COVID-19 Vaccine (BNT162, PF-07302048)

IND 19736

Request for Comments and Advice Regarding Adolescent (12-15 Years of Age) Supplemental BLA Proposed Clinical Package

August 2021

1. INTRODUCTION

Reference is made to Investigational New Drug (IND) 19736 for COVID-19 mRNA Vaccine (BNT162; PF-07302048), which Pfizer and BioNTech are developing for the indication of active immunization to prevent COVID-19 caused by SARS-CoV-2. The IND was effective on 29 April 2020.

Reference is also made to Biologics License Application (BLA) STN 125742/0 for COVID-19 mRNA Vaccine (COMIRNATY) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age, currently under review by CBER.

Individuals 12-15 years of age are currently eligible for vaccination with the COVID-19 mRNA Vaccine (Pfizer-BioNTech COVID-19 Vaccine) under Emergency Use Authorization (EUA 27034) which was authorized by CBER on 10 May 2021.

Pfizer/BioNTech are planning for a supplemental BLA (sBLA) for the COVID-19 mRNA Vaccine for the adolescent (12-15 years of age) group in pivotal Phase 1/2/3 Study C4591001. The present submission provides a Request for Comments and Advice regarding the proposed scope of this sBLA.

Pfizer/BioNTech respectfully request CBER's feedback by 17 August 2021.

2. QUESTIONS FOR CBER

2.1. Question 1

Does CBER agree with the proposed clinical safety analyses in the planned sBLA to support an indication for individuals ≥12 years of age?

Pfizer/BioNTech propose the same approach used for BLA 125742 that included data from approximately 44,000 participants ≥16 years of age, among whom approximately 12,000 had at least 6 months of follow-up after Dose 2 of BNT162b2. The sBLA would include safety data for all of the approximately 2200 participants 12-15 years of age enrolled in Study C4591001, among whom approximately 1100 would have at least 6 months of follow-up after Dose 2 of BNT162b2. Participants have been unblinded to treatment assignment as they have become eligible for vaccination under EUA; therefore safety data would be presented from blinded placebo-controlled and open-label periods as follows:

a. *Blinded placebo-controlled period*: Dose 1 to 1 month after Dose 2, and Dose 1 to the unblinding date, for Phase 3 participants 12-15 years of age randomized 1:1 to BNT162b2 vs placebo
   - Safety subgroup analyses by sex, race, ethnicity, and baseline SARS-CoV-2 status from Dose 1 to the unblinding date

b. *Open-label observational period*: unblinding date to the sBLA data cutoff date
   - Phase 3 participants 12-15 years of age originally randomized to BNT162b2

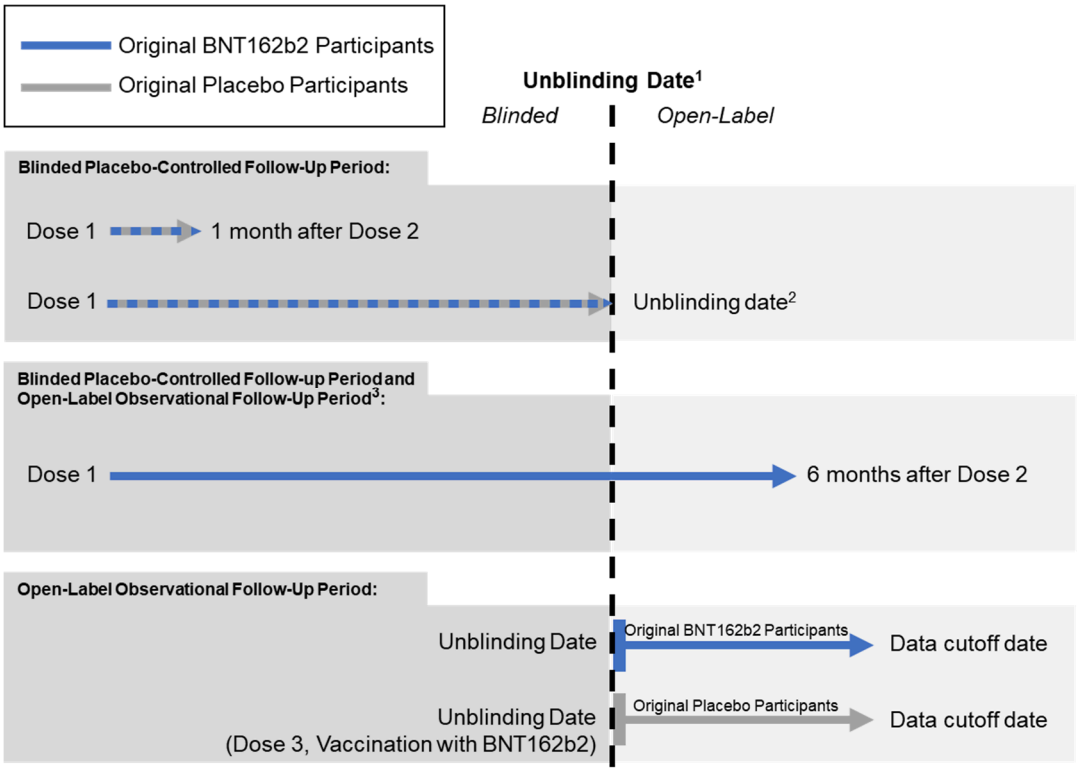
- Phase 3 participants 12-15 years of age originally randomized to placebo (Dose 1 and Dose 2) who then received open-label BNT162b2 (Dose 3 and Dose 4)
  - Safety subgroup analysis of participants originally randomized to placebo who had confirmed COVID-19 prior to unblinding to receive open-label BNT162b2

c. *Cumulative follow-up from Dose 1 to 6 months after Dose 2*: Phase 3 participants 12-15 years of age originally randomized to BNT162b2 (inclusive of blinded data and open-label data)

Note that AE analyses which begin or end at the unblinding date would be summarized as incidence rates (IR) adjusted for exposure time to account for variable timing of unblinding for individual participants (per protocol) to receive BNT162b2 under EUA.

The analysis of safety by time period and analysis group is illustrated in Figure 1.

Figure 1. Study C4591001 Phase 3 Safety Analysis Time Periods and Analysis Groups



Dashed horizontal blue/gray line indicates randomized blinded BNT162b2 vs placebo vaccination period.
Dose 3 refers to first of two doses of open-label BNT162b2 administered to participants originally randomized to placebo (Dose 1 and Dose 2) who then received open-label BNT162b2 (Dose 3 and Dose 4)

[1] AE data analyzed from Dose 1 to the unblinding date or from unblinding date to the sBLA data cutoff date will be reported as incidence rates per person-years adjusted for exposure time (which varies per participant).
[2] Blinded placebo-controlled follow-up period until unblinding has duration of <6 months after Dose 2.
[3] Cumulative follow-up is to ≥6 months after Dose 2 for participants originally randomized to the BNT162b2 group, inclusive of blinded and open-label data.

2.2. Question 2

Does CBER agree with the proposed criteria for safety narratives in the planned sBLA for Study C4591001 participants 12-15 years of age?

Hybrid (programmed and prose) narratives would be prepared for participants 12-15 years of age using the same criteria as agreed by CBER for the EUA and BLA:

- Deaths, vaccine-related SAEs, safety-related withdrawals
- AEs of interest requested by FDA* (ie, anaphylaxis, Bell's palsy, appendicitis, and pregnancy exposures and outcomes, myocarditis/pericarditis)
- AEs corresponding to the CDC list of AEs of special interest (AESIs) for COVID-19, if there is a numerical imbalance with a higher frequency (or incidence rate) in the BNT162b2 group vs placebo group for events that led to withdrawal, considered to be vaccine-related, or otherwise considered biologically plausible.
- COVID-19 cases for participants with severe and/or multiple episodes.

* In lieu of individual narratives on lymphadenopathy, which typically are related AEs with little additional information, we propose to provide programmed tables summarizing incidence, timing relative to Dose 1 or 2, duration, severity, and resolution of events.

2.3. Question 3

Does CBER agree that the planned sBLA can be comprised of safety and efficacy data through at least 6-month follow-up for Study C4591001 participants 12-15 years of age?

Immunogenicity and efficacy data in the 12-15 years of age group were previously submitted for EUA. These data demonstrated that BNT162b2-elicited immune responses in the 12-15 years of age group were noninferior to immune responses in the 16-25 years of age group, meeting immunobridging success criteria, and participants 12-15 years of age had an observed vaccine efficacy of 100%.

In addition to proposed safety analyses (see Question 1), we propose the sBLA to include updated efficacy analyses of confirmed COVID-19 cases accrued in placebo-controlled blinded follow-up through the sBLA data cutoff date, similar to the updated efficacy analyses performed for the BLA, but limited to the 12-15 years of age group. Given that successful immunobridging has already been demonstrated for this group, no new immunogenicity analyses are planned to be performed for the sBLA.

In order to expediently submit an sBLA to obtain licensure for individuals ≥12 years of age, ideally by early 4th quarter 2021, we propose to submit only updated safety and efficacy data in the sBLA. If CBER requires submission of updated immunogenicity data, this will delay the sBLA submission due to the additional time needed to analyze the data. We estimate this could result in submission of the sBLA at the end of 4th quarter 2021 or early 2022.

2.4. Question 4

Does CBER agree with the proposal to submit an sBLA with clinical documents limited to an interim Clinical Study Report and a Module 2.5 Clinical Overview to report 6-month follow-up data from Study C4591001 participants 12-15 years of age?

The proposed sBLA data are derived from a single study/group and can be fully described in an interim Clinical Study Report and in a Module 2.5 Clinical Overview (in which additional benefit:risk context can be provided).

Module 2.7.3 (Summary of Clinical Efficacy) and Module 2.7.4 (Summary of Clinical Safety) would not include any additional or unique content.

Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
Harkins Tull, Elisa	03-Aug-2021 12:37:11	Regulatory Affairs Approval