Ramachandra Naik -S

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS

DATE: **September 24, 2021** **PAGES: 4**

TO: **BioNTech SE/Pfizer., Inc.**
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FROM: **Ramachandra Naik, Ph.D.**
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CBER Reference: IND 19736 amendment 434

IND Title: Human Coronavirus mRNA Vaccines (SARS-CoV-2 Spike Protein; BNT162a1 (uRNA; variant RBL063.3); BNT162b1 (modRNA; variant RBP020.3); BNT162b2 (modRNA; variant RBP020.2); BNT162c2 (saRNA; variant RBS004.2)) in Lipid Nanoparticles (ALC-0315, ALC-0159, DSPC and Cholesterol)

SUBJECT: CBER responses to the Request for Comments and Advice regarding the supplemental BLA for adolescents 12 through 15 years of age

Dear Mr. Patel:

Reference is made to amendment 434 (dated August 3, 2021) to your IND 19736 that contained a Request for Comments and Advice regarding a proposal to submit a supplemental Biologics License Application (sBLA) to expand the indication to include use in adolescents 12 through 15 years of age. We have the following responses to the questions you posed in the Request for Comments and Advice document.

Sponsor 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?

FDA Response to Question 1:
We have the following additional requests for the clinical safety analyses in the planned sBLA for individuals ≥12 years of age:

a. In addition to the listed safety analyses, please include an interim summary of new or updated safety events that occurred/have been updated since the data cutoff used for the EUA Amendment submission for individuals 12 through 15 years of age, using the same time periods, and insert a flag into the datasets to indicate which safety events are new/updated.

b. Please submit the safety data and results for this age group from the dose ranging portion of Study C4591007, to support the selected dose level for this age group.

c. In addition to the AE analyses provided as incidence rates to account for exposure time, please also provide all AE analyses to summarize the number/percentage of subjects with each AE, regardless of exposure time.

Sponsor 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?

FDA Response to Question 2:
We have the following additional requests for the proposed criteria for safety narratives in the planned sBLA for individuals ≥12 years of age:

a. Please include hyperlinks from the interim study report to the narrative document, which will identify the specific subject narrative location within the narrative document.

b. Please include participant listings for all AEs, which include actual study arm, age, sex and race and time to event from last vaccination.

c. With regards to the proposed programmed tables summarizing lymphadenopathy events, please report these by treatment group, include absolute numbers of the events, and provide narratives for any lymphadenopathy events that meet criteria as outlined for SAEs, safety-related withdrawals, or any other criteria.

d. Please submit any safety narratives for this age group from the dose ranging portion of Study C4591007, that also meet the stated criteria.

Sponsor 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?

FDA Response to Question 3:
We agree that updated efficacy analyses of confirmed COVID-19 cases accrued in the placebo-controlled blinded follow-up period through the sBLA data cutoff will be sufficient, and additional immunogenicity evaluations will not be requested from Study C4591001. We have the following additional requests:

a. Similar to the BLA package, please submit the following additional information:

   i. for all confirmed COVID-19 cases contributing to the vaccine efficacy analysis, please provide available viral sequencing information to identify the SARS-CoV-2 strain for each case and a summary of the variants of concern and variants of interest, and

   ii. a post-hoc analysis of breakthrough cases [i.e., protocol-specified COVID-19 cases accrued during the current delta variant surge (e.g., during a defined time period beginning July 1, 2021 and through the data cut-off)] comparing participants who completed the 2-dose vaccination series early in the study (i.e., those who were originally randomized to BNT162b2) vs. those who completed the 2-dose vaccination series later in the study (i.e., those who were originally randomized to placebo and then crossed over to BNT162b2).

b. Please submit the data and immunogenicity results for this age group from the dose ranging portion of Study C4591007, to support the selected dose level for this age group.

Sponsor 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?

FDA Response to Question 4:
We have the following comments regarding the clinical documents for inclusion with the planned sBLA for individuals ≥12 years of age:

a. Please refer to our response to Question 1; this interim summary of safety events that occurred or have been updated since the data cutoff for the EUA Amendment can be provided within the interim Clinical Study Report or as a stand-alone document. Please alert us to the location of this information within the submission.

b. Because the data, analyses, and your interpretation of the dose-ranging portion of Study C4591007 are expected to be part of the planned sBLA submission, please plan to revise your proposal to include an interim Clinical Study Report for Study C4591007, limited to the 12 through 15 year age group, to describe the dose-ranging portion of the study. Because the number of subjects 12 through 15 years of age evaluated in Phase 1 of Study C4591007 is small, we agree that Summaries of Clinical Efficacy and Safety in Module 2 would not be required for the planned sBLA submission.

Additional FDA Questions/Comments:

1. We also request that the data and analyses from the Postmarketing Required Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of COMIRNATY in a subset of participants 5 through 15 years of age be submitted to inform the risk benefit analysis of the proposed sBLA for individuals ≥12 years of age.

2. We will also provide shell tables specific to this sBLA submission for individuals ≥12 years of age.

Please provide your responses in an amendment to your IND 19736. In your reply to this communication, we recommend that you restate the item and follow it with your response. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference.

END