U.S. FOOD & DRUG ADMINISTRATION

MAY MONTHLY MEETING SUMMARY

Application number:	BLA 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:	May 6, 2022; 12:30 - 1:30 PM EST
Committee Chair:	Ramachandra Naik, Ph.D.
Meeting Recorders:	CAPT Michael Smith, Ph.D. and Laura Gottschalk, Ph.D.

Laura B. Gottschalk -S
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1. 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 any issues, and plan the remainder of the review, including if action can be taken on this supplement before the end of May or if it will need to be deprioritized to take action after June 17, 2022.

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** BD: Tsai-Lien, PhD	**DD: John Scott, PhD** **DDD: Shiowjen Lee, PhD**

Epidemiological/Pharmacovigilance Benefit-Risk Assessment Real World Evidence	**Deborah Thompson, MD, MSPH** **Hong Yang, PhD** **Osman Yogurtcu, PhD** **Patrick Funk, PhD** **Yun Lu, PhD**	BC: Manette Niu, MD **Sup: Richard Forshee, PhD** **Sup: Richard Forshee, PhD**	**DD: Narayan Nair, MD** **DDD: Meghna Alimchandani, MD**
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
CDSIC Consult	**Brenda Baldwin, PhD**	BC: Elizabeth Sutkowski, PhD	**DD: Loris McVittie, PhD** **SA: Kirk Prutzman, PhD**

Additional Attendees: Steven Anderson, Karen Farizo, Theresa Finn, Meghan Maguire Thon, and Ujwani Nukala

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):	31-MAR-2022
Mid-Cycle Meeting (Internal):	06-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:	20-APR-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 6, 2022, 1:00PM-2:30PM
Monthly Committee Meetings:

March 2, 2022; 1:00 – 2:00 pm
May 6, 2022; 3:00 – 4:00 pm
Labeling Meetings:
April 8, 2022 (w/o MGMT); 12:30 – 2:00 pm
April 20, 2022; 2:00 – 4:00 pm (First set of comments sent)
May 3, 2022; 3:00 – 5:00pm
May 11, 2022; 2:00 – 4:00pm

2. Discussion Topics

2.1 Opening remarks from the Chair and RPMs

- Currently only one outstanding Information Request (IR).
- The submission was discussed at the May 3rd PeRC meeting and PeRC agreed with the pediatric assessment.
- Labeling negotiations for the PI are almost completed with two outstanding items to be addressed:
  1. Clarification on the number of nausea events in dataset (current outstanding IR)
  2. Chemical name used for ALC-0159 in section 11

2.2 Review of milestones and internal/projected target dates

2.3 Status update from each member of the review committee

- Clinical (Susan Wollersheim):
  - Previously provided targeted review completion date: May 6, 2022.
  - No new issues have been identified and the review is almost complete. The clinical team is waiting on the last outstanding IR to clarify the number of nausea events in the dataset so that the number is accurate in label for placebo recipients.
- Statistics (Lei Huang):
  - Previously provided targeted review completion date: May 31, 2022
  - No substantial issues have been identified and the statistical team is also waiting on the response for the last outstanding IR. The statistics review is almost complete.
- Benefit-Risk assessment (Hong Yang, Osman Yogurtcu and Patrick Funk):
  - Previously provided targeted review completion date: May 18, 2022
  - A quantitative analysis was conducted for ages 16 and 17 years during the original BLA. The reviewers acknowledged that the benefits of the vaccine are lower now with the spread of Omicron variant and more widespread

seroprevalence than August of 2021 when Delta was the predominant variant. However, this lowered benefit is not specific to this age group. Additionally, the risk of myocarditis is lower in ages 12 through 15 years than 16 through 17 years. Both benefit and risk are lower in this age group, but that does not seem to change the overall balance; therefore, a formal calculation of benefit-risk will not be done for this submission. There is no clear reason not to approve this supplement based on the safety and effectiveness data and post-authorization experience that we have.

- The reviewer also presented slides demonstrating a decreased benefit for individuals who were vaccinated within 6 months of a prior SARS-CoV-2 infection, but it was noted that this lowered benefit is not specific to COMIRNATY or this age group. It was agreed that this lowered benefit (b) (5) does not need to be included in the COMIRNATY label. (b) (5)

- Real World Evidence (Yun Lu):
  - Previously provided targeted review completion date: May 18, 2022
  - Additional articles containing real world evidence of vaccine effectiveness against Omicron variant in this age group are being reviewed since none were included in the submission.

- Epidemiology/Pharmacovigilance Plan (Deborah Thompson):
  - The review is complete and is being routed for signature.
  - There were no new safety issues for this submission that would require new PMCs or PMRs.

- BIMO (Kanaeko Ravenell and Char-Dell Edwards):
  - Previously provided targeted review completion date: 30 days after receipt of the completed Establishment Inspection Report (EIR) package.
  - All three clinical investigations for the supplement are completed and no 483s were issued. BIMO will complete their review and memo by end of May 2022.

- CMC (Xiao Wang):
  - The CMC review is complete, and the memo was uploaded on May 2, 2022.

- APLB (Oluchi Elekwachi):
  - Previously provided targeted review completion date: May 10, 2022.

- Labeling negotiations are in progress and the review is on target for completion by May 10, 2022.

- CDISC (Brenda Baldwin):
  - The review is complete, and the memo was uploaded on April 22, 2022.

2.4 Other Discussion Items

- Chemical name of ALC-0159 in Package Insert (PI)
  - The chemical name for ALC-0159 in the PIs and Fact Sheets (FSs) is currently listed as: 2-((polyethylene glycol)-2000)-N,N-ditetradecylacetamide
  - The UNII Code Subject Matter Expert has proposed that the name be revised to be more fully meaningful and include the methoxy group at the end of the chain: 2-(ω-methoxy-(polyethylene glycol)-2000)-N,N-ditetradecylacetamide
  - Given that the name of this ingredient in the PI and FSs is listed on the FDA UNII code website as an accepted synonym, the review team and management agreed that we should not change the name on the FSs and the PIs.

- Action due date for submission
  - The review team should continue to work on their reviews as they can, and we can assess management's bandwidth to review those documents as soon as they are ready.
  - We will continue to move forward with the ADD of June 17th but may take action earlier if possible.

3. 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. 03/08/2022: Follow-up response to Pfizer's March 8, 2022 clarification question to the review team's March 7, 2022 IR

6. 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.

7. 04/20/2022: Request to update the PVP to include both Tris/Sucrose and PBS/Sucrose formulations.

8. 04/20/2022: First set of labeling comments on the PI

9. 04/22/2022: Request for a revised study protocol for Study C4591022 - pregnancy registry study (postmarketing commitment [PMC] #10 as described in the STN 125742/0 approval letter)

10. 05/04/2022: Request for clarification regarding the number of placebo recipients who reported nausea from Dose 1 through 1 month after Dose 2, based on the September 2, 2021 data cutoff

4. Amendments:

1. STN 125742/45.1 (01/28/2022) – Response to January 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 January 19, 2022 request regarding datasets.

3. STN 125742/45.3 (03/01/2022) – Response to February 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 March 14, 2022 follow-up question regarding Pfizer' response in STN 125742/45.4 to our 3/7/22 clinical and statistical questions.

8. STN 125742/45.8 (04/29/2022) – Revised Comirnaty Package Insert (response to CBER's April 20, 2022 comments)

9. STN 125742/45.9 (05/02/2022) – Revised Pharmacovigilance Plan to include both Tris/Sucrose and PBS/Sucrose formulations (response to CBER's April 20, 2022 comments)

10. STN 125742/45.10 (05/04/2022) – Response to CBER's April 22, 2022 request to revise the study protocol for C4591022 to include pregnant individuals of all ages.

11. STN 125742/45.11 (05/09/2022) – Response to May 5, 2022 request for clarification regarding the number of placebo recipients who reported nausea from Dose 1 through 1 month after Dose 2, based on the September 2, 2021 data cutoff