant data received from literature sources.

O/E analysis

Cumulative for myocarditis in the EEA, O/E ratios were above 1 for the following groups (although the 95% CI crossed 1 for some groups)

- 14-day risk window:
  - Males 5+ years
  - Females 5+ years
  - Overall, monovalent dose 1, dose 2, and additional doses
  - Overall
- 21-day risk window:
  - Males 5+ years
  - Females 12+ years
  - Overall, monovalent dose 1, dose 2, and additional doses
  - Overall

Cumulative for myocarditis/pericarditis in the EEA, O/E ratios were above 1 for the following groups (although the 95% CI crossed 1 for some groups)

- 14-day risk window:
  - Males 12-24 years
  - Females 12+ years
  - Overall, monovalent dose 1 and dose 2
  - Overall
- 21-day risk window:
  - Males 12-24 years
  - Females 12-49 years
  - Overall, monovalent dose 2
  - Overall

The cost-effectiveness analysis up until May 15, 2023, was conducted for acute disseminated encephalomyelitis (ADEM, narrow definition), ADEM and encephalitis (broad definition), autoimmune thyroiditis, myasthenia gravis, polymyalgia rheumatica, and type 1 diabetes mellitus. All O/E ratios were below 1, except for ADEM with the narrow definition in the age groups of 18-24 years, 25-49 years, and 50-59 years using the 21-day risk window (Table 4), and in the 25-49 age group using the 42-day risk window (Table 5).

The review of these cases, along with age-group analyses, O/E ratios, and comparisons between original and bivalent vaccines, did not reveal any significant new safety information. Safety monitoring will continue.

Illustration 218 : Pfizer Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 – AESI analysis

O/E analysis

- O/E analysis through 15 May 2023 was performed for Acute disseminated encephalomyelitis (ADEM)(narrow definition), ADEM and encephalitis (broad definition), Autoimmune thyroiditis, Myasthenia gravis, Polymyalgia rheumatica, and Type 1 diabetes mellitus. All O/E ratios were <1, except for ADEM narrow definition in the 18-24 years, 25-49 years, and 50-59 years age groups using the 21-day risk window (table 4) and in the 25-49 years age group using the 42-day risk window (table 5):

Table 4. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 21-Day Risk Window, Cumulative Period

	<5 years		5-11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio [a,b,c]	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
ADEM, narrow definition	0.000	-	0.135	0.016, 0.486	0.493	0.263, 0.843	1.016	0.525, 1.775	1.870	1.466, 2.352	1.473	0.970, 2.143	0.749	0.437, 1.200	0.816	0.491, 1.274
ADEM and encephalitis, broad definition	0.000	-	0.071	0.029, 0.147	0.149	0.097, 0.218	0.098	0.062, 0.145	0.119	0.100, 0.139	0.062	0.047, 0.081	0.042	0.031, 0.054	0.042	0.034, 0.052

Table 5. Age-Stratified Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI) in European Economic Area Countries and the United States, 42-Day Risk Window, Cumulative Period

	<5 years		5-11 years		12-17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
AESI	O/E Ratio [a,b,c]	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
ADEM, narrow definition	0.000	-	0.089	0.011, 0.322	0.364	0.204, 0.601	0.741	0.405, 1.243	1.235	0.976, 1.542	0.882	0.581, 1.284	0.433	0.252, 0.694	0.547	0.343, 0.828
ADEM and encephalitis, broad definition	0.000	-	0.047	0.019, 0.097	0.110	0.074, 0.157	0.074	0.049, 0.106	0.088	0.075, 0.102	0.043	0.033, 0.055	0.029	0.022, 0.036	0.027	0.022, 0.033

MAH's conclusion

No new significant safety information was identified based on the review of these cases and on the analyses by age group, O/E, and original vs bivalent vaccines. Safety surveillance will continue.

The report indicated <u>1.8 million cases</u> reported to pharmacovigilance since the begining of the vaccination campaign with 6 millions AEs **(pages 14 of the PDF).**

The number of deaths is not indicated.

Illustration 219 : Pfizer Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 – Cases

Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

Appendix 2.2 of the PSUR (not reproduced here) provides the overall (including original and bivalent vaccines) cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources. Appendix 2.2.1 through Appendix 2.2.4 of the PSUR (not reproduced here) provide cumulative and interval summary tabulation of adverse drug reactions by PT from post-marketing sources by vaccine type [BNT162b2 original and BNT162b2 bivalent (Omi BA.1, Omi BA.4/BA.5, Omi)]. These tabulations include serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources.

Rapporteur assessment comment:

During the interval period, post-marketing there were 74,102 cases reporting 242,787 AEs.

Cumulatively, a total of 1,839,454 cases with 6,059,820 AEs were reported in MAH's safety database.

Regarding pregnant women, the document still states: *« The safety profile of the vaccine in pregnant and/or breastfeeding women **<u>was not studied</u> in the pivotal clinical trial and the maternal clinical trial was terminated early due to participant recruitment difficulties. <u>Many pregnant women have chosen to be vaccinated despite the lack of clinical trial safety data</u>**. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. **The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy is not yet fully understood** and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-Co V-2 will influence the benefit risk considerations for use of the vaccine. Cases indicative of use in pregnancy and while breastfeeding received during the reporting interval are summarised in Section 16.3.5.2 Use in Pregnant/Lactating Women.* »

Note the « have chosen » !

Illustration 220 : Pfizer – Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 – Information on pregnant women

16.4.2. Description of Missing Information

Table 57 describes missing information associated with the use of BNT162b2.

Table 57. Description of Missing Information

Topic	Description
Use in pregnancy and while breast feeding	The safety profile of the vaccine in pregnant and/or breastfeeding women was not studied in the pivotal clinical trial and the maternal clinical trial was terminated early due to participant recruitment difficulties. Many pregnant women have chosen to be vaccinated despite the lack of clinical trial safety data. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy is not yet fully understood and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine. Cases indicative of use in pregnancy and while breastfeeding received during the reporting interval are summarised in Section 16.3.5.2 *Use in Pregnant/Lactating Women*.

Regarding the missing information (page 128 of the PDF), as of June 18, 2023, the PSUR still cites gaps in data on use in pregnant or breastfeeding women, use in immunocompromised patients, and use in frail patients with comorbidities (COPD, diabetes, chronic neurological disease, cardiovascular conditions). The interaction with other vaccines also remained unknown, as well as long-term tolerance.

Illustration 221 : Pfizer – Periodic Safety Report 5 (PSUR5) –18 December 2022 through 18 June 2023 - Description of missing information

2.4.2. Description of missing information

- Use in pregnancy and while breast feeding
- Use in immunocompromised patients
- Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
- Use in patients with autoimmune or inflammatory disorders
- Interaction with other vaccines
- Long term safety data

Rapporteur assessment comment:

The information on the missing information has been updated with no consequence on the known safety profile. The missing information remain unchanged.

At the April 19, 2023 meeting of the Advisory Committee on Immunization Practices (ACIP), the CDC presented data related to further analyses of a **preliminary safety signal for individuals aged 65 and older** who received the Pfizer-BioNTech bivalent COVID-19

vaccine. This signal concerning **ischemic stroke** was identified through the Vaccine Safety Datalink (VSD) surveillance system.

https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cdc-and-fda-identify-preliminary-covid-19-vaccine-safety-signal-persons-aged-65-years-and-older

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/03-COVID-Shimabukuro-508.pdf

The safety report 5 indicates that an additional semi-annual PSUR was to be submitted, followed by the first annual PSUR with a data lock point (DLP) in December 2024. No report has been published on the EMA website.

13.12 European Pharmacovigilance Data

Pharmacovigilance data from the Eudravigilance website can be accessed on the site Eudravigilance, which contains reports on adverse drug reactions for medicines authorized in the European Economic Area.
https://www.adrreports.eu/fr/disclaimer.html
https://dap.ema.europa.eu/analytics/saw.dll?PortalPages&PortalPath=%2Fshared%2FPHV%20DAP%2F_portal%2FDAP&Action=Navigate&P0=1&P1=eq&P2=%22Line%20Listing%20Objects%22.%22Substance%20High%20Level%20Code%22&P3=1+42325700

Regarding the first authorized vaccine (COVID-19 MRNA VACCINE PFIZER-BIONTECH (TOZINAMERAN)), more than **1.2 million cases have been reported**, with nearly 40% submitted by healthcare professionals. Seventy percent of these cases concern women, and 3% involve individuals under the age of 17. **Forty percent of all cases are considered serious**.

For the **ORIGINAL/OMICRON BA.4-5 vaccine (TOZINAMERAN, FAMTOZINAMERAN)**, 12,025 cases have been reported, with 65% classified as serious.

For the **ORIGINAL/OMICRON BA.1 vaccine (TOZINAMERAN, RILTOZINAMERAN)**, 7,054 cases have been reported, with more than 50% being serious.

For the **OMICRON XBB.1.5 vaccine (RAXTOZINAMERAN)**, 7,501 cases have been reported, with over 60% considered serious.

Illustration 222 : EMA – Eudravigilance – number of cases - TOZINAMERAN - May 26, 2024

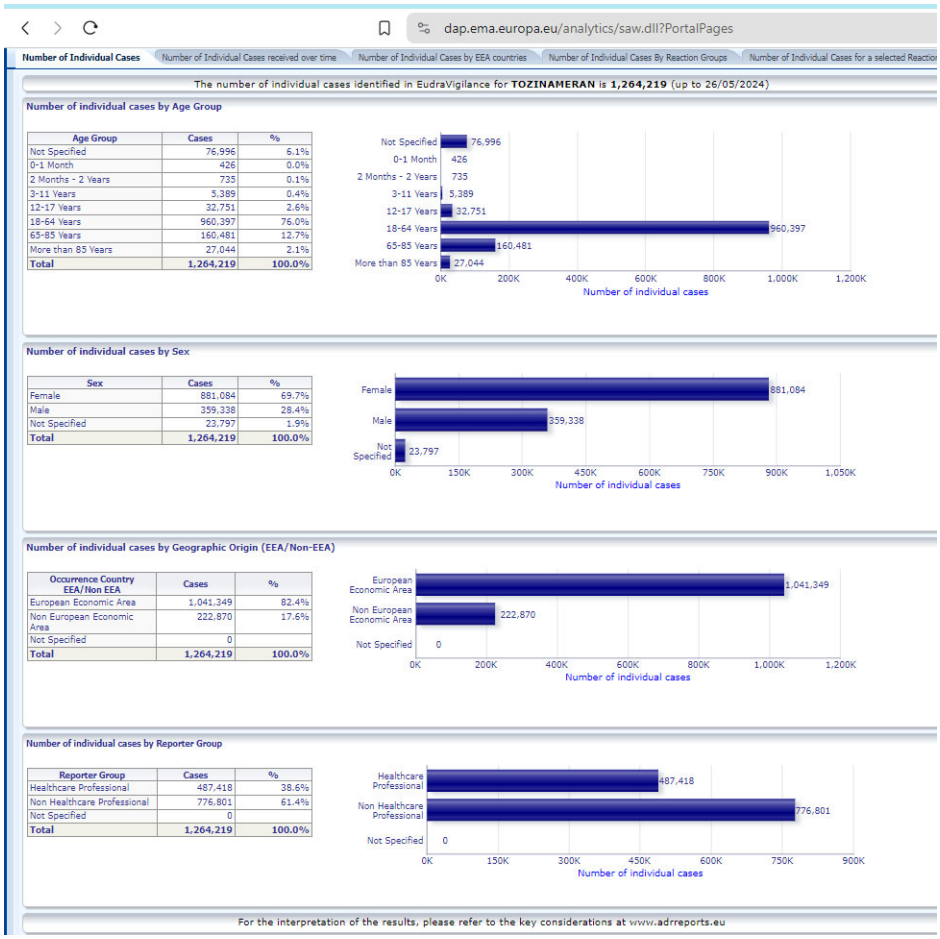
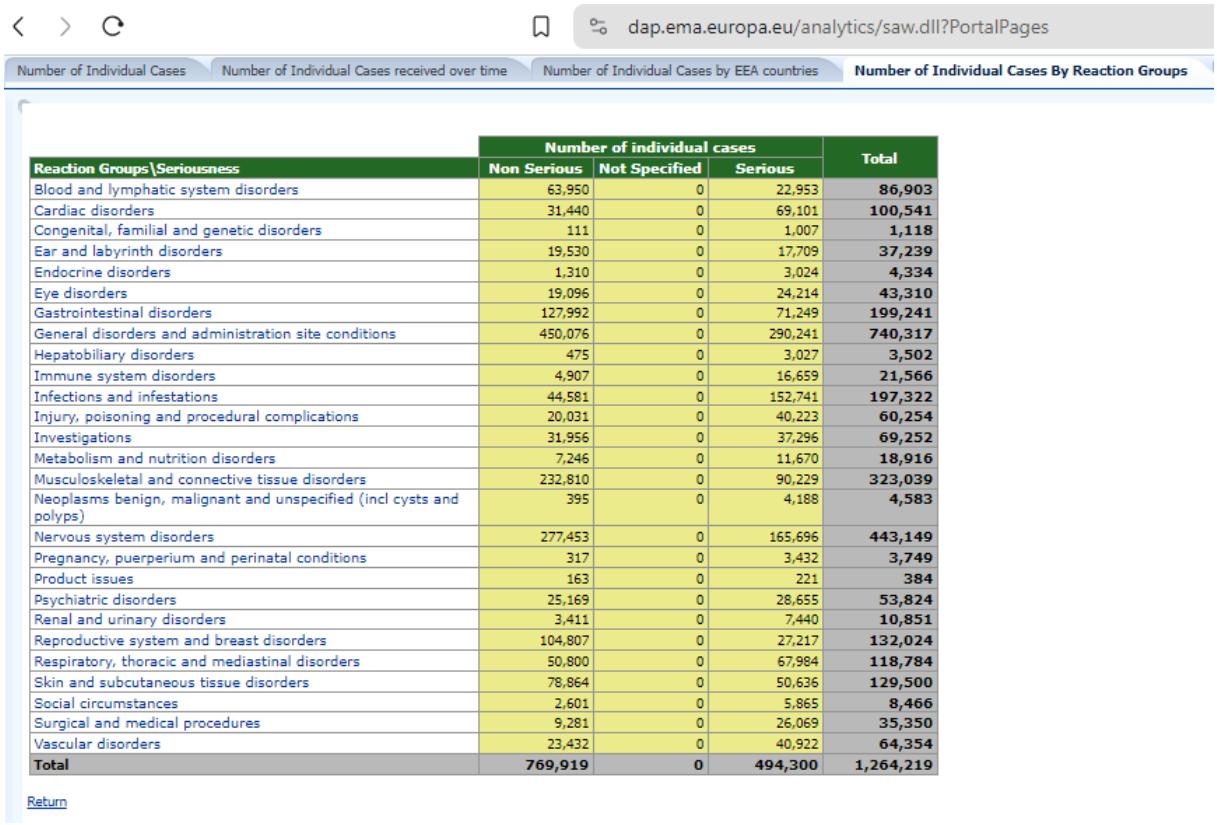


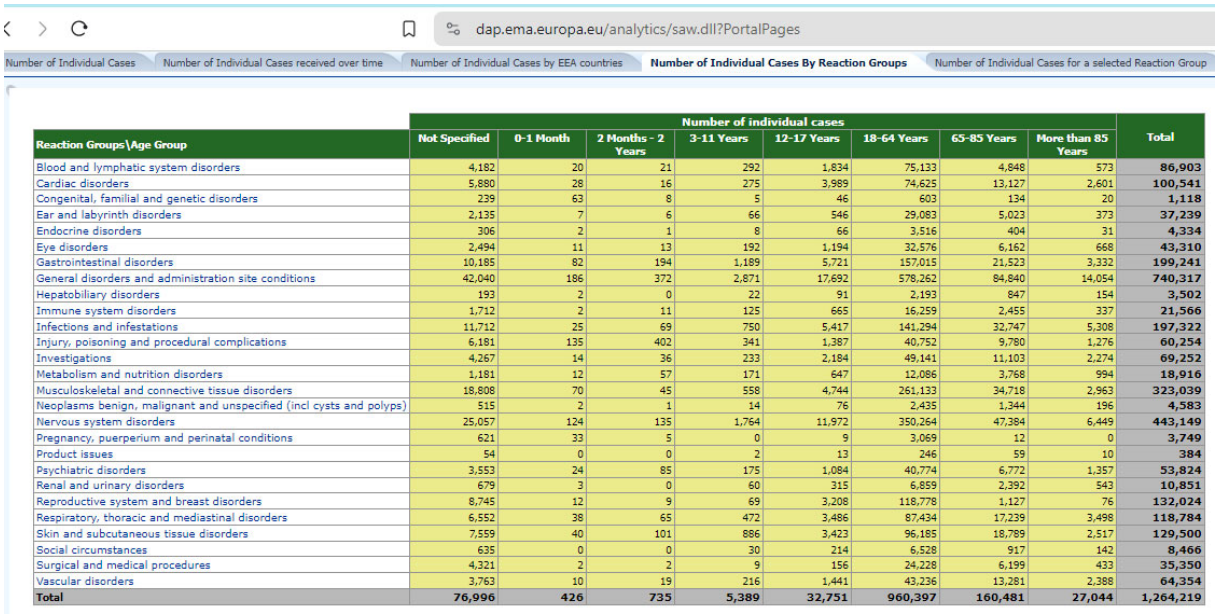
Illustration 223 : EMA – Eudravigilance – number of serious cases by System Organ Class- TOZINAMERAN - May 26, 2024



Reaction Groups\Seriousness	Number of individual cases			Total
	Non Serious	Not Specified	Serious	
Blood and lymphatic system disorders	63,950	0	22,953	**86,903**
Cardiac disorders	31,440	0	69,101	**100,541**
Congenital, familial and genetic disorders	111	0	1,007	**1,118**
Ear and labyrinth disorders	19,530	0	17,709	**37,239**
Endocrine disorders	1,310	0	3,024	**4,334**
Eye disorders	19,096	0	24,214	**43,310**
Gastrointestinal disorders	127,992	0	71,249	**199,241**
General disorders and administration site conditions	450,076	0	290,241	**740,317**
Hepatobiliary disorders	475	0	3,027	**3,502**
Immune system disorders	4,907	0	16,659	**21,566**
Infections and infestations	44,581	0	152,741	**197,322**
Injury, poisoning and procedural complications	20,031	0	40,223	**60,254**
Investigations	31,956	0	37,296	**69,252**
Metabolism and nutrition disorders	7,246	0	11,670	**18,916**
Musculoskeletal and connective tissue disorders	232,810	0	90,229	**323,039**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	395	0	4,188	**4,583**
Nervous system disorders	277,453	0	165,696	**443,149**
Pregnancy, puerperium and perinatal conditions	317	0	3,432	**3,749**
Product issues	163	0	221	**384**
Psychiatric disorders	25,169	0	28,655	**53,824**
Renal and urinary disorders	3,411	0	7,440	**10,851**
Reproductive system and breast disorders	104,807	0	27,217	**132,024**
Respiratory, thoracic and mediastinal disorders	50,800	0	67,984	**118,784**
Skin and subcutaneous tissue disorders	78,864	0	50,636	**129,500**
Social circumstances	2,601	0	5,865	**8,466**
Surgical and medical procedures	9,281	0	26,069	**35,350**
Vascular disorders	23,432	0	40,922	**64,354**
Total	**769,919**	**0**	**494,300**	**1,264,219**

Return

Illustration 224 : EMA – Eudravigilance – number of cases by System Organ Class and Age- TOZINAMERAN - May 26, 2024



Reaction Groups\Age Group	Number of individual cases								Total
	Not Specified	0-1 Month	2 Months - 2 Years	3-11 Years	12-17 Years	18-64 Years	65-85 Years	More than 85 Years	
Blood and lymphatic system disorders	4,182	20	21	292	1,834	75,133	4,848	573	**86,903**
Cardiac disorders	5,880	28	16	275	3,989	74,625	13,127	2,601	**100,541**
Congenital, familial and genetic disorders	239	63	8	5	46	603	134	20	**1,118**
Ear and labyrinth disorders	2,135	7	6	66	546	29,083	5,023	373	**37,239**
Endocrine disorders	306	2	1	8	66	3,516	404	31	**4,334**
Eye disorders	2,494	11	13	192	1,194	32,576	6,162	668	**43,310**
Gastrointestinal disorders	10,185	82	194	1,189	5,721	157,015	21,523	3,332	**199,241**
General disorders and administration site conditions	42,040	186	372	2,871	17,692	578,262	84,840	14,054	**740,317**
Hepatobiliary disorders	193	2	0	22	91	2,193	847	154	**3,502**
Immune system disorders	1,712	2	11	125	665	16,259	2,455	337	**21,566**
Infections and infestations	11,712	25	69	750	5,417	141,294	32,747	5,308	**197,322**
Injury, poisoning and procedural complications	6,181	135	402	341	1,387	40,752	9,780	1,276	**60,254**
Investigations	4,267	14	36	233	2,184	49,141	11,103	2,274	**69,252**
Metabolism and nutrition disorders	1,181	12	57	171	647	12,086	3,768	994	**18,916**
Musculoskeletal and connective tissue disorders	18,808	70	45	558	4,744	261,133	34,718	2,963	**323,039**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	515	2	1	14	76	2,435	1,344	196	**4,583**
Nervous system disorders	25,057	124	135	1,764	11,972	350,264	47,384	6,449	**443,149**
Pregnancy, puerperium and perinatal conditions	621	33	5	0	9	3,069	12	0	**3,749**
Product issues	54	0	0	2	13	246	59	10	**384**
Psychiatric disorders	3,553	24	85	175	1,084	40,774	6,772	1,357	**53,824**
Renal and urinary disorders	679	3	0	60	315	6,859	2,392	543	**10,851**
Reproductive system and breast disorders	8,745	12	9	69	3,208	118,778	1,127	76	**132,024**
Respiratory, thoracic and mediastinal disorders	6,552	38	65	472	3,486	87,434	17,239	3,498	**118,784**
Skin and subcutaneous tissue disorders	7,559	40	101	886	3,423	96,185	18,789	2,517	**129,500**
Social circumstances	635	0	0	30	214	6,528	917	142	**8,466**
Surgical and medical procedures	4,321	2	2	9	156	24,228	6,199	433	**35,350**
Vascular disorders	3,763	10	19	216	1,441	43,236	13,281	2,388	**64,354**
Total	**76,996**	**426**	**735**	**5,389**	**32,751**	**960,397**	**160,481**	**27,044**	**1,264,219**

Illustration 225 : EMA – Eudravigilance – number of cases - ORIGINAL/OMICRON BA.4-5 (TOZINAMERAN, FAMTOZINAMERAN) - May 26, 2024

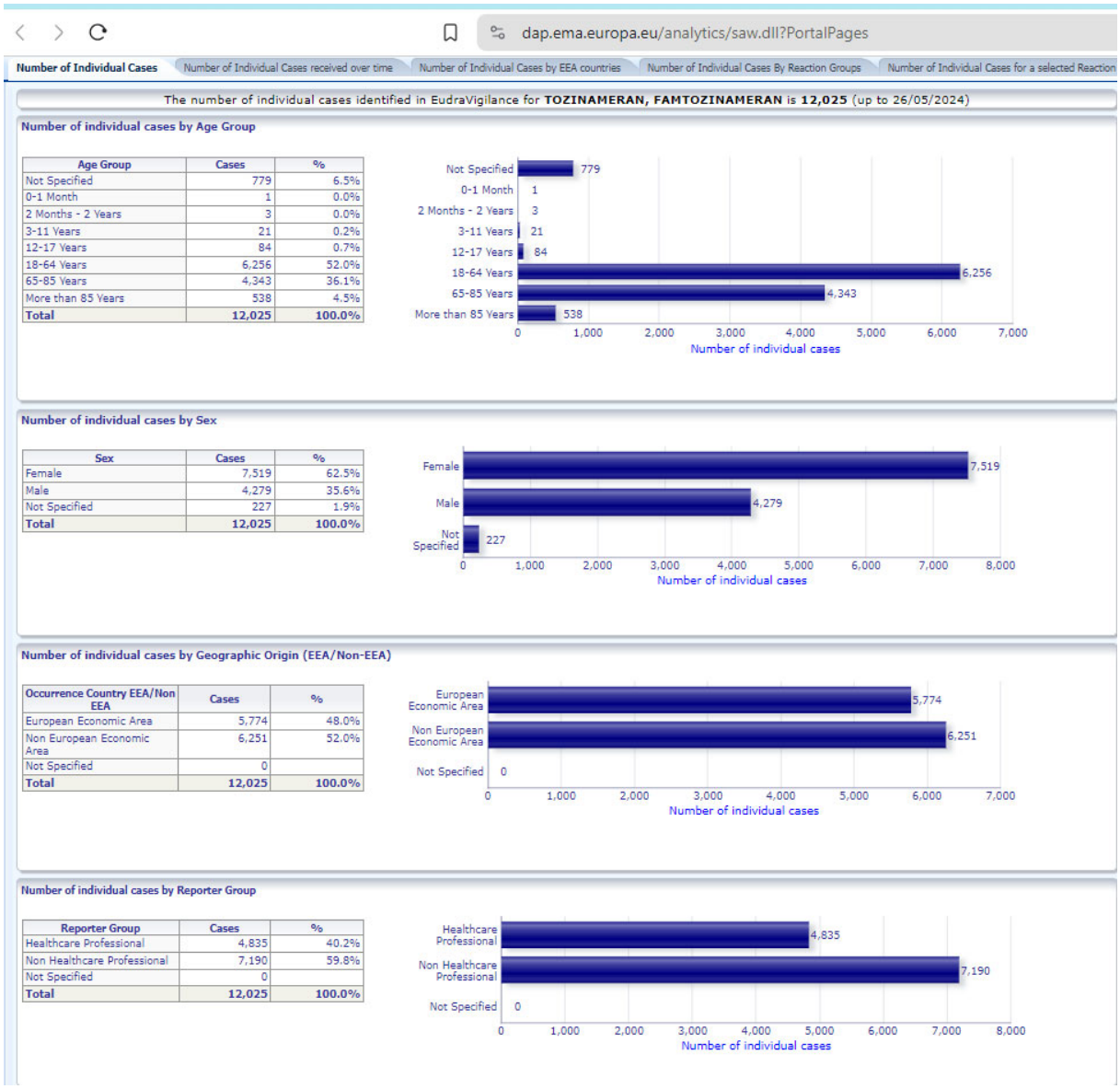


Illustration 226 : EMA – Eudravigilance – number of cases - cas OMICRON XBB.1.5 (RAXTOZINAMERAN - May 26, 2024

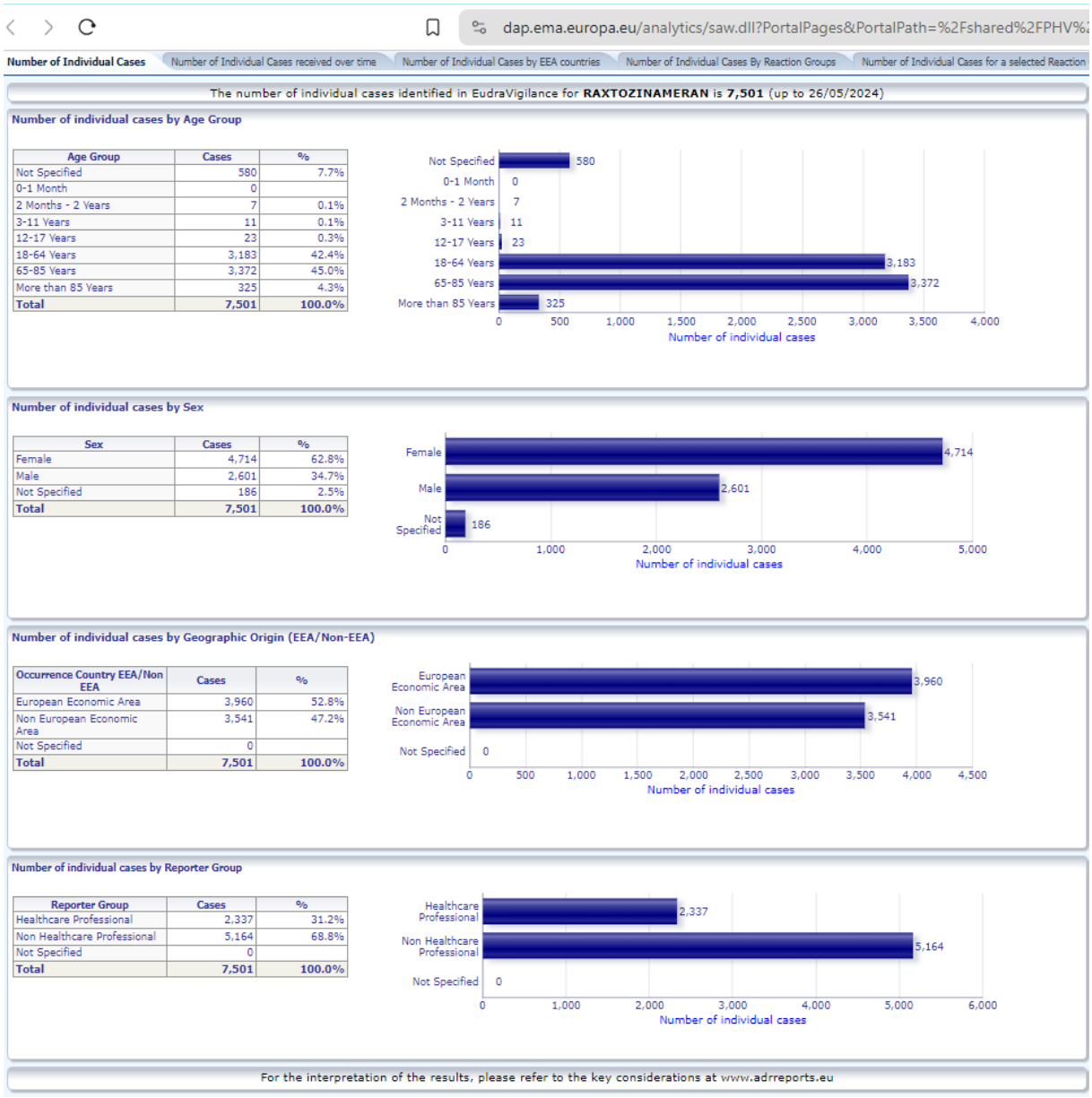
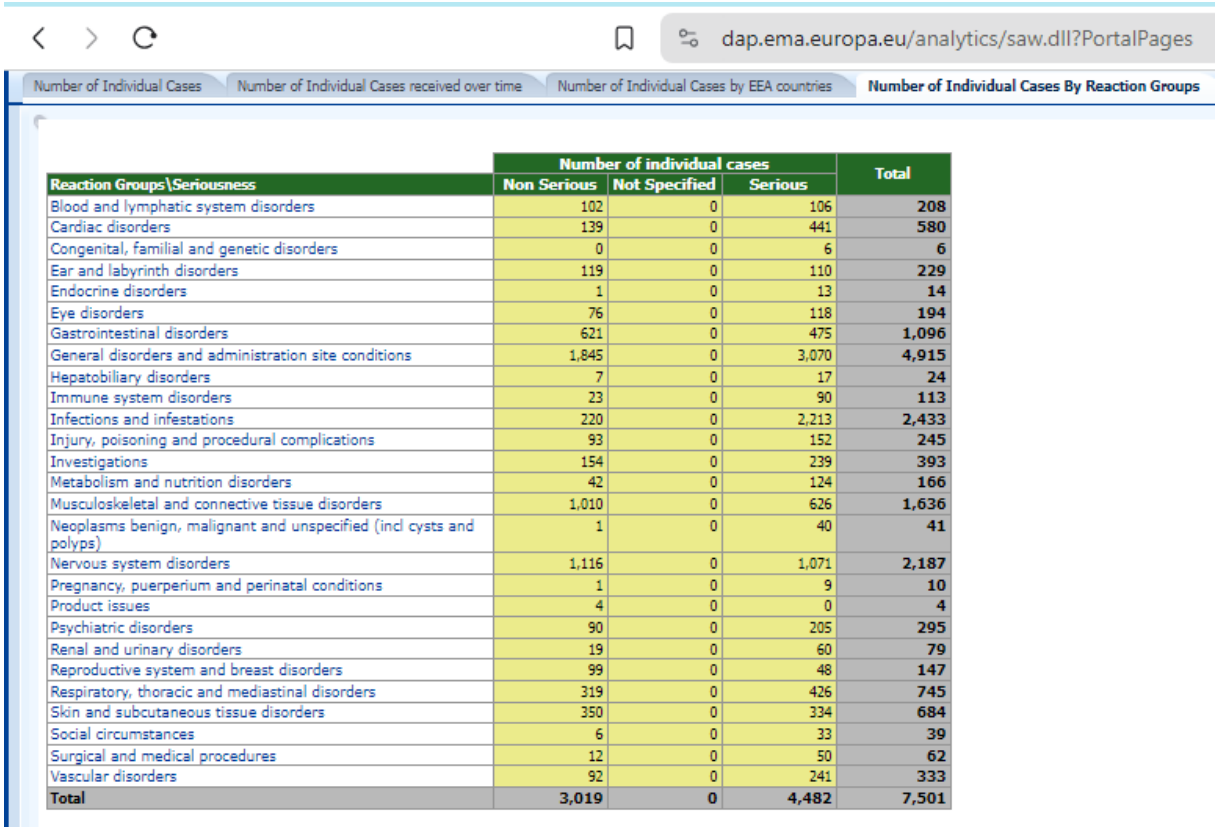


Illustration 227 : EMA – Eudravigilance – number of serious cases by Système Organ Class - OMICRON XBB.1.5 (RAXTOZINAMERAN - May 26, 2024



	Number of individual cases			Total
Reaction Groups\Seriousness	Non Serious	Not Specified	Serious	
Blood and lymphatic system disorders	102	0	106	**208**
Cardiac disorders	139	0	441	**580**
Congenital, familial and genetic disorders	0	0	6	**6**
Ear and labyrinth disorders	119	0	110	**229**
Endocrine disorders	1	0	13	**14**
Eye disorders	76	0	118	**194**
Gastrointestinal disorders	621	0	475	**1,096**
General disorders and administration site conditions	1,845	0	3,070	**4,915**
Hepatobiliary disorders	7	0	17	**24**
Immune system disorders	23	0	90	**113**
Infections and infestations	220	0	2,213	**2,433**
Injury, poisoning and procedural complications	93	0	152	**245**
Investigations	154	0	239	**393**
Metabolism and nutrition disorders	42	0	124	**166**
Musculoskeletal and connective tissue disorders	1,010	0	626	**1,636**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0	40	**41**
Nervous system disorders	1,116	0	1,071	**2,187**
Pregnancy, puerperium and perinatal conditions	1	0	9	**10**
Product issues	4	0	0	**4**
Psychiatric disorders	90	0	205	**295**
Renal and urinary disorders	19	0	60	**79**
Reproductive system and breast disorders	99	0	48	**147**
Respiratory, thoracic and mediastinal disorders	319	0	426	**745**
Skin and subcutaneous tissue disorders	350	0	334	**684**
Social circumstances	6	0	33	**39**
Surgical and medical procedures	12	0	50	**62**
Vascular disorders	92	0	241	**333**
Total	**3,019**	**0**	**4,482**	**7,501**

14 Doubts about data quality, the cases of Ventavia and Madeline de Garay

14.1 The case of the Clinical Research Organization Ventavia

According to an article in the British Medical Journal, Ms. BrookJackson regional director with 20 years of experience in clinical trial coordination and management, hired by CRO Ventavia Research Group (https://www.ventaviaresearch.com/) on September 7, 2020, to oversee operations, **recruitment and quality assurance for the company's clinics, is alleging serious breaches of Good Clinical Practice** and other misconduct.

Source : Thacker P D. Covid-19: Researcher blows the whistle on data integrity issues in Pfizer's vaccine trial BMJ 2021; 375 :n2635 https://www.bmj.com/content/375/bmj.n2635

According to the document "***Reflection paper on risk based quality management in clinical trials",*** "***Good clinical practice*** *(GCP) is a set of internationally recognised* ***ethical and scientific standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.***

ICH GCP requires in Section 5.1, that the sponsor implements and maintains systems for quality assurance and quality control; similarly, the Article 2 of the GCP Directive 2005/28/EC requires the implementation of procedures necessary to secure the quality of every aspect of the trial.

The key elements of the quality system include:

- *documented procedures and validated methods being developed, implemented and kept up-todate;*
- *documentation system that preserves and allows for the retrieval of any information/documentation (quality records/essential documents) to show actions taken, decisions made and results;*
- *appropriate training of sponsor personnel as well as of the personnel in affiliates, at the Contract Research Organisations (CROs), vendors or other service providers and at trial sites;*
- *validation of computerised systems;*
- *quality control, for example monitoring of trial sites and central technical facilities on-site and/or by using centralised monitoring techniques;*
- *quality assurance including internal and external audits performed by independent auditors*

The aim of these quality management procedures is to provide assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

The same requirements apply to Contract Research Organisations (CROs), vendors or other service providers to whom the sponsor has delegated any trial related duties and functions of the sponsor."

Illustration 228 : EMA - Compliance and Inspection: Reflection Paper on Risk-Based Quality Management in Clinical Trials, November 18, 2013 – Good Clinical Practice

1. Introduction

Good clinical practice (GCP)[1], is a set of internationally recognised ethical and scientific standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.

ICH GCP requires in Section 5.1, that the sponsor implements and maintains systems for quality assurance and quality control; similarly the Article 2 of the GCP Directive 2005/28/EC requires the implementation of procedures necessary to secure the quality of every aspect of the trial. The aim of these quality management procedures is to provide assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible. The same requirements apply to Contract Research Organisations (CROs), vendors or other service providers to whom the sponsor has delegated any trial related duties and functions of the sponsor.

The key elements of the quality system include:

- documented procedures and validated methods being developed, implemented and kept up-to-date;
- documentation system that preserves and allows for the retrieval of any information/documentation (quality records/essential documents) to show actions taken, decisions made and results;
- appropriate training of sponsor personnel as well as of the personnel in affiliates, at the Contract Research Organisations (CROs), vendors or other service providers and at trial sites;

- validation of computerised systems;
- quality control, for example monitoring of trial sites and central technical facilities on-site and/or by using centralised monitoring techniques;
- quality assurance including internal and external audits performed by independent auditors.

Source: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

During her months of involvement in Pfizer/BioNtech's Phase 2/3 COVID-19 trial, Ms. Jackson, along with two other employees who wished to remain anonymous, accused Ventavia of the following:

- **Storing vaccines at incorrect temperatures**
- **Falsifying data**
- **Failing to maintain participant anonymity**: Staff at the trial sites were allegedly informed of the actual product administered to participants, even though the trial was supposed to be blinded.
- **Employing inadequately trained vaccinators**
- **Delaying follow-up on reported adverse events**: As evidenced by an email from the contract research organization (CRO) ICON, which was chosen by Pfizer to manage the trial:

"The subject reported severe symptoms/reactions... According to the protocol, subjects with Grade 3 local reactions must be contacted. Please confirm whether an UNSCHEDULED CONTACT was made and update the corresponding form accordingly." According to the trial protocol, a phone call should have taken place "to obtain additional details and determine if an on-site visit is clinically indicated."

- **Making significant errors in handling samples**, such as mislabeling them, with documented evidence found in "laboratory handling logs" completed by staff.
- **Failing to enter data within required timeframes**, leading to a reprimand from the CRO ICON: "The expectation for this study is that all queries are addressed within 24 hours."

This set of allegations **points to potential breaches in trial protocol**, patient safety, and data integrity, raising serious concerns about the conduct of the clinical trial.

Ventavia did not have enough employees to collect samples from all trial participants who reported COVID-19-like symptoms to test for infection. This information may partially explain the numerous symptomatic COVID-19 cases that were not confirmed by PCR testing, casting doubt on the validity of the COVID-19 case count used for the primary endpoint.

These issues constitute serious violations of Good Clinical Practice (GCP).

The document titled "***Compliance and Inspection: Reflection Paper on Risk-Based Quality Management in Clinical Trials***" also defines the concept of acceptable risks as follows:

"*Risks might be acceptable* ***if they have limited impact on subject's safety and rights as well as data integrity and reliability.*** *If a risk is not acceptable, it needs to be reduced by appropriate risk mitigation actions. Those need to be specified in a risk management plan. The latter needs to be reviewed and adapted accordingly*."

Illustration 229 : EMA – Compliance and Inspection: Reflection Paper on Risk-Based Quality Management in Clinical Trials, November 18, 2013 – Risk mitigation

> ***5.1. Risk mitigation/risk acceptance***
>
> Risks might be acceptable if they have limited impact on subject's safety and rights as well as data integrity and reliability.
>
> If a risk is not acceptable, it needs to be reduced by appropriate risk mitigation actions. Those need to be specified in a risk management plan. The latter needs to be reviewed and adapted accordingly.

Chapter 5.2. Quality Tolerance Limits states that, concerning the **Trial Data**, it is necessary to "*consider the precision, the accuracy and the timing of clinical measurements. In particular in relation to the importance of the variable in terms of the trial objectives including safety monitoring (e.g. the occasional omission of some measurements, or early or late performance of some study visits may be in some cases less critical than in others)*".

Illustration 230 : EMA – Compliance and Inspection: Reflection Paper on Risk-Based Quality Management in Clinical Trials, November 18, 2013 – Trial data

1. Trial data

Consider the precision, the accuracy and the timing of clinical measurements. In particular in relation to the importance of the variable in terms of the trial objectives including safety monitoring (e.g. the occasional omission of some measurements, or early or late performance of some study visits may be in some cases less critical than in others).

Brook Jackson's complaints align with the risks highlighted throughout this document, as do all the demonstrated elements.

Brook Jackson claims **she was unable to quantify the types and number of errors they were finding when reviewing clinical trial documents** for quality control due to the sheer volume. The experienced former research director was fired by her employer on the same day she filed her official complaint with the FDA, on September 25, 2020, reporting all the serious violations and issues encountered at Ventavia Research Group.

The CRO (Contract Research Organization) issued a statement denying the claims, asserting that "none of her professional responsibilities pertained to the clinical trials in question." However, two former Ventavia employees corroborated Jackson's allegations. Despite this, participant recruitment was suspended to address a list of "common" quality control deficiencies under review, but Ventavia did not inform Pfizer of the reason for the pause, as required, and allegedly engaged in a cover-up of its misconduct.

Brook Jackson reportedly possesses a document listing Ventavia's "action items" still pending, which include discussions with trial coordinators about serious violations of data integrity, thereby putting patients at risk.

The Ventavia case involves only 3 centers with 1,000 participants, but if the allegations are proven true, it highlights that the primary endpoint is flawed, and that Pfizer did not adequately monitor and manage the trial. **This raises suspicion about the management of all other centers.**

The issues cited in the Ventavia case (incorrect product storage, failure to maintain participant anonymity, sample handling errors, disorganized follow-up on serious adverse events, etc.) **are particularly serious in clinical trials as they constitute major violations of Good Clinical Practice (GCP).**

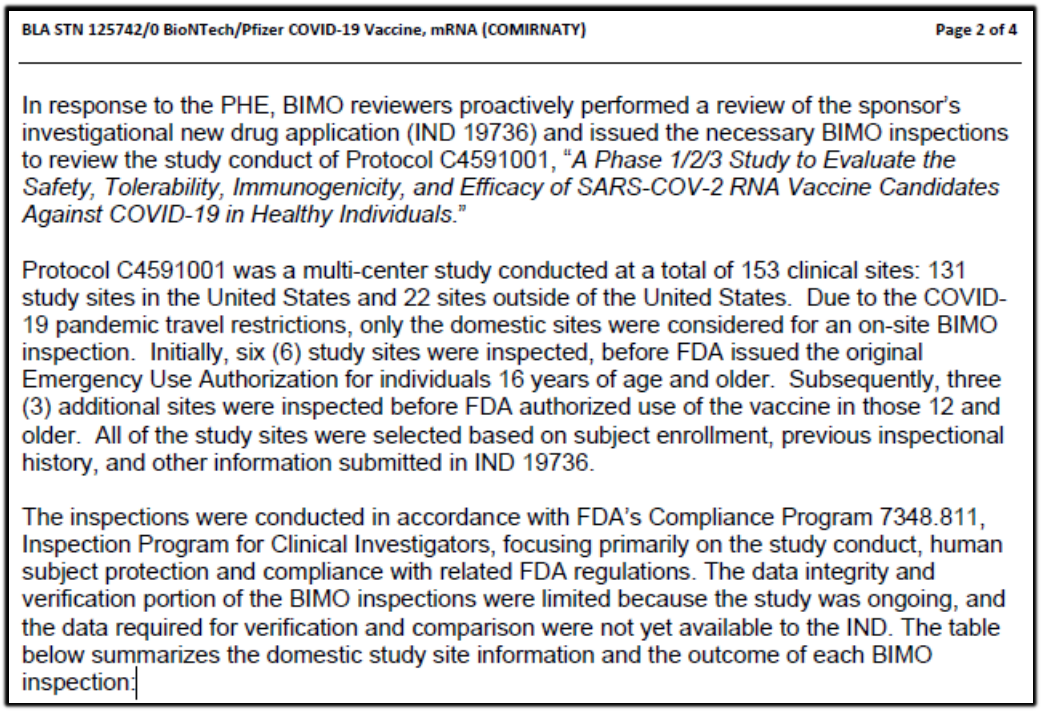
La FDA indique sur son site sur la page relative au vaccin, dans sa section « *Supporting Documents / Approval History, Letters, Reviews, and Related Documents – COMIRNATY »* et plus précisément dans le document « *Bioresearch Monitoring Discipline Review Memo, August 13, 2021 – COMIRNATY* » **avoir réalisé une inspection de 6 sites sur les 153 sites** cliniques ayant inclus les participants de la phase 3.

The FDA justifies this low 3.9% audit rate on a product with such innovative features as Comirnaty by the fact that, of the 153 sites, 131 were in the United States and 22 sites outside the United States. Due to travel restrictions related to the COVID-19 pandemic, only domestic sites were considered for on-site BIMO (bioresearch monitoring) inspection.

Yet, the lockdown restrictions did not visibly hinder the recruitment and follow-up of 44,000 participants.

The FDA states in the document that it has audited 3 additional sites before approving the vaccine for use in ages 12 and older.

Illustration 231 : FDA - August 13, 2021 audit



BLA STN 125742/0 BioNTech/Pfizer COVID-19 Vaccine, mRNA (COMIRNATY) Page 2 of 4

In response to the PHE, BIMO reviewers proactively performed a review of the sponsor's investigational new drug application (IND 19736) and issued the necessary BIMO inspections to review the study conduct of Protocol C4591001, "*A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals.*"

Protocol C4591001 was a multi-center study conducted at a total of 153 clinical sites: 131 study sites in the United States and 22 sites outside of the United States. Due to the COVID-19 pandemic travel restrictions, only the domestic sites were considered for an on-site BIMO inspection. Initially, six (6) study sites were inspected, before FDA issued the original Emergency Use Authorization for individuals 16 years of age and older. Subsequently, three (3) additional sites were inspected before FDA authorized use of the vaccine in those 12 and older. All of the study sites were selected based on subject enrollment, previous inspectional history, and other information submitted in IND 19736.

The inspections were conducted in accordance with FDA's Compliance Program 7348.811, Inspection Program for Clinical Investigators, focusing primarily on the study conduct, human subject protection and compliance with related FDA regulations. The data integrity and verification portion of the BIMO inspections were limited because the study was ongoing, and the data required for verification and comparison were not yet available to the IND. The table below summarizes the domestic study site information and the outcome of each BIMO inspection:

Illustration 232 : FDA - August 13, 2021 – Listing of audited sites

Site ID	Site Location	Form FDA 483 Issued	Final Classification
1007	Cincinnati Children's Hospital Medical Center Cincinnati Center for Clinical Research Cincinnati, OH	No	No Action Indicated (NAI)
1009	J. Lewis Research Inc./ Foothill Family Clinic South, Salt Lake City, UT	No	NAI
1044	Virginia Research Center, LLC. Midlothian, VA	No	NAI
1056	Indago Research and Health Center, Inc. Hialeah, FL	No	NAI
1109	Deland Clinical Research Unit DeLand, FL	No	NAI
1118	Meridian Clinical Research, LLC. Binghamton, NY	No	NAI
1125	Meridian Clinical Research, LLC Norfolk, NE	No	NAI
1133	Research Centers of America Hollywood, FL	No	NAI
1149	Collaborative Neuroscience Research, LLC at two locations: Long Beach & Garden Grove, CA	No	NAI

Source : Bioresearch Monitoring Discipline Review Memo, August 13, 2021 – COMIRNATY - Approval History, Letters, Reviews, and Related Documents – COMIRNATY https://www.fda.gov/vaccines-blood-biologics/comirnaty

According to the FDA, the audits did not raise any major issues.

However, in its letter, the FDA states that the inspection program focused primarily on the conduct of the study, protection of participants, and compliance with related FDA regulations. It states that "***The data integrity and verification portion of the BIMO [biological research monitoring] inspections was limited because the study was ongoing and the data required for verification and comparison were not yet available for the IND [investigational new drug]***"(see Illustration 231))

It is surprising that the sites managed by Ventavia (located in Dallas, Galveston, Texas, Houston) are not among the sites inspected despite the letter sent by Ms. Jackson who had reported major violations of Good Clinical Practice to the FDA.

It is also very surprising that the data required for an inspection was not available at the time of the audit, since the Trial Master File containing all the documents must be updated regularly and it is highly unlikely that the FDA did not notify the centres so that they could retrieve the missing elements in order to present them to the auditor.

Even more surprisingly, no problems were identified at the Cincinnati Children's Hospital Medical centre, which had enrolled Garay's Maddie who participated in the Pfizer Phase 3 trial for 12-15 year olds.

14.2 The case of Maddie de Garay

The letter sent to the FDA by the family's lawyer, Aaron Siri, who specializes in medical litigation, provides an insight into the effects suffered by Maddie: "Maddie de Garay was a typical 12-year-old little girl: full of energy, spunk, gymnastic moves, and TikTok dances. Maddie, along with her two brothers, **took part in Pfizer's pediatric clinical trial for the COVID-19 vaccine**.

Since the day she received the second dose of the vaccine, the vibrant girl Maddie's parents once knew has disappeared, replaced with a girl who lives her life in agony.

Within 24 hours of arriving at the trial site with her dad and receiving her second shot, Maddie developed **crippling, scream-inducing pain that landed her in the emergency room. She was experiencing abdominal, muscle, and nerve pain, described as the feeling of someone "ripping [her] heart out through [her] neck**."

Over the next three months, Maddie was admitted to the hospital three times, visited doctors and emergency rooms more than that, and developed additional life-changing symptoms including: gastroparesis, erratic blood pressure, erratic heart rate, memory loss, brain fog, dizziness, fainting, seizures, verbal tics, motor tics, loss of feeling from her waist through her toes, muscle weakness, drastic and adverse changes in her vision, urinary retention, loss of bladder control, and the start of and severely irregular menstrual cycles. Maddie currently has an **NG tube** and uses a **wheelchair** for assistance. »

Illustration 233 : October 22, 2021 A. Siri letter

B. Potential Risks in Vaccinating Children for COVID-19

Since it is exceedingly rare for a child to have a permanent injury from being infected with SARS-CoV-2, it must be determined that the vaccine presents even less risk.

1. Maddie de Garay

Maddie de Garay was a typical 12-year-old little girl: full of energy, spunk, gymnastic moves, and TikTok dances. Maddie, along with her two brothers, took part in Pfizer's pediatric clinical trial for the COVID-19 vaccine. Since the day she received the second dose of the vaccine, the vibrant girl Maddie's parents once knew has disappeared, replaced with a girl who lives her life in agony.

Within 24 hours of arriving at the trial site with her dad and receiving her second shot, Maddie developed crippling, scream-inducing pain that landed her in the emergency room. She was experiencing abdominal, muscle, and nerve pain, described as the feeling of someone "ripping [her] heart out through [her] neck."

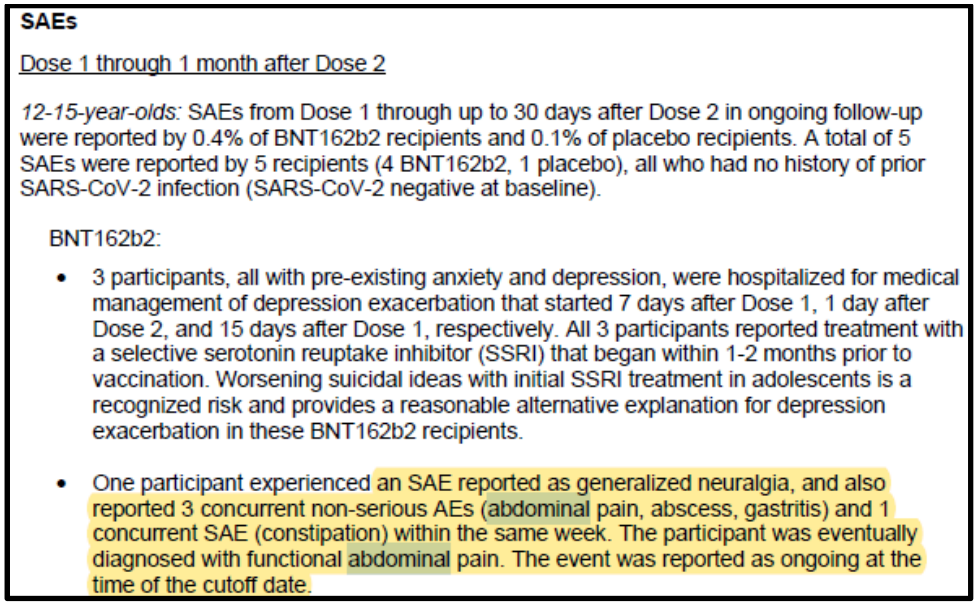
Over the next three months, Maddie was admitted to the hospital three times, visited doctors and emergency rooms more than that, and developed additional life-changing symptoms including: gastroparesis, erratic blood pressure, erratic heart rate, memory loss, brain fog, dizziness, fainting, seizures, verbal tics, motor tics, loss of feeling from her waist through her toes, muscle weakness, drastic and adverse changes in her vision, urinary retention, loss of bladder control, and the start of and severely irregular menstrual cycles. Maddie currently has an NG tube and uses a wheelchair for assistance.

Source : https://www.sirillp.com/wp-content/uploads/2021/10/Letter-to-Federal-Health-Agencies-Regarding-Maddie-and-Clinical-Trials-for-Children.pdf

Maddie's mother says she had great difficulty reaching the center.

Despite this impressive list of symptoms, Maddie's case appears as "**abdominal pain**" instead of "permanent paralysis" in the clinical report on the 12-15 age group

Illustration 234 : Pfizer – October 26, 2021 Clinical Study Report – Serious Adverse Events



SAEs

Dose 1 through 1 month after Dose 2

12-15-year-olds: SAEs from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of BNT162b2 recipients and 0.1% of placebo recipients. A total of 5 SAEs were reported by 5 recipients (4 BNT162b2, 1 placebo), all who had no history of prior SARS-CoV-2 infection (SARS-CoV-2 negative at baseline).

BNT162b2:

- 3 participants, all with pre-existing anxiety and depression, were hospitalized for medical management of depression exacerbation that started 7 days after Dose 1, 1 day after Dose 2, and 15 days after Dose 1, respectively. All 3 participants reported treatment with a selective serotonin reuptake inhibitor (SSRI) that began within 1-2 months prior to vaccination. Worsening suicidal ideas with initial SSRI treatment in adolescents is a recognized risk and provides a reasonable alternative explanation for depression exacerbation in these BNT162b2 recipients.

- One participant experienced an SAE reported as generalized neuralgia, and also reported 3 concurrent non-serious AEs (abdominal pain, abscess, gastritis) and 1 concurrent SAE (constipation) within the same week. The participant was eventually diagnosed with functional abdominal pain. The event was reported as ongoing at the time of the cutoff date.

Source : https://www.fda.gov/media/148542/download

On August 23, 2021, the medical review by Drs. Wollersheim and Schwartz reported in section 3.3 that 7 investigators had conflicts of interest out of the 1,834 who participated in the clinical studies.

In addition, they named the efforts made to eliminate bias in the studies.

These included the following:

- "***The trial was double-blind and multicentre***"
  The number of participants at each center is not known at this time, and no analysis by center was provided to conclude that the multicenter design of this study was free of bias.

- "***The statistical methods used are in accordance with the statistical analysis plan.***"
  This is not a proof of the absence of bias, and it is the case for almost all clinical trials. There is no discussion of the identification of symptomatic COVID-19 cases, which is a more than questionable point.

- ***"Frequent monitoring of investigators' trial sites and auditing of study sites.***"
  The monitoring elements are not sufficiently explicit in the reports provided to be able to conclude that the monitoring of the sites was done adequately, especially in the middle of a pandemic, any remote verification of the data being less reliable than on-site visits by the CRAs.

- **"*The validity of the data collected was confirmed by standard monitoring procedures*."**
  In other words, no special procedures were implemented to manage this critical trial, even though the vaccine was expected to be administered to billions of people.
- **"*Data processing involved cleaning checks (querying data through electronic edit checks) to ensure that errors were identified and corrected*."**
  This refers to the work of data managers, who edit electronic correction requests for missing, incomplete or inconsistent data. Wollersheim and Schwartz's report found no problems with the corrections made. As a reminder, there were no issues with the data in the December 10, 2020 report either, in which 5 deaths were missing.
- **"*Data were reviewed by clinicians and queries were generated in case of inconsistencies during the course of the trial"***
  These arguments also efer to the checks programmed by the data managers to retrieve missing data and correct inconsistent data. This is the least that can be done in a serious clinical trial.
- **"*The study report was reviewed by the project team and quality control*."**
  It would be interesting to know what comments were made on the reports.
- ***"The study sites performing the safety assessments were deemed acceptable based on appropriate certification or historical performance and/or qualifications and credentials*."**
  Again, it is the least we can do to recruit competent investigators to participate in a study of this importance.

Illustration 235 : Dr Wollersheim & Schwartz - August 23, 2021 BLA Clinical Review Memorandum – Minimization of bias

Efforts reported to eliminate bias for the covered studies consisted of the following:

- Randomized, double-blind and multicenter study design as well as pre-specified statistical methods as per the statistical analysis plan
- Frequent monitoring of investigator trial sites and auditing of study sites
- Validity of data collected was confirmed by standard monitoring procedures
- Data processing involved cleaning checks (querying data through electronic edit checks) to ensure that errors were identified and corrected
- Data were reviewed by clinicians and queries were generated in case of inconsistencies during the course of the trial
- The study report underwent review by the project team and Quality Control; and

15

Clinical Reviewers: Susan Wollersheim, MD and **Ann Schwartz, MD**
STN:125742

- Study sites performing safety evaluations were determined acceptable based on appropriate certification or historical performance and/or qualifications and credentials.

  Reviewer Comment: The Applicant satisfactorily addressed possible study investigator financial interests that could impact clinical data quality.

Source https://www.fda.gov/media/152256/download

According to this report, "**no major statistical problems were identified by CBER** (Center for Biologics Evaluation and Research) statistical reviewers in this application. The key statistical analyses concerning safety and efficacy were confirmed by the CBER statistical reviewers".

The authors conclude in section "4.7 Risk and Benefit Assessment" that :

« t*he benefit-risk estimates are* ***limited*** ***by uncertainties*** *associated with the dynamics of pandemics.*

The major ***uncertainties in benefits*** *are related to potential changes in COVID-19 incidence over time and vaccine efficacy and duration of protection in the face of emerging virus variants.*

The major risk uncertainty is the data on vaccine-related myocarditis cases and deaths. » !

Illustration 236 : Dr Wollersheim & Schwartz - August 23, 2021 BLA Clinical Review Memorandum – Risk-Benefit Assessment

respectively. The excess myocarditis/pericarditis cases and associated hospitalizations and deaths attributable to the vaccine are 196, 196, and 0 per million vaccinated individuals in this age group, respectively. Even with the conservative assumption on the myocarditis/pericarditis death rate, the model predicted 0 deaths associated with myocarditis/pericarditis. The model predicts a higher number of myocarditis/pericarditis-related hospitalizations compared to prevented COVID-19 hospitalizations. However, considering the differential clinical outcomes of the hospitalization from two difference causes, FDA considers the benefits of the vaccine still outweigh the risks for the highest risk group, males 16-17 years old, under this worst-case scenario.

The benefit-risk estimates are limited by uncertainties associated with the dynamics of pandemics. The major uncertainties in benefits are related to potential changes in COVID-19 incidence over time and vaccine efficacy and duration of protection in the face of emerging virus variants. The major risk uncertainty is the data on vaccine-related myocarditis cases and deaths.

Source : https://www.fda.gov/media/152256/download

In summary,

the Maddie de Garay case confirm the **dubious quality of the data**, both for efficacy (PCR tests not carried out) and for safety, and the impossibility of reporting serious effects, thus considerably distorting the evaluation of the real number of events and therefore the evaluation of the real risks run by people who are vaccinated

This **underestimation of serious adverse events** can only be amplified by the workload of the investigating centers, which have broken records in recruiting participants.

The results of the FDA audits **cannot be taken into account to comfort on the integrity of the data** since, against all expectations, and for reasons of sanitary restrictions, they have not been subject to on-site verification.

The medical review report of August 25, 2021 is not particularly comforting on the quality of the controls carried out, as it refers to classic and obvious validations in the pharmaceutical industry, the conclusions are more than trivial and non specific.

15 Change in manufacturing Process

We know from the study protocol available in the appendices of the December 2020 New England Journal of Medicine (NEJM) publication that Pfizer/BioNTech developed a new manufacturing process during the clinical trial. This "**process 2**" was referenced in amendment 7 of the protocol on October 6, 2020, and then in amendment 8 on October 15, 2020, as indicated in the protocol change history.

Illustration 237 : Pfizer – October 29, 2020 Pivotal clinical trial protocol – Document history

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001
Protocol Amendment 9, 29 October 2020

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2."
Protocol amendment 8	15 October 2020	• Removed "N-binding antibody" and "SARS-CoV-2 detection by NAAT" as endpoints from the third exploratory objective, as these results are used for the determination of the population, and are not endpoints. • Clarified that the "Process 1" participants included in the descriptive analysis of "Process 1"- and "Process 2"-manufactured study interventions will be selected randomly. • Clarified that surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study. • Further modified the circumstances in which a local NAAT result may be used in the COVID-19 case definition. • Clarified that for participants who are not in the reactogenicity subset, local reactions and systemic events following vaccination should be detected and reported as AEs. • Clarified that premenarchal females are not WOCBP.

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https://www.nejm.org/doi/full/10.1056/NEJMoa2034577
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2034577/suppl_file/nejmoa2034577_protocol.pdf

This manufacturing process change is also mentioned in paragraph 6.1.1. of the protocol. The plan was to administer vaccines produced using manufacturing process 2 to 250 participants per batch.

To ensure that the protection against the virus was similar between the two processes, the protocol outlined a **comparison of antibody levels** between participants who received vaccines from process 2 and a randomly selected sample of 250 participants from the tens of thousands vaccinated with the product manufactured using process 1.

To check that process 2 did not present more toxicity than process 1, the protocol specified a **comparison of adverse events** between these two groups of participants (vaccines manufactured using process 1 versus vaccines manufactured using process 2).

Illustration 238 : Pfizer – October 29, 2020 Pivotal clinical trial protocol – Manufacturing process

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

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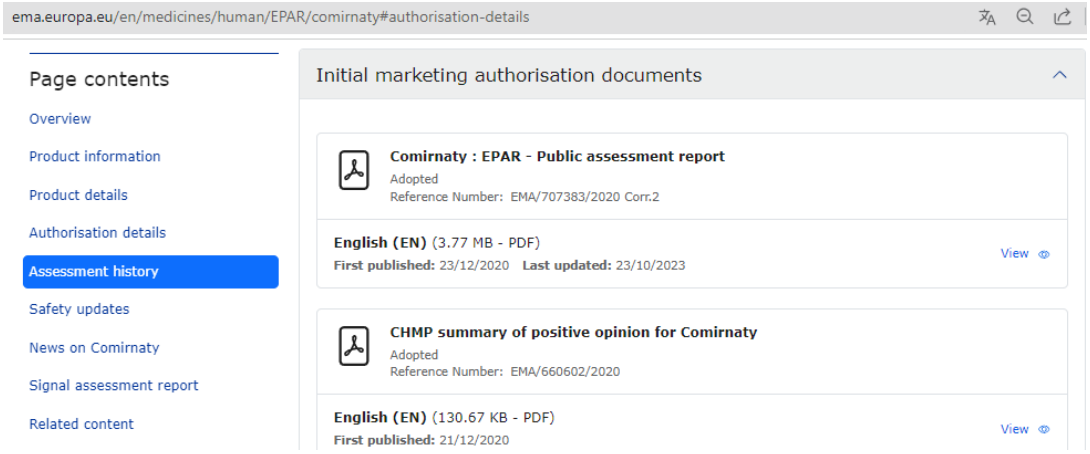
The EMA Assessment Report (Procedure Number: EMEA/H/C/005735/0000), available at https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf confirmed this change in the manufacturing process and identified several issues related to it.

Illustration 239 : EMA– Website – List of initial marketin authorization documents



Here is an excerpt from the EMA's observations, **Chapter 2.2.2, Active Substance**, sections "**Manufacturers**," "**Process Validation**," and "**Manufacturing Process Development**," which every global citizen should be informed about.

The EMA highlighted several issues concerning Good Manufacturing Practices (GMP) for the active substance and regarding the sites that manufacture and control the finished product in preparation for batch release : « *During the procedure, a* ***number of issues were highlighted relating to the GMP*** *status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release, the comparability between clinical and commercial material and the* ***absence of validation*** ***data on finished product manufactured at the commercial site****.* ***These issues were classified as Major Objections (MOs). »***

Illustration 240 :EMA–February 19, 2021 - Assessment Report – Manufacturers

Manufacturers

The active substance is manufactured and controlled by either Wyeth BioPharma Division, Andover, United States or by BioNTech Manufacturing GmbH, Mainz, Germany, and Rentschler Biopharma SE, Laupheim, Germany.

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release. These issues were classified as a Major Objection (MO). After further information was obtained from the sites and inspectors, the MO was considered resolved.

EU GMP certificates for the manufacturing and testing sites were subsequently obtained. In conclusion, appropriate manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing sites.

« *In comparability studies,* ***a decrease in RNA integrity*** ***was observed for the initial Process 2 batches compared to Process 1 batches****. This is further discussed in the subsequent section on manufacturing process development. After adjustment of process parameters for CTP and ATP volumes, RNA integrity level is more consistent and verify that the volume adjustments made for ATP and CTP volumes consistently provide reproducible results with RNA integrity levels more similar to levels achieved in Process 1 batches. Since the target volumes for ATP and CTP have been increased, the proven acceptable ranges (PARs) ranges need to be adjusted and the dossier updated accordingly (REC8).*

The robustness of the DNase digestion step is NOT considered comprehensively demonstrated *although there is routine control of residual DNA impurities at the active substance level. It has been confirmed that studies to enhance the robustness of this step are ongoing and these should be reported (REC7).* »

Illustration 241 : EMA–February 19, 2021 - Assessment Report – Process validation

Process validation

The BNT162b2 active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial process validation/ process performance qualification batches at all sites. All acceptance criteria for the critical operational parameters and acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

In comparability studies, a decrease in RNA integrity was observed for the initial Process 2 batches compared to Process 1 batches. This is further discussed in the subsequent section on manufacturing process development. After adjustment of process parameters for CTP and ATP volumes, RNA integrity level is more consistent and verify that the volume adjustments made for ATP and CTP volumes consistently provide reproducible results with RNA integrity levels more similar to levels achieved in Process 1 batches. Since the target volumes for ATP and CTP have been increased, the proven acceptable ranges (PARs) ranges need to be adjusted and the dossier updated accordingly **(REC8)**. The robustness of the DNase digestion step is not considered comprehensively demonstrated although there is routine control of residual DNA impurities at the active substance level. It has been confirmed that studies to enhance the robustness of this step are ongoing and these should be reported **(REC7)**. The finalised indirect filter qualification assessment, according to the applicant, already available and should be provided for evaluation **(REC6)**.

Relevant hold times and transport times have been defined and were validated by appropriate studies.

The shipping qualification strategy is described in detail and considers both thermal and mechanical aspects of shipping. The shipping procedures and configuration for transport of frozen AS to the

Source : https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

« *Process development changes were adequately summarised. Two active substance processes have been used during the development history;* ***Process 1 (clinical trial material)*** *and* ***Process 2 (commercial process)****. Details about process differences, justification for making changes, and results from a comparability study are provided. The major changes between active substance process versions were described in the dossier.*

Batch analysis results showing comparability between non-clinical and clinical batches are provided. ***Additional characterization*** ***of product-related species and their relation to final product specifications will be provided as a specific obligation****.*

Electropherograms were presented demonstrating similarities in the peak pattern of RNA species, but ***some differences between Process 1 and 2 were also noted. It can therefore NOT be concluded that identical species are obtained by the processes****. It is likely that the fragmented species will not result in expressed proteins, due to their expected poor stability and poor translational efficiency (see below).*

However, the lack of experimental data on the truncated RNA and expressed proteins does not permit a definitive conclusion and ***needs further characterisation****. Therefore, additional characterisation data remain to be provided as a specific obligation (SO1).*

Regarding the 5' cap end of the AS, reversed phase high performance liquid chromatography-UV and mass spectrometry (LC- UV/MS) characterisation confirmed that the 5'-capped and uncapped structures are the same but that there is a slight shift towards higher 5'-capping levels in Process 2. The reported quality attribute 'capped-intact RNA' is intended to reflect the proportion of the RNA molecules in the active substance that are a fully intact molecule and have the 5'-cap. It is noted that the capped-intact RNA is not measured, but only calculated from the results of 5'-cap and % RNA integrity tests. ***Therefore, this argument alone CANNOT fully confirm the comparability of Process 2 versus Process 1, and further characterisation data and justification of specifications were requested.***»

Illustration 242 : EMA–February 19, 2021 - Assessment Report – Manufacturing process development

Manufacturing process development

Process development changes were adequately summarised. Two active substance processes have been used during the development history; Process 1 (clinical trial material) and Process 2 (commercial process). Details about process differences, justification for making changes, and results from a comparability study are provided. The major changes between active substance process versions were described in the dossier.

Batch analysis results showing comparability between non-clinical and clinical batches are provided. Additional characterization of product-related species and their relation to final product specifications will be provided as a specific obligation.

Electropherograms were presented demonstrating similarities in the peak pattern of RNA species, but some differences between Process 1 and 2 were also noted. It can therefore not be concluded that identical species are obtained by the processes. It is likely that the fragmented species will not result in expressed proteins, due to their expected poor stability and poor translational efficiency (see below). However, the lack of experimental data on the truncated RNA and expressed proteins does not permit a definitive conclusion and needs further characterisation. Therefore, additional characterisation data remain to be provided as a specific obligation **(SO1)**.

Regarding the 5′ cap end of the AS, reversed phase high performance liquid chromatography-UV and mass spectrometry (LC- UV/MS) characterisation confirmed that the 5'-capped and uncapped structures are the same but that there is a slight shift towards higher 5'-capping levels in Process 2. The reported quality attribute 'capped-intact RNA' is intended to reflect the proportion of the RNA molecules in the active substance that are a fully intact molecule and have the 5′-cap. It is noted that the capped-intact RNA is not measured, but only calculated from the results of 5′-cap and %RNA integrity tests. Therefore, this argument alone cannot fully confirm the comparability of Process 2 versus Process 1, and further characterisation data and justification of specifications were requested.

Source : https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

The manufacturing process 2 does not yield the product used during the clinical trial, and the European Agency has requested further investigations.

The evaluation report on post-authorization measures from the Committee for Medicinal Products for Human Use (CHMP) dated May 20, 2021 (document EMA/CHMP/284816/2021 REC 027 Comirnaty) documents that the manufacturing process was far from finalized as of May 2021.

« Recommendation number 7 to provide the results of the studies performed to enhance the robustness of the DNase digestion step has only been partly fulfilled. ***Further actions are required to fulfil Recommendation 7 including submission of a detailed summary of the results*** *from the studies and inclusion of these data in Module 3.2.5.2.5 of the dossier by the*

end of second quarter 2021. It also recommended that Recommendations 3 and 7 are grouped. »

Illustration 243 :EMA– Assessment .Report for the Post-Authorisation Measure REC 027 – Overall conclusion

4. Overall conclusion

The Recommendation number 7 is only considered as partly fulfilled.

☐ **PAM fulfilled (all commitments fulfilled) - No further action required**

☒ **PAM not fulfilled (not all commitments fulfilled) and further action, as specified below, required by the end of second quarter 2021**

Recommendation number 7 to provide the results of the studies performed to enhance the robustness of the DNase digestion step has only been partly fulfilled. Further actions are required to fulfil Recommendation 7 including submission of a detailed summary of the results from the studies and inclusion of these data in Module 3.2.S.2.5 of the dossier by the end of second quarter 2021.
It also recommended that Recommendations 3 and 7 are grouped.

Source: https://www.docdroid.net/71rc66n/assessment-report-for-the-post-authorization-measure-rec-027-pdf

The Australian Therapeutic Goods Administration (TGA) also explains the differences between the two manufacturing processes:

« *the process used to generate the DNA template has been changed from a PCR product (process 1) to a linearised plasmid (process 2) and the purification process has changed from magnetic beads (process 1) to tangential flow filtration following proteinase K treatment (process 2). Additionally, the production scale has been increased, and additional manufacturing sites added (see Table 6). Process 2 incorporates the production of the DNA template via a plasmid DNA process as well as the TFF purification process for production of drug substance (see Figure 1), which will be scaled up further to support commercial supply.*

Illustration 244 : FOI - TGA - September 18, 2020 Pre-Submission Meeting

Document 3 Part 1

COVID-19 Vaccine (BNT162, PF-07302048)
TGA Briefing Document September 2020

7. CHEMISTRY, MANUFACTURING AND CONTROLS

7.1. Manufacturing Process

Initial clinical trial drug substance material has been manufactured using a PCR-amplified DNA template with RNA purification by magnetic beads at BNT's clinical manufacturing facility (IMFS). LNP fabrication and drug product manufacture have been performed at Polymun. Additional changes in the mRNA drug substance manufacturing process are planned to continue to enable the manufacture of maximum supply. Specifically, the process used to generate the DNA template has been changed from a PCR product (process 1) to a linearised plasmid (process 2) and the purification process has changed from magnetic beads (process 1) to tangential flow filtration following proteinase K treatment (process 2). Additionally, the production scale has been increased, and additional manufacturing sites added (see Table 6). Process 2 incorporates the production of the DNA template via a plasmid DNA process as well as the TFF purification process for production of drug substance (see **Figure 1**), which will be scaled up further to support commercial supply.

Source : https://www.tga.gov.au/sites/default/files/foi-2389-03-1.pdf)

The Japanese Health Agency also mentionned that the process 2 is the commercial product in a report dated January 29, 2021.

« *The active substance used for nonclinical and clinical studies are manufactured by Process 1, and the active substance in the proposed commercial formulation by Process 2. In Process 1, the active substance is manufactured by in vitro transcription of the template DNA prepared by *****, followed by ********* and purification through **********. In Process 2, the active substance is manufactured by in vitro transcription of the linear template DNA prepared from the plasmid DNA, followed by *********, **********, and purification through ********* and ********.* »

Illustration 245 : PMDA : January 29, 2021 Report on the Deliberation Results

2.1.4 Manufacturing process development (comparability)

The following are main changes in the manufacturing process during the development of the active substance:
The active substance used for nonclinical and clinical studies are manufactured by Process 1, and the active substance in the proposed commercial formulation by Process 2. In Process 1, the active substance is manufactured by *in vitro* transcription of the template DNA prepared by [redacted], followed by [redacted] and purification through [redacted]. In Process 2, the active substance is manufactured by *in vitro* transcription of the linear template DNA prepared from the plasmid DNA, followed by [redacted], [redacted], and purification through [redacted] and [redacted]. The comparability of quality attributes between pre-change and post-change active substances has been demonstrated.

Quality by design (QbD) approach was used in the development of the manufacturing process of the active substance [see Section 2.3].

Source : https://www.pmda.go.jp/files/000243206.pdf

In response to FOI request 23/510 from Mr. Nick Hunt, the Medicines & Healthcare products Regulatory Agency (MHRA) of the United Kingdom confirmed that "*the first clinical batch which contained process 2 drug active substance was dosed 19th October 2020, in the US.*"

Illustration 246 : MHRA answer to FOI 23/510 – Confirmation of process used in real life

i) whether the relevant information was identified

The original responses directed you to the clinical data repository hosted by the EMA. The review finds that the responses were not compliant with the Act and did not provide or address the specific information that your questions asked for.

At internal review, we hope to be able to provide direct responses and address the questions which you raise directly.

> ***Request 1 : please can you tell me if any human was vaccinated (in UK or elsewhere) using 'Process 2' product prior to 2 December 2020, and if so, when and where.***

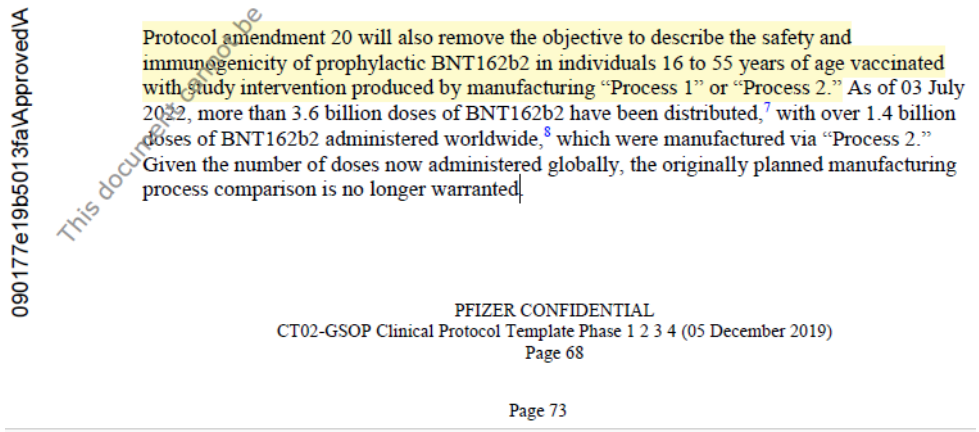
Answer:
This information was not held at the time of your request; this should have been indicated under section 1(1)(a).

Further to this, we can advise that Pfizer/BioNTech confirmed that the first clinical batch which contained process 2 drug substance was dosed 19th October 2020 in US.

Source : https://assets.publishing.service.gov.uk/media/661516fbeb8a1b68a805e364/Further_response_FOI_23-510_internal_review_redacted_.pdf

The comparisons between processes 1 and 2, intended to verify the comparability of tolerance profiles and antibody levels, were completely annulled by amendment 20 of the protocol from September 2022, as stated in section 2.2. Background.

Illustration 247 : September 15, 2022 final Protocol – Amendment 20



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Protocol amendment 20 will also remove the objective to describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." As of 03 July 2022, more than 3.6 billion doses of BNT162b2 have been distributed,[7] with over 1.4 billion doses of BNT162b2 administered worldwide,[8] which were manufactured via "Process 2." Given the number of doses now administered globally, the originally planned manufacturing process comparison is no longer warranted

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*« Protocol amendment 20 will also remove the objective to describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." As of 03 July 2022, more than 3.6 billion doses of BNT162b2 have been distributed,7 with over 1.4 billion doses of BNT162b2 administered worldwide,8 which were manufactured via "Process 2." **Given the number of doses now administered globally, the originally planned manufacturing process comparison is no longer warranted**. »*

Despite the countless recommendations present in the pharmaceutical industry to ensure the safety of individuals, various authorizations were granted without any results regarding efficacy, tolerance, or immunogenicity (antibody titration) being provided. This has led the public to believe that they were receiving the vaccine with the announced 95% efficacy.

On October 14, 2021, the CHMP Assessment Report on the extension of the marketing authorization for COMIRNATY - Procedure Number: EMEA/H/C/005735/X/0044/G mentioned a **new change in the manufacturing process** with the introduction of tromethamine, also known as Tris.

Illustration 248 : EMA – October 14, 2021 CMPH – New product

The new Ready-to-Use (RTU) formulation is based on the current approved vaccine except that:

- The formulation buffer has been changed from phosphate buffered saline to Tris buffer without sodium chloride and potassium chloride while maintaining the same target pH.
- The RNA concentration is lower.
- The finished product does not require dilution for administration.

There are no changes to the active substance, or the lipids used to produce the lipid nanoparticles (LNPs) in the bulk finished product.

Both the applied RTU formulation (Tris/Sucrose finished product) and the approved concentrate (PBS/Sucrose finished product) are administered intramuscularly (IM), 30 µg doses (0.3 mL).

https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-x-0044-g-epar-assessment-report-extension_en.pdf

The list of ingredients for the new vaccine is presented in the table below.

Illustration 249 : EMA – October 14, 2021 CMPH – New product composition

The composition of the finished product, including quality standard, function, concentration and amount per dose are given in Table 2.

Table 2 *Composition of BNT162b2 Tris/Sucrose Finished Product, Multi-dose Vial (225 µg/vial)*

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per 0.3 mL dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.1	30 µg
ALC-0315	In-house specification	Functional lipid	1.43	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.05 mg
DSPC	In-house specification	Structural lipid	0.31	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	0.19 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	31 mg[b]
Tromethamine (Tris base)	USP-NF, Ph. Eur.	Buffer component	0.20	0.06
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)	In-house specification	Buffer component	1.32	0.4
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.

Source : https://www.fda.gov/media/154357/download

On October 19, 2021, the FDA approved this new formulation for children of 5 years and older **without any clinical trial results**, relying instead on a comparability study involving three batches of Tris/Sucrose finished products for ICH stability testing, compared to the previously approved PBS/Sucrose finished product, as indicated in the section titled "Demonstration of Comparability."

« *On October 29, 2021, based on additional clinical trial data, the FDA further amended the EUA to authorize use of a Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series in children 5 through 11 years of age.* ***In the October 29, 2021 revision****, FDA* ***also authorized a manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses tromethamine (Tris) buffer instead of phosphate buffered saline (PBS)*** *used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine. Pfizer-BioNTech's currently authorized indication is for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals age 5 years and older.* »

Illustration 250 : FDA – November 19, 2021 memorandum – New formulation

exposure to SARS-CoV-2. Then, on October 20, 2021, the FDA authorized the use of a heterologous booster dose for currently available (i.e., FDA-authorized or approved) COVID-19 vaccines. On October

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29, 2021, based on additional clinical trial data, the FDA further amended the EUA to authorize use of a Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series in children 5 through 11 years of age. In the October 29, 2021 revision, FDA also authorized a manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses tromethamine (Tris) buffer instead of phosphate buffered saline (PBS) used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine.[1] Pfizer-BioNTech's currently authorized indication is for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals age 5 years and older.

« *A comparability study has been performed for **three primary Tris/Sucrose finished product lots** for ICH stability testing compared to the currently approved PBS/Sucrose finished product. Comparisons used to evaluate comparability were made using the finished product specification acceptance criteria, to predetermined comparability acceptance criteria from historical release test data for 94 PBS/Sucrose finished product lots as well as to extended characterization testing including a well-characterized reference lot (EL8983).*

*Tris/Sucrose finished product release data and the extended characterization testing results demonstrated that the Tris/Sucrose finished product lots are comparable to the registered PBS/Sucrose lots, **with only few and minor differences noted that are not expected to impact efficacy and safety**. All three Tris/Sucrose finished products lots for stability testing met all of the release specifications for the Tris/Sucrose finished product. These three lots also met the established acceptance criteria for the extended characterization testing.*»

Illustration 251 : EMA – October 14, 2021 CMPH – Demonstration of comparability

Demonstration of comparability

A comparability study has been performed for three primary Tris/Sucrose finished product lots for ICH stability testing compared to the currently approved PBS/Sucrose finished product. Comparisons used to evaluate comparability were made using the finished product specification acceptance criteria, to pre-determined comparability acceptance criteria from historical release test data for 94 PBS/Sucrose finished product lots as well as to extended characterization testing including a well-characterized reference lot (EL8983).

Tris/Sucrose finished product release data and the extended characterization testing results demonstrated that the Tris/Sucrose finished product lots are comparable to the registered PBS/Sucrose lots, with only few and minor differences noted that are not expected to impact efficacy and safety. All three Tris/Sucrose finished products lots for stability testing met all of the release specifications for the Tris/Sucrose finished product. These three lots also met the established acceptance criteria for the extended characterization testing.

The design of the comparability study utilized for the ICH stability lots has been repeated for three commercial scale PPQ lots. The release data and the extended characterization testing results demonstrated that the Tris/Sucrose PPQ lots product lots are comparable to the registered PBS/Sucrose lots, with only few and minor differences noted that are not expected to impact efficacy and safety. All three Tris/Sucrose PPQ lots met all of the release specifications for the Tris/Sucrose finished product. These three PPQ lots also met the established acceptance criteria for the extended characterization testing.

Take note of the phrase « ***some minor differences that are NOT EXPECTED to impact the product's EFFICACY and SAFETY***! »

The product's composition was therefore modified for children without any clinical trial results being provided and without any evidence of no impact on efficacy or safety. Although no patient had received this new formulation, the introduction of tromethamine did not result in an amendment to the Risk Management Plan.

Illustration 252 : EMA – CMPH du 14 octobre 2021 –Pharmacovigilance Plan

2.7. Risk Management Plan

2.7.1. Safety concerns

No change in this section in the RMP submitted with this application.

2.7.2. Pharmacovigilance plan

The MAH has included a discussion on the potential for medication errors with the new formulation. In response to the two outstanding issues, the MAH confirmed that the existing and the new formulation would co-exist on the EU market until the end of 2022, and that adequate measures have been put in place to monitor and report any emerging trend in the pattern of reporting that might be related to the new formulation.

No change in the additional pharmacovigilance activities proposed in the RMP submitted with this application.

2.7.3. Risk minimisation measures

No change in this section in the RMP submitted with this application.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 2.4 is acceptable.

Regarding the first manufacturing process change, it is possible to compare the adverse effects of the two manufacturing processes using the publicly available database.

The analysis focuses on participants aged 16 to 55, recruited exclusively within the United States from sites 1133, 1135, 1146, and 1170, who received batch EE8493 as identified by Joshu Guetzlov and are part of the safety population.

All participants in the second manufacturing process were recruited by U.S. centers. The group consists of 146 men (57.9%) and 106 women (42.1%), aged 16 to 55 (50% under 42 years), predominantly of white race (80.6%). Of these, 100 participants (19.8%) have comorbidities, and 165 (32.7%) are obese. Additionally, 22 (4.4%) had a confirmed COVID-19 infection through serology prior to participating in the clinical trial. Notably, obesity was not considered a comorbidity by the manufacturer.

To randomly select participants with similar profiles from those who received the product manufactured using the first process, we selected only patients recruited by U.S. centers within the same age group.

Adverse events collected after doses 3 and 4, as well as those that occurred prior to the first vaccination, were excluded from the analysis.

Several random selections were conducted:

- By fixing the proportion of participants with comorbidities (2 samples)
- By fixing the proportion of men and women (2 samples)
- By fixing the proportion of obese individuals (2 samples)

The analysis was performed using SAS® software, which was also employed to generate the tables and graphs included in various reports submitted to health authorities. The

SURVEYSELECT procedure in SAS® was used for the random selection of 252 participants who received the vaccine produced using manufacturing process 1, referred to as the clinical trial material.

The results provided relate to the number of participants with at least one:

- Treatment-emergent adverse event (AE)
- Serious adverse event (SAE)
- Life-threatening adverse event (AE leading to life-threatening conditions)
- Adverse event leading to premature withdrawal
- Adverse event leading to death
- Product-related adverse event (related AE)
- Grade 3 or 4 adverse event
- Adverse event that persists or results in significant disability/incapacity
- Adverse event requiring hospitalization or an increase in the length of hospitalization

Chi-square tests were conducted to compare the proportions of participants with at least one adverse event and at least one product-related adverse event between the two processes for each type of event.

Illustration 253 : Comparison of Adverse Events Between the Two Manufacturing Processes – Sample 1 – Fixed Percentage of Comorbidities

		BNT162 b2 Process1 N=252	**BNT162 b2 Process2 N=252**	**Total N=504**	**p-value**
Treatment emergent AE (TE AE)	N	**86 (34.1%)**	**155 (61.5%) X 1.8**	241 (47.8%)	p <.0001 (chi-square)
TE Serious Adverse Event	N	5 (2.0%)	0	5 (1.0%)	
TE AE leading to life threatening	N	0	0	0	
TE AE leading to premature withdrawal	N	0	0	0	
TE AE leading to death	N	0	0	0	
TE AE related	N	**66 (26.2%)**	**148 (58.7%) X 2.2**	214 (42.5%)	p <.0001 (chi-square
TE AE Grade 3 or 4	N	0	0	0	
TE AE Persist or Signif Disability/Incapacity	N	0	0	0	
TE AE Requires or Prolongs Hospitalization	N	4 (1.6%)	0	4 (0.8%)	

Illustration 254 : Comparison of Adverse Events Between the Two Manufacturing Processes – Sample 2 – Fixed Percentage of Comorbidities

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504	p-value
Treatment emergent AE (TE AE)	N	**74 (29.4%)**	**155 (61.5%) X 2.1**	229 (45.4%)	p <.0001 (chi-square)
TE Serious Adverse Event	N	0	0	0	
TE AE leading to life threatening	N				
TE AE leading to premature withdrawal	N	1 (0.4%)	0	1 (0.2%)	
TE AE leading to death	N				
TE AE related	N	**53 (21.0%)**	**148 (58.7%) X 2**	201 (39.9%)	p <.0001 (chi-square
TE AE Grade 3 or 4	N	3 (1.2%)	0	3 (0.6%)	
TE AE Persist or Signif Disability/Incapacity	N	0	0	0	
TE AE Requires or Prolongs Hospitalization	N	0	0	0	

Illustration 255 : Comparison of Adverse Events Between the Two Manufacturing Processes – Sample 3 – Fixed Percentage of Men/Women

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504	p-value
Treatment emergent AE (TE AE)	N	**74 (29.4%)**	**155 (61.5%) X 2.1**	229 (45.4%)	p <.0001 (chi-square)
TE Serious Adverse Event	N	2 (0.8%)	0	2 (0.4%)	
TE AE leading to life threatening	N	0	0	0	
TE AE leading to premature withdrawal	N	1 (0.4%)	0	1 (0.2%)	
TE AE leading to death	N	0	0	0	
TE AE related	N	**54 (21.4%)**	**148 (58.7%) X 2.7**	202 (40.1%)	p <.0001 (chi-square
TE AE Grade 3 or 4	N	4 (1.6%)	0	4 (0.8%)	
TE AE Persist or Signif Disability/Incapacity	N	0	0	0	
TE AE Requires or Prolongs Hospitalization	N	1 (0.4%)	0	1 (0.2%)	

Illustration 256 : Comparison of Adverse Events Between the Two Manufacturing Processes – Sample 4 – Fixed Percentage of Men/Women

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504	p-value
Treatment emergent AE (TE AE)	N	**77 (30.6%)**	**155 (61.5%) X 2**	**232 (46.0%)**	p <.0001 (chi-square)
TE Serious Adverse Event	N	2 (0.8%)	0	2 (0.4%)	
TE AE leading to life threatening	N	0	0	0	
TE AE leading to premature withdrawal	N	0	0	0	
TE AE leading to death	N	0	0	0	
TE AE related	N	**61 (24.2%)**	**148 (58.7%) X 2.4**	209 (41.5%)	p <.0001 (chi-square
TE AE Grade 3 or 4	N	2 (0.8%)	0	2 (0.4%)	
TE AE Persist or Signif Disability/Incapacity	N	0	0	0	
TE AE Requires or Prolongs Hospitalization	N	1 (0.4%)	0	1 (0.2%)	

Illustration 257 : Comparison of Adverse Events Between the Two Manufacturing Processes – Sample 5 – Fixed Percentage of obese

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504	p-value
Treatment emergent AE (TE AE)	N	**75 (29.8%)**	**155 (61.5%) X 2**	230 (45.6%)	p <.0001 (chi-square)
TE Serious Adverse Event	N	2 (0.8%)	0	2 (0.4%)	
TE AE leading to life threatening	N	0	0	0	
TE AE leading to premature withdrawal	N	2 (0.8%)	0	2 (0.4%)	
TE AE leading to death	N	0	0	0	
TE AE related	N	**51 (20.2%)**	**148 (58.7%)**	199 (39.5%)	p <.0001 (chi-square
TE AE Grade 3 or 4	N	4 (1.6%)	0	4 (0.8%)	
TE AE Persist or Signif Disability/Incapacity	N	0	0	0	
TE AE Requires or Prolongs Hospitalization	N	2 (0.8%)	0	2 (0.4%)	

Illustration 258 : Comparison of Adverse Events Between the Two Manufacturing Processes – Sample 6 – Fixed Percentage of obese

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504	p-value
Treatment emergent AE (TE AE)	N	**83 (32.9%)**	**155 (61.5%)**	238 (47.2%)	p <.0001 (chi-square)
TE Serious Adverse Event	N	1 (0.4%)	0	1 (0.2%)	
TE AE leading to life threatening	N	1 (0.4%)	0	1 (0.2%)	
TE AE leading to premature withdrawal	N	1 (0.4%)	0	1 (0.2%)	
TE AE leading to death	N	0	0	0	
TE AE related	N	**68 (27.0%)**	**148 (58.7%)**	216 (42.9%)	p <.0001 (chi-square
TE AE Grade 3 or 4	N	3 (1.2%)	0	3 (0.6%)	
TE AE Persist or Signif Disability/Incapacity	N	0	0	0	
TE AE Requires or Prolongs Hospitalization	N	1 (0.4%)	0	1 (0.2%)	

498 adverse events were reported for Process 2, affecting 155 participants, which represents 61.5%. Among the participants from Process 2, no serious adverse events were reported—no fatalities, life-threatening events, or hospitalizations.

The tables organized by system organ class and preferred terms (see Annexes) reveal a significant increase in the following conditions: chills, fatigue, pain, pyrexia, myalgia, headache, diarrhea, and arthralgia, indicating that the product from Process 2 elicited a stronger bodily reaction.

Calculations demonstrate that the two processes are not identical in terms of toxicity.

In summary,

Pfizer modified the manufacturing process of its vaccine between the study phase and its market release in October 2020. The Process 1 is clearly identified as “clinical trial material” and the Process 2 as “commercial process”.

On the 19th of February, 2021, the Committee for Medicinal Products for Human Use (CMPH) of EMA raised **Major Objections regarding Good manufacturing Practice**.

Despite the batchs comparison provided, it is NOT formally proven <u>that the two processes result in the production of the same product</u>.

To ensure that the protection against the virus was similar between the two manufacturing processes, the protocol planned to compare the antibody levels of participants who received vaccines from Process 2 with those of a randomly selected sample of 250 participants from the tens of thousands vaccinated with the product manufactured under Process 1.

To ensure that Process 2 did not present more toxicity than Process 1, the October 2020 protocol intended to compare the adverse effects between the two groups of participants (those who received vaccines manufactured under Process 1 versus Process 2).

These analyses were entirely canceled by Protocol Amendment 20.

The toxicity analysis of Process 2, after randomly selecting multiple samples of 252 participants who had received vaccines manufactured under Process 1 and comparing them to Process 2, demonstrated that Process 2 caused at least twice as many adverse effects attributed to the product by Pfizer compared to Process 1.

As a result, in December 2020, the population unknowingly received a product with NO data on efficacy, immunogenicity, or tolerance.

In October 2021, a new change in the composition was submitted to the FDA regarding vaccines for youg children (children 5 through 11 years of age).

Once again, the authorization was granted by FDA and EMA without any result on the efficacy and safety.

16 General Conclusion

This report complements and replaces the report written in January 2022[8], whose conclusions were presented on April 5, 2022, to the Parliamentary Office for the Evaluation of Scientific and Technological Choices (OPECST) and on July 1, 2022, to the French National Agency for Medicines and Health Products Safety (ANSM). It was established after reviewing the following elements concerning the vaccines BNT162b2, BNT162b2 Bivalent (Original and Omicron BA.1) (tozinameran/riltozinameran), and the BNT162b2 Bivalent vaccine (Original and Omicron BA.4/BA.5) (tozinameran/famtozinameran) from Pfizer/BioNTech :

- Clinical report of December 10, 2020 – Three-month interim analysis on adults over 16 years of age:
  https://www.fda.gov/media/144246/download
- Six-month interim analysis on adults over 16 years of age from September 15, 2021:
  New England Journal of Medicine:
  https://pubmed.ncbi.nlm.nih.gov/34525277/

  https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110345
- Clinical report on the third dose or booster from September 17, 2021:
  https://www.fda.gov/media/152161/download
- Final clinical report for those over 16 years of age from July 28, 2023:

  https://mega.nz/file/XJ5mGTQY#6sGKu79MXyJXxhiWlEYOOrxeuea1wSTRMO01cppULOQ
- Clinical report on the adolescent population aged 12 to 15 years from April 9, 2021:
  https://www.fda.gov/media/148542/download
- Clinical report on children aged 5 to 11 years from October 26, 2021:
  https://www.fda.gov/media/153409/download
- Clinical report on children aged 6 months to under 5 years from June 14-15, 2022:

  https://www.fda.gov/media/159193/download
- Results from trials on bivalent vaccines:
  https://www.has-sante.fr/upload/docs/application/pdf/2022-09/rapport_evaluation_place_des_vaccins_cominarty_bivalents_original.omicron_ba.1_et_origninal._omicron_ba.4-5.pdf
- Successive Risk Management Plans:

  https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty
- Documents from the pregnant women's trial:

  https://classic.clinicaltrials.gov/ProvidedDocs/94/NCT04754594/Prot_000.pdf
  https://clinicaltrials.gov/study/NCT04754594?tab=history&a=24#version-content-panel
- Compliance and inspection: Reflection paper on risk-based quality management in clinical trials:

  https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

[8] https://christinecotton.com/english_expertise

- Periodic Safety Update Reports (PSURs):

  https://tkp.at/wp-content/uploads/2023/10/OCR_R-Comirnaty-19-Dec-2020-To-18-June-2021-PSUR-1_body.pdf

  https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-june-2021-18-december-2021_en.pdf

  https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-december-2021-18-june-2022_en.pdf-0

  https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-june-2022-18-december-2022_en.pdf

  https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-december-2022-18-june-2023_en.pdf

- Pivotal clinical trial database, participants' case report forms released by court ruling and made available to the public:

  https://phmpt.org/pfizer-16-plus-documents

- Other documents from Healths agencies: FDA, EMA, TGA, ANSM, HAS…
- European pharmacovigilance database (Eudravigilance):

  https://www.adrreports.eu/fr/disclaimer.html

  https://dap.ema.europa.eu/analytics/saw.dll?PortalPages&PortalPath=%2Fshared%2FPHV%20DAP%2F_portal%2FDAP&Action=Navigate&P0=1&P1=eq&P2=%22Line%20Listing%20Objects%22.%22Substance%20High%20Level%20Code%22&P3=1+42325700

…

The conclusions are as follows:

16.1 Regarding participant management

This report highlights the following points.

Participants are **responsible for assessing and reporting their symptoms** to the investigator who recruited them in order to undergo PCR testing.

The PCR test was therefore not systematically performed for all participants but only for participants reporting symptoms and on the advice of the investigator.

The diagnostic method chosen although usual in the clinical trials on vaccines is very surprising in the context of a pandemic where any person infected with COVID-19 could contaminate those around him or her, transmitting a **potentially fatal disease**.

First, any erroneous assessment or incomplete reporting of symptoms by the participant does not trigger PCR testing to confirm or not the presence of COVID-19, we will conclude on this point later in this report.

Secondly, the way to manage participants in this trial (not conducting PCR tests for everyone, phone calls to report symptoms**) endangered their lives** and the lifes of **any person he could met**—a risk that seemingly did not concern the company much.

This apparent disregard for participant safety raises significant concerns about the laboratory's commitment **to basic patient protection laws**, **such as the Helsinki Declaration. The pivotal trial and all the trials managed similarly present violation of basic patient protection laws**

Moreover, the use of electronic diaries is not suitable for an elderly population, which is the group most susceptible to contracting SARS-CoV-2.

Pfizer cannot claim to have followed the standard format for vaccine protocols, as, in the context of a global pandemic that led to exceptional emergency measures allowing an accelerated development, the protocol should have been adapted accordingly. Participants should not have been left to manage on their own without being offered systematic and regular testing, as one would have expected in such a situation.

16.2 Regarding criteria not assessed in the trial

The efficacy in preventing transmission has never been demonstrated, as it was never studied in the clinical trials, regardless of the population. This is confirmed by the French National Authority for Health (HAS) in December 2020:
"*At this stage, there is no available data on the impact of vaccination on viral* ***transmission***."

Illustration 259 : December 23, 2020 French National Authority for Health (HAS) statement

Par ailleurs, la HAS note, à ce stade que :

- l'efficacité vaccinale n'a pu être évaluée chez les sujets les plus jeunes (<18 ans);
- l'efficacité vaccinale sur la transmission virale n'a pas été évaluée ;
- la tolérance du vaccin chez les sujets ayant un antécédent de Covid-19 (documenté par sérologie positive ou test PCR positif) était bonne.

La HAS insiste donc sur le fait que l'essai de phase 3 devra être poursuivi afin de pouvoir disposer de données d'immunogénicité, d'efficacité et de tolérance à plus long terme et souhaite être informée des résultats des analyses plus fines en sous-groupes dans l'essai de phase 3, ainsi que des études mises en place dans le cadre du Plan de Gestion des Risques (PGR). La HAS encourage la mise en place :

- d'études post-autorisation notamment sur les populations vaccinées dans la première phase de la campagne (Ehpad).
- d'une étude avec séquençage des souches virales, afin de suivre l'évolution de nouvelles souches, notamment chez les patients infectés après vaccination

Cet avis sera revu en fonction de l'évolution des connaissances, notamment au regard des résultats complets des essais de phase 3 de chaque candidat vaccin et des données épidémiologiques.

Source ; https://www.has-sante.fr/upload/docs/application/pdf/2020-12/strategie_vaccination_covid_19_place_vaccin_a_arnm_comirnaty_bnt162b2.pdf

The level of evidence from the trials is **clearly insufficient to argue for a collective benefit from mass vaccination,** particularly for individuals at low risk of severe COVID. **Any communication aimed at promoting vaccination based on such an argument is therefore unsupported by scientific evidence.**

In this regard, the information provided in the product leaflet itself is therefore incorrect[9].

« *Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is a vaccine used for preventing COVID-19 caused by SARS-CoV-2 virus.*»

The laboratory could, at most, have written:

« *The Pfizer-BioNTech/Comirnaty COVID-19 mRNA vaccine is a vaccine used to prevent symptomatic COVID-19 caused by the SARS-CoV-2 virus.* »

[9] *https://www.fda.gov.ph/wp-content/uploads/2021/11/Pfizer-BioNTech-and-Comirnaty-Product-Information-for-vaccine-recipients.pdf*

Illustration 260 : Pfizer - Package leafet: Information for the User

Package leaflet: Information for the user

Pfizer-BioNTech/Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is and what it is used for
2. What you need to know before you receive Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine
3. How Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is given
4. Possible side effects
5. How to store Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine
6. Contents of the pack and other information

1. What Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is and what it is used for

Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is a vaccine used for preventing COVID-19 caused by SARS-CoV-2 virus.

16.3 Regarding the main efficacy criteria

The primary efficacy criteria or primary endpoint was the number of participants with a first occurrence of a symptomatic COVID-19 <u>from 7 days after dose 2</u> in the 2 groups, BNT162b2 and placebo. These number were to be used to compute vaccine efficacy.

In order to diagnose a symptomatic COVID-19, it was necessary to identify, for each subject,

- **if he had one of the following symptoms,**
    - Fever,
    - New or increased cough;,
    - New or increased shortness of breath,
    - Chills,
    - New or increased muscle pain,
    - New loss of taste or smell,
    - Sore throat,
    - Diarrhea,
    - Vomiting.

and

- **A Positive PCR Test** *during or within the 4 days before or after the symptomatic*. The nasal swab should be sent to a central laboratory in order to get homogenous results for all participants.

  If no central result was available, the result of a local laboratory should be used to confirm a COVID-19 case.

Each participant was responsible to evaluate and report these symptoms to the site as discussed in the Participant management section.

The Pfizer laboratory was thus well aware of the importance of the postponement of symptoms since section 8.14 of the protocol insists on this point
"***In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events <u>are not missed</u>.***"

For a study of this magnitude, conducted on an innovative product within a record time frame, placing the responsibility on participants to report their symptoms—with all the potential errors in judgment that entails, given that participants do not have the clinical expertise to assess their own health—is particularly questionable.

In order to report his symptoms, the participant could chose to **contact the site directly** and not to make an appointment with his usual doctor. However, the protocol specified that symptoms that could be possible **reactions** to the experimental product (fever, chills, muscle aches ...) <u>should not trigger a visit for a potential COVID-19</u> disease, **unless**

- *If, in the opinion of the investigator, such a visit was necessary.*
- *If, in the opinion of the investigator, the clinical picture was more indicative of possible COVID-19-related disease than vaccine reactogenicity.*

- *If, in the opinion of the investigator, the symptoms were more likely to be vaccine reactogenicity, **a local test for SARS-CoV-2** could be performed.*

Then, this method of diagnosis implies that the participant has correctly assessed **all** his/her symptoms, as **any incomplete or erroneous reporting of symptoms could therefore lead to an erroneous assessment by the investigator,** especially if the participant is behind a screen in a teleconsultation setting.

This also meant that center staff responded **very quickly to calls** from participants reporting symptoms so that PCR testing could be performed as quickly as possible. Given the number of participants recruited per clinical investigation center (on average 293) in record time, in the midst of the COVID-19 pandemic and travel restrictions, did the investigative sites have the capacity to respond to all participant calls?
As some symptoms are both possible reactions to the vaccination and symptoms of COVID-19 such as fever, chills, muscle aches, diarrhea, vomiting, how could an investigator differentiate **between reactions** due to the injection of the experimental product **and COVID-19 symptoms** during teleconsultations, without examining the participant, on the basis of some data reported by the participant himself?

Any participant with any of the symptoms of interest should logically have had a PCR test done immediately to classify the symptom as an adverse event or COVID-19, **without giving the investigator any option to decide otherwise**.

This approach induces a major bias in the evaluation of the occurrence of COVID-19 because it is well understood that no PCR test means no symptomatic COVID-19, so any symptomatic participant without PCR test is de facto classified as a therapeutic success.

Even worse, any symptomatic participant who has a PCR+ test result via their local laboratory but is unable to reach the investigator site is also classified as a therapeutic success.

In order to overcome this major bias, it would have been much more appropriate to perform PCR tests not only for participants reporting symptoms, but for **all** participants, this would also have allowed the detection of asymptomatic COVID-19 who are also vectors of the disease.

Considering the choice of the primary endpoint itself, we can conclude that the Pfizer vaccine efficacy is only evaluated on symptomatic cases and not all COVID-19 cases.

It is also important to note that any use of antipyretics suppresses fever and reduces or even eliminates pain, symptoms that are among the first signals that may suggest COVID-19 and that should trigger the test to confirm the presence of the virus or not.
It is therefore already clear that **the use of antipyretics introduces a bias by eliminating symptoms and therefore potential COVID-19 cases.**

Moreover, we have confirmation **from the database** that participants who received the vaccine were tested less frequently than those in the placebo group, introducing a major bias in counting the number of COVID-19 cases, which is the primary efficacy endpoint, and this bias favors the vaccine.

Based on the above elements, we can conclude that t**he method used to identify symptomatic COVID-19 cases inevitably leads to an underestimation of the actual number of cases, in favor of the vaccine, rendering the conclusions about the demonstrated vaccine efficacy unreliable.**

All results concerning this endpoint cannot be considered accurate, regardless of the population, and this applies to all analyses (the 3-month interim, 6-month, and final analysis) and all trials managed the same way.

16.4 Regarding unsatisfactory results

- The efficacy **against severe cases was not statistically demonstrated after 2 doses**, due to a lack of cases in December 2020 and across all other populations at the time of authorization requests (adolescents in April 2021, children aged 5 to 11 in October 2021, young children aged 6 months to 4 years in June 2022).
  The results are no more reliable than those for the primary efficacy endpoint, as they are based on the same data collection method. In fact, the statistical significance obtained in the 6-month analysis is biased by the participant management method and the calculation of the endpoint. Therefore, it cannot, by itself, provide conclusive evidence of the vaccine's efficacy against severe cases.

- In December 2020, the efficacy **in individuals over 75 years old was not statistically demonstrated**. This was confirmed by the French National Authority for Health (HAS): "*Due to a lack of power, it is not possible to draw specific conclusions for patients over 75 years old*."

  https://www.has-sante.fr/upload/docs/application/pdf/2020-12/strategie_vaccination_covid_19_place_vaccin_a_arnm_comirnaty_bnt162b2.pdf

  Any subsequent demonstrated efficacy is questionable due to the method used to count cases.
- The efficacy **in preventing hospitalizations** has not been statistically demonstrated for any population or analysis.
- The efficacy in preventing COVID-19-related mortality has not been statistically demonstrated for any population or analysis. This was confirmed by the French National Authority for Health (HAS) in December 2020 for individuals over 16 years old:

  https://www.has-sante.fr/upload/docs/application/pdf/2020-12/strategie_vaccination_covid_19_place_vaccin_a_arnm_comirnaty_bnt162b2.pdf

- The efficacy **against asymptomatic cases**, tested only on participants without evidence of infection until the start of the asymptomatic surveillance period (January 2021), was not statistically demonstrated for the entire trial. The efficacy against asymptomatic cases in the total population was not studied.

  The estimated efficacy against asymptomatic disease, based on antinucleocapsid Serology (seroconversion), was only **52.9% in the final report from July 2023**. The results on seroconversion for both asymptomatic and symptomatic infections were not provided, preventing any comparison with the efficacy determined through case counting.

- The efficacy i**n children aged 2 to under 5 years and children aged 6 months to under 2 years** yielded very poor results, with no demonstrated efficacy against the Delta and Omicron variants. Severe cases were more frequent in the vaccinated group compared to the placebo group.

16.5 Regarding immunogenicity

The duration of protection is discussed in Section 4.7 of the Clinical Review Memorandum for the Biologics License Application (BLA) dated August 23, 2021, by Drs. Susan Wollersheim and Ann Schwartz.

The FDA conducted a quantitative benefit-risk assessment through a model evaluating the benefits of preventable COVID-19 cases through vaccination, hospitalizations, ICU admissions, and deaths, as well as the risks of excess cases of myocarditis/pericarditis, hospitalizations, and vaccination-related deaths. This analysis was performed for groups stratified by age and sex combinations (12-15 years, 16-17 years, 18-24 years, and 25-29 years).

From this modeling, the most likely scenario predicted a vaccine protection duration of 6 months.

Illustration 261 : August 23, 2021 BLA Clinical Review Memorandum – Risk-Benefit Assessment

> The most likely scenario assumed vaccine protection duration of 6 months, 10x COVID-19 case incidence and 4x COVID-19 hospitalization incidence as compared with those of July 10 (recent nadir), 70% vaccine efficacy against COVID-19 case, 80% vaccine efficacy against hospitalization, and no vaccine-related myocarditis death. The model results indicate that, for all age/sex groups and across all model outcomes, the benefits clearly outweigh the risks. For males 16-17 years old—the group with the highest risk of myocarditis/pericarditis—the model predicts that prevented COVID cases, hospitalizations, ICU admissions, and deaths are 136,000, 506, 166 and 4 per million vaccinated individuals, respectively. The excess myocarditis/pericarditis cases, associated hospitalizations, and deaths attributable to vaccine are 196, 196, and 0 per million vaccinated individuals, respectively.

Source: https://www.fda.gov/media/152256/download

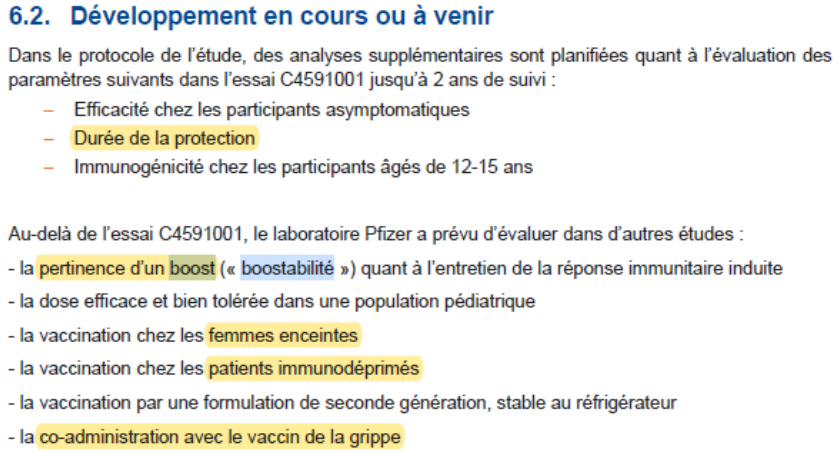
It has been acknowledged since May 2021 that the protection provided by the vaccine would not exceed six months.

The measurement of neutralizing antibodies presented in the report from December 10, 2020, already indicated a decline in immunity to below two months after the second dose.

As of September 22, 2021 [10], Pfizer publicly admitted to a **decline in antibodies six to eight months after the second dose**. This decline could have been observed earlier if the interim analysis had been conducted after six months instead of the two-month median, as permitted by the FDA's Emergency Use Authorization. Additionally, if the trial had included visits between one month and six months after the second dose, it would have seemed prudent, especially for such an innovative vaccine.

[10] *https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/02-COVID-Gruber-508.pdf*

In December 2020, the opinion of the HAS indicated that a booster was already planned. It proved quite convenient not to measure antibodies at three months, as this would have hindered the Emergency Use Authorization in the United States and the conditional marketing authorization in Europe. Who would authorize a vaccine whose protection does not exceed six months? No one.



6.2. Développement en cours ou à venir

Dans le protocole de l'étude, des analyses supplémentaires sont planifiées quant à l'évaluation des paramètres suivants dans l'essai C4591001 jusqu'à 2 ans de suivi :

- Efficacité chez les participants asymptomatiques
- Durée de la protection
- Immunogénicité chez les participants âgés de 12-15 ans

Au-delà de l'essai C4591001, le laboratoire Pfizer a prévu d'évaluer dans d'autres études :

- la pertinence d'un boost (« boostabilité ») quant à l'entretien de la réponse immunitaire induite
- la dose efficace et bien tolérée dans une population pédiatrique
- la vaccination chez les femmes enceintes
- la vaccination chez les patients immunodéprimés
- la vaccination par une formulation de seconde génération, stable au réfrigérateur
- la co-administration avec le vaccin de la grippe

The design of the trial allowed for the avoidance of measuring antibodies beyond two months after the second dose, **contributing to the concealment of their decline, which was foreseeable based on studies in macaques, and which was confirmed in the following months**.

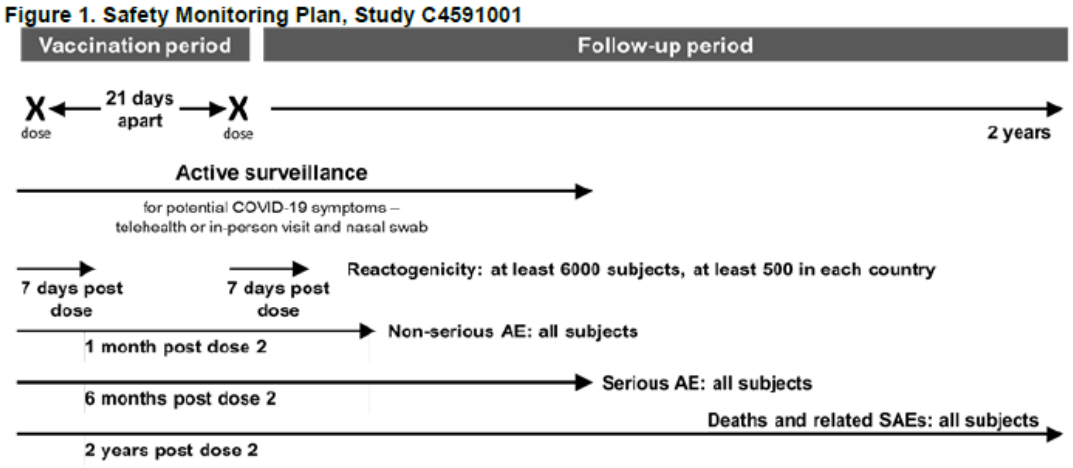
This represents a **serious oversight, if not a methodological fraud**, that proved to be quite convenient, as no authorization would have been granted for a vaccine whose protection lasts only four to five months. **This lack of measurement also facilitated the administration of boosters, as well as the fourth, fifth, sixth, and seventh doses, among others**.

16.6 Regarding safety

In all the clinical reports presented—the report from December 10, the report from April 2021, the report from October 2021, and the report from June 2022—the results were based on a median follow-up time of two months (with 50% of participants followed for less than two months and a maximum follow-up of four months).

The total duration of the clinical trial was planned to be two years, as indicated in the memorandum signed by Marion Gruber, Director of the Office of Vaccines Research and Review (OVRR) of the FDA, dated December 11, 2020.

Illustration 262 : FDA : December 11, 2020 Memorandum – Safety monitoring plan



Source : https://www.fda.gov/media/144416/download

This follow-up period was authorized by the new regulations issued urgently by the U.S. Food and Drug Administration in October 2020 ("Emergency Use Authorization for Vaccines to Prevent COVID-19"[11])) and contradicts the recommendations of the World Health Organization from 2010 [12] regarding vaccines, which advocated **for a <u>one-year follow-up to conclude efficacy</u> and <u>six months to properly assess safety</u> in order to obtain valid and reliable results**.

The reduced observation period for participants does not allow for an assessment of long-term safety, which is mentioned in Pfizer/BioNTech's Comirnaty Risk Management Plan **since December 2020** in chapter SVII.3.2, "Presentation of the Missing Information".

<u>The long-term safety profile remains UNKNOWN to this day.</u>

[11] *https://www.fda.gov/media/142749/download*

[12] *https://web.archive.org/web/20131031205225/https://www.who.int/immunization_standards/vaccine_quality/clinical_considerations_oct10.pdf*

Serious adverse effects have not been reported in the database. <u>The safety results provided in the reports from December 2020 and April 2021 are therefore erroneous</u>.

- Case of Augusto Roux, a lawyer at the High Court of Justice in Buenos Aires: a participant in the trial in Argentina, he experienced serious adverse effects after receiving his second dose, including pericarditis, which was diagnosed as vaccine-related. The pericarditis was not reported and does not appear in the database or the report. Other effects were reclassified as potential COVID cases by the sponsor, even inventing convenient psychiatric disorders to discredit Mr. Roux's allegations of fraud with health agencies.

  Augusto Roux contacted the FDA, EMA, and other regulatory bodies, which refrained from examining his case with the seriousness it warranted. He has opened a **criminal investigation in Argentina against Fernando Polack**, the principal investigator at the Argentine site, for falsification of public documents and neglect of a person.

- Case of Maddy de Garay, a 15-year-old participant in the adolescent trial: she suffered from over thirty adverse effects after receiving the vaccine. Her condition continued to decline rapidly and ultimately necessitated the continuous use of a feeding tube and a wheelchair. The de Garay family received no attention from Pfizer or the FDA. In the report submitted to health authorities for the approval of the vaccine for adolescents aged 12 to 15 years, only one serious adverse effect was listed: "**functional abdominal pain.**"

  The de Garay family requested information regarding their daughter's participation in the clinical trial through legal channels and has been heard multiple times by U.S. senators.

  https://phmpt.org/wp-content/uploads/2023/05/001-Complaint-PHMPT-de-Garay-v.-FDA-2022-10-11.pdf

<u>Regarding deaths</u>, a crucial point since they allow for the evaluation of the vaccine's efficacy in cases of death due to COVID-19 as well as the product's safety, it is noted that the number of deaths in the vaccinated group significantly exceeds the number of deaths in the placebo group (85 deaths in the vaccinated group from the onset of the study, 62 deaths among participants who received the placebo followed by the vaccine, and 23 deaths in the placebo group).

An examination of the Case Report Forms containing publicly available participant data reveals **delays, errors, and concealment of deaths**, despite the laboratory's awareness of these issues in the December 2020 report.

Among the **four unreported deaths for the vaccine**, two participants aged 58 and 63 died from **cardiac arrest** within three months following the second dose. In two instances, there were data entry errors, with the dates of death entered into the computerized system set up for data collection later corrected through correction requests.

Centers are obligated to report serious adverse effects to the laboratory within 24 hours, making these delays or persistent data entry errors regarding death dates during such a

significant interim analysis completely unusual, as data managers and pharmacovigilance staff are particularly vigilant regarding death reporting.

These issues constitute a serious breach that undermines the tolerance results, as in December 2020, there were not two deaths in the vaccinated group as indicated in the report, but six, including three from cardiac arrest, which casts suspicion on all provided results.

This analysis was confirmed by Dr. Jeyanthi Kunadhasan in her correspondence with the Australian Therapeutic Goods Administration (TGA). These exchanges, sent and made public on behalf of the Australian Medical Professional Society (AMPS), consist of an initial letter dated March 21, 2024, the response from the professor of the Health Products Regulation Group at the TGA dated March 27, 2024, and the response from the professor of the AMPS dated March 27, 2024.

These findings corroborate our investigations within the database and the participant notebooks made public throughout 2023. **Four deaths are missing in the vaccinated group and one death in the placebo group.** Therefore, the reporting rate for deaths is 33% in the vaccinated group and 80% in the placebo group (four reported deaths out of five).

By adding deaths that occurred a few days after the data freeze date for the December 2020 interim analysis, we must include three additional fatal cardiac issues (atherosclerosis/hypertensive heart disease, cardiopulmonary arrest, congestive heart failure) among men aged 84, 53, and 54 years.

Regarding children aged 5 to 11 years, the small sample size did not allow for the detection of myocarditis, which was nonetheless identified in adolescents aged 12 to 15 years. The estimation of the risks of myocarditis/pericarditis was based on "**predictions**."

"*Based on this information, it is reasonable to predict that the rates of post-vaccination myocarditis will likely be even lower in children aged 5 to <12 years than those observed in adolescents aged 12 to 15 years.*"

Risk assessment must rely on evidence, not predictions.

Based on the elements outlined above, we can conclude that the methods employed to identify adverse effects (trial design, timing of scheduled visits, absence of visits between one month after the second dose and six months after the second dose, method of reporting adverse effects, participant follow-up by the investigative site, duration of participant follow-up during interim analyses, and the number of participants in analyses involving younger populations) **lead to an underestimation of the number of adverse effects, rendering the tolerance results unreliable.**

The unreported deaths indicate a manifest fraud aimed at concealing the product's toxicity.

This also highlights the risk taken by health agencies in granting authorization for such an innovative product based **on an interim analysis** with only three months of follow-up. Since the data are not finalized, the results presented are largely incomplete, if not false.

16.7 Regarding violation to Good Clinical Practice

The **Ventavia** [13] case highlighted uncertainties regarding the training, supervision, and monitoring of clinical trial sites by the sponsor, as well as concerns about the quality of participant follow-up at these sites. Nearly 44,000 patients were recruited and followed between July 27, 2020, and November 14, 2020, across 150 clinical trial sites in the United States, Germany, Turkey, South Africa, Brazil, and Argentina. This amounted to an average of 293 participants per clinical investigation site during the COVID-19 pandemic, when travel restrictions were in place.

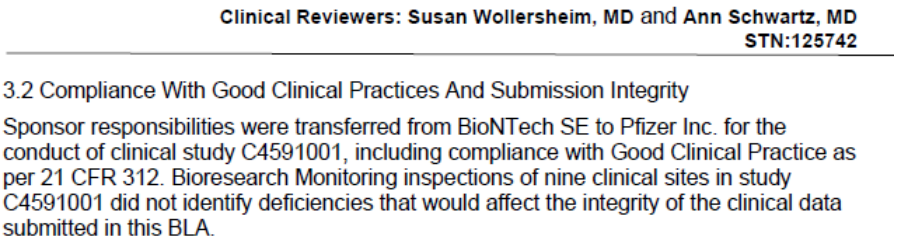
- Suspicion of fraud at Cincinnati Hospital, which recruited Maddie de Garay.
- Fraud at the Argentine site: the creation of a virtual site to recruit additional participants, as seen in the case of Augusto Roux.
- No analysis was conducted without these sites, despite questionable data integrity.
- Protocol deviations were assessed during blinded meetings for each population analysis, which is highly **unusual** in clinical trials.
- **Missing death data at the time of the December 2020 analysis.**

The results provided in the various clinical reports from Pfizer, which were urgently reviewed by health authorities, regarding efficacy (e.g., symptomatic cases, severe cases), immunogenicity, and safety, **cannot be considered as trustworthy or reliable from a Good Clinical Practice (GCP) guidelines.** This undermines the assessment of the benefit-risk ratio, which was presumed to favor the Comirnaty vaccine and its subsequent formulations.

The **FDA** [14] audit, conducted across 9 sites, does not resolve these concerns, as, by the FDA's own admission, during the audits of the sites, "the section on data integrity and the verification of BIMO (Bioresearch Monitoring) inspections was limited because the study was ongoing and the data required for verification and comparison were not yet available for the IND."

The memorandum on the clinical review of the Biologics License Application (BLA) by Drs. Wollersheim and Schwartz, dated August 23, 2021, states on page 15 that « s***ponsor responsibilities were transferred from BioNTech SE to Pfizer Inc. for the conduct of clinical study C4591001, including compliance with Good Clinical Practice as per 21 CFR 312.*** »

Illustration 263 : FDA : Mémorandum d'examen du 23 août 2021- Respect des PBC



Clinical Reviewers: Susan Wollersheim, MD and Ann Schwartz, MD
STN:125742

3.2 Compliance With Good Clinical Practices And Submission Integrity

Sponsor responsibilities were transferred from BioNTech SE to Pfizer Inc. for the conduct of clinical study C4591001, including compliance with Good Clinical Practice as per 21 CFR 312. Bioresearch Monitoring inspections of nine clinical sites in study C4591001 did not identify deficiencies that would affect the integrity of the clinical data submitted in this BLA.

Source: https://www.fda.gov/media/152256/download

The review offers little reassurance regarding the quality of the controls conducted, as it refers to **standard validations** in the pharmaceutical industry, stating that "no major statistical issues were identified."

[13] https://www.bmj.com/content/375/bmj.n2635
[14] https://www.fda.gov/vaccines-blood-biologics/comirnaty

In the section titled « 4.7 Risk-Benefit Assessment », the authors conclude that « the benefit-risk estimates are limited by uncertainties associated with the dynamics of pandemics. The major uncertainties in benefits are related to potential changes in COVID-19 incidence over time and vaccine efficacy and duration of protection in the face of emerging virus variants. The major risk uncertainty is the data on vaccine-related myocarditis cases and deaths. »

One should ask these doctors how many clinical trial methodologies they have written, how many analysis plans they have developed, and how many results they have provided in order to assess their qualifications to evaluate a clinical trial methodology.

Finally, given the accelerated clinical development that the vaccine underwent, facilitated by the COVID-19-specific "Emergency Use" procedure established by the Food and Drug Administration (FDA) in October 2020, as well as the "Fast-Track" system, which allows for the use of non-standard methods to expedite development, it is highly likely that this trial contains additional major deviations from Good Clinical Practice (GCP) that have not yet been identified.

As we have extensively demonstrated in this document, this clinical trial does not adhere to Good Clinical Practice (GCP), and its conclusions are therefore flawed. The statement in the July 2023 report regarding compliance with GCP is, therefore, misleading.

16.8 Regarding the approval of a product that is not the one used in the clinical trial

Pfizer modified the manufacturing process of its vaccine between the study phase and the market launch.

This is indicated in the study protocol published in the New England Journal of Medicine in December 2020, (§ 6.1.1, research protocol for the Pfizer BioNTech/Pfizer clinical trial C4591001, appended as a supplement to the first journal article on phases 2 and 3 of the trial: "Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine." N Engl J Med Dec. 2020).

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2034577/suppl_file/nejmoa2034577_protocol.pdf)

The existence of a second manufacturing process is confirmed by :

- **the EMA evaluation report from February 2021.**
  « *Two active substance processes have been used during the development history; Process 1 (clinical trial material) and Process 2 (commercial process).*. »
  EMA, « Assessment report Comirnaty Common name: COVID-19 mRNA vaccine (nucleoside-modified) », 19 February 2021
  https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

- **The Australian Therapeutic Goods Administration (TGA) also explains the differences between the two manufacturing processes::**
  In Process 1, the DNA template for mRNA transcription is produced through PCR amplification.
  In Process 2, linearized plasmid DNA is cultured in E. coli bacteria. Linearized plasmid DNA involves the use of plasmid DNA, which is a double-stranded circular DNA molecule typically found in bacteria..
  (TGA, « Pfizer/BioNTech COVID-19 mRNA vaccine (BNT162, PF-07302048) », Sept. 18, 2020, pp. 21 et 23
  https://www.tga.gov.au/sites/default/files/foi-2389-03-1.pdf)

- A report from the Japanese Health Agency, dated January 29, 2021.
  « *The active substance used for nonclinical and clinical studies are manufactured by Process 1, and the active substance in the proposed commercial formulation by Process 2. In Process 1, the active substance is manufactured by in vitro transcription of the template DNA prepared by *****, followed by ********* and purification through *********. In Process 2, the active substance is manufactured by in vitro transcription of the linear template DNA prepared from the plasmid DNA, followed by *********, **************, and purification through ********* and ********.* »
  (PMDA, « Report on special approval for emergency »
  https://www.pmda.go.jp/files/000243206.pdf)

To ensure that Process 2 did not present greater toxicity than Process 1, the October 2020 protocol provided for a comparison of the adverse effects between the two participant groups (vaccines manufactured using Process 1 versus vaccines manufactured using Process 2).

These analyses were completely canceled by Amendment 20 to the protocol.

Joshua GUETZKOW, an academic researcher with a PhD in Sociology from Princeton University and a postdoctoral fellowship in Health Policy from Harvard University, Associate Professor in the Department of Sociology and Anthropology, and at the Institute of Criminology at the Hebrew University of Tel Aviv in Israel, has worked extensively on this topic.

The research conducted using the Pfizer clinical trial database shows that only 252 individuals were tested with a single batch from Process 2, batch EE8493.

The toxicity analysis of Process 2, after random sampling of several groups of 252 participants who received Process 1 and comparing it with Process 2, shows that Process 2 caused at least twice as many adverse effects, which were attributed by Pfizer to the product, compared to Process 1.

The change in the manufacturing process can not be considered as minor as it significantly affects the safety of the product. It then requires new clinical studies or additional data to assess its impact and a new Marketing application or a substantial change to the MA.

In December 2020, the population received a product without any results on efficacy, immunogenicity, or safety, and this was done without their knowledge.

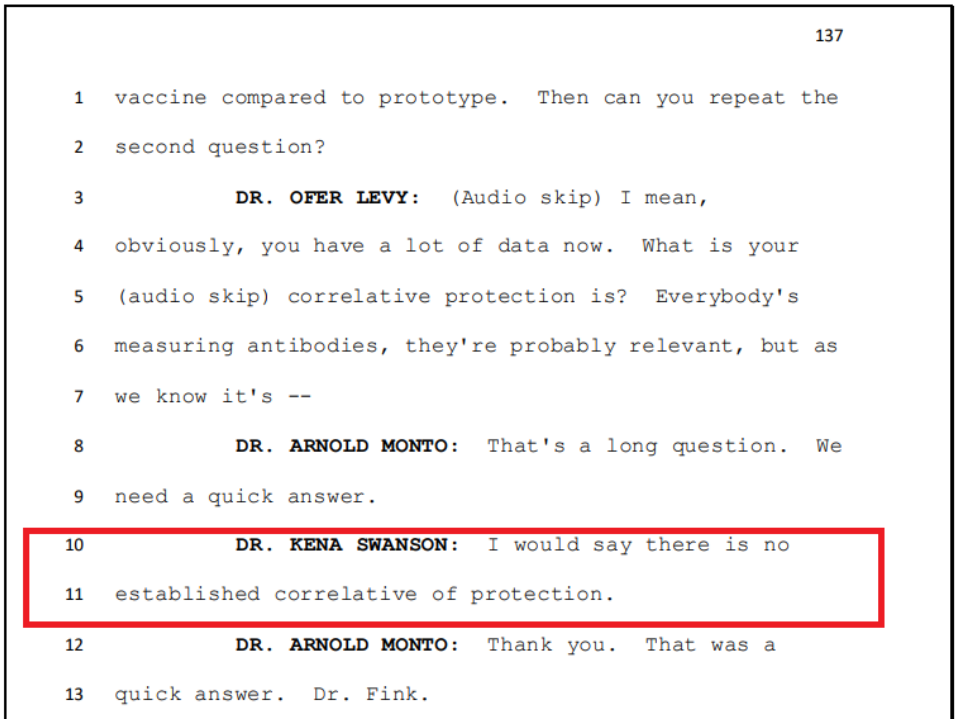
16.9 Regarding clinical trials on the booster and bivalent vaccines

The trials primarily, if not exclusively, study the antibody levels by comparing them to those of the original BNT162b2, **assuming** that a high antibody level equates to good protection against SARS-CoV-2.

However, the document *"Emergency Use Authorization for Vaccines to Prevent COVID-19 »*[15] written by the FDA stated **that no immune marker had been identified to establish protection against COVID-19**, and neutralizing antibodies were therefore used, by default, to assess immunogenicity.

Moreover, during an FDA meeting on June 28, 2022, Kena Swanson, Vice President of Pfizer for Viral Vaccines, acknowledged that "there is no established correlative of protection" between antibody levels and protection against the disease.

Illustration 264 : FDA – Center for Biologics Evaluation and Research (CBER)- 175th Vaccines and Related Biological Products Advisory Committee (VRBPAC) du 28 juin 2022 – Transcription – Réponse de Kena Swanson



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vaccine compared to prototype. Then can you repeat the second question?

DR. OFER LEVY: (Audio skip) I mean, obviously, you have a lot of data now. What is your (audio skip) correlative protection is? Everybody's measuring antibodies, they're probably relevant, but as we know it's --

DR. ARNOLD MONTO: That's a long question. We need a quick answer.

DR. KENA SWANSON: I would say there is no established correlative of protection.

DR. ARNOLD MONTO: Thank you. That was a quick answer. Dr. Fink.

Source ; https://www.fda.gov/media/160778/download

Increasing antibody levels is therefore not sufficient to prevent individuals from becoming ill.

Thus, all trials measuring only antibody levels do not constitute evidence of the vaccines' effectiveness against SARS-CoV-2 disease.

[15] *Emergency Use Authorization for Vaccines to Prevent COVID-19 - Guidance for Industry » , « Autorisation d'Urgence pour les vaccins contre la COVID-19 ».https://www.fda.gov/media/142749/download*

16.10 Regarding risks and missing information

The missing information regarding the vaccine was already cited in the clinical report from April 9, 2021, on adolescents aged 11 to 15 [16].

« *The unknown benefits and data gaps associated with the Pfizer-BioNTech COVID-19 vaccine when used in adolescents 12-15 years of age are the same as those detailed in the memorandum authorizing the vaccine for emergency use in for the individuals 16 years of age and older.*

They relate to:

- *Duration of protection*
- *Effectiveness in certain populations at high risk of severe COVID-19*
- *Effectiveness in individuals previously infected with SARS-CoV-2*
- *Future vaccine effectiveness as influenced by characteristics of the pandemic, changes*
- *in the virus, and/or potential effects of co-infections*
- *Vaccine effectiveness against asymptomatic infection*
- *Vaccine effectiveness against long-term effects of COVID-19 disease*
- *Vaccine effectiveness against mortality*
- *Vaccine effectiveness against transmission of SARS-CoV-2* »

Pfizer publicly acknowledged here, albeit indirectly, the ineffectiveness of its vaccine against asymptomatic infections and, consequently, its inability to curb the transmission of the virus. **As previously demonstrated in this report, the primary endpoint selected could not claim any effectiveness in this regard.**

The missing data had also been included in the Comirnaty Risk Management Plan for months, and still pertained as of November 25, 2021 [17].

- *Use in pregnancy and while breast feeding*
- *Use in immunocompromised patients*
- *Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)*
- *Use in patients with autoimmune or inflammatory disorders*
- *Interaction with other vaccines*
- *Long term safety data*
  - *La tolérance à long terme :* ***Les données continueront d'être recueillies auprès de participants à l'étude en cours C4591001 jusqu'à 2 ans après la 2ème dose du vaccin***

The clinical report from April 2021 and the Risk Management Plan from November 2021 clearly demonstrate, due to the overwhelming amount of missing information, that **the risk assessment presented is entirely incomplete.**

[16] *https://www.fda.gov/media/148542/download*

[17] https://web.archive.org/web/20211228225313/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf

The same conclusions apply to the reports from June 14 and 15, 2022, regarding children under the age of 5. [18].

In section « ***6.2. Uncertainties Related to Benefits*** » (page 59), it is stated:

« ***The uncertainties*** *associated with benefits of the Pfizer-BioNTech COVID-19 vaccine when used in children 6 months through 4 years of age include the following:*

- *Duration of vaccine effectiveness: the blinded, placebo-controlled evaluation period for descriptive efficacy analyses was* ***limited****, and* ***waning of protection*** *following a primary series has been observed in older age groups.*
- *Need for a booster dose: based on experience with adults, it is likely that a* ***booster dose will be needed in addition to the three-dose primary series to increase robustness****, breadth, and duration of protection against currently circulating and emerging SARS-CoV-2 variants in children 6 months through 4 years of age. A booster dose could be considered for authorization with submission of supportive data in a future amendment to the EUA.*
- *Effectiveness* ***in certain populations at high risk of severe COVID-19****, including immunocompromised individuals.*
- *Benefits in individuals previously infected with SARS-CoV-2: descriptive post-Dose 3 efficacy analyses do not include cases in previously infected participants. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred by natural immunity.53 Additionally, for individuals previously infected with the Omicron variant of SARS-CoV-2, a vaccine based on the ancestral strain S protein could provide a greater breadth of protection against SARS-CoV-2 variants.*
- *Effectiveness* ***in preventing post-acute sequelae of COVID-19****: available data are not conclusive on the effectiveness of COVID-19 vaccines currently in use against long-term sequelae of COVID-19 among individuals who are infected despite vaccination. Additional evaluation is needed to assess the effect of this vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.*
- ***Future vaccine effectiveness*** *as influenced by characteristics of the pandemic, including emergence of new variants: the continued evolution of the pandemic, including changes in the virus infectivity, antigenically significant mutations to the S protein, and changes in practice of nonpharmacologic interventions to mitigate against transmission, will likely influence vaccine effectiveness over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical.*
- ***Vaccine effectiveness against asymptomatic infection and transmission of SARS-CoV-2****: Available data for COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against symptomatic COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections »*

[18] https://www.fda.gov/media/159195/download

It was clearly documented that vaccination was not effective for individuals with long COVID. However, some public health organizations and medical professionals recommended that long COVID patients get vaccinated in order to alleviate their symptoms.

The successive Risk Management Plans have helped identify safety issues over time since December 2020.

Anaphylaxis and Vaccine-Associated Disease Exacerbation (VAED), including Vaccine-Associated Exacerbated Respiratory Disease (VAERD), were removed from the list of identified risks, while myocarditis and pericarditis were added.

Menstrual disorders and heavy bleeding were added as side effects for Comirnaty and Spikevax by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), as indicated in its statement from October 28, 2022[19], without being mentioned in the safety issues outlined in the Risk Management Plans.

A preliminary signal of **potential cerebral ischemic accident was also identified by the CDC** for the bivalent BNT162b2 - Omicron BA.4/BA.5 vaccine in older adults.

Regarding the missing information, little has changed since the product was first marketed, with no results provided on...

- Pregnant or breastfeeding women due to their exclusion from the phase 3 study.
- Immunocompromised patients.
- Frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological diseases, cardiovascular disorders) (see Table 44 of the Risk Management Plan).
- Patients with autoimmune diseases or inflammatory conditions.

The interaction between the COVID vaccine and the flu vaccine was removed from the missing data, based on a trial that did not test efficacy regarding the onset of COVID or flu, but rather focused on antibody levels[20]. **This trial therefore does not constitute scientific evidence, as previously demonstrated**.

The long-term tolerance remains unknown.

The administration of the vaccines posed a real risk to the population due to the numerous unknowns regarding their efficacy and safety, particularly for children and pregnant women.

These groups were repeatedly cited as part of the populations that were not studied, and for which no results were available.

The Pfizer clinical trial on pregnant women, which began on February 16, 2021, concluded on July 15, 2022, with 683 women included out of an initial target of 4,000. The first results were published on July 13, 2023, with no efficacy results provided.

[19] https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10581992/

The protocol for this trial, dated March 5, 2022, confirms the absence of data at that time regarding "*the risk of obstetric and/or neonatal adverse effects following vaccination during pregnancy*."

https://classic.clinicaltrials.gov/ProvidedDocs/94/NCT04754594/Prot_000.pdf

In April 2022, while vaccination had been recommended for pregnant women for over a year, the risks to their health and that of their baby were still unknown.

The missing results were finally published on June 24, 2024, nearly two years after the conclusion of the trial, which is highly unusual. Biostatisticians typically provide results within a month of the study's completion. The reported **vaccine efficacy** was just 3.8%.

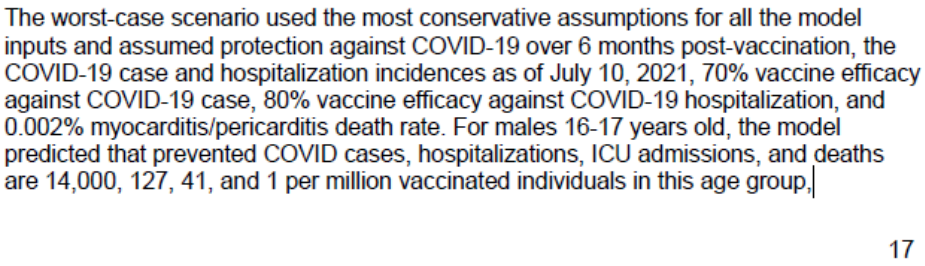
Therefore, no statistically significant efficacy of the Pfizer/BioNTech vaccine has ever been demonstrated in pregnant women.

16.11 Regarding the Benefit/Risk Assessments

The benefit-risk assessment was regularly conducted in the safety reports (PSURs) prepared by health agencies, considering the efficacy established in the clinical trials, which we have demonstrated to be largely insufficient and even erroneous, and through modeling based on assumptions of efficacy.

The memorandum on the clinical review of the BLA by Drs. Wollersheim and Schwartz from August 23, 2021, projected, in its most pessimistic scenario, a vaccine efficacy of 70% against COVID-19 cases, an 80% vaccine efficacy against COVID-19 hospitalizations, and a **myocarditis/pericarditis mortality rate of 0.002%.**

Illustration 265 : Memorandum Wollersheim et Schwartz du 23 août 2021 – Modélisation rapport bénéfices/risques



The worst-case scenario used the most conservative assumptions for all the model inputs and assumed protection against COVID-19 over 6 months post-vaccination, the COVID-19 case and hospitalization incidences as of July 10, 2021, 70% vaccine efficacy against COVID-19 case, 80% vaccine efficacy against COVID-19 hospitalization, and 0.002% myocarditis/pericarditis death rate. For males 16-17 years old, the model predicted that prevented COVID cases, hospitalizations, ICU admissions, and deaths are 14,000, 127, 41, and 1 per million vaccinated individuals in this age group,

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Source https://www.fda.gov/media/152256/download

Regarding the risks, they were estimated solely based on the occurrence of myocarditis/pericarditis. The memorandum, dated May 2021, projected an excess of **196 cases of myocarditis/pericarditis, 196 hospitalizations, and 0 deaths associated with the vaccine per million vaccinated individuals for males aged 16 to 17, the group considered to be at the highest risk**.

Since the use of the authorized Comirnaty and subsequent vaccines, a significant number of serious adverse events have been reported on pharmacovigilance sites. Pfizer/BioNTech had identified a number of these events, as they were already included in their cumulative safety data analysis following the market authorization, from December 1, 2020, to February 28, 2021 (document 5.3.6, Cumulative Analysis of Post-authorization Adverse Event Reports [21]).

In February 2021, the WHO detected **a signal of sudden hearing loss and tinnitus**, with a statistically higher number of reported cases than expected. These hearing issues primarily affected young, healthy adults without comorbidities and appeared within minutes to several hours after vaccination. The WHO recommended that pharmaceutical companies closely monitor these cases.

https://www.who.int/publications/i/item/9789240042452

Health authorities, including the Centers for Disease Control and Prevention (CDC), also conducted pharmacovigilance signal calculations. However, by only **considering adverse events within 21 days of injection,** while long-term safety data were precisely lacking, the

[21]: *https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf*

method employed by the CDC minimized the actual number of events, which were serious and could even result in death. One might have expected even more stringent monitoring from the authorities for such an innovative product developed in such a short time, especially given the emergency recommendations issued.

Regarding the safety reports:

Between December 19, 2020, and June 18, 2021, **327,827 cases were reported, accounting for 1,172,887 adverse events.** Of these, 100,808 cases were classified as serious, representing 30%. There were 5,115 reported deaths, including 46 during the clinical trials.

In the Safety Report 2 covering the period from June 18, 2021, to December 18, 2021, of the 657,528 cases (2,173,477 reported adverse events), 542,562 were classified as serious and 1,631,402 as non-serious. **There were 5,413 reported deaths, including 46 during the clinical trials**.

The Safety Report 3, covering the period from December 18, 2021, to June 18, 2022, reported 1.3 million cases since the start of the vaccination campaign, with a total of 4.9 million adverse events (AE).

In the Safety Report 4, covering the period from June 19, 2022, to December 18, 2022, a total of 1.7 million cases were reported to pharmacovigilance, including 14,945 deaths.

The Safety Report 5, coverint the period from 18 December 2022 through 18 June 2023, indicates more than 1,8 millions cases for more than 6 millions of adverse events. **The number of deaths is not indicated.**

These reports highlighted the occurrence of multiple safety signals affecting all organs, including:

- Amenorrhea
- Anaphylaxis
- Hemolytic anemia
- Appendicitis
- Hypertensive crisis with intracranial hemorrhage
- Asthenia
- Lymphocytic colitis
- Diarrhea
- Decreased appetite
- Pain in the extremity (arm)
- Pain and swelling of the closed eyes
- Dizziness
- Thromboembolic events
- Exacerbation and/or flare-up of underlying autoimmune diseases or inflammatory disorders
- Significant swelling of the limbs
- Hypersensitivity, other than anaphylaxis
- Hyperhidrosis
- Lethargy
- Herpes zoster, including ophthalmic shingles
- Insomnia
- Irritability
- Myocarditis and pericarditis

- Myositis
- Retinal vascular occlusion
- Hearing loss and tinnitus
- Sensorineural hearing loss
- Polymyalgia rheumatica
- Reaction to dermal filler products
- Facial nerve paralysis
- Pemphigus and pemphigoid
- Loss/alteration of taste and smell
- Pruritus at the injection site
- Delayed skin reaction
- Corneal transplant rejection
- Heavy menstrual bleeding
- Night sweats
- Delayed syncope
- Multisystem inflammatory syndrome in children/adults
- Capillary leak syndrome
- Immune thrombocytopenia
- Cerebral venous sinus thrombosis (CVST)
- Stroke
- Subacute thyroiditis
- Chronic urticaria
- Uveitis
- Vasculitis
- Vomiting …

An impressive list of more or less serious, disabling, or even fatal pathologies that the population was never informed about.

The EMA mentions in section 18.2, Benefit-Risk Assessment in PSUR 5[22], the limitations of the benefit-risk analysis.

« *Some limitations of the benefit-risk analysis may include missing information in certain special populations and the inherent limitations of the various data sources.* »

The EMA also highlights the following three points:

These limitations were considered when evaluating the overall benefit-risk profile of BNT162b2.

Clinical trials:

a) The participants in clinical trials are a relatively homogeneous group as they all meet study inclusion criteria. Importantly, certain populations may be excluded.

b) Close monitoring required as part of study participation likely identifies relatively common events. Events that are dose-related and pharmacologically predictable events may be distinguished. However, clinical studies may not be powered to pick up rare safety issues.

[22] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-december-2022-18-june-2023_en.pdf

Non-interventional (observational) study data:

*a) There is **limited control over patient assessment** as patient monitoring and diagnostics are per standard of care; no additional clinical monitoring is generally conducted.*

*b) Patient specific methodological challenges such as **potential biases from patient selection,** loss of patients through study attrition, and overall patient recall are also inherent limitations.*

Post-marketing data:

*a) Reports originate from multiple sources (consumer and healthcare professional) and they can be **poorly characterised from a medical perspective**.*

*b) **Limited or incomplete information is common**, including indication, medical history, concomitant medication use, and reason for reporting as an AE, making it difficult to fully characterise events and associated risk factors.*

*c) **Difficult to contextualise quantitatively, as voluntary and sporadic reporting do not allow complete knowledge of total exposure or total number of events** ever experienced in the exposed population. These data are generally not suitable to make between-drug compansons. »*

Illustration 266 : Pfizer – Periodic Safety Update Report 5- December 18, 2022 to June 18, 2023 - Study limitations identified by the EMA

Limitations

Some limitations of the benefit-risk analysis may include missing information in certain special populations and the inherent limitations of the various data sources, as summarised below.

These limitations were considered when evaluating the overall benefit-risk profile of BNT162b2.

Clinical trials:

a) The participants in clinical trials are a relatively homogeneous group as they all meet study inclusion criteria. Importantly, certain populations may be excluded.

b) Close monitoring required as part of study participation likely identifies relatively common events. Events that are dose-related and pharmacologically predictable events may be distinguished. However, clinical studies may not be powered to pick up rare safety issues.

Non-interventional (observational) study data:

a) There is limited control over patient assessment as patient monitoring and diagnostics are per standard of care; no additional clinical monitoring is generally conducted.

b) Patient specific methodological challenges such as potential biases from patient selection, loss of patients through study attrition, and overall patient recall are also inherent limitations.

Post-marketing data:

a) Reports originate from multiple sources (consumer and healthcare professional) and they can be poorly characterised from a medical perspective.

b) Limited or incomplete information is common, including indication, medical history, concomitant medication use, and reason for reporting as an AE, making it difficult to fully characterise events and associated risk factors.

c) Difficult to contextualise quantitatively, as voluntary and sporadic reporting do not allow complete knowledge of total exposure or total number of events ever experienced in the exposed population. These data are generally not suitable to make between-drug comparisons.

Source : https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-december-2022-18-june-2023_en.pdf

Le PRAC de l'EMA lui-même reconnaît que les « *limitations des données de pharmacovigilance sont des facteurs importants qui empêchent une évaluation médicale correcte de la causalité entre la survenue de l'événement et l'administration du vaccin.* »

The EMA's PRAC itself acknowledges that "limitations in pharmacovigilance data are significant factors that prevent a proper medical assessment of the causality between the occurrence of the event and the administration of the vaccine."

In PSUR 5, page 137 of the PDF, the EMA admits that « *the limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:*

• Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

• Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to

make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing. »

Illustration 267 : Pfizer – – Periodic Safety Update Report 5- December 18, 2022 to June 18, 2023 - Study limitations due to the underreporting of adverse effects identified by the EMA

Cumulative review of ADEM cases

A cumulative review of ADEM cases within Pfizer's global safety database up to the DLP of the PSUR (18 Jun 2023) was performed. The database was searched for all BNT162b2; BNT162b2/BNT162b2 OMI BA.1; BNT162b2/BNT162b2 OMI BA.4-5 and BNT162b2 OMI cases reporting the MedDRA version 26.0 PT Acute disseminated encephalomyelitis (ADEM). The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.
- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.
- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.
- An accumulation of AE reports does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

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Finally, the EMA acknowledges that the impact (including long-term effects) of repeated administration (e.g., annually) of booster doses (with or without updated strains) remains unknown.

Hundreds of scientific papers, which we will not address in this report as they warrant a report of their own, are regularly published regarding adverse effects and deaths occurring after vaccination. These papers signal an **incomplete assessment of safety during the trials**, to the extent that certain health authorities have already taken measures to compensate individuals who suffered from adverse effects, and even suspended the use of the vaccines in certain populations.

Given all these factors, it appears that the benefit-risk balance is extremely difficult to assess due to the underreporting of adverse effects and the challenges in evaluating the product's causality.

The multitude of emerging signals should have prompted health agencies to exercise caution, especially considering that deaths were recorded in the younger populations.

16.12 Recommandations

In light of all these factors, as a biostatistician, former director of a contract research organization specializing in clinical trial data management since 1995, and former quality assurance officer of my company, I not only confirm my conclusions from January 2022 but also call for the withdrawal of all COVID-19 vaccines from Pfizer/BioNTech.

Continuing to use the vaccines developed by Pfizer/BioNTech, including the mRNA COVID-19 vaccine COMIRNATY, the BNT162b2 Bivalent (Original and Omicron BA.1) (tozinameran/riltozinameran), the BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) (tozinameran/famtozinameran), and other bivalent vaccines in real-world settings presents a significant risk to people's lives.

Furthermore, given the numerous methodological issues highlighted in the documents and clinical trial databases, **this trial appears to resemble a massive fraud aimed at showcasing a significant efficacy that never existed, while concealing the decline in antibodies and hiding the associated risks.**

It is necessary to ask the Health Authorities how, despite the countless recommendations within the pharmaceutical industry to ensure the safety of individuals, they were able to authorize a product in December 2020 for which we had no data on safety, efficacy, or immunogenicity.

It would also be pertinent to question why they did not contradict any media representatives, journalists, or politicians who touted the 95% efficacy rate, leading the public to believe they were receiving a vaccine with the claimed 95% effectiveness.

The failure to disclose the change in the manufacturing process constitutes a serious endangerment of lives, as **individuals unknowingly participated in a clinical trial.**

To highlight any **errors, attempts at concealment, or blatant fraud** by the laboratory itself or the participating centers, it is necessary to:

- Request Pfizer to provide the "frozen" database (final database) of the trial in order to verify the calculations provided (in SAS® format).

- Request Pfizer to provide the files documenting participant phone calls, follow-up calls made by the center, as well as the results of PCR tests, whether they come from local laboratories or the central laboratory. This would help clarify the algorithm used to determine symptomatic COVID-19 cases.

- Request Pfizer to provide the file detailing the values, dates of entry, and modifications made to the data by the various parties involved at the investigator sites, known as the "Audit Trail." This would allow identification of any data modifications aimed at concealing deficiencies in the execution of the main tasks of the trial by the investigator sites, such as the failure to perform PCR tests for suspected COVID-19 cases or the lack of follow-up for participants who reported experiencing adverse effects.

  The Pfizer report of 2023 mentions the audit trail in Section 3.6.5, Clinical Data Management, in accordance with the regulations of 21 CFR Part 11 concerning the use of electronic data capture forms, as previously discussed in this document.

Illustration 268 : Pfizer – Rapport juillet 2023 –Mention de l'audit-trail

3.6.5. Clinical Data Management

CRF data were captured via data entry in a sponsor agent database system. Data quality checks were applied using manual and electronic verification methods. An audit trail was maintained to support data query resolution and any modification to the data.

The audit trail is used by inspectors to verify data quality and compliance with Good Clinical Practice (GCP), as outlined in numerous publications. A November 2020 article on Data Integrity in Global Clinical Trials: Discussions from the FDA and UK Medicines and Healthcare Products Regulatory Agency (MHRA) Workshop emphasizes the critical role of the audit trail during inspections. This article highlights how the audit trail is vital for ensuring transparency, accountability, and the proper management of clinical trial data, especially when assessing the integrity of the data collected during clinical trials.

Illustration 269 : Article - Data Integrity in Global Clinical Trials: Discussions From Joint US Food and Drug Administration and UK Medicines and Healthcare Products Regulatory Agency Good Clinical Practice Workshop

EFFECTIVE USE OF AUDIT TRAILS

Audit trails are an integral component of the electronic systems (eSystems) used in clinical trials for the capture of study data as they provide the ability to trace both data changes and system activity. Use of eSystems with well-designed and controlled audit trails can ensure GCP compliance and improve the quality of the system performance.

Source : Khin NA, Francis G, Mulinde J, Grandinetti C, Skeete R, Yu B, Ayalew K, Cho SJ, Fisher A, Kleppinger C, Ayala R, Bonapace C, Dasgupta A, Kronstein PD, Vinter S. Data Integrity in Global Clinical Trials: Discussions From Joint US Food and Drug Administration and UK Medicines and Healthcare Products Regulatory Agency Good Clinical Practice Workshop. Clin Pharmacol Ther. **2020 Nov**;108(5):949-963. doi: 10.1002/cpt.1794. Epub 2020 Mar 28. PMID: 31958142.
https://pubmed.ncbi.nlm.nih.gov/31958142/

It is crucial to conduct a comprehensive audit of the clinical trial, ideally by external auditors who are independent of any organization involved in the development and approval of the Comirnaty vaccine. This should involve delegating quality assurance teams to review all available records at the trial sites that could not be directly verified due to procedures such as Fast Track or Emergency Use, which allowed for remote monitoring. The audit should cover several key aspects:

- **Participant records**: including informed consent forms, vaccination dates, and visit logs.
- **Participant interactions**: telephone calls for symptom or adverse event reporting, as well as follow-up calls made by the center.
- **Adherence to blinding protocols**: ensuring that the decoding of products was not prematurely revealed, maintaining the integrity of the randomization process for personnel involved in the trial.
- **Product storage conditions**: verifying that vaccines were stored under the correct conditions.

- **Source documents**: reviewing all documents at the trial sites to ensure full compliance with regulatory requirements and GCP standards.

This thorough review is essential to confirm the accuracy and integrity of the data, ensuring that all trial procedures were conducted according to established guidelines and that any potential deviations are identified and addressed.

Moreover, **Safety Report** 4 [23] highlights significant variability in the number of adverse events reported across different vaccine lots. For example, **14,556 cases** were reported for lot **FD6840**, and **13,982 cases** for lot **FE6208**, as indicated in the following table:

Illustration 270 : Rapport de sécurité 4 - Problèmes liés aux lots

6.3.1.3.3. Batch-Related issues

The most frequently reported lot numbers in PM case reports (≥3000 cases) are listed in Table 41 below.

Table 41. Most Frequently Reported Lot Numbers

Lot Number[a]	Number of Cases
FD6840	14556
FE6208	13982
FD4555	11490
FD1921	9556
FD0168	9195
FF0680	6982
FC0681	5671
FF3318	5621
FC2473	5384
EJ6797	4377
EY7015	4272
FA4598	4199
EY3014	3806
FE8244	3165

a. The lots/batches reported in the table were all manufactured at Pfizer Puurs (Belgium).

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The AEs most frequently reported (≥ 4%) with these lot numbers included COVID-19 (38,033), Inappropriate schedule of product administration (19,898), Vaccination failure (19,651), Drug ineffective (18,420), Vaccination site pain (5534), Headache (3730), and Fatigue (3356). These AEs do not differ from those reported in the overall incremental dataset.

There were no safety issues related to quality identified during product complaint investigations.

Overall, the most frequently (> 40 occurrences) reported product issues regardless of lot number included the following PTs: Product temperature excursion issue (7464), Product label issue (115), Product expiration date issue (58), Product distribution issue (51), and Liquid product physical issue (42).

[23] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-june-2022-18-december-2022_en.pdf

It is therefore imperative to request that **Pfizer**:

- Provide the **lot analysis reports** for each batch of the vaccine administered.
- Supply **vials from different lots** to allow for independent analysis in order to identify potential contaminants or undeclared substances.

This step is essential to ensure the quality and safety of the vaccine, especially given the discrepancies observed in the number of reported adverse events across different lots. Independent testing can help determine if there are any variations in the vaccine formulation or manufacturing process that may contribute to these differences, and whether the vaccine meets the required safety and efficacy standards for all patients.

17 APPENDICES – Comparison Process 1 – Process 2 results

17.1 Sample 1

Table 1 : Patient s characteristics [N=504 patients] – Sample 1

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Age	N	252	252	504
	Missing	0	0	0
	Mean (s.d.)	39.2 (11.1)	40.7 (10.1)	40.0 (10.6)
	Median	41.0	42.0	42.0
	Q1 - Q3	31.0 - 48.0	34.0 - 49.0	32.5 - 49.0
	Min - Max	16.0 - 55.0	17.0 - 55.0	16.0 - 55.0
Sex	N	252	252	504
	Missing	0	0	0
	F	125 (49.6%)	106 (42.1%)	231 (45.8%)
	M	127 (50.4%)	146 (57.9%)	273 (54.2%)
Race	N	252	252	504
	Missing	0	0	0
	AMERICAN INDIAN OR ALASKA NATIVE	4 (1.6%)	0	4 (0.8%)
	ASIAN	15 (6.0%)	27 (10.7%)	42 (8.3%)
	BLACK OR AFRICAN AMERICAN	25 (9.9%)	19 (7.5%)	44 (8.7%)
	MULTIPLE	4 (1.6%)	2 (0.8%)	6 (1.2%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.4%)	0	1 (0.2%)
	NOT REPORTED	0	1 (0.4%)	1 (0.2%)
	WHITE	203 (80.6%)	203 (80.6%)	406 (80.6%)
Pooled Race Group 1	N	252	252	504
	Missing	0	0	0
	ALL OTHERS	24 (9.5%)	30 (11.9%)	54 (10.7%)
	BLACK OR AFRICAN AMERICAN	25 (9.9%)	19 (7.5%)	44 (8.7%)
	WHITE	203 (80.6%)	203 (80.6%)	406 (80.6%)
Comorbidities	N	252	252	504
	Missing	0	0	0

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
	No	202 (80.2%)	202 (80.2%)	404 (80.2%)
	Yes	**50 (19.8%)**	**50 (19.8%)**	**100 (19.8%)**
OBESE	N	252	252	504
	Missing	0	0	0
	No	164 (65.1%)	173 (68.7%)	337 (66.9%)
	Yes	88 (34.9%)	79 (31.3%)	167 (33.1%)
Japanese	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
N-binding Antibody Neg at Visit	N	252	252	504
	Missing	0	0	0
	No	9 (3.6%)	10 (4.0%)	19 (3.8%)
	Yes	243 (96.4%)	242 (96.0%)	485 (96.2%)

Table 2 : Number of events [N=504 patients] – Sample 1

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Treatment emergent AE	N	252	252	504
	Missing	0	0	0
	No	166 (65.9%)	97 (38.5%)	263 (52.2%)
	Yes	86 (34.1%)	155 (61.5%)	241 (47.8%)
Serious Adverse Event	N	252	252	504
	Missing	0	0	0
	No	247 (98.0%)	252 (100.0%)	499 (99.0%)
	Yes	5 (2.0%)	0	5 (1.0%)
AE leading to life threatening	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE leading to premature withdrawal	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE leading to death	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE related	N	252	252	504
	Missing	0	0	0
	No	186 (73.8%)	104 (41.3%)	290 (57.5%)
	Yes	66 (26.2%)	148 (58.7%)	214 (42.5%)
Grade 3 or 4	N	252	252	504
	Missing	0	0	0
	No	246 (97.6%)	252 (100.0%)	498 (98.8%)
	Yes	6 (2.4%)	0	6 (1.2%)
Persist or Signif Disability/Incapacity	N	252	252	504
	Missing	0	0	0

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
Requires or Prolongs Hospitalization	N	252	252	504
	Missing	0	0	0
	No	248 (98.4%)	252 (100.0%)	500 (99.2%)
	Yes	4 (1.6%)	0	4 (0.8%)

The FREQ Procedure

Table of TEAE by Process			
TEAE(Treatment emergent AE)	**Process**		
Frequency Percent Row Pct Col Pct	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	166 32.94 63.12 65.87	97 19.25 36.88 38.49	263 52.18
Yes	86 17.06 35.68 34.13	155 30.75 64.32 61.51	241 47.82
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of TEAE by Process

Statistic	DF	Value	Prob
Chi-Square	1	37.8578	<.0001
Likelihood Ratio Chi-Square	1	38.3506	<.0001
Continuity Adj. Chi-Square	1	36.7685	<.0001
Mantel-Haenszel Chi-Square	1	37.7827	<.0001
Phi Coefficient		0.2741	
Contingency Coefficient		0.2643	
Cramer's V		0.2741	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	166
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

The FREQ Procedure

Table of sae by Process			
sae(Serious Adverse Event)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	247 49.01 49.50 98.02	252 50.00 50.50 100.00	499 99.01
Yes	5 0.99 100.00 1.98	0 0.00 0.00 0.00	5 0.99
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of sae by Process

Statistic	DF	Value	Prob
Chi-Square	1	5.0501	0.0246
Likelihood Ratio Chi-Square	1	6.9816	0.0082
Continuity Adj. Chi-Square	1	3.2321	0.0722
Mantel-Haenszel Chi-Square	1	5.0401	0.0248
Phi Coefficient		-0.1001	
Contingency Coefficient		0.0996	
Cramer's V		-0.1001	
WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.			

Fisher's Exact Test	
Cell (1,1) Frequency (F)	247
Left-sided Pr <= F	0.0306
Right-sided Pr >= F	1.0000
Table Probability (P)	0.0306
Two-sided Pr <= P	0.0613

Sample Size = 504

The FREQ Procedure

Table of REL by Process			
REL(AE related)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	186 36.90 64.14 73.81	104 20.63 35.86 41.27	290 57.54
Yes	66 13.10 30.84 26.19	148 29.37 69.16 58.73	214 42.46
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of REL by Process

Statistic	DF	Value	Prob
Chi-Square	1	54.6068	<.0001
Likelihood Ratio Chi-Square	1	55.7440	<.0001
Continuity Adj. Chi-Square	1	53.2830	<.0001
Mantel-Haenszel Chi-Square	1	54.4984	<.0001
Phi Coefficient		0.3292	
Contingency Coefficient		0.3127	
Cramer's V		0.3292	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	186
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

By System Organ Class and Preferred Term - Long table

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
All	**All**	179	87	34.52	498	155	61.51	677	242	48.02
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**All**	3	3	1.19	2	2	0.79	5	5	0.99
	Lymph node pain	-	-	-	1	1	0.40	1	1	0.20
	Lymphadenopathy	3	3	1.19	1	1	0.40	4	4	0.79
EAR AND LABYRINTH DISORDERS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Ear discomfort	1	1	0.40	-	-	-	1	1	0.20
	Vertigo	1	1	0.40	2	2	0.79	3	3	0.60
GASTROINTESTINAL DISORDERS	**All**	10	9	3.57	17	13	5.16	27	22	4.37
	Abdominal discomfort	-	-	-	1	1	0.40	1	1	0.20
	Coeliac disease	1	1	0.40	-	-	-	1	1	0.20
	Diarrhoea	2	2	0.79	9	9	3.57	11	11	2.18
	Nausea	5	5	1.98	6	6	2.38	11	11	2.18
	Noninfective gingivitis	1	1	0.40	-	-	-	1	1	0.20
	Pancreatitis	1	1	0.40	-	-	-	1	1	0.20
	Vomiting	-	-	-	1	1	0.40	1	1	0.20
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**All**	89	56	22.22	334	140	55.56	423	196	38.89
	Chills	14	14	5.56	58	**58**	**23.02**	72	72	14.29
	Fatigue	13	13	5.16	73	**73**	**28.97**	86	86	17.06
	Feeling abnormal	-	-	-	1	1	0.40	1	1	0.20
	Influenza like illness	2	2	0.79	-	-	-	2	2	0.40
	Injection site erythema	2	2	0.79	8	8	3.17	10	10	1.98
	Injection site pain	34	34	13.49	97	**97**	**38.49**	131	131	25.99
	Injection site pruritus	1	1	0.40	-	-	-	1	1	0.20
	Injection site reaction	-	-	-	1	1	0.40	1	1	0.20
	Injection site swelling	3	3	1.19	10	**10**	**3.97**	13	13	2.58
	Malaise	2	2	0.79	5	5	1.98	7	7	1.39
	Pain	4	4	1.59	31	**31**	**12.30**	35	35	6.94
	Pyrexia	14	14	5.56	50	**50**	**19.84**	64	64	12.70
INFECTIONS AND INFESTATIONS	**All**	4	4	1.59	3	3	1.19	7	7	1.39
	Cellulitis	1	1	0.40	-	-	-	1	1	0.20
	Ear infection	-	-	-	1	1	0.40	1	1	0.20
	Sinusitis	1	1	0.40	-	-	-	1	1	0.20
	Sinusitis bacterial	1	1	0.40	-	-	-	1	1	0.20
	Upper respiratory tract infection	1	1	0.40	1	1	0.40	2	2	0.40
	Urinary tract infection	-	-	-	1	1	0.40	1	1	0.20
	All	9	8	3.17	-	-	-	9	8	1.59

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**Corneal abrasion**	1	1	0.40	-	-	-	1	1	0.20
	Exposure during pregnancy	2	2	0.79	-	-	-	2	2	0.40
	Incorrect dosage administered	1	1	0.40	-	-	-	1	1	0.20
	Product storage error	4	4	1.59	-	-	-	4	4	0.79
	Vaccination complication	1	1	0.40	-	-	-	1	1	0.20
INVESTIGATIONS	**All**	4	3	1.19	2	2	0.79	6	5	0.99
	Blood creatinine decreased	1	1	0.40	-	-	-	1	1	0.20
	Body temperature increased	1	1	0.40	2	2	0.79	3	3	0.60
	Herpes simplex test positive	1	1	0.40	-	-	-	1	1	0.20
	Low density lipoprotein increased	1	1	0.40	-	-	-	1	1	0.20
METABOLISM AND NUTRITION DISORDERS	**All**	-	-	-	2	2	0.79	2	2	0.40
	Iron deficiency	-	-	-	1	1	0.40	1	1	0.20
	Vitamin D deficiency	-	-	-	1	1	0.40	1	1	0.20
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**All**	29	26	10.32	61	52	20.63	90	78	15.48
	Arthralgia	4	4	1.59	**11**	**11**	**4.37**	15	15	2.98
	Back pain	-	-	-	1	1	0.40	1	1	0.20
	Bursitis	1	1	0.40	1	1	0.40	2	2	0.40
	Exostosis	-	-	-	1	1	0.40	1	1	0.20
	Muscle spasms	-	-	-	2	2	0.79	2	2	0.40
	Muscle twitching	-	-	-	1	1	0.40	1	1	0.20
	Myalgia	17	17	6.75	42	**42**	**16.67**	59	59	11.71
	Neck pain	1	1	0.40	1	1	0.40	2	2	0.40
	Osteoarthritis	1	1	0.40	-	-	-	1	1	0.20
	Pain in extremity	5	5	1.98	1	1	0.40	6	6	1.19
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**All**	1	1	0.40	1	1	0.40	2	2	0.40
	Benign uterine neoplasm	1	1	0.40	-	-	-	1	1	0.20
	Uterine leiomyoma	-	-	-	1	1	0.40	1	1	0.20
NERVOUS SYSTEM DISORDERS	**All**	17	17	6.75	68	64	25.40	85	81	16.07
	Dizziness	-	-	-	4	4	1.59	4	4	0.79
	Dysgeusia	-	-	-	3	3	1.19	3	3	0.60
	Headache	12	12	4.76	56	**56**	**22.22**	68	68	13.49
	Hyperaesthesia	1	1	0.40	-	-	-	1	1	0.20
	Idiopathic intracranial hypertension	1	1	0.40	-	-	-	1	1	0.20
	Lethargy	-	-	-	1	1	0.40	1	1	0.20
	Migraine	2	2	0.79	1	1	0.40	3	3	0.60

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
	Paraesthesia	-	-	-	2	2	0.79	2	2	0.40
	Parosmia	-	-	-	1	1	0.40	1	1	0.20
	Seizure	1	1	0.40	-	-	-	1	1	0.20
PRODUCT ISSUES	**All**	1	1	0.40	-	-	-	1	1	0.20
	Product temperature excursion issue	1	1	0.40	-	-	-	1	1	0.20
PSYCHIATRIC DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Depression	1	1	0.40	-	-	-	1	1	0.20
RENAL AND URINARY DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Nephrolithiasis	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Asthma	1	1	0.40	-	-	-	1	1	0.20
	Oropharyngeal pain	1	1	0.40	1	1	0.40	2	2	0.40
	Rhinorrhoea	-	-	-	1	1	0.40	1	1	0.20
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**All**	5	4	1.59	2	2	0.79	7	6	1.19
	Dermatitis contact	1	1	0.40	-	-	-	1	1	0.20
	Erythema	1	1	0.40	-	-	-	1	1	0.20
	Night sweats	-	-	-	1	1	0.40	1	1	0.20
	Pruritus	1	1	0.40	-	-	-	1	1	0.20
	Rash	2	2	0.79	-	-	-	2	2	0.40
	Urticaria	-	-	-	1	1	0.40	1	1	0.20
VASCULAR DISORDERS	**All**	1	1	0.40	2	2	0.79	3	3	0.60
	Flushing	-	-	-	1	1	0.40	1	1	0.20
	Hypertension	1	1	0.40	1	1	0.40	2	2	0.40

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

ADR Process1 vs Process 2 - Sample 1

By System Organ Class

System organ class / Preferred term [a]	BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
	NAE	N	%	NAE	N	%	NAE	N	%
All	179	87	34.52	498	155	61.51	677	242	48.02
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3	3	1.19	2	2	0.79	5	5	0.99
EAR AND LABYRINTH DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
GASTROINTESTINAL DISORDERS	10	9	3.57	17	13	5.16	27	22	4.37
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	89	56	22.22	334	140	55.56	423	196	38.89
INFECTIONS AND INFESTATIONS	4	4	1.59	3	3	1.19	7	7	1.39
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	9	8	3.17	-	-	-	9	8	1.59
INVESTIGATIONS	4	3	1.19	2	2	0.79	6	5	0.99
METABOLISM AND NUTRITION DISORDERS	-	-	-	2	2	0.79	2	2	0.40
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	29	26	10.32	61	52	20.63	90	78	15.48
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	1	0.40	1	1	0.40	2	2	0.40
NERVOUS SYSTEM DISORDERS	17	17	6.75	68	64	25.40	85	81	16.07
PRODUCT ISSUES	1	1	0.40	-	-	-	1	1	0.20
PSYCHIATRIC DISORDERS	1	1	0.40	-	-	-	1	1	0.20
RENAL AND URINARY DISORDERS	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5	4	1.59	2	2	0.79	7	6	1.19
VASCULAR DISORDERS	1	1	0.40	2	2	0.79	3	3	0.60

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

1.1 Sample 2

Table 3 : Patient s characteristics [N=504 patients] – Sample 2

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Age	N	252	252	504
	Missing	0	0	0
	Mean (s.d.)	38.7 (11.1)	40.7 (10.1)	39.7 (10.6)
	Median	39.0	42.0	41.0
	Q1 - Q3	30.0 - 49.0	34.0 - 49.0	31.0 - 49.0
	Min - Max	16.0 - 55.0	17.0 - 55.0	16.0 - 55.0
Sex	N	252	252	504
	Missing	0	0	0
	F	113 (44.8%)	106 (42.1%)	219 (43.5%)
	M	139 (55.2%)	146 (57.9%)	285 (56.5%)
Race	N	252	252	504
	Missing	0	0	0
	AMERICAN INDIAN OR ALASKA NATIVE	4 (1.6%)	0	4 (0.8%)
	ASIAN	18 (7.1%)	27 (10.7%)	45 (8.9%)
	BLACK OR AFRICAN AMERICAN	25 (9.9%)	19 (7.5%)	44 (8.7%)
	MULTIPLE	4 (1.6%)	2 (0.8%)	6 (1.2%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.4%)	0	1 (0.2%)
	NOT REPORTED	4 (1.6%)	1 (0.4%)	5 (1.0%)
	WHITE	196 (77.8%)	203 (80.6%)	399 (79.2%)
Pooled Race Group 1	N	252	252	504
	Missing	0	0	0
	ALL OTHERS	31 (12.3%)	30 (11.9%)	61 (12.1%)
	BLACK OR AFRICAN AMERICAN	25 (9.9%)	19 (7.5%)	44 (8.7%)
	WHITE	196 (77.8%)	203 (80.6%)	399 (79.2%)
Comorbidities	N	252	252	504
	Missing	0	0	0
	No	202 (80.2%)	202 (80.2%)	404 (80.2%)

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
	Yes	50 (19.8%)	50 (19.8%)	100 (19.8%)
OBESE	N	252	252	504
	Missing	0	0	0
	No	166 (65.9%)	173 (68.7%)	339 (67.3%)
	Yes	86 (34.1%)	79 (31.3%)	165 (32.7%)
Japanese	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)
N-binding Antibody Neg at Visit	N	248	252	500
	Missing	4	0	4
	No	12 (4.8%)	10 (4.0%)	22 (4.4%)
	Yes	236 (95.2%)	242 (96.0%)	478 (95.6%)

Table 4 : Number of events [N=504 patients] – Sample 2

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Treatment emergent AE	N	252	252	504
	Missing	0	0	0
	No	178 (70.6%)	97 (38.5%)	275 (54.6%)
	Yes	74 (29.4%)	155 (61.5%)	229 (45.4%)
Serious Adverse Event	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE leading to life threatening	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE leading to premature withdrawal	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)
AE leading to death	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE related	N	252	252	504
	Missing	0	0	0
	No	199 (79.0%)	104 (41.3%)	303 (60.1%)
	Yes	53 (21.0%)	148 (58.7%)	201 (39.9%)
Grade 3 or 4	N	252	252	504
	Missing	0	0	0
	No	249 (98.8%)	252 (100.0%)	501 (99.4%)
	Yes	3 (1.2%)	0	3 (0.6%)

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Persist or Signif Disability/Incapacity	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
Requires or Prolongs Hospitalization	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)

The FREQ Procedure

Table of TEAE by Process			
TEAE(Treatment emergent AE)	**Process**		
Frequency Percent Row Pct Col Pct	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	178 35.32 64.73 70.63	97 19.25 35.27 38.49	275 54.56
Yes	74 14.68 32.31 29.37	155 30.75 67.69 61.51	229 45.44
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of TEAE by Process

Statistic	DF	Value	Prob
Chi-Square	1	52.5088	<.0001
Likelihood Ratio Chi-Square	1	53.4959	<.0001
Continuity Adj. Chi-Square	1	51.2203	<.0001
Mantel-Haenszel Chi-Square	1	52.4047	<.0001
Phi Coefficient		0.3228	
Contingency Coefficient		0.3072	
Cramer's V		0.3228	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	178
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

The FREQ Procedure

Table of REL by Process			
REL(AE related)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	199 39.48 65.68 78.97	104 20.63 34.32 41.27	303 60.12
Yes	53 10.52 26.37 21.03	148 29.37 73.63 58.73	201 39.88
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of REL by Process

Statistic	DF	Value	Prob
Chi-Square	1	74.6860	<.0001
Likelihood Ratio Chi-Square	1	77.0361	<.0001
Continuity Adj. Chi-Square	1	73.1219	<.0001
Mantel-Haenszel Chi-Square	1	74.5378	<.0001
Phi Coefficient		0.3849	
Contingency Coefficient		0.3593	
Cramer's V		0.3849	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	199
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

ADR Process1 vs Process 2 - Sample 2
By System Organ Class and Preferred Term - Long table

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
All	**All**	185	74	29.37	498	155	61.51	683	229	45.44
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**All**	1	1	0.40	2	2	0.79	3	3	0.60
	Lymph node pain	-	-	-	1	1	0.40	1	1	0.20
	Lymphadenopathy	1	1	0.40	1	1	0.40	2	2	0.40
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Benign familial pemphigus	1	1	0.40	-	-	-	1	1	0.20
EAR AND LABYRINTH DISORDERS	**All**	-	-	-	2	2	0.79	2	2	0.40
	Vertigo	-	-	-	2	2	0.79	2	2	0.40
EYE DISORDERS	**All**	2	2	0.79	-	-	-	2	2	0.40
	Eye irritation	1	1	0.40	-	-	-	1	1	0.20
	Glaucoma	1	1	0.40	-	-	-	1	1	0.20
GASTROINTESTINAL DISORDERS	**All**	10	7	2.78	17	13	5.16	27	20	3.97
	Abdominal discomfort	-	-	-	1	1	0.40	1	1	0.20
	Diarrhoea	3	3	1.19	**9**	**9**	**3.57**	12	12	2.38
	Food poisoning	1	1	0.40	-	-	-	1	1	0.20
	Intra-abdominal fluid collection	1	1	0.40	-	-	-	1	1	0.20
	Nausea	4	4	1.59	6	6	2.38	10	10	1.98
	Vomiting	1	1	0.40	1	1	0.40	2	2	0.40
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**All**	106	52	20.63	**334**	**140**	**55.56**	440	192	38.10
	Chills	26	26	10.32	**58**	**58**	**23.02**	84	84	16.67
	Fatigue	17	17	6.75	**73**	**73**	**28.97**	90	90	17.86
	Feeling abnormal	-	-	-	1	1	0.40	1	1	0.20
	Injection site erythema	3	3	1.19	8	8	3.17	11	11	2.18
	Injection site pain	35	35	13.89	**97**	**97**	**38.49**	132	132	26.19
	Injection site pruritus	1	1	0.40	-	-	-	1	1	0.20
	Injection site reaction	-	-	-	1	1	0.40	1	1	0.20
	Injection site swelling	-	-	-	10	10	3.97	10	10	1.98
	Malaise	-	-	-	5	5	1.98	5	5	0.99
	Pain	10	10	3.97	**31**	**31**	**12.30**	41	41	8.13
	Pyrexia	14	14	5.56	**50**	**50**	**19.84**	64	64	12.70
INFECTIONS AND INFESTATIONS	**All**	1	1	0.40	3	3	1.19	4	4	0.79
	Bacterial vulvovaginitis	1	1	0.40	-	-	-	1	1	0.20
	Ear infection	-	-	-	1	1	0.40	1	1	0.20
	Upper respiratory tract infection	-	-	-	1	1	0.40	1	1	0.20
	Urinary tract infection	-	-	-	1	1	0.40	1	1	0.20

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**All**	11	10	3.97	-	-	-	11	10	1.98
	Concussion	1	1	0.40	-	-	-	1	1	0.20
	Exposure during pregnancy	3	3	1.19	-	-	-	3	3	0.60
	Foreign body in eye	1	1	0.40	-	-	-	1	1	0.20
	Incorrect dosage administered	2	2	0.79	-	-	-	2	2	0.40
	Ligament sprain	1	1	0.40	-	-	-	1	1	0.20
	Product storage error	2	2	0.79	-	-	-	2	2	0.40
	Road traffic accident	1	1	0.40	-	-	-	1	1	0.20
INVESTIGATIONS	**All**	4	4	1.59	2	2	0.79	6	6	1.19
	Blood cholesterol increased	2	2	0.79	-	-	-	2	2	0.40
	Blood pressure increased	1	1	0.40	-	-	-	1	1	0.20
	Body temperature increased	1	1	0.40	2	2	0.79	3	3	0.60
METABOLISM AND NUTRITION DISORDERS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Diabetes mellitus	1	1	0.40	-	-	-	1	1	0.20
	Hypercholesterolaemia	1	1	0.40	-	-	-	1	1	0.20
	Iron deficiency	-	-	-	1	1	0.40	1	1	0.20
	Vitamin D deficiency	-	-	-	1	1	0.40	1	1	0.20
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**All**	19	16	6.35	**61**	**52**	**20.63**	80	68	13.49
	Arthralgia	2	2	0.79	11	11	4.37	13	13	2.58
	Back pain	3	3	1.19	1	1	0.40	4	4	0.79
	Bursitis	-	-	-	1	1	0.40	1	1	0.20
	Exostosis	1	1	0.40	1	1	0.40	2	2	0.40
	Muscle spasms	1	1	0.40	2	2	0.79	3	3	0.60
	Muscle twitching	-	-	-	1	1	0.40	1	1	0.20
	Myalgia	10	10	3.97	**42**	**42**	**16.67**	52	52	10.32
	Neck pain	1	1	0.40	1	1	0.40	2	2	0.40
	Pain in extremity	-	-	-	1	1	0.40	1	1	0.20
	Synovial cyst	1	1	0.40	-	-	-	1	1	0.20
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**All**	-	-	-	1	1	0.40	1	1	0.20
	Uterine leiomyoma	-	-	-	1	1	0.40	1	1	0.20
NERVOUS SYSTEM DISORDERS	**All**	23	22	8.73	68	64	25.40	91	86	17.06
	Dizziness	-	-	-	4	4	1.59	4	4	0.79
	Dysgeusia	-	-	-	3	3	1.19	3	3	0.60
	Headache	18	18	7.14	**56**	**56**	**22.22**	74	74	14.68
	Lethargy	-	-	-	1	1	0.40	1	1	0.20
	Migraine	2	2	0.79	1	1	0.40	3	3	0.60
	Paraesthesia	1	1	0.40	2	2	0.79	3	3	0.60
	Parosmia	-	-	-	1	1	0.40	1	1	0.20

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
	Seizure like phenomena	1	1	0.40	-	-	-	1	1	0.20
	Tension headache	1	1	0.40	-	-	-	1	1	0.20
PSYCHIATRIC DISORDERS	**All**	2	2	0.79	-	-	-	2	2	0.40
	Depression	1	1	0.40	-	-	-	1	1	0.20
	Sleep disorder	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**All**	1	1	0.40	2	2	0.79	3	3	0.60
	Oropharyngeal pain	-	-	-	1	1	0.40	1	1	0.20
	Rhinorrhoea	1	1	0.40	1	1	0.40	2	2	0.40
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Diabetic foot	1	1	0.40	-	-	-	1	1	0.20
	Night sweats	-	-	-	1	1	0.40	1	1	0.20
	Rash	1	1	0.40	-	-	-	1	1	0.20
	Urticaria	-	-	-	1	1	0.40	1	1	0.20
VASCULAR DISORDERS	**All**	-	-	-	2	2	0.79	2	2	0.40
	Flushing	-	-	-	1	1	0.40	1	1	0.20
	Hypertension	-	-	-	1	1	0.40	1	1	0.20

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

ADR Process1 vs Process 2 - Sample 2
By System Organ Class

System organ class / Preferred term [a]	BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
	NAE	N	%	NAE	N	%	NAE	N	%
All	185	74	29.37	498	155	61.51	683	229	45.44
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	1	0.40	2	2	0.79	3	3	0.60
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1	1	0.40	-	-	-	1	1	0.20
EAR AND LABYRINTH DISORDERS	-	-	-	2	2	0.79	2	2	0.40
EYE DISORDERS	2	2	0.79	-	-	-	2	2	0.40
GASTROINTESTINAL DISORDERS	10	7	2.78	17	13	5.16	27	20	3.97
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	106	52	20.63	334	140	55.56	440	192	38.10
INFECTIONS AND INFESTATIONS	1	1	0.40	3	3	1.19	4	4	0.79
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11	10	3.97	-	-	-	11	10	1.98
INVESTIGATIONS	4	4	1.59	2	2	0.79	6	6	1.19
METABOLISM AND NUTRITION DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	19	16	6.35	61	52	20.63	80	68	13.49
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	-	-	-	1	1	0.40	1	1	0.20
NERVOUS SYSTEM DISORDERS	23	22	8.73	68	64	25.40	91	86	17.06
PSYCHIATRIC DISORDERS	2	2	0.79	-	-	-	2	2	0.40
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	1	0.40	2	2	0.79	3	3	0.60
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
VASCULAR DISORDERS	-	-	-	2	2	0.79	2	2	0.40

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

1.2 Sample 3

ADR Process1 vs Process 2 - Sample 3
Patient s characteristics

Table 5 : Patient s characteristics [N=504 patients]

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Age	N	252	252	504
	Missing	0	0	0
	Mean (s.d.)	39.2 (10.9)	40.7 (10.1)	39.9 (10.5)
	Median	40.0	42.0	41.0
	Q1 - Q3	31.5 - 48.0	34.0 - 49.0	33.0 - 49.0
	Min - Max	16.0 - 55.0	17.0 - 55.0	16.0 - 55.0
Sex	N	252	252	504
	Missing	0	0	0
	F	106 (42.1%)	106 (42.1%)	212 (42.1%)
	M	146 (57.9%)	146 (57.9%)	292 (57.9%)
Race	N	252	252	504
	Missing	0	0	0
	AMERICAN INDIAN OR ALASKA NATIVE	8 (3.2%)	0	8 (1.6%)
	ASIAN	19 (7.5%)	27 (10.7%)	46 (9.1%)
	BLACK OR AFRICAN AMERICAN	30 (11.9%)	19 (7.5%)	49 (9.7%)
	MULTIPLE	0	2 (0.8%)	2 (0.4%)
	NOT REPORTED	4 (1.6%)	1 (0.4%)	5 (1.0%)
	WHITE	191 (75.8%)	203 (80.6%)	394 (78.2%)
Pooled Race Group 1	N	252	252	504
	Missing	0	0	0
	ALL OTHERS	31 (12.3%)	30 (11.9%)	61 (12.1%)
	BLACK OR AFRICAN AMERICAN	30 (11.9%)	19 (7.5%)	49 (9.7%)
	WHITE	191 (75.8%)	203 (80.6%)	394 (78.2%)
Comorbidities	N	252	252	504
	Missing	0	0	0

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
	No	220 (87.3%)	202 (80.2%)	422 (83.7%)
	Yes	32 (12.7%)	50 (19.8%)	82 (16.3%)
OBESE	N	252	252	504
	Missing	0	0	0
	No	158 (62.7%)	173 (68.7%)	331 (65.7%)
	Yes	94 (37.3%)	79 (31.3%)	173 (34.3%)
Japanese	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)
N-binding Antibody Neg at Visit	N	252	252	504
	Missing	0	0	0
	No	11 (4.4%)	10 (4.0%)	21 (4.2%)
	Yes	241 (95.6%)	242 (96.0%)	483 (95.8%)

ADR Process1 vs Process 2 - Sample 3

Outcomes

Table 6 : Number of events [N=504 patients]

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Treatment emergent AE	N	252	252	504
	Missing	0	0	0
	No	178 (70.6%)	97 (38.5%)	275 (54.6%)
	Yes	74 (29.4%)	155 (61.5%)	229 (45.4%)
Serious Adverse Event	N	252	252	504
	Missing	0	0	0
	No	250 (99.2%)	252 (100.0%)	502 (99.6%)
	Yes	2 (0.8%)	0	2 (0.4%)
AE leading to life threatening	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE leading to premature withdrawal	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)
AE leading to death	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE related	N	252	252	504
	Missing	0	0	0
	No	198 (78.6%)	104 (41.3%)	302 (59.9%)
	Yes	54 (21.4%)	148 (58.7%)	202 (40.1%)
Grade 3 or 4	N	252	252	504
	Missing	0	0	0
	No	248 (98.4%)	252 (100.0%)	500 (99.2%)
	Yes	4 (1.6%)	0	4 (0.8%)

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Persist or Signif Disability/Incapacity	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
Requires or Prolongs Hospitalization	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)

The FREQ Procedure

Table of TEAE by Process			
TEAE(Treatment emergent AE)	**Process**		
Frequency Percent Row Pct Col Pct	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	178 35.32 64.73 70.63	97 19.25 35.27 38.49	275 54.56
Yes	74 14.68 32.31 29.37	155 30.75 67.69 61.51	229 45.44
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of TEAE by Process

Statistic	DF	Value	Prob
Chi-Square	1	52.5088	<.0001
Likelihood Ratio Chi-Square	1	53.4959	<.0001
Continuity Adj. Chi-Square	1	51.2203	<.0001
Mantel-Haenszel Chi-Square	1	52.4047	<.0001
Phi Coefficient		0.3228	
Contingency Coefficient		0.3072	
Cramer's V		0.3228	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	178
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

The FREQ Procedure

Table of sae by Process			
sae(Serious Adverse Event)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	250 49.60 49.80 99.21	252 50.00 50.20 100.00	502 99.60
Yes	2 0.40 100.00 0.79	0 0.00 0.00 0.00	2 0.40
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of sae by Process

Statistic	DF	Value	Prob
Chi-Square	1	2.0080	0.1565
Likelihood Ratio Chi-Square	1	2.7806	0.0954
Continuity Adj. Chi-Square	1	0.5020	0.4786
Mantel-Haenszel Chi-Square	1	2.0040	0.1569
Phi Coefficient		-0.0631	
Contingency Coefficient		0.0630	
Cramer's V		-0.0631	
WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.			

Fisher's Exact Test	
Cell (1,1) Frequency (F)	250
Left-sided Pr <= F	0.2495
Right-sided Pr >= F	1.0000
Table Probability (P)	0.2495
Two-sided Pr <= P	0.4990

Sample Size = 504

The FREQ Procedure

Table of REL by Process			
REL(AE related)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	198 39.29 65.56 78.57	104 20.63 34.44 41.27	302 59.92
Yes	54 10.71 26.73 21.43	148 29.37 73.27 58.73	202 40.08
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of REL by Process

Statistic	DF	Value	Prob
Chi-Square	1	73.0009	<.0001
Likelihood Ratio Chi-Square	1	75.2265	<.0001
Continuity Adj. Chi-Square	1	71.4559	<.0001
Mantel-Haenszel Chi-Square	1	72.8560	<.0001
Phi Coefficient		0.3806	
Contingency Coefficient		0.3557	
Cramer's V		0.3806	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	198
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

ADR Process1 vs Process 2 - Sample 3

By System Organ Class and Preferred Term - Long table

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
All	**All**	163	74	29.37	498	155	61.51	661	229	45.44
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Lymph node pain	-	-	-	1	1	0.40	1	1	0.20
	Lymphadenopathy	2	2	0.79	1	1	0.40	3	3	0.60
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Congenital cystic kidney disease	1	1	0.40	-	-	-	1	1	0.20
EAR AND LABYRINTH DISORDERS	**All**	-	-	-	2	2	0.79	2	2	0.40
	Vertigo	-	-	-	2	2	0.79	2	2	0.40
GASTROINTESTINAL DISORDERS	**All**	13	10	3.97	17	13	5.16	30	23	4.56
	Abdominal discomfort	-	-	-	1	1	0.40	1	1	0.20
	Abdominal pain	1	1	0.40	-	-	-	1	1	0.20
	Diarrhoea	4	4	1.59	9	9	3.57	13	13	2.58
	Nausea	5	5	1.98	6	6	2.38	11	11	2.18
	Toothache	1	1	0.40	-	-	-	1	1	0.20
	Vomiting	2	2	0.79	1	1	0.40	3	3	0.60
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**All**	84	42	16.67	334	140	55.56	418	182	36.11
	Chills	18	18	7.14	**58**	**58**	**23.02**	76	76	15.08
	Fatigue	15	15	5.95	**73**	**73**	**28.97**	88	88	17.46
	Feeling abnormal	-	-	-	1	1	0.40	1	1	0.20
	Feeling cold	1	1	0.40	-	-	-	1	1	0.20
	Injection site erythema	2	2	0.79	**8**	**8**	**3.17**	10	10	1.98
	Injection site pain	20	20	7.94	**97**	**97**	**38.49**	117	117	23.21
	Injection site pruritus	1	1	0.40	-	-	-	1	1	0.20
	Injection site reaction	-	-	-	1	1	0.40	1	1	0.20
	Injection site swelling	1	1	0.40	**10**	**10**	**3.97**	11	11	2.18
	Malaise	-	-	-	**5**	**5**	**1.98**	5	5	0.99
	Pain	6	6	2.38	**31**	**31**	**12.30**	37	37	7.34
	Pyrexia	20	20	7.94	**50**	**50**	**19.84**	70	70	13.89
HEPATOBILIARY DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Cholecystitis acute	1	1	0.40	-	-	-	1	1	0.20
INFECTIONS AND INFESTATIONS	**All**	2	2	0.79	3	3	1.19	5	5	0.99
	Ear infection	1	1	0.40	1	1	0.40	2	2	0.40
	Upper respiratory tract infection	1	1	0.40	1	1	0.40	2	2	0.40
	Urinary tract infection	-	-	-	1	1	0.40	1	1	0.20
	All	12	9	3.57	-	-	-	12	9	1.79
	Chest injury	1	1	0.40	-	-	-	1	1	0.20

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**Contusion**	1	1	0.40	-	-	-	1	1	0.20
	Fall	1	1	0.40	-	-	-	1	1	0.20
	Hip fracture	1	1	0.40	-	-	-	1	1	0.20
	Product administration error	1	1	0.40	-	-	-	1	1	0.20
	Product storage error	2	2	0.79	-	-	-	2	2	0.40
	Road traffic accident	1	1	0.40	-	-	-	1	1	0.20
	Skin laceration	1	1	0.40	-	-	-	1	1	0.20
	Tooth fracture	1	1	0.40	-	-	-	1	1	0.20
	Vaccination complication	1	1	0.40	-	-	-	1	1	0.20
	Wrong product administered	1	1	0.40	-	-	-	1	1	0.20
INVESTIGATIONS	**All**	1	1	0.40	2	2	0.79	3	3	0.60
	Blood cholesterol increased	1	1	0.40	-	-	-	1	1	0.20
	Body temperature increased	-	-	-	2	2	0.79	2	2	0.40
METABOLISM AND NUTRITION DISORDERS	**All**	5	3	1.19	2	2	0.79	7	5	0.99
	Decreased appetite	1	1	0.40	-	-	-	1	1	0.20
	Folate deficiency	1	1	0.40	-	-	-	1	1	0.20
	Gout	1	1	0.40	-	-	-	1	1	0.20
	Iron deficiency	-	-	-	1	1	0.40	1	1	0.20
	Vitamin B12 deficiency	1	1	0.40	-	-	-	1	1	0.20
	Vitamin D deficiency	1	1	0.40	1	1	0.40	2	2	0.40
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**All**	17	17	6.75	61	52	20.63	78	69	13.69
	Arthralgia	3	3	1.19	**11**	**11**	**4.37**	14	14	2.78
	Back pain	-	-	-	1	1	0.40	1	1	0.20
	Bursitis	1	1	0.40	1	1	0.40	2	2	0.40
	Coccydynia	1	1	0.40	-	-	-	1	1	0.20
	Exostosis	-	-	-	1	1	0.40	1	1	0.20
	Muscle spasms	-	-	-	2	2	0.79	2	2	0.40
	Muscle twitching	-	-	-	1	1	0.40	1	1	0.20
	Myalgia	8	8	3.17	**42**	**42**	**16.67**	50	50	9.92
	Neck pain	-	-	-	1	1	0.40	1	1	0.20
	Pain in extremity	4	4	1.59	1	1	0.40	5	5	0.99
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**All**	2	2	0.79	1	1	0.40	3	3	0.60
	Adenocarcinoma gastric	1	1	0.40	-	-	-	1	1	0.20
	Benign uterine neoplasm	1	1	0.40	-	-	-	1	1	0.20
	Uterine leiomyoma	-	-	-	1	1	0.40	1	1	0.20
	All	15	14	5.56	68	64	25.40	83	78	15.48

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
NERVOUS SYSTEM DISORDERS	Cervical radiculopathy	1	1	0.40	-	-	-	1	1	0.20
	Dizziness	-	-	-	4	4	1.59	4	4	0.79
	Dysgeusia	-	-	-	3	3	1.19	3	3	0.60
	Headache	12	12	4.76	**56**	**56**	**22.22**	68	68	13.49
	Lethargy	-	-	-	1	1	0.40	1	1	0.20
	Migraine	-	-	-	1	1	0.40	1	1	0.20
	Paraesthesia	1	1	0.40	2	2	0.79	3	3	0.60
	Parosmia	-	-	-	1	1	0.40	1	1	0.20
	Somnolence	1	1	0.40	-	-	-	1	1	0.20
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	All	1	1	0.40	-	-	-	1	1	0.20
	Exposure during pregnancy	1	1	0.40	-	-	-	1	1	0.20
PSYCHIATRIC DISORDERS	All	2	2	0.79	-	-	-	2	2	0.40
	Abnormal dreams	1	1	0.40	-	-	-	1	1	0.20
	Irritability	1	1	0.40	-	-	-	1	1	0.20
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	All	1	1	0.40	-	-	-	1	1	0.20
	Dysmenorrhoea	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	All	2	2	0.79	2	2	0.79	4	4	0.79
	Dyspnoea	2	2	0.79	-	-	-	2	2	0.40
	Oropharyngeal pain	-	-	-	1	1	0.40	1	1	0.20
	Rhinorrhoea	-	-	-	1	1	0.40	1	1	0.20
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	All	-	-	-	2	2	0.79	2	2	0.40
	Night sweats	-	-	-	1	1	0.40	1	1	0.20
	Urticaria	-	-	-	1	1	0.40	1	1	0.20
SURGICAL AND MEDICAL PROCEDURES	All	1	1	0.40	-	-	-	1	1	0.20
	Wisdom teeth removal	1	1	0.40	-	-	-	1	1	0.20
VASCULAR DISORDERS	All	1	1	0.40	2	2	0.79	3	3	0.60
	Flushing	-	-	-	1	1	0.40	1	1	0.20
	Hypertension	1	1	0.40	1	1	0.40	2	2	0.40

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

ADR Process1 vs Process 2 - Sample 3

By System Organ Class

System organ class / Preferred term [a]	BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
	NAE	N	%	NAE	N	%	NAE	N	%
All	163	74	29.37	498	155	61.51	661	229	45.44
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1	1	0.40	-	-	-	1	1	0.20
EAR AND LABYRINTH DISORDERS	-	-	-	2	2	0.79	2	2	0.40
GASTROINTESTINAL DISORDERS	13	10	3.97	17	13	5.16	30	23	4.56
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	84	42	16.67	334	140	55.56	418	182	36.11
HEPATOBILIARY DISORDERS	1	1	0.40	-	-	-	1	1	0.20
INFECTIONS AND INFESTATIONS	2	2	0.79	3	3	1.19	5	5	0.99
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	12	9	3.57	-	-	-	12	9	1.79
INVESTIGATIONS	1	1	0.40	2	2	0.79	3	3	0.60
METABOLISM AND NUTRITION DISORDERS	5	3	1.19	2	2	0.79	7	5	0.99
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	17	17	6.75	61	52	20.63	78	69	13.69
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2	2	0.79	1	1	0.40	3	3	0.60
NERVOUS SYSTEM DISORDERS	15	14	5.56	68	64	25.40	83	78	15.48
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1	1	0.40	-	-	-	1	1	0.20
PSYCHIATRIC DISORDERS	2	2	0.79	-	-	-	2	2	0.40
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	-	-	-	2	2	0.79	2	2	0.40
SURGICAL AND MEDICAL PROCEDURES	1	1	0.40	-	-	-	1	1	0.20
VASCULAR DISORDERS	1	1	0.40	2	2	0.79	3	3	0.60

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

1.3 Sample 4

ADR Process1 vs Process 2 - Sample 4
Patient s characteristics

Table 7 : Patient s characteristics [N=504 patients]

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Age	N	252	252	504
	Missing	0	0	0
	Mean (s.d.)	39.4 (11.1)	40.7 (10.1)	40.1 (10.6)
	Median	42.0	42.0	42.0
	Q1 - Q3	30.0 - 49.0	34.0 - 49.0	32.0 - 49.0
	Min - Max	16.0 - 55.0	17.0 - 55.0	16.0 - 55.0
Sex	N	252	252	504
	Missing	0	0	0
	F	106 (42.1%)	106 (42.1%)	212 (42.1%)
	M	146 (57.9%)	146 (57.9%)	292 (57.9%)
Race	N	252	252	504
	Missing	0	0	0
	AMERICAN INDIAN OR ALASKA NATIVE	9 (3.6%)	0	9 (1.8%)
	ASIAN	17 (6.7%)	27 (10.7%)	44 (8.7%)
	BLACK OR AFRICAN AMERICAN	28 (11.1%)	19 (7.5%)	47 (9.3%)
	MULTIPLE	4 (1.6%)	2 (0.8%)	6 (1.2%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.4%)	0	1 (0.2%)
	NOT REPORTED	2 (0.8%)	1 (0.4%)	3 (0.6%)
	WHITE	191 (75.8%)	203 (80.6%)	394 (78.2%)
Pooled Race Group 1	N	252	252	504
	Missing	0	0	0
	ALL OTHERS	33 (13.1%)	30 (11.9%)	63 (12.5%)
	BLACK OR AFRICAN AMERICAN	28 (11.1%)	19 (7.5%)	47 (9.3%)
	WHITE	191 (75.8%)	203 (80.6%)	394 (78.2%)

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Comorbidities	N	252	252	504
	Missing	0	0	0
	No	213 (84.5%)	202 (80.2%)	415 (82.3%)
	Yes	39 (15.5%)	50 (19.8%)	89 (17.7%)
OBESE	N	252	252	504
	Missing	0	0	0
	No	163 (64.7%)	173 (68.7%)	336 (66.7%)
	Yes	89 (35.3%)	79 (31.3%)	168 (33.3%)
Japanese	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
N-binding Antibody Neg at Visit	N	250	252	502
	Missing	2	0	2
	No	9 (3.6%)	10 (4.0%)	19 (3.8%)
	Yes	241 (96.4%)	242 (96.0%)	483 (96.2%)

Table 8 : Number of events [N=504 patients]

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Treatment emergent AE	N	252	252	504
	Missing	0	0	0
	No	175 (69.4%)	97 (38.5%)	272 (54.0%)
	Yes	77 (30.6%)	155 (61.5%)	232 (46.0%)
Serious Adverse Event	N	252	252	504
	Missing	0	0	0
	No	250 (99.2%)	252 (100.0%)	502 (99.6%)
	Yes	2 (0.8%)	0	2 (0.4%)
AE leading to life threatening	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE leading to premature withdrawal	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE leading to death	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE related	N	252	252	504
	Missing	0	0	0
	No	191 (75.8%)	104 (41.3%)	295 (58.5%)
	Yes	61 (24.2%)	148 (58.7%)	209 (41.5%)
SAE related	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
Death related	N	252	252	504

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
Grade 3 or 4	N	252	252	504
	Missing	0	0	0
	No	250 (99.2%)	252 (100.0%)	502 (99.6%)
	Yes	2 (0.8%)	0	2 (0.4%)
Persist or Signif Disability/Incapacity	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
Requires or Prolongs Hospitalization	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)

ADR Process1 vs Process 2 - Sample 4

Outcomes

The FREQ Procedure

Table of TEAE by Process			
TEAE(Treatment emergent AE)	**Process**		
Frequency Percent Row Pct Col Pct	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	175 34.72 64.34 69.44	97 19.25 35.66 38.49	272 53.97
Yes	77 15.28 33.19 30.56	155 30.75 66.81 61.51	232 46.03
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of TEAE by Process

Statistic	DF	Value	Prob
Chi-Square	1	48.5918	<.0001
Likelihood Ratio Chi-Square	1	49.4267	<.0001
Continuity Adj. Chi-Square	1	47.3538	<.0001
Mantel-Haenszel Chi-Square	1	48.4954	<.0001
Phi Coefficient		0.3105	
Contingency Coefficient		0.2965	
Cramer's V		0.3105	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	175
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

ADR Process1 vs Process 2 - Sample 4

Outcomes

The FREQ Procedure

Table of sae by Process			
sae(Serious Adverse Event)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	250 49.60 49.80 99.21	252 50.00 50.20 100.00	502 99.60
Yes	2 0.40 100.00 0.79	0 0.00 0.00 0.00	2 0.40
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of sae by Process

Statistic	DF	Value	Prob
Chi-Square	1	2.0080	0.1565
Likelihood Ratio Chi-Square	1	2.7806	0.0954
Continuity Adj. Chi-Square	1	0.5020	0.4786
Mantel-Haenszel Chi-Square	1	2.0040	0.1569
Phi Coefficient		-0.0631	
Contingency Coefficient		0.0630	
Cramer's V		-0.0631	
WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.			

Fisher's Exact Test	
Cell (1,1) Frequency (F)	250
Left-sided Pr <= F	0.2495
Right-sided Pr >= F	1.0000
Table Probability (P)	0.2495
Two-sided Pr <= P	0.4990

Sample Size = 504

The FREQ Procedure

Table of LifeThreat by Process			
LifeThreat(AE leading to life threatening)	**Process**		
Frequency **Percent** **Row Pct** **Col Pct**	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	252 50.00 50.00 100.00	252 50.00 50.00 100.00	504 100.00
Total	252 50.00	252 50.00	504 100.00

Outcomes

The FREQ Procedure

Table of REL by Process			
REL(AE related)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	191 37.90 64.75 75.79	104 20.63 35.25 41.27	295 58.53
Yes	61 12.10 29.19 24.21	148 29.37 70.81 58.73	209 41.47
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of REL by Process

Statistic	DF	Value	Prob
Chi-Square	1	61.8729	<.0001
Likelihood Ratio Chi-Square	1	63.3844	<.0001
Continuity Adj. Chi-Square	1	60.4587	<.0001
Mantel-Haenszel Chi-Square	1	61.7502	<.0001
Phi Coefficient		0.3504	
Contingency Coefficient		0.3307	
Cramer's V		0.3504	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	191
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

ADR Process1 vs Process 2 - Sample 4

By System Organ Class and Preferred Term - Long table

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
All	All	192	78	30.95	498	155	61.51	690	233	46.23
BLOOD AND LYMPHATIC SYSTEM DISORDERS	All	2	2	0.79	2	2	0.79	4	4	0.79
	Lymph node pain	-	-	-	1	1	0.40	1	1	0.20
	Lymphadenopathy	2	2	0.79	1	1	0.40	3	3	0.60
EAR AND LABYRINTH DISORDERS	All	3	3	1.19	2	2	0.79	5	5	0.99
	Ear pain	1	1	0.40	-	-	-	1	1	0.20
	Tinnitus	1	1	0.40	-	-	-	1	1	0.20
	Vertigo	1	1	0.40	2	2	0.79	3	3	0.60
GASTROINTESTINAL DISORDERS	All	13	8	3.17	17	13	5.16	30	21	4.17
	Abdominal discomfort	-	-	-	1	1	0.40	1	1	0.20
	Abdominal pain	1	1	0.40	-	-	-	1	1	0.20
	Abdominal pain upper	2	2	0.79	-	-	-	2	2	0.40
	Aphthous ulcer	1	1	0.40	-	-	-	1	1	0.20
	Constipation	2	2	0.79	-	-	-	2	2	0.40
	Diarrhoea	1	1	0.40	9	9	3.57	10	10	1.98
	Flatulence	1	1	0.40	-	-	-	1	1	0.20
	Gastrointestinal disorder	1	1	0.40	-	-	-	1	1	0.20
	Nausea	3	3	1.19	6	6	2.38	9	9	1.79
	Vomiting	1	1	0.40	1	1	0.40	2	2	0.40
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	All	108	54	21.43	334	140	55.56	442	194	38.49
	Chest discomfort	1	1	0.40	-	-	-	1	1	0.20
	Chills	23	23	9.13	58	58	23.02	81	81	16.07
	Fatigue	17	17	6.75	73	73	28.97	90	90	17.86
	Feeling abnormal	-	-	-	1	1	0.40	1	1	0.20
	Injection site erythema	3	3	1.19	8	8	3.17	11	11	2.18
	Injection site pain	32	32	12.70	97	97	38.49	129	129	25.60
	Injection site reaction	-	-	-	1	1	0.40	1	1	0.20
	Injection site swelling	2	2	0.79	10	10	3.97	12	12	2.38
	Malaise	3	3	1.19	5	5	1.98	8	8	1.59
	Pain	11	11	4.37	31	31	12.30	42	42	8.33
	Pyrexia	15	15	5.95	50	50	19.84	65	65	12.90
	Sensation of foreign body	1	1	0.40	-	-	-	1	1	0.20
HEPATOBILIARY DISORDERS	All	1	1	0.40	-	-	-	1	1	0.20
	Cholecystitis	1	1	0.40	-	-	-	1	1	0.20
INFECTIONS AND INFESTATIONS	All	4	3	1.19	3	3	1.19	7	6	1.19
	Ear infection	-	-	-	1	1	0.40	1	1	0.20

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
	Hordeolum	1	1	0.40	-	-	-	1	1	0.20
	Nasopharyngitis	1	1	0.40	-	-	-	1	1	0.20
	Upper respiratory tract infection	1	1	0.40	1	1	0.40	2	2	0.40
	Urinary tract infection	1	1	0.40	1	1	0.40	2	2	0.40
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**All**	5	4	1.59	-	-	-	5	4	0.79
	Exposure during pregnancy	1	1	0.40	-	-	-	1	1	0.20
	Muscle strain	1	1	0.40	-	-	-	1	1	0.20
	Product storage error	2	2	0.79	-	-	-	2	2	0.40
	Thermal burn	1	1	0.40	-	-	-	1	1	0.20
INVESTIGATIONS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Blood pressure increased	1	1	0.40	-	-	-	1	1	0.20
	Body temperature increased	1	1	0.40	2	2	0.79	3	3	0.60
METABOLISM AND NUTRITION DISORDERS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Glucose tolerance impaired	1	1	0.40	-	-	-	1	1	0.20
	Hyperlipidaemia	1	1	0.40	-	-	-	1	1	0.20
	Iron deficiency	-	-	-	1	1	0.40	1	1	0.20
	Vitamin D deficiency	-	-	-	1	1	0.40	1	1	0.20
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**All**	27	26	10.32	61	52	20.63	88	78	15.48
	Arthralgia	4	4	1.59	11	11	4.37	15	15	2.98
	Back pain	-	-	-	1	1	0.40	1	1	0.20
	Bursitis	1	1	0.40	1	1	0.40	2	2	0.40
	Exostosis	-	-	-	1	1	0.40	1	1	0.20
	Muscle spasms	1	1	0.40	2	2	0.79	3	3	0.60
	Muscle twitching	-	-	-	1	1	0.40	1	1	0.20
	Musculoskeletal chest pain	1	1	0.40	-	-	-	1	1	0.20
	Myalgia	17	17	6.75	42	42	16.67	59	59	11.71
	Neck pain	-	-	-	1	1	0.40	1	1	0.20
	Pain in extremity	3	3	1.19	1	1	0.40	4	4	0.79
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**All**	-	-	-	1	1	0.40	1	1	0.20
	Uterine leiomyoma	-	-	-	1	1	0.40	1	1	0.20
NERVOUS SYSTEM DISORDERS	**All**	14	13	5.16	68	64	25.40	82	77	15.28
	Dizziness	-	-	-	4	4	1.59	4	4	0.79
	Dysgeusia	-	-	-	3	3	1.19	3	3	0.60
	Headache	12	12	4.76	56	56	22.22	68	68	13.49
	Hypoaesthesia	1	1	0.40	-	-	-	1	1	0.20

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
	Idiopathic intracranial hypertension	1	1	0.40	-	-	-	1	1	0.20
	Lethargy	-	-	-	1	1	0.40	1	1	0.20
	Migraine	-	-	-	1	1	0.40	1	1	0.20
	Paraesthesia	-	-	-	2	2	0.79	2	2	0.40
	Parosmia	-	-	-	1	1	0.40	1	1	0.20
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Polycystic ovaries	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**All**	4	3	1.19	2	2	0.79	6	5	0.99
	Dyspnoea	1	1	0.40	-	-	-	1	1	0.20
	Oropharyngeal pain	1	1	0.40	1	1	0.40	2	2	0.40
	Rhinorrhoea	-	-	-	1	1	0.40	1	1	0.20
	Sinus congestion	1	1	0.40	-	-	-	1	1	0.20
	Wheezing	1	1	0.40	-	-	-	1	1	0.20
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**All**	5	5	1.98	2	2	0.79	7	7	1.39
	Acne	1	1	0.40	-	-	-	1	1	0.20
	Dermatitis contact	2	2	0.79	-	-	-	2	2	0.40
	Hyperhidrosis	1	1	0.40	-	-	-	1	1	0.20
	Night sweats	-	-	-	1	1	0.40	1	1	0.20
	Rash	1	1	0.40	-	-	-	1	1	0.20
	Urticaria	-	-	-	1	1	0.40	1	1	0.20
SURGICAL AND MEDICAL PROCEDURES	**All**	1	1	0.40	-	-	-	1	1	0.20
	Wisdom teeth removal	1	1	0.40	-	-	-	1	1	0.20
VASCULAR DISORDERS	**All**	-	-	-	2	2	0.79	2	2	0.40
	Flushing	-	-	-	1	1	0.40	1	1	0.20
	Hypertension	-	-	-	1	1	0.40	1	1	0.20

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

ADR Process1 vs Process 2 - Sample 4

By System Organ Class

System organ class / Preferred term [a]	BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
	NAE	N	%	NAE	N	%	NAE	N	%
All	192	78	30.95	498	155	61.51	690	233	46.23
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
EAR AND LABYRINTH DISORDERS	3	3	1.19	2	2	0.79	5	5	0.99
GASTROINTESTINAL DISORDERS	13	8	3.17	17	13	5.16	30	21	4.17
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	108	54	21.43	334	140	55.56	442	194	38.49
HEPATOBILIARY DISORDERS	1	1	0.40	-	-	-	1	1	0.20
INFECTIONS AND INFESTATIONS	4	3	1.19	3	3	1.19	7	6	1.19
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5	4	1.59	-	-	-	5	4	0.79
INVESTIGATIONS	2	2	0.79	2	2	0.79	4	4	0.79
METABOLISM AND NUTRITION DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	27	26	10.32	61	52	20.63	88	78	15.48
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	-	-	-	1	1	0.40	1	1	0.20
NERVOUS SYSTEM DISORDERS	14	13	5.16	68	64	25.40	82	77	15.28
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4	3	1.19	2	2	0.79	6	5	0.99
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5	5	1.98	2	2	0.79	7	7	1.39
SURGICAL AND MEDICAL PROCEDURES	1	1	0.40	-	-	-	1	1	0.20
VASCULAR DISORDERS	-	-	-	2	2	0.79	2	2	0.40

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

1.4 Sample 5

ADR Process1 vs Process 2 - Sample 5
Patient s characteristics

Table 9 : Patient s characteristics [N=504 patients]

		BNT162 b2 Process1 N=252	**BNT162 b2 Process2 N=252**	**Total N=504**
Age	N	252	252	504
	Missing	0	0	0
	Mean (s.d.)	39.1 (11.3)	40.7 (10.1)	39.9 (10.7)
	Median	41.0	42.0	41.0
	Q1 - Q3	30.0 - 49.0	34.0 - 49.0	31.0 - 49.0
	Min - Max	16.0 - 55.0	17.0 - 55.0	16.0 - 55.0
Sex	N	252	252	504
	Missing	0	0	0
	F	135 (53.6%)	106 (42.1%)	241 (47.8%)
	M	117 (46.4%)	146 (57.9%)	263 (52.2%)
Race	N	252	252	504
	Missing	0	0	0
	AMERICAN INDIAN OR ALASKA NATIVE	8 (3.2%)	0	8 (1.6%)
	ASIAN	17 (6.7%)	27 (10.7%)	44 (8.7%)
	BLACK OR AFRICAN AMERICAN	30 (11.9%)	19 (7.5%)	49 (9.7%)
	MULTIPLE	1 (0.4%)	2 (0.8%)	3 (0.6%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	2 (0.8%)	0	2 (0.4%)
	NOT REPORTED	1 (0.4%)	1 (0.4%)	2 (0.4%)
	WHITE	193 (76.6%)	203 (80.6%)	396 (78.6%)
Pooled Race Group 1	N	252	252	504
	Missing	0	0	0
	ALL OTHERS	29 (11.5%)	30 (11.9%)	59 (11.7%)
	BLACK OR AFRICAN AMERICAN	30 (11.9%)	19 (7.5%)	49 (9.7%)
	WHITE	193 (76.6%)	203 (80.6%)	396 (78.6%)

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Comorbidities	N	252	252	504
	Missing	0	0	0
	No	222 (88.1%)	202 (80.2%)	424 (84.1%)
	Yes	30 (11.9%)	50 (19.8%)	80 (15.9%)
OBESE	N	252	252	504
	Missing	0	0	0
	No	173 (68.7%)	173 (68.7%)	346 (68.7%)
	Yes	79 (31.3%)	79 (31.3%)	158 (31.3%)
Japanese	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
N-binding Antibody Neg at Visit	N	252	252	504
	Missing	0	0	0
	No	7 (2.8%)	10 (4.0%)	17 (3.4%)
	Yes	245 (97.2%)	242 (96.0%)	487 (96.6%)

ADR Process1 vs Process 2 - Sample 5

Outcomes

Table 10 : Number of events [N=504 patients]

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Treatment emergent AE	N	252	252	504
	Missing	0	0	0
	No	177 (70.2%)	97 (38.5%)	274 (54.4%)
	Yes	75 (29.8%)	155 (61.5%)	230 (45.6%)
Serious Adverse Event	N	252	252	504
	Missing	0	0	0
	No	250 (99.2%)	252 (100.0%)	502 (99.6%)
	Yes	2 (0.8%)	0	2 (0.4%)
AE leading to life threatening	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE leading to premature withdrawal	N	252	252	504
	Missing	0	0	0
	No	250 (99.2%)	252 (100.0%)	502 (99.6%)
	Yes	2 (0.8%)	0	2 (0.4%)
AE leading to death	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE related	N	252	252	504
	Missing	0	0	0
	No	201 (79.8%)	104 (41.3%)	305 (60.5%)
	Yes	51 (20.2%)	148 (58.7%)	199 (39.5%)
Grade 3 or 4	N	252	252	504
	Missing	0	0	0
	No	248 (98.4%)	252 (100.0%)	500 (99.2%)
	Yes	4 (1.6%)	0	4 (0.8%)

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Persist or Signif Disability/Incapacity	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
Requires or Prolongs Hospitalization	N	252	252	504
	Missing	0	0	0
	No	250 (99.2%)	252 (100.0%)	502 (99.6%)
	Yes	2 (0.8%)	0	2 (0.4%)

The FREQ Procedure

Table of TEAE by Process			
TEAE(Treatment emergent AE)	**Process**		
Frequency Percent Row Pct Col Pct	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	177 35.12 64.60 70.24	97 19.25 35.40 38.49	274 54.37
Yes	75 14.88 32.61 29.76	155 30.75 67.39 61.51	230 45.63
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of TEAE by Process

Statistic	DF	Value	Prob
Chi-Square	1	51.1838	<.0001
Likelihood Ratio Chi-Square	1	52.1176	<.0001
Continuity Adj. Chi-Square	1	49.9122	<.0001
Mantel-Haenszel Chi-Square	1	51.0822	<.0001
Phi Coefficient		0.3187	
Contingency Coefficient		0.3036	
Cramer's V		0.3187	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	177
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

The FREQ Procedure

Table of sae by Process			
sae(Serious Adverse Event)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	250 49.60 49.80 99.21	252 50.00 50.20 100.00	502 99.60
Yes	2 0.40 100.00 0.79	0 0.00 0.00 0.00	2 0.40
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of sae by Process

Statistic	DF	Value	Prob
Chi-Square	1	2.0080	0.1565
Likelihood Ratio Chi-Square	1	2.7806	0.0954
Continuity Adj. Chi-Square	1	0.5020	0.4786
Mantel-Haenszel Chi-Square	1	2.0040	0.1569
Phi Coefficient		-0.0631	
Contingency Coefficient		0.0630	
Cramer's V		-0.0631	
WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.			

Fisher's Exact Test	
Cell (1,1) Frequency (F)	250
Left-sided Pr <= F	0.2495
Right-sided Pr >= F	1.0000
Table Probability (P)	0.2495
Two-sided Pr <= P	0.4990

Sample Size = 504

The FREQ Procedure

Table of REL by Process			
REL(AE related)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	201 39.88 65.90 79.76	104 20.63 34.10 41.27	305 60.52
Yes	51 10.12 25.63 20.24	148 29.37 74.37 58.73	199 39.48
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of REL by Process

Statistic	DF	Value	Prob
Chi-Square	1	78.1306	<.0001
Likelihood Ratio Chi-Square	1	80.7498	<.0001
Continuity Adj. Chi-Square	1	76.5280	<.0001
Mantel-Haenszel Chi-Square	1	77.9756	<.0001
Phi Coefficient		0.3937	
Contingency Coefficient		0.3664	
Cramer's V		0.3937	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	201
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

ADR Process1 vs Process 2 - Sample 5

By System Organ Class and Preferred Term - Long table

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
All	**All**	185	76	30.16	498	155	61.51	683	231	45.83
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**All**	3	2	0.79	2	2	0.79	5	4	0.79
	Anaemia	1	1	0.40	-	-	-	1	1	0.20
	Lymph node pain	1	1	0.40	1	1	0.40	2	2	0.40
	Lymphadenopathy	1	1	0.40	1	1	0.40	2	2	0.40
CARDIAC DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Tachycardia	1	1	0.40	-	-	-	1	1	0.20
EAR AND LABYRINTH DISORDERS	**All**	-	-	-	2	2	0.79	2	2	0.40
	Vertigo	-	-	-	2	2	0.79	2	2	0.40
GASTROINTESTINAL DISORDERS	**All**	9	8	3.17	17	13	5.16	26	21	4.17
	Abdominal discomfort	-	-	-	1	1	0.40	1	1	0.20
	Constipation	1	1	0.40	-	-	-	1	1	0.20
	Diarrhoea	1	1	0.40	9	9	3.57	10	10	1.98
	Nausea	6	6	2.38	6	6	2.38	12	12	2.38
	Vomiting	1	1	0.40	1	1	0.40	2	2	0.40
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**All**	91	48	19.05	**334**	**140**	**55.56**	425	188	37.30
	Chills	16	16	6.35	**58**	**58**	**23.02**	74	74	14.68
	Fatigue	17	17	6.75	**73**	**73**	**28.97**	90	90	17.86
	Feeling abnormal	-	-	-	1	1	0.40	1	1	0.20
	Influenza like illness	1	1	0.40	-	-	-	1	1	0.20
	Injection site erythema	3	3	1.19	8	8	3.17	11	11	2.18
	Injection site induration	1	1	0.40	-	-	-	1	1	0.20
	Injection site pain	26	26	10.32	**97**	**97**	**38.49**	123	123	24.40
	Injection site reaction	-	-	-	1	1	0.40	1	1	0.20
	Injection site swelling	1	1	0.40	10	10	3.97	11	11	2.18
	Malaise	-	-	-	5	5	1.98	5	5	0.99
	Pain	11	11	4.37	**31**	**31**	**12.30**	42	42	8.33
	Pyrexia	15	15	5.95	**50**	**50**	**19.84**	65	65	12.90
IMMUNE SYSTEM DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Seasonal allergy	1	1	0.40	-	-	-	1	1	0.20
INFECTIONS AND INFESTATIONS	**All**	9	8	3.17	3	3	1.19	12	11	2.18
	Appendicitis	1	1	0.40	-	-	-	1	1	0.20
	Cellulitis	1	1	0.40	-	-	-	1	1	0.20
	Diverticulitis	1	1	0.40	-	-	-	1	1	0.20
	Ear infection	-	-	-	1	1	0.40	1	1	0.20
	Gonorrhoea	1	1	0.40	-	-	-	1	1	0.20

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
	Herpes zoster	1	1	0.40	-	-	-	1	1	0.20
	Sinusitis	1	1	0.40	-	-	-	1	1	0.20
	Upper respiratory tract infection	1	1	0.40	1	1	0.40	2	2	0.40
	Urinary tract infection	1	1	0.40	1	1	0.40	2	2	0.40
	Wound infection	1	1	0.40	-	-	-	1	1	0.20
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**All**	14	14	5.56	-	-	-	14	14	2.78
	Arthropod bite	1	1	0.40	-	-	-	1	1	0.20
	Exposure during pregnancy	1	1	0.40	-	-	-	1	1	0.20
	Head injury	1	1	0.40	-	-	-	1	1	0.20
	Incorrect dosage administered	2	2	0.79	-	-	-	2	2	0.40
	Meniscus injury	1	1	0.40	-	-	-	1	1	0.20
	Product administration error	1	1	0.40	-	-	-	1	1	0.20
	Product storage error	4	4	1.59	-	-	-	4	4	0.79
	Tooth fracture	1	1	0.40	-	-	-	1	1	0.20
	Wrong product administered	2	2	0.79	-	-	-	2	2	0.40
INVESTIGATIONS	**All**	1	1	0.40	2	2	0.79	3	3	0.60
	Blood cholesterol increased	1	1	0.40	-	-	-	1	1	0.20
	Body temperature increased	-	-	-	2	2	0.79	2	2	0.40
METABOLISM AND NUTRITION DISORDERS	**All**	5	3	1.19	2	2	0.79	7	5	0.99
	Decreased appetite	1	1	0.40	-	-	-	1	1	0.20
	Folate deficiency	1	1	0.40	-	-	-	1	1	0.20
	Hypercholesterolaemia	1	1	0.40	-	-	-	1	1	0.20
	Iron deficiency	-	-	-	1	1	0.40	1	1	0.20
	Vitamin B12 deficiency	1	1	0.40	-	-	-	1	1	0.20
	Vitamin D deficiency	1	1	0.40	1	1	0.40	2	2	0.40
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**All**	19	19	7.54	61	52	20.63	80	71	14.09
	Arthralgia	2	2	0.79	**11**	**11**	**4.37**	13	13	2.58
	Back pain	2	2	0.79	1	1	0.40	3	3	0.60
	Bursitis	-	-	-	1	1	0.40	1	1	0.20
	Exostosis	-	-	-	1	1	0.40	1	1	0.20
	Muscle spasms	1	1	0.40	2	2	0.79	3	3	0.60
	Muscle twitching	-	-	-	1	1	0.40	1	1	0.20
	Myalgia	11	11	4.37	**42**	**42**	**16.67**	53	53	10.52
	Neck pain	-	-	-	1	1	0.40	1	1	0.20
	Pain in extremity	3	3	1.19	1	1	0.40	4	4	0.79
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**All**	-	-	-	1	1	0.40	1	1	0.20
	Uterine leiomyoma	-	-	-	1	1	0.40	1	1	0.20

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
NERVOUS SYSTEM DISORDERS	**All**	18	18	7.14	68	64	25.40	86	82	16.27
	Dizziness	1	1	0.40	4	4	1.59	5	5	0.99
	Dysgeusia	-	-	-	3	3	1.19	3	3	0.60
	Headache	14	14	5.56	**56**	**56**	**22.22**	70	70	13.89
	Lethargy	1	1	0.40	1	1	0.40	2	2	0.40
	Migraine	-	-	-	1	1	0.40	1	1	0.20
	Paraesthesia	-	-	-	2	2	0.79	2	2	0.40
	Parosmia	-	-	-	1	1	0.40	1	1	0.20
	Subarachnoid haemorrhage	1	1	0.40	-	-	-	1	1	0.20
	Tension headache	1	1	0.40	-	-	-	1	1	0.20
PSYCHIATRIC DISORDERS	**All**	4	2	0.79	-	-	-	4	2	0.40
	Anxiety	1	1	0.40	-	-	-	1	1	0.20
	Depression	1	1	0.40	-	-	-	1	1	0.20
	Insomnia	1	1	0.40	-	-	-	1	1	0.20
	Schizophrenia	1	1	0.40	-	-	-	1	1	0.20
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**All**	1	1	0.40	-	-	-	1	1	0.20
	Benign prostatic hyperplasia	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Cough	1	1	0.40	-	-	-	1	1	0.20
	Dry throat	1	1	0.40	-	-	-	1	1	0.20
	Oropharyngeal pain	-	-	-	1	1	0.40	1	1	0.20
	Rhinorrhoea	-	-	-	1	1	0.40	1	1	0.20
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**All**	6	5	1.98	2	2	0.79	8	7	1.39
	Alopecia	1	1	0.40	-	-	-	1	1	0.20
	Eczema	2	2	0.79	-	-	-	2	2	0.40
	Hyperhidrosis	1	1	0.40	-	-	-	1	1	0.20
	Night sweats	-	-	-	1	1	0.40	1	1	0.20
	Pruritus	1	1	0.40	-	-	-	1	1	0.20
	Rash	1	1	0.40	-	-	-	1	1	0.20
	Urticaria	-	-	-	1	1	0.40	1	1	0.20
VASCULAR DISORDERS	**All**	1	1	0.40	2	2	0.79	3	3	0.60
	Flushing	-	-	-	1	1	0.40	1	1	0.20
	Hypertension	1	1	0.40	1	1	0.40	2	2	0.40

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

ADR Process1 vs Process 2 - Sample 5

By System Organ Class

System organ class / Preferred term [a]	BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
	NAE	N	%	NAE	N	%	NAE	N	%
All	185	76	30.16	498	155	61.51	683	231	45.83
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3	2	0.79	2	2	0.79	5	4	0.79
CARDIAC DISORDERS	1	1	0.40	-	-	-	1	1	0.20
EAR AND LABYRINTH DISORDERS	-	-	-	2	2	0.79	2	2	0.40
GASTROINTESTINAL DISORDERS	9	8	3.17	17	13	5.16	26	21	4.17
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	91	48	19.05	334	140	55.56	425	188	37.30
IMMUNE SYSTEM DISORDERS	1	1	0.40	-	-	-	1	1	0.20
INFECTIONS AND INFESTATIONS	9	8	3.17	3	3	1.19	12	11	2.18
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	14	14	5.56	-	-	-	14	14	2.78
INVESTIGATIONS	1	1	0.40	2	2	0.79	3	3	0.60
METABOLISM AND NUTRITION DISORDERS	5	3	1.19	2	2	0.79	7	5	0.99
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	19	19	7.54	61	52	20.63	80	71	14.09
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	-	-	-	1	1	0.40	1	1	0.20
NERVOUS SYSTEM DISORDERS	18	18	7.14	68	64	25.40	86	82	16.27
PSYCHIATRIC DISORDERS	4	2	0.79	-	-	-	4	2	0.40
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	1	0.40	-	-	-	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6	5	1.98	2	2	0.79	8	7	1.39
VASCULAR DISORDERS	1	1	0.40	2	2	0.79	3	3	0.60

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

1.5 Sample 6

ADR Process1 vs Process 2 - Sample 6
Patient s characteristics

Table 11 : Patient s characteristics [N=504 patients]

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Age	N	252	252	504
	Missing	0	0	0
	Mean (s.d.)	38.1 (10.9)	40.7 (10.1)	39.4 (10.6)
	Median	39.0	42.0	41.0
	Q1 - Q3	30.0 - 47.0	34.0 - 49.0	31.0 - 48.0
	Min - Max	16.0 - 55.0	17.0 - 55.0	16.0 - 55.0
Sex	N	252	252	504
	Missing	0	0	0
	F	135 (53.6%)	106 (42.1%)	241 (47.8%)
	M	117 (46.4%)	146 (57.9%)	263 (52.2%)
Race	N	252	252	504
	Missing	0	0	0
	ASIAN	29 (11.5%)	27 (10.7%)	56 (11.1%)
	BLACK OR AFRICAN AMERICAN	29 (11.5%)	19 (7.5%)	48 (9.5%)
	MULTIPLE	1 (0.4%)	2 (0.8%)	3 (0.6%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.4%)	0	1 (0.2%)
	NOT REPORTED	0	1 (0.4%)	1 (0.2%)
	WHITE	192 (76.2%)	203 (80.6%)	395 (78.4%)
Pooled Race Group 1	N	252	252	504
	Missing	0	0	0
	ALL OTHERS	31 (12.3%)	30 (11.9%)	61 (12.1%)
	BLACK OR AFRICAN AMERICAN	29 (11.5%)	19 (7.5%)	48 (9.5%)
	WHITE	192 (76.2%)	203 (80.6%)	395 (78.4%)
Comorbidities	N	252	252	504
	Missing	0	0	0

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
	No	213 (84.5%)	202 (80.2%)	415 (82.3%)
	Yes	39 (15.5%)	50 (19.8%)	89 (17.7%)
OBESE	N	252	252	504
	Missing	0	0	0
	No	173 (68.7%)	173 (68.7%)	346 (68.7%)
	Yes	79 (31.3%)	79 (31.3%)	158 (31.3%)
Japanese	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)
N-binding Antibody Neg at Visit	N	252	252	504
	Missing	0	0	0
	No	10 (4.0%)	10 (4.0%)	20 (4.0%)
	Yes	242 (96.0%)	242 (96.0%)	484 (96.0%)

Table 12 : Number of events [N=504 patients]

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
Treatment emergent AE	N	252	252	504
	Missing	0	0	0
	No	169 (67.1%)	97 (38.5%)	266 (52.8%)
	Yes	83 (32.9%)	155 (61.5%)	238 (47.2%)
Serious Adverse Event	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)
AE leading to life threatening	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)
AE leading to premature withdrawal	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)
AE leading to death	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
AE related	N	252	252	504
	Missing	0	0	0
	No	184 (73.0%)	104 (41.3%)	288 (57.1%)
	Yes	68 (27.0%)	148 (58.7%)	216 (42.9%)
Grade 3 or 4	N	252	252	504
	Missing	0	0	0
	No	249 (98.8%)	252 (100.0%)	501 (99.4%)

		BNT162 b2 Process1 N=252	BNT162 b2 Process2 N=252	Total N=504
	Yes	3 (1.2%)	0	3 (0.6%)
Persist or Signif Disability/Incapacity	N	252	252	504
	Missing	0	0	0
	No	252 (100.0%)	252 (100.0%)	504 (100.0%)
Requires or Prolongs Hospitalization	N	252	252	504
	Missing	0	0	0
	No	251 (99.6%)	252 (100.0%)	503 (99.8%)
	Yes	1 (0.4%)	0	1 (0.2%)

Outcomes

The FREQ Procedure

Table of TEAE by Process			
TEAE(Treatment emergent AE)	**Process**		
Frequency Percent Row Pct Col Pct	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	169 33.53 63.53 67.06	97 19.25 36.47 38.49	266 52.78
Yes	83 16.47 34.87 32.94	155 30.75 65.13 61.51	238 47.22
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of TEAE by Process

Statistic	DF	Value	Prob
Chi-Square	1	41.2702	<.0001
Likelihood Ratio Chi-Square	1	41.8605	<.0001
Continuity Adj. Chi-Square	1	40.1318	<.0001
Mantel-Haenszel Chi-Square	1	41.1883	<.0001
Phi Coefficient		0.2862	
Contingency Coefficient		0.2751	
Cramer's V		0.2862	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	169
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

ADR Process1 vs Process 2 - Sample 6

Outcomes

The FREQ Procedure

Table of sae by Process			
sae(Serious Adverse Event)	Process		
Frequency Percent Row Pct Col Pct	BNT162 b2 Process1	BNT162 b2 Process2	Total
No	251 49.80 49.90 99.60	252 50.00 50.10 100.00	503 99.80
Yes	1 0.20 100.00 0.40	0 0.00 0.00 0.00	1 0.20
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of sae by Process

Statistic	DF	Value	Prob
Chi-Square	1	1.0020	0.3168
Likelihood Ratio Chi-Square	1	1.3883	0.2387
Continuity Adj. Chi-Square	1	0.0000	1.0000
Mantel-Haenszel Chi-Square	1	1.0000	0.3173
Phi Coefficient		-0.0446	
Contingency Coefficient		0.0445	
Cramer's V		-0.0446	
WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.			

Fisher's Exact Test	
Cell (1,1) Frequency (F)	251
Left-sided Pr <= F	0.5000
Right-sided Pr >= F	1.0000
Table Probability (P)	0.5000
Two-sided Pr <= P	1.0000

Sample Size = 504

ADR Process1 vs Process 2 - Sample 6

Outcomes

The FREQ Procedure

Table of LifeThreat by Process			
LifeThreat(AE leading to life threatening)	**Process**		
Frequency Percent Row Pct Col Pct	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	251 49.80 49.90 99.60	252 50.00 50.10 100.00	503 99.80
Yes	1 0.20 100.00 0.40	0 0.00 0.00 0.00	1 0.20
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of LifeThreat by Process

Statistic	DF	Value	Prob
Chi-Square	1	1.0020	0.3168
Likelihood Ratio Chi-Square	1	1.3883	0.2387
Continuity Adj. Chi-Square	1	0.0000	1.0000
Mantel-Haenszel Chi-Square	1	1.0000	0.3173
Phi Coefficient		-0.0446	
Contingency Coefficient		0.0445	
Cramer's V		-0.0446	
WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.			

Fisher's Exact Test	
Cell (1,1) Frequency (F)	251
Left-sided Pr <= F	0.5000
Right-sided Pr >= F	1.0000
Table Probability (P)	0.5000
Two-sided Pr <= P	1.0000

Sample Size = 504

ADR Process1 vs Process 2 - Sample 6

Outcomes

The FREQ Procedure

Table of REL by Process			
REL(AE related)	**Process**		
Frequency Percent Row Pct Col Pct	**BNT162 b2 Process1**	**BNT162 b2 Process2**	**Total**
No	184 36.51 63.89 73.02	104 20.63 36.11 41.27	288 57.14
Yes	68 13.49 31.48 26.98	148 29.37 68.52 58.73	216 42.86
Total	252 50.00	252 50.00	504 100.00

Statistics for Table of REL by Process

Statistic	DF	Value	Prob
Chi-Square	1	51.8519	<.0001
Likelihood Ratio Chi-Square	1	52.8644	<.0001
Continuity Adj. Chi-Square	1	50.5637	<.0001
Mantel-Haenszel Chi-Square	1	51.7490	<.0001
Phi Coefficient		0.3208	
Contingency Coefficient		0.3054	
Cramer's V		0.3208	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	184
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	<.0001
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 504

ADR Process1 vs Process 2 - Sample 6

By System Organ Class and Preferred Term - Long table

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
All	All	211	84	33.33	498	155	61.51	709	239	47.42
BLOOD AND LYMPHATIC SYSTEM DISORDERS	All	2	2	0.79	2	2	0.79	4	4	0.79
	Lymph node pain	1	1	0.40	1	1	0.40	2	2	0.40
	Lymphadenopathy	1	1	0.40	1	1	0.40	2	2	0.40
CARDIAC DISORDERS	All	3	2	0.79	-	-	-	3	2	0.40
	Acute myocardial infarction	1	1	0.40	-	-	-	1	1	0.20
	Coronary artery disease	1	1	0.40	-	-	-	1	1	0.20
	Tachycardia	1	1	0.40	-	-	-	1	1	0.20
EAR AND LABYRINTH DISORDERS	All	-	-	-	2	2	0.79	2	2	0.40
	Vertigo	-	-	-	2	2	0.79	2	2	0.40
EYE DISORDERS	All	1	1	0.40	-	-	-	1	1	0.20
	Eye irritation	1	1	0.40	-	-	-	1	1	0.20
GASTROINTESTINAL DISORDERS	All	8	8	3.17	17	13	5.16	25	21	4.17
	Abdominal discomfort	-	-	-	1	1	0.40	1	1	0.20
	Abdominal pain upper	1	1	0.40	-	-	-	1	1	0.20
	Dental caries	1	1	0.40	-	-	-	1	1	0.20
	Diarrhoea	2	2	0.79	9	9	3.57	11	11	2.18
	Eosinophilic oesophagitis	1	1	0.40	-	-	-	1	1	0.20
	Nausea	3	3	1.19	6	6	2.38	9	9	1.79
	Vomiting	-	-	-	1	1	0.40	1	1	0.20
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	All	125	61	24.21	334	140	55.56	459	201	39.88
	Adverse drug reaction	1	1	0.40	-	-	-	1	1	0.20
	Chills	27	27	10.71	58	58	23.02	85	85	16.87
	Fatigue	19	19	7.54	73	73	28.97	92	92	18.25
	Feeling abnormal	-	-	-	1	1	0.40	1	1	0.20
	Influenza like illness	2	2	0.79	-	-	-	2	2	0.40
	Injection site erythema	5	5	1.98	8	8	3.17	13	13	2.58
	Injection site pain	37	37	14.68	97	97	38.49	134	134	26.59
	Injection site pruritus	1	1	0.40	-	-	-	1	1	0.20
	Injection site reaction	-	-	-	1	1	0.40	1	1	0.20
	Injection site swelling	-	-	-	10	10	3.97	10	10	1.98
	Malaise	6	6	2.38	5	5	1.98	11	11	2.18
	Pain	11	11	4.37	31	31	12.30	42	42	8.33
	Pyrexia	16	16	6.35	50	50	19.84	66	66	13.10
	All	4	4	1.59	3	3	1.19	7	7	1.39

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
INFECTIONS AND INFESTATIONS	Bacterial blepharitis	1	1	0.40	-	-	-	1	1	0.20
	Ear infection	-	-	-	1	1	0.40	1	1	0.20
	Herpes zoster	1	1	0.40	-	-	-	1	1	0.20
	Tooth abscess	1	1	0.40	-	-	-	1	1	0.20
	Upper respiratory tract infection	1	1	0.40	1	1	0.40	2	2	0.40
	Urinary tract infection	-	-	-	1	1	0.40	1	1	0.20
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	All	8	5	1.98	-	-	-	8	5	0.99
	Concussion	1	1	0.40	-	-	-	1	1	0.20
	Ear injury	1	1	0.40	-	-	-	1	1	0.20
	Exposure during pregnancy	2	2	0.79	-	-	-	2	2	0.40
	Fall	1	1	0.40	-	-	-	1	1	0.20
	Muscle strain	1	1	0.40	-	-	-	1	1	0.20
	Skin laceration	1	1	0.40	-	-	-	1	1	0.20
	Thermal burn	1	1	0.40	-	-	-	1	1	0.20
INVESTIGATIONS	All	2	2	0.79	2	2	0.79	4	4	0.79
	Body temperature increased	1	1	0.40	2	2	0.79	3	3	0.60
	Weight increased	1	1	0.40	-	-	-	1	1	0.20
METABOLISM AND NUTRITION DISORDERS	All	-	-	-	2	2	0.79	2	2	0.40
	Iron deficiency	-	-	-	1	1	0.40	1	1	0.20
	Vitamin D deficiency	-	-	-	1	1	0.40	1	1	0.20
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	All	29	25	9.92	61	52	20.63	90	77	15.28
	Arthralgia	2	2	0.79	11	11	4.37	13	13	2.58
	Back pain	1	1	0.40	1	1	0.40	2	2	0.40
	Bursitis	-	-	-	1	1	0.40	1	1	0.20
	Exostosis	-	-	-	1	1	0.40	1	1	0.20
	Muscle spasms	1	1	0.40	2	2	0.79	3	3	0.60
	Muscle twitching	-	-	-	1	1	0.40	1	1	0.20
	Myalgia	18	18	7.14	42	42	16.67	60	60	11.90
	Neck pain	1	1	0.40	1	1	0.40	2	2	0.40
	Pain in extremity	6	6	2.38	1	1	0.40	7	7	1.39
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	All	1	1	0.40	1	1	0.40	2	2	0.40
	Transitional cell carcinoma	1	1	0.40	-	-	-	1	1	0.20
	Uterine leiomyoma	-	-	-	1	1	0.40	1	1	0.20
NERVOUS SYSTEM DISORDERS	All	18	18	7.14	68	64	25.40	86	82	16.27
	Dizziness	-	-	-	4	4	1.59	4	4	0.79
	Dysgeusia	-	-	-	3	3	1.19	3	3	0.60

System organ class / Preferred term [a]		BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
		NAE	NP	%	NAE	NP	%	NAE	NP	%
	Headache	17	17	6.75	56	56	22.22	73	73	14.48
	Lethargy	-	-	-	1	1	0.40	1	1	0.20
	Migraine	-	-	-	1	1	0.40	1	1	0.20
	Paraesthesia	1	1	0.40	2	2	0.79	3	3	0.60
	Parosmia	-	-	-	1	1	0.40	1	1	0.20
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**All**	2	2	0.79	2	2	0.79	4	4	0.79
	Oropharyngeal pain	1	1	0.40	1	1	0.40	2	2	0.40
	Paranasal sinus discomfort	1	1	0.40	-	-	-	1	1	0.20
	Rhinorrhoea	-	-	-	1	1	0.40	1	1	0.20
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**All**	5	5	1.98	2	2	0.79	7	7	1.39
	Acne	1	1	0.40	-	-	-	1	1	0.20
	Alopecia	1	1	0.40	-	-	-	1	1	0.20
	Diabetic foot	1	1	0.40	-	-	-	1	1	0.20
	Night sweats	-	-	-	1	1	0.40	1	1	0.20
	Rash	1	1	0.40	-	-	-	1	1	0.20
	Urticaria	1	1	0.40	1	1	0.40	2	2	0.40
SURGICAL AND MEDICAL PROCEDURES	**All**	2	2	0.79	-	-	-	2	2	0.40
	Dental implantation	1	1	0.40	-	-	-	1	1	0.20
	Wisdom teeth removal	1	1	0.40	-	-	-	1	1	0.20
VASCULAR DISORDERS	**All**	1	1	0.40	2	2	0.79	3	3	0.60
	Flushing	-	-	-	1	1	0.40	1	1	0.20
	Hypertension	1	1	0.40	1	1	0.40	2	2	0.40

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)

ADR Process1 vs Process 2 - Sample 6

By System Organ Class

System organ class / Preferred term [a]	BNT162 b2 Process1			BNT162 b2 Process2			TOTAL		
	NAE	N	%	NAE	N	%	NAE	N	%
All	211	84	33.33	498	155	61.51	709	239	47.42
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
CARDIAC DISORDERS	3	2	0.79	-	-	-	3	2	0.40
EAR AND LABYRINTH DISORDERS	-	-	-	2	2	0.79	2	2	0.40
EYE DISORDERS	1	1	0.40	-	-	-	1	1	0.20
GASTROINTESTINAL DISORDERS	8	8	3.17	17	13	5.16	25	21	4.17
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	125	61	24.21	334	140	55.56	459	201	39.88
INFECTIONS AND INFESTATIONS	4	4	1.59	3	3	1.19	7	7	1.39
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8	5	1.98	-	-	-	8	5	0.99
INVESTIGATIONS	2	2	0.79	2	2	0.79	4	4	0.79
METABOLISM AND NUTRITION DISORDERS	-	-	-	2	2	0.79	2	2	0.40
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	29	25	9.92	61	52	20.63	90	77	15.28
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	1	0.40	1	1	0.40	2	2	0.40
NERVOUS SYSTEM DISORDERS	18	18	7.14	68	64	25.40	86	82	16.27
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	2	0.79	2	2	0.79	4	4	0.79
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5	5	1.98	2	2	0.79	7	7	1.39
SURGICAL AND MEDICAL PROCEDURES	2	2	0.79	-	-	-	2	2	0.40
VASCULAR DISORDERS	1	1	0.40	2	2	0.79	3	3	0.60

[a] ADR are coded using MedDRA dictionary (V23.1).
N: Number of patients with at least an ADR by SOC (system organ class)
Nae: Number of ADRs in a class
% (Number of patients concerned (N) / Number de patients in DB)