Mid-Cycle Meeting Summary

Application type and number: sBLA STN 125742/45

Product name: COVID-19 Vaccine, mRNA (COMIRNATY)

Proposed Indication: Active immunization to prevent coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older

Applicant: BioNTech Manufacturing GmbH

Meeting date & time: April 7, 2022; 11:00 AM – 12:30 PM EDT

Committee Chair: Ramachandra Naik, PhD

RPMs: CAPT Michael Smith, PhD and Laura Gottschalk, PhD

Background:
COMIRNATY (COVID-19 Vaccine, mRNA) was originally approved on August 23, 2021, for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. The current application, received on December 16, 2021, is an efficacy supplement from BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.) for COMIRNATY to extend the indication to adolescents 12 through 15 years of age.

The purpose of this meeting was to discuss the progress of the review; identify and present substantive issues/major deficiencies and plans to address substantive issues; plan the remainder of the review including dates for further deliverables and interactions; and obtain supervisory feedback.

Table 1: Review Committee (bold font indicates attendance at the meeting)

Review Responsibility	Committee Member	Team Leader/Supervisor	Division Director (and DDD)
Chair	**Ramachandra Naik, PhD**	**BC: Elizabeth Sutkowski, PhD**	**DD: Loris McVittie, PhD** **SA: Kirk Prutzman, PhD**
Regulatory Project Managers	**CAPT Mike Smith, PhD** **Laura Gottschalk, PhD**	**BC: Elizabeth Sutkowski, PhD**	**DD: Loris McVittie, PhD** **SA: Kirk Prutzman, PhD**
Clinical	**Susan Wollersheim, MD**	**TL: Lucia Lee, MD** **BC: Maria Allende, MD**	**DD: Doran Fink, MD, PhD** **SA: Rebecca Reindel, MD** **Douglas Pratt, MD**
DVP – CMC	**Xiao Wang, PhD**	**LC: Keith Peden, PhD** **Cc: Anissa Cheung, MSc**	DD: Jerry Weir, PhD **DDD: Robin Levis, PhD**
Statistics – Clinical (Immunogenicity and Safety)	**Ye Yang, PhD**	**TL: Lei Huang, PhD** **BC: Tsai-Lien, PhD**	DD: John Scott, PhD **DDD: Shiowjen Lee, PhD**
Epidemiological/ Pharmacovigilance	**Deborah Thompson, MD, MSPH**	**BC: Manette Niu, MD**	**DD: Narayan Nair, MD** DDD: Meghna Alimchandani, MD

Benefit-Risk Assessment Real World Evidence	**Hong Yang, PhD** **Osman Yogurtcu, PhD** **Patrick Funk, PhD** **Yun Lu, PhD**	**Sup: Richard Forshee, PhD** **Sup: Richard Forshee, PhD**	
BIMO	**Kanaeko Ravenell** **Char-Dell Edwards**	**BC: Dennis Cato**	**DD: Carrie Mampilly, MPH**
APLB Labeling	**CAPT Oluchi Elekwachi, PharmD, MPH**	**BC: Lisa Stockbridge, PhD**	**DD: Robert Sausville**
CDISC Consult	**Brenda Baldwin, PhD**	**BC: Elizabeth Sutkowski, PhD**	**DD: Loris McVittie, PhD** **SA: Kirk Prutzman, PhD**

Additional attendees: Steven Anderson, David Cho, Tatiana Claro da Silva, Karen Farizo, Theresa Finn, Cara Fiore, Brynn Hollingsworth, Sana Hussain, Hector Izurieta, Meghan MaguireThon, Peter Marks, Sylvia Park, David Rouse

Review Timetable (PDUFA Milestones are in blue)

Review Milestone	**Target Due Date**
Submitted:	16-DEC-2021
Received:	16-DEC-2021
Committee Assignment:	30-DEC-2021
First Committee Meeting:	06-JAN-2022
Filing reviews complete:	25-JAN-2022
Confirm BIMO (GCP) Inspection Sites	30-JAN-2022
Filing Meeting:	31-JAN-2022
Filing Action:	14-FEB-2022
Deficiencies Identified:	28-FEB-2022
Primary Draft Reviews & Reviewer Reports Due (4 days prior to Mid-Cycle meeting):	01-APR-2022
Determine if Advisory Committee Meeting is Necessary:	16-MAR-2022
Mid-Cycle Meeting (Internal):	**07-APR-2022**
Notify Safety Working Group (SWG)	18-APR-2022
PeRC Briefing materials due:	19-APR-2022
PeRC Meeting:	03-MAY-2022
Labeling Comments to Applicant:	18-MAY-2022
Final draft primary reviews with supervisory Concurrence (upload not required):	18-MAY-2022
Notify OCOD of pending approval:	18-MAY-2022
Notify Applicant of PMC/PMR:	18-MAY-2022
Final reviews & addenda signed & uploaded:	12-JUN-2022
PDUFA ADD:	**17-JUN-2022**

Table 2: Scheduled Meetings

PDUFA Meetings:
First Committee Meeting: January 6, 2022 (by email)
Filing Meeting: January 31, 2022, 12:00PM – 1:00PM
Internal Mid-Cycle: April 7, 2022, 1:00PM-2:30PM

Monthly Committee Meetings:
March 2, 2022; 1:00 – 2:00 pm
May 6, 2022; 12:30 – 1:30 pm
Labeling Meetings:
April 8, 2022 (w/o MGMT); 12:30 – 2:00 pm
April 20, 2022; 2:00 – 4:00 pm
April 21, 2022; 3:00 – 5:00pm
May 3, 2022; 3:00 – 5:00pm
May 11, 2022; 2:00 – 4:00pm

Discussion Summary:

- The ADD for the supplement, June 17, 2022, was discussed in the context of submissions related to COVID-19 vaccines in the near future. Due to the increased OVRR workload anticipated for June, the ADD may be difficult to meet. Therefore, the review team will complete as much as possible in the next month with a check-in to occur in early to mid-May to determine if the action on the sBLA can be taken before the end of May or if it will need to be deprioritized to take action after June 17th.

- The clinical reviewer presented the key findings from the supplement and also highlighted the differences between the data that were submitted to support the EUA versus the sBLA.

Report and Discuss:

1. Reviewer Reports

   a. Clinical (Susan Wollersheim)
      - The review is ongoing and no substantive issues have been identified.
      - The remaining items to be reviewed/completed are:
        i. Subgroup analyses for immunogenicity and safety
        ii. Narrative details of SAEs
        iii. PeRC paperwork
      - PMR/PMC studies are not needed.
      - Target date the review will be completed: May 2, 2022. Moving the deadline upwards will depend on supervisory input and their workload.

   b. Biostatistics (Ye Yang)
      - The review is ongoing, and no substantive issues have been identified.
      - Target date the review will be completed: May 31, 2022
      - The majority of the review is completed. The date of completion is flexible, and it can be moved up if needed.

- There have been minor updates to the solicited reactions and immunobinding data, and these updates will need to be included in the PI.

c. Benefit-Risk Assessment (Hong Yang, Osman Yogurtcu and Patrick Funk)
    - The real-world effectiveness data for this age group are similar to those for the older pediatric age group 16-18 years of age. The vaccine efficacy information included in the submission is also similar between these age groups.
    - We do not expect new data for myocarditis in this age group from FDA BEST due to limited sample size. However, available VAERS data and data from Israel indicated a relatively lower myocarditis risk for this age group compared to the group 16-18 years of age.
    - A recently conducted seroprevalence study by the CDC demonstrated that about 57% of the unvaccinated population tested positive for SARS-CoV-2 antibodies, indicating a great extent of exposure to the SARS-CoV-2 among the unvaccinated population. The reviewers questioned how much protection prior exposure could provide, and how this could potentially lower the benefit of the vaccine.
    - Management summarized several studies which demonstrate an added benefit of vaccination for individuals with prior infection; therefore, there is agreement that there are still added benefit from the vaccination for the people with prior infection. Management will share the referenced studies/presentations with the reviewers. [Post-meeting note: Management shared the CDC slides and other literature with the reviewers.]
    - The reviewers will review the information and vaccine benefit. Additional quantitative benefit-risk analysis may not be needed for this age group.
    - Target date the review will be completed: May 18, 2022 (can be flexible if needed).

d. Real World Evidence (Yun Lu)
    - Target date the review will be completed: May 18, 2022 (can be flexible if needed).
    - Real World Evidence (RWE) studies show high effectiveness in this age group. However, the studies that were submitted were conducted during the pre-Delta or Delta predominant period, and there is no RWE associated with this age group during the Omicron predominant period.
    - The reviewer does not consider this a major concern since there are publications outside of this submission which can be reviewed. She will look for new publications with Omicron data and will update the team.

e. Epidemiology/Pharmacovigilance (Deborah Thompson)
    - Date the review will be completed: Review is complete.
    - No substantive issues were identified, and the draft review memo is under supervisory review.

- The PMRs and PMCs are the same as those identified in the August 23, 2021, Comirnaty Approval Letter. During the authorization of emergency use for younger age groups, including adolescents 12-15 years of age, we requested that relevant age groups be included in post-authorization studies. PMRs #7, #8 and #9 are specifically focused on younger age groups and include individuals 12-15 years of age. The respective protocols have already been revised, if needed, to include this age group with the exception of PMC #10 Pregnancy Registry Study (C4591022). An IR will be sent asking the sponsor to revise the Pregnancy Registry Study protocol and SAP to include pregnant individuals of all ages.
- No safety issues have been identified that would warrant new PMRs or PMCs. The clinical reviewer concurred with this decision.

f. BIMO (Kanaeko Ravenell and Char-Dell Edwards)
   - Target date the review will be completed: 30 days after receipt of the completed Establishment Inspection Report (EIR) package.
   - All BIMO inspections have been completed and no FDA form 483s were issued. The review will be completed within two weeks of receiving the EIRs if the reviewer concurs with ORA's recommendations.

g. CMC (Xiao Wang)
   - Target date the review will be completed: April 15, 2022.
   - There are no updates at this time, and no substantive issues have been identified.

h. APLB (Oluchi Elekwachi)
   - Target date the review will be completed: May 10, 2022.
   - Comments will be discussed during the upcoming labeling meetings.

i. CDISC (Brenda Baldwin)
   - Target date the review will be completed: by the end of April 2022.
   - There are no new comments at this time.

2. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.
   No. At the January 31, 2022 Filing meeting, DVRPA management confirmed that this application does not need to go to VRBPAC.

3. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.
   No safety issues have been identified that would warrant new PMRs or PMCs beyond those that were included in the August 23, 2021 Approval Letter for the original Comirnaty BLA (STN 125742/0).

4. National Drug Code (NDC) assignments to product/packaging (excludes devices).
   N/A

5. Proper naming convention.
   N/A

6. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).
   No GMP inspections are needed.
   Three clinical inspections were issued on February 17, 2022, and all BIMO inspections are completed. No additional BiMO inspections are anticipated for this submission.

Review

7. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g., Late-Cycle meeting, Advisory Committee, labeling discussion).
   Please see Review Timetable above.

8. Establish a labeling review plan and agree on future labeling meeting activities.
   Please see Table 2 above for all scheduled labeling meetings. The first labeling meeting, without management, is scheduled for April 8, 2022. Labeling comments must be sent to the Applicant no later than May 18, 2022.

Confirm, as applicable

9. Components Information Table was obtained, and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.
   Not Applicable as there is no change in product formulation/information.

10. New facility information is included in the application, requiring implementation of regulatory job aid JA 910.01: Manufacturing Facility Data Entry . If not complete, indicate date it will be completed.
    N/A

11. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.
    N/A

12. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid JA 900.01: Unique Ingredient Identifier (UNII) Code for additional information.
    N/A

13. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.
PeRC review is scheduled for May 3, 2022, and materials are due by April 19, 2022.

14. **Information Requests**

1. 01/19/2022: Three questions regarding datasets.

2. 01/25/2022: Request for an updated FDA form 356h and an Environmental Assessment or claim of Categorical Exclusion.

3. 02/23/2022: Two questions on cumulative analysis of post-authorization adverse event reports.

4. 03/07/2022: Two clinical-statistical comments regarding updated immunobridging analyses and solicited adverse reaction frequencies

5. 03/14/2022: Statistical follow-up IR re: Pfizer's response in STN 125742/45.4 to our 03/07/2022 clinical and statistical questions.

15. **Amendments**

1. STN 125742/45.1 (01/28/2022) – Response to 01/25/2022 request regarding submitting (1) updated Form 356h to include information regarding all establishments and manufacturing facilities, and (2) an Environmental Assessment or Claim of Categorical Exclusion.

2. STN 125742/45.2 (02/02/2022) – Response to 01/19/2022 request regarding datasets.

3. STN 125742/45.3 (03/01/2022) – Response to 02/23/2022 request regarding cumulative analysis of post-authorization adverse event reports.

4. STN 125742/45.4 (03/11/2022) – Response to 03/07/2022 request regarding two clinical-statistical comments on updated immunobridging analyses and solicited adverse reaction frequencies.

5. *STN 125742/45.5 (03/15/2022) – Request for comments and advice on acceptability of applying for licensures of a booster dose for adolescents 12 through 15 years of age in the same sBLA planned to apply for licensure of a booster dose for individuals 16 years of age and older as a single submission.*

6. *STN 125742/45.6 (03/16/2022) – Request to withdraw amendment 5, request for comments and advice.*

7. STN 125742/45.7 (03/18/2022) - Response to 03/14/2022 request regarding statistical follow-up IR re: Pfizer's response in STN 125742/45.4 to our 03/07/2022 clinical and statistical questions.

Concurrence Page for the Meeting Summary

Application Type and Number: BLA 125742/45

Communication Type: Mid-Cycle Meeting Summary

Review History: Sent for review via email to the following:

4/18/2022: Susan Wollersheim, Lucia Lee, Maria Allende, Elizabeth Sutkowski, Xiao Wang, Keith Peden, Anissa Cheung, Ye Yang, Lei Huang, Tsai-Lien Lin, Deborah Thompson, Manette Niu, Hong Yang, Osman Yogurtcu, Patrick Funk, Tun Lu, Kanaeko Ravenell, Char-Dell Edwards, Dennis Cato, Oluchi Elekwachi, Lisa Stockbridge, Brenda Baldwin, Tatiana ClarodaSilva, Cara Fiore, Brynn Hollingworth, Sans Hussain, Sylvia Park, David Rouse, Richard Forshee

4/21/2022: Douglas Pratt, Rebecca Reindel, Doran Fink, Loris McVittie, Kirk Prutzman, Shiowjen Lee, Robin Levis, Narayan Nair, Carrie Mampilly, Robert Sausville, Steven Anderson, David Cho, Karen Farizo, Theresa Fill, Peter Marks

Concurrence:

Office/Division	Name	Signature/Date
OVRR/DVRPA	Laura Gottschalk	Laura B. Gottschalk -S Digitally signed by Laura B. Gottschalk -S Date: 2022.04.26 12:00:07 -04'00'
OVRR/DVRPA	Michael Smith	Michael J. Smith -S4 Digitally signed by Michael J. Smith -S4 Date: 2022.04.26 12:20:38 -04'00'
OVRR/DVRPA	Ramachandra Naik	Ramachandra Naik -S Digitally signed by Ramachandra Naik -S Date: 2022.04.26 12:22:34 -04'00'
OVRR/DVRPA	Loris McVittie	Loris D. Mcvittie -S Digitally signed by Loris D. Mcvittie -S Date: 2022.04.27 13:25:19 -04'00'

Laura B. Gottschalk -S
Digitally signed by Laura B. Gottschalk -S
Date: 2022.04.28 09:49:48 -04'00'