BLA 125742/EUA 27034 Data validation Report Summary and Subsequent follow-up with Pfizer

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

Sponsor: Pfizer-BioNTech SE

Product: COVID-19 (BNT162b2)

Proposed Indication: Prevention of COVID-19 in individuals 16 years of age and older.

On May 7, 2021 the BLA was submitted and included datasets for C4591001 and BNT162-01. However, prior to this time we had also received part of the datasets or all of the datasets in the EUA 27034 as described below.

On November 20, 2020, the sponsor submitted the Emergency Use Authorization for individuals 16 years of age and older. Two clinical trial datasets were submitted:

- **BNT162-01** - Phase 1/2, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of Four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-19 Using Different Dosing Regimens in Healthy Adults
- **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 datasets included analyses for follow-up up to 2 months after Dose 2.

On November 23, 2020, the eDATA team discussed the validation results with the review committee for EUA 27034. Three study datasets were validated – BNT162-01, C4591001-ia-efficacy (IA efficacy cutoff of Nov 4, 2020) and C4591001-safety-fa-eff (which is the final efficacy/EUA safety analysis- data cutoff of Nov 14, 2020).

On November 24, 2020 an IR was sent regarding clarification on discrepancies already found either by the clinical/stats reviewers or by the validation. On November 25, 2020, a teleconference was held with Pfizer in which they provided an explanation for the discrepancies.

Based on the validation results (beginning page 6 below) and a deeper dive into the study datasets, the following limitations were identified:

1. The datasets are not clean so results may not be entirely accurate.
2. There are events in CE that maybe should be in AE and there are events in AE that should be in CE
3. Temperature was not always reported in VS to back up "fever." Temperature was also missing for several of the days. Data is missing for the other solicited events also.

4. The signs and symptoms for those subjects with COVID-like symptoms but were determined to be negative for COVID were also reported in the FACE dataset. This is ok except many of them overlap events that could be considered systemic reactions to the vaccine. This is not reported as an AE and thus would not be included in the analysis.

5. In matching up COVID positive subjects with MH with BMI I have noticed that obesity is not consistently used across the board, e.g. one subject with BMI of 31.5 is marked as obese whereas another with BMI of 40.1 is not, so I don't think we can rely solely on the MH terms. Vital signs may be more accurate.

Even with these limitations, the datasets were still able to be used to confirm the safety and efficacy results following several IRs to Pfizer. The EUA for adults 16 years of age and older was authorized on December 11, 2020.

On March 15, 2021, Pfizer sent via email the following question regarding the planned BLA submission:

> Pfizer/BioNTech would like to make a further clarification on the SDTM mapping for reactogenicity data for C4591001. Specifically, Pfizer/BioNTech will provide the same mapping logic as in the EUA and also stated in the pre-BLA briefing document Section 1.3 whereby the SDTM mapping rules will be applied to provide a flat model (FACE, CE, VS, etc.) solely for reactogenicity data collected via e-diary per study design and data collection (e.g., not from an AE form). Pfizer/BioNTech will not be submitting a supplemental format schema as part of the BLA as most recently described in the Response to CBER Comment #1 of the 08 January 2021 Information Request regarding Trumenba (Meningococcal Group B Vaccine) submitted on 12 March 2021 (STN 125549/737). If required, Pfizer/BioNTech can submit tables using the new mapping if required. Does CBER agree?

On April 1, 2021, we responded to their question with the following:

> Your reference to a supplemental format schema as described under STN 125549/737 is unclear. We recommend standardizing the CE dataset format, as previously communicated in correspondences under IND 19736 and IND (b) (4) and summarized below:
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> • Reactogenicity events that begin within the prespecified assessment period but are currently reported in the AE dataset should be transferred from AE to FACE, or be flagged in AE so that we know that it is being included in the CE dataset.
>
> • Records covering the entire event duration (which could go beyond the protocol-defined assessment period) be created in the ADaM3 ADCEVD dataset 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.

• Include all individual supporting assessments (daily e-diary and any unplanned assessments) in the FACE domain and the assessor for each finding can be identified using FAEVAL (STUDY SUBJECT or INVESTIGATOR).

• 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).

• 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.

On April 8, 2021, a teleconference was held to discuss our request for the BLA submission. Pfizer agreed to include a separate set of datasets (supplemental tabulation and analysis) in which all "solicited events" whether it be from the diary or investigator are combined in the upcoming BLA.

On April 9, 2021, the sponsor submitted an amendment (132) to the EUA to extend the authorization to individuals 12-15 years of age. The data presented in this EUA amendment from pivotal study C4591001 (conducted under IND 19736) consists of the immune response measured by SARS-CoV-2 neutralizing antibody titers in this adolescent group compared to young adults 16-25 years of age, which serves as immunobridging for adolescents; efficacy data in the 12-15 years of age group; and safety data in approximately 2200 adolescents with a median follow-up time of at least 2 months after Dose 2. Additionally, safety data in adolescents are compared to the larger data safety data set of individuals 16-55 years of age. The datasets also contain the information from the adult portion of the study.

On April 14, 2021, the eDATA team discussed the validation results with the review committee for EUA 27034 amendment 132. One study's datasets were validated – C4591001 which included all 48,901 subjects. There were no major dataset concerns as the data were much cleaner. The datasets were additionally validated for only those subjects 55 years of age and younger (n=29, 417). See validation results for Part II (all subjects) and Part III (16 to 55 years of age) (beginning page … below).

The EUA for adolescents 12 to 15 years of age was authorized on May 10, 2021.

On May 7, 2021 the BLA was submitted and included datasets for C4591001 and BNT162-01. This BLA (STN 125742/0) contains cumulative follow-up from Dose 1 to 6 months after Dose 2, as well as updated Efficacy analyses in blinded placebo-controlled follow-up evaluated duration of protection (data cutoff date: 13 March 2021), and immunogenicity analyses of adults (18 to 85 years of age) including data up to 1 month after Dose 2 in Phase 2, and up to 6 months after Dose 2 in Phase 1. The updated datasets for C4591001 were also submitted to EUA 27034 amendment 132 so they do not need to be validated again. The updated datasets for BNT162-01 (6-Month Follow-Up Data from subjects 16 Years of Age and Older) were submitted in EUA 27034 amendment 174; however, they were not validated at that time.

For C4591001: As agreed by Pfizer, they also submitted a set of SDTM-SUPPL and ADaM-SUPPL, which is for: Supplemental analysis package created as a supplement to the BLA esub package to revise the reactogenicity SDTM and ADaM data to address the agreements made with CBER. SDTM includes DM, EX and updated domains (AE, CE, FACE, VS, SUPPAE, SUPPCE, SUPPFACE, SUPPVS, RELREC), define and aCRF. ADaM includes ADSL and updated datasets (ADAE, ADCEVD, ADFACEVD). Based on what needed to be reviewed with this data we determined that the supplemental datasets did not need to be validated.

On May 18, 2021, an IR was sent regarding the C4591001 datasets submitted thus far and Pfizer responded with the following:

1. Pfizer/BioNTech confirm that the datasets submitted in the EUA 27034-amendment 132 are identical to the datasets submitted to BLA STN 125742/0.
2. Pfizer/BioNTech confirm that the datasets submitted as SDTM-SUPPL and ADaM-SUPPL contain the reactogenicity data changes as requested (including flags) in the teleconference held on April 8, 2021 and nothing additional.
3. No data were changed in the supplemental EX and DM datasets. They were included in the supplemental package because these two datasets would be required for pinnacle 21 check in case FDA wants to run its own check.

For study BNT162-01, we only needed to look at immunogenicity data for 24 subjects that received BNT162b2 (12 subjects in the 18-55 age group and 12 subjects in the 56-85 yr age group who received the 30mcg dose) so validation is not necessary. I looked at the DM, IS and EX datasets to determine if data was acceptable. Immunogenicity data was not provided for 12 of the 24 subjects.

On June 8, 2021, an IR was sent requesting the immunogenicity data for the 12 subjects in BNT162-01. Pfizer responded on June 16, 2021 (amendment 6). They indicated that the data were not available at the time of immunogenicity cut-off for this report because the samples were put on hold due to necessary testing prioritizations at the Pfizer labs (eg C4591001 6-month stability and booster; C4591007). Pfizer has now resumed testing of these samples and an updated BNT162-01 study report will be provided once it is available. Pfizer did not believe

these data to be material to the review of the BLA. Please see clinical review regarding the immunogenicity data results.