125742/45 Data validation Report Summary and Subsequent follow-up with Pfizer

Our Reference: STN 125742/45 (studied under IND 19736/EUA 27034)

Sponsor: Pfizer-BioNTech SE

Product: COVID-19 (BNT162b2)

Proposed Indication: Prevention of COVID-19 in individuals 12 through 15 years of age

On December 16, 2021, the sBLA was submitted and included datasets for C4591001.

- **C4591001** - Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals. The proposed dosage is 30 µg via intramuscular (IM) injection following a dosing regimen of two 0.3-mL doses given 3 weeks apart. Data cutoff date is Sep 2, 2021.

On January 6, 2022, the eDATA team discussed the validation results of C4591001 with the review committee for STN 125742/45. Based on the validation results (beginning page 3 below) and a deeper dive into the study datasets, the following concerns were identified:

1. There are 2 subjects (10961068 and 11631062) with AE records that have AEACN = DRUG WITHDRAWN, but they only have COMPLETED records in DS. Please explain.
2. We have found that subject 11311279 was included in SDTM DM but not ADSL. Please explain.
3. As previously communicated and discussed under BLA 125742 and other BLAs/INDs reactogenicity events that begin within the prespecified assessment period should have been reported in FACE and summarized with the subject diary data in CE. Since this was not implemented, we request that:
    a. reactogenicity events that begin within the prespecified assessment period that are currently reported in the AE dataset be included in FACE, and then be flagged in AE so that we know that it is being included in the FACE dataset.
    b. Include all individual supporting assessments (daily e-diary and any unplanned assessments) and the assessor for each finding (identified using FAEVAL=STUDY SUBJECT or INVESTIGATOR) in the FACE domain.
    c. Maintain one row per subject/vaccination/symptom in the CE domain, with CE summarizing the duration of the event and maximum severity. Maximum severity (CESEV) should be based on the highest-level severity

reported by the subject (via e-diary) or investigator (in the unplanned assessment CRF).

d. Use SUPPCE CESEV1 and CEDIFFRS to show assessment of severity by study subject and reason investigator's assessment of severity differed from study subject as needed for events reported in CE.
e. Update the analysis dataset(s) with records covering the entire event duration (which could go beyond the protocol-defined assessment period) with start/end dates and durations (based on first and last days the symptom was present as recorded in the e-diary and/or Symptom Resolved Dates CRF, ignoring any gaps) derived from both the e-diary and CRF data.

These comments were conveyed to Pfizer on January 19, 2022. On February 2, 2022, Pfizer provided their responses in amendment 2.

In response to comment 1, Pfizer provided clarifications and also indicated that these subjects are not included in the analysis of the age group under review in this supplement as neither are adolescents.

In response to comment 2, Pfizer stated that Participant 11311279 was 15 years of age at the time of enrollment but turned 16 years of age at the time of vaccination, therefore, this participant was not included in the ADSL.

In response to comment 3, Pfizer indicated that the tabulation and analysis package submitted to FDA in the original 125742/0 submission on May 06, 2021 included the data to support the review for participants 12-15 years of age (in legacy tabulation datasets). With this response, Pfizer/BioNTech are providing additional documents including a roadmap, supplemental ADRG, reactogenicity tables with tracked changes, summary of differences between CSR and updated reactogenicity data, and reactogenicity supplemental TLFs. These are specific to the 12 to 15 year old adolescents.

All explanations are acceptable.

Data Fitness Findings Report

BLA125742

BioNTech SE and Pfizer, December 2021

Findings	Notes
C4591001 – 1mth - sBLA (12-15 Years of Age) **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.*	

Document / Standard	Version	Notes
annotated CRF		Seems fine
SDTM Implementation Guide	SDTM-IG v3.2	
SDTM Controlled Terminology	2020-03-27	
SDTM define.xml	V2.0	Seems fine
Medications Dictionary	WHODD GLOBALV3Mar20	
Medical Events Dictionary (MedDRA)	V23.1	
SDTM Reviewer's Guide	PhUSE template	Seems fine

From ADRG: All data up through 13Mar2021 cutoff are included in the SDTM datasets and used for ADaM datasets and analyses. Furthermore, any data related to the booster portion of the Phase 1 subjects was also programmatically excluded from SDTM data.

C4591001 – 6mth - sBLA Analysis for Participants, 12-15 Years of Age

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.*

Document / Standard	Version	Notes
annotated CRF		Seems fine
SDTM Implementation Guide	SDTM-IG v3.2	
SDTM Controlled Terminology	2020-03-27	
SDTM define.xml	V2.0	Seems fine
Medications Dictionary	WHODD GLOBALB3Mar21	
Medical Events Dictionary (MedDRA)	V24.0	
SDTM Reviewer's Guide	PhUSE template	Seems fine

From ADRG: All data up through 02Sep2021 cutoff are included in the SDTM datasets and used for ADaM datasets and analyses.

Data Issues	

The cSDRG/ADRG do not really clearly explain the difference in number of subjects/records between the 2 versions of data
• Study C4591001 1mth – **48,091** subjects total
  ○ Subjects included have ages from 12 to 91
• Study C4591001 6mth – **2,265** subjects total
  ○ Subjects included have ages from 12 to 15
  ○ Note that there are 42 additional subjects from the 1mth version, with ages from 12 to 15, that weren't included in the 6mth version of the data…but these are all SCREEN FAILURE or NOT ASSIGNED subjects	

There are subjects with AE records that have AEACN = DRUG WITHDRAWN, but they only have COMPLETED records in DS • Study C4591001 1mth – 2 subjects ○ See report "BLA125742 - c4591001 - 1mth - subjects with AE DRUG WITHDRAWN but only COMPLETED records in DS.xlsx"	

Application: BLA125742
Study: c4591001-6mth
EDR Sequence: 0211

Generated: 2021-12-28T17:14:00
Version: 2.5.3
Data Standards Training
EDR Link: \\cber-fs3\m\eCTD_Submissions\BLA125742\0211\m5\datasets\c4591001\tabulations\sdtm-6mth
EDR Link: \\cber-fs3\m\eCTD_Submissions\BLA125742\0211\m5\datasets\c4591001\analysis\adam\datasets-6mth

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 ADULTS

Summary

Documents

- SDTM Define.xml
- Study Data Reviewer's Guide
- ADaM Define xml
- Analysis Data Reviewer's Guide

Standards / Dictionaries

- SDTM-IG 3 2
- MedDRA 24.0

Subjects / Actual Arms

- 2265 - Subjects
- 1132 (50 0%) - B2_P23_30
- 1129 (49 8%) - PLACEBO
- 4 (0.2%) - Likely Not Treated

Datasets

- 42 - Total SDTM Datasets
- 0 - Custom Datasets
- 15 - Suppqual Datasets
- 9 - ADaM Datasets (ADAE, ADC19EF, ADCM, ADDS, ADDV, ADMH, ADSL, ADSYMPT, ADXB)

Reports to Help Basic Review Activities

Deaths
No mention of death in any dataset
Adverse Events
Adverse Events Coding Quality
Disposition
Disposition Coding Quality
Supplemental Info
Supplemental Contents

Potential Data Quality Findings

Demographics
53 of 2 265 (2.3%) RACE values not found in CDISC codelist
4 of 2,265 (0 2%) subjects have a different actual arm than planned
Disposition
16 of 15 919 (0.1%) disposition statuses or protocol milestones are potential duplicates
Exposure
59 of 6 511 (0.9%) treatments have ended after the last disposition date
Adverse Events and Potential Adverse Events
34 of 1,558 (2.2%) adverse events have started after the last disposition date
1 558 of 1 558 (100.0%) adverse events are missing treatment emergent flag in SUPPAE
480 of 1,558 (30.8%) adverse events have neither severity or toxicity grade populated
Clinical Events
169 of 54 538 (0.3%) events are missing start time-point
Laboratory
Laboratory results use inconsistent values for Standard Units (LBSTRESU)
1 of 645 (0 2%) observations are missing Reference Range Upper Limit in Standard Units (LBSTNRHI)
2 261 of 2 265 (99.8%) subjects are either missing a lab test or a baseline value
Vital Signs
No significant findings
General Findings
Study events are missing end time-points
Study subjects are missing all baseline flags for all tests present in the dataset
Traceability
1 of 2,265 (< 0.1%) subjects in SDTM DM are not included in ADSL
481 of 1 558 (30.9%) Adverse Events in SDTM AE are not present in ADAE