STUDY PROTOCOL

Study information

Title	Safety Profile of BNT162b2 mRNA SARS-Cov-2 Vaccine in Indonesia: A National Passive Surveillance.
Protocol number	C4591050
Protocol version identifier	Version 2.0
Date	26 April 2023
Active substance	ATC code: J07BX03 Tozinameran - Nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2
Medicinal product	BNT162b2 mRNA Vaccine
Research question and objectives	The objective of the study is to characterize descriptively the BNT162b2 vaccination experience among the Indonesian population, by analyzing structured data within Indonesia Vaccine Safety Databaseas requested by Indonesia Food and Drug Monitoring Agency (BPOM). Specific data elements include: A. Primary outcome measure : A1. SAE (Serious Adverse Event) : SAE after primary dose and/or booster dose A2. Total AE reported after primary dose and/or booster dose B. Secondary outcome measure : B1. SAE onset : ≤30 mins or > 30 mins

	B2. Causality of SAE : coincidence, ISRR (Immunization Stress Related Response), vaccine reaction, unclassifiable, or indeterminate B3. Type of AE : B3.1. Serious and Non-serious B3.2. Solicited and unsolicited B4. Solicited AEs: B4.1.. Local reactions : pain, swelling, redness, thickness. B4.2. Systemic reactions: fever, myalgia, malaise B5. Unsolicited AEs: B5.1. Local reactions: abscess, bleeding, etc. B5.2. Systemic reactions: headache, nausea, arthralgia, etc.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BPOM	Indonesia Food and Drug Monitoring Agency
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus Disease 19
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
IBM-SPSS	Intelligence Based Manufacturing – Statistical Package of Social Science
IRB	Institutional Review Board
ISRR	Immunization Stress Related Response
IQR	Interquartiles Ranges
modRNA	Modified Ribonucleocid Acid
MoH	Ministry of Health
mRNA	Messenger Ribonucleic Acid
NCAEFI	National Committee of Adverse Event Following Immunization
NI	Non Interventional
SAE	Serious Adverse Events

SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Dr. PPD	PPD	Pfizer	PPD
Dr. PPD	PPD	Pfizer	PPD
Dr. PPD	PPD	Pfizer	PPD
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4. ABSTRACT

None

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 administrative	26 Apr 2023	Section 6 MILESTONES	Modified Milestone	NA
		Section 9 RESEARCH METHODS	Deletion of text of SAP: Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP),etc	Align with study team's decision.

6. MILESTONES

Milestone	Planned date
Start of data collection	*16 March 2023*
End of data collection	28 March 2023
Final study report	*19 June 2023*

7. RATIONALE AND BACKGROUND

BPOM (Indonesia National Regulatory Authority) has issued an Emergency Use Authorization (EUA) to permit the emergency use of Comirnaty 30 mg/dose for primary and 15 mg/dose for booster concentrate for dispersion for injection. Comirnaty is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older in Indonesia. For detailed information please refer to the BPOM (Indonesia National Regulatory Authority) approved Fact Sheet For Health Care Providers EUA Of Comirnaty.

The safety of the primary series Pfizer-BioNTech COVID-19 Vaccine was evaluated in participants 6 months of age and older in 3 clinical studies conducted in the United States(US), Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) was a Phase 1/2, second-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dosefinding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 46,000 participants, 12 years of age or older. Of these, approximately 43,448 participants [21,720 Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA); 21,728 placebo] in Phase 2/3 are 16 years of age or older (including 138 and 145 participants 16 and 17 years of age in the vaccine and placebo groups, respectively) and 2,260 participants are 12 through 15 years of age (1,131 and 1,129 in the vaccine and placebo groups, respectively). Study C4591007 (Study 3) is a Phase 1/2/3 multicenter, randomized, dose-finding, open-label (Phase 1) and multinational, saline placebo-controlled, observer-blind, immunogenicity and efficacy (Phase 2/3) study that has enrolled 4,695 participants 5 through 11 years of age, of whom 3,109 participants received Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA) and 1,538 participants received placebo in Phase 2/3. Study

3 also enrolled 1,776 participants 6 through 23 months of age, of whom 1,178 participants were in the Pfizer-BioNTech COVID-19 Vaccine (3 mcg modRNA) group and 598 participants in the placebo group; and also enrolled 2,750 participants 2 through 4 years of age, of whom 1,835 participants were in the Pfizer-BioNTech COVID-19 Vaccine group and 915 participants in the placebo group in Phase 2/3. Results from these clinical studies have been published in peer-reviewed journals.

BPOM (Indonesia National Regulatory Authority) has requested to conduct an analysis of AEs reported in the Indonesia NC AEFI database following administration of BNT162b2 mRNA vaccine.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of the study is to characterize descriptively the BNT162b2 vaccination safety experience among the Indonesian population, by analyzing structured data within Indonesia Vaccine Safety Website (Ministry of Health) as requested by BPOM (Indonesia National Regulatory Authority).

9. RESEARCH METHODS

9.1. Study design

This is a descriptive study for secondary data collection and analysis of structured data regarding AEs reported in Indonesia Vaccine Safety Website, following administration of primary and booster dose BNT162b2 mRNA vaccine. This study will not provide or make recommendations on any vaccine use.

A. The AEs reported in Indonesia Vaccine Safety Database, following administration of BNT162b2 mRNA vaccine, are expected to be structured and anonymized/ coded. Individual vaccine recipient identification information will not be collected in this study. The following data elements will be collected from the IndonesiaVaccine Safety Website for further analysis. Primary outcome measure :

   A1. SAE (Serious Adverse Event) : SAE after primary dose and/or booster dose

   A2. Total AE reported after primary dose and/or booster dose

B. Secondary outcome measure :

   B1. SAE onset : ≤30 mins or > 30 mins

   B2. Causality of SAE : coincidence, ISRR (Immunization Stress Related Response), vaccine reaction, unclassifiable, or indeterminate

B3. Type of AE :

B3.1. Serious and Non-serious

B3.2. Solicited and unsolicited

B4. Solicited AEs:

B4.1.. Local reactions : pain, swelling, redness, thickness.

B4.2. Systemic reactions: fever, myalgia, malaise

B5. Unsolicited AEs:

B5.1. Local reactions: abscess, bleeding, etc.

B5.2. Systemic reactions: headache, nausea, arthralgia, etc.

Since the study doesn't involve primary data collection from any participants, there will be no requirement of individual consent/ assent.

9.2. Setting

The secondary data collection will be exclusively from the Indonesia Vaccine Safety Website as requested by BPOM (Indonesia National Regulatory Authority). After the study protocol is approved by BPOM (Indonesia National Regulatory Authority), structured data will be obtained retrospectively for all AEs reported following administration of the BNT162b2 mRNA vaccine, starting from the time of vaccine availablein Indonesia. Structured anonymized data for events which includes the following information will be collected and used for analysis:

A. Primary outcome measure :

A1. SAE (Serious Adverse Event) : SAE after primary dose and/or booster dose

A2. Total AE reported after primary dose and/or booster dose

B. Secondary outcome measure :

B1. SAE onset : ≤30 mins or > 30 mins

B2. Causality of SAE : coincidence, ISRR (Immunization Stress Related Response), vaccine reaction, unclassifiable, or indeterminate

B3. Type of AE :

B3.1. Serious and Non-serious

B3.2. Solicited and unsolicited

B4. Solicited AEs:

B4.1.. Local reactions : pain, swelling, redness, thickness.

B4.2. Systemic reactions: fever, myalgia, malaise

B5. Unsolicited AEs:

B5.1. Local reactions: abscess, bleeding, etc.

B5.2. Systemic reactions: headache, nausea, arthralgia, etc.

Events for which either of the above is missing will not be recorded for analysis.

9.2.1. Inclusion criteria

This study will include adverse events reported in Indonesia NC AEFI database for individuals 12 years of age and older

9.2.2. Exclusion criteria

The incomplete data in the database will be excluded

9.3. Variables

Variable	Role	Data source(s)	Operational definition
The type of vaccination with BNT162b2 mRNA vaccine following which SAE was reported	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was reported after primary series or booster vaccination
Onset of SAE	Baseline characteristic	Indonesia Vaccine Safety Website	Whether the serious AE onset ≤ 30 mins or > 30 mins
Causality	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the SAE was caused by the vaccine. Causality of the AE with BNT162b2 – classified as WHO criteria as coincidence, ISRR, vaccine reaction, unclassifiable, or indeterminate)
Type of AE	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was Serious and Non-serious or solicited and unsolicited

Type of solicited reaction	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was local or systemic
Type of Solicited Local reaction	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was pain, swelling, redness or thickness
Type of Solicited Systemic reaction	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was fever, myalgia, malaise
Type of unsolicited reaction	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was local or systemic and the term reported
Type of unsolicited local reaction	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was abscess, bleeding, etc.
Type of unsolicited systemic reaction	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was headache, nausea, athralgia, fatigue, etc
Seriousness	Baseline characteristics	Indonesia Vaccine Safety Website	Whether the AE was serious according to Indonesia MoH decree (require hospitalization, life-threatening, cause persistent or significant disability/ incapacity, or suspected to cause death) or non-serious

9.4. Data sources

In Indonesia Vaccine Safety Website for AEs reported following administration of BNT162b2 mRNA vaccine

9.5. Study size

This is a descriptive study without a statistical hypothesis and hence sample size calculation is not applicable. In this study all the AEs reported following administration of BNT162b2 mRNA vaccine

will be collected retrospectively from the onset of this vaccine administration in Indonesia till the time of approval of this study.

9.6. Data management

Data will be obtained from the Indonesia Vaccine Safety Website for AEs reported following administration of BNT162b2 mRNA vaccine as per the variables listed in section 9.3. A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection and analysis.

9.7. Data analysis

Descriptive Summary statistics will be presented to describe characteristics of events reports. Categorical covariates such as gender will be described by frequency distributions while continuous covariates such as age expressed will be summarized by in terms of their means and standard deviations or medians and interquartile ranges (IQR) as appropriate.

In addition, incidence rates will be computed as the number of events divided by the total number of vaccines administered.

All analyses will be done by Microsoft Excel

9.8. Quality control

Not applicable

9.9. Limitations of the research methods

This is a retrospective, observational study for secondary data collection and analysis of structured data regarding AEs reported in Indonesia NC AEFI database, following administration of BNT162b2 mRNA vaccine. The data availability will be contingent on the data provision by Indonesia NC AEFI post study approval by BPOM (Indonesia National Regulatory Authority). Since the data will originate and be owned by the Indonesia NC AEFI database, data validation and external quality control measures will not be applicable as a part of this study.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Patient withdrawal

Not applicable

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety
  2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891
- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).
  http://www.ispor.org/workpaper/practices_index.asp
- Good practices for real-world data studies of treatment and/or comparative effectiveness:
  Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in

health care decision making.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/

- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS).
https://cioms.ch/shop/product/international-ethical-guidelines-for-epidemiological-studies/
- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.
http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml
- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance
Practices and Pharmacoepidemiologic Assessment.
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/
ucm071696.pdf
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance
s/UCM243537.pdf
- FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.
http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the

minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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1. US FDA. Fact sheet for healthcare providers administering vaccine (vaccination providers): Emergency use authorization (EUA) of the Pfizer-Biontech COVID-19 vaccine to prevent coronavirus Disease 2019 (COVID-19); June 2022. https://www.fda.gov/media/159312/download accessed on 5 August 2022
2. BPOM. Fact Sheet For Health Care Providers Emergency Use Authorization (EUA) Of Comirnaty; July 2022.
3. Thomas SJ et al.; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021 Nov 4;385(19):1761-1773. doi: 10.1056/NEJMoa2110345. Epub 2021 Sep 15.
4. Thomas S.J., et al. (2021). "Safety and Efficacy of the BNT162b2 mRNACovid-19 Vaccine through 6 Months." *N Engl J Med.* 385(19):1761-1773. 2. Frenck, R. W., Jr., et al. (2021). "Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents." *N Engl J Med.* 385(3): 239-250. 3. Walter, E. B., et al. (2021). (2022) "Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age." *N Engl J Med.* 386(1):35-46.
5. Frenck RW Jr et al.; C4591001 Clinical Trial Group. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021 Jul 15;385(3):239-250. doi: 10.1056/NEJMoa2107456. Epub 2021 May 27.

6. Polack FP et al.; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 31;383(27):2603-2615. doi: 10.1056/NEJMoa2034577. Epub 2020 Dec 10.
7. Mulligan MJ et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020 Oct;586(7830):589-593. doi: 10.1038/s41586-020-2639-4. Epub 2020 Aug 12. Erratum in: Nature. 2021 Feb;590(7844):E26.

14. LIST OF TABLES

None

15. LIST OF FIGURES

None