



Our STN: BLA 125819/0

**MID-CYCLE COMMUNICATION
SUMMARY**

September 18, 2024

GlaxoSmithKline Biologicals
Attention: Wendy Valinski
14200 Shady Grove Road
Vr1500
Rockville, MD 20850-7464

Dear Ms. Valinski:

Attached is a copy of the summary of your August 19, 2024, Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN 125819/0 in your future submissions related to Meningococcal Groups A, B, C, Y, W Vaccine (PENMENVY).

If you have any questions, please contact Maria Bagh, PhD and Lynsay Ehui, PA-C, MPH at 301-796-2640 or by email at Maria.Bagh@fda.hhs.gov or Lynsay.Ehui@fda.hhs.gov, respectively.

Sincerely,

Loris D. McVittie, Ph.D.
Director
Division of Review Management and Regulatory Review
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Summary

Application Type and Number: BLA STN 125819/0

Product Name: Meningococcal Groups A, B, C, Y, W Vaccine (PENMENVY)

Proposed Indication for Use: Active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y.

Applicant: GlaxoSmithKline Biologicals

Meeting Date & Time: August 19, 2024, 11:30-1:00 pm ET

Committee Chair: CAPT Edward Wolfgang, PhD

RPMs: Maria Bagh, PhD
Lynsay Ehui PA-C, MPH

CBER Attendees:

Kouassi Ayikoe	Lunhua Liu
Maria Bagh	Adamma Mba-Jonas
Brenda Baldwin	Tina Mongeau
Margaret Bash	Nancy Murray
Marcos Battistel	Tao Pan
Karin Bok	Douglas Pratt
Rebecca Brady	Kirk Prutzman
Jennifer Bridgewater	Anuja Rastogi
Fang Chen	Maria Said
Mark Connelly	Michael Schmitt
Lynsay Ehui	John Scott
Ada Ezenekwe	Michael Smith
Hussein Ezzeldin	Elizabeth Sutkowski
Jared Greenleaf	Matthew Swierzbinski
Alaina Halbach	Willie Vann
Maria Haurat	Leslie Wagner
Harry Houghton	Robin Wisch
David Kaslow	Edward Wolfgang
Jennifer Kirk	Hong Yang
Tsai-Lien Lin	Rachel Zhang

GSK Attendees:

Steven Rubin, Global Regulatory Affairs
(b) (4), Global Regulatory Affairs
Wendy Valinski, Global Regulatory Affairs
Martina Gensini, Global Regulatory Affairs
(b) (4), Vaccine Development, R&D
Maria Lattanzi, Vaccines Clinical Sciences
(b) (4), Vaccines Clinical Sciences
Ellen Ypma, Head, Clinical Statistics
Dominique Boutriau, Clinical Laboratory Readout
Danielle Morelle, Clinical Laboratory Readout
Simone Gallo, CMC
(b) (4) CMC Stat
(b) (4), Technical Development
Nicoletta Fineschi, Global Supply Chain
Leonardo Gherardini, Quality Assurance
Benedetta Romi Quality Control
Wendy Sohn, Global Medical
Cindy Burman, US Medical

Discussion Summary:

Agenda items:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.
 - a. Clinical:

Our review of the totality of the submitted immunogenicity data has identified important differences in the *N. meningitidis* serogroup B (MenB) responses following PENMENVY (0, 6m) as compared with the primary comparator regimen of 2-doses of BEXSERO administered 6 months apart [BEXSERO (0, 6m)]. Data from the pivotal Study V72_72 that support these differences include:

 - i. Analyses of the differences in the exogenous complement hSBA responses against the MenB indicator strains following PENMENVY (0, 6m) and BEXSERO (0, 6m) for which the lower limit of the confidence intervals (CIs) for analyses of the NHBA, OMV and composite responses are less than -10%,
 - ii. Analyses of the endogenous complement hSBA (enc-hSBA) responses against a panel of 110 MenB strains that met the pre-specified statistical criteria for the primary endpoints but demonstrate important differences with the point estimates of the enc-hSBA responses following PENMENVY (0, 6m) as compared with the BEXSERO (0, 6m). These differences were

also evident with subgroup analyses of enc-hSBA responses in U.S. participants.

The estimated relative vaccine effectiveness of (b) (4) for PENMENVY (0, 6m) as compared with BEXSERO (0, 6m) provides additional support for the importance of the observed differences in the enc-hSBA responses. This estimate was calculated with the approach used by GSK in the February 13, 2020, Type C meeting.

These data suggest a clinically meaningful decrease in protection against invasive MenB disease following PENMENVY (0, 6m) as compared to BEXSERO (0, 6m).

Meeting Discussion:

The FDA clinical reviewer assigned to this BLA discussed the above information and in summary indicated that meaningful differences in protection between the PENMENVY (0, 6m) and the BEXSERO (0, 6m) treatment groups exist in study V72_72. Specifically, lower immunogenicity in the exogenous hSBA for PorA and NHBA antigens and an estimated relative vaccine effectiveness (rVE) of (b) (4) in the endogenous hSBA for PENMENVY.

GSK acknowledged that the immune responses for indicator strains PorA and NHBA measured by exogenous hSBA were higher with BEXSERO but indicated that since killing is mediated by cooperative antibody activity to multiple antigens, which is not reflected in this assay, it is difficult to appreciate the clinical meaning of these results. CBER responded that the intent of Mid-Cycle Communication teleconferences is not to engage in lengthy discussions on technical details, but rather to inform GSK (the Applicant) of potential review issues identified to date.

GSK mentioned that a prior agreement was reached to not base success criteria in study V72_72 on relative vaccine effectiveness (rVE), but rather to base success on a NI margin of -5% since the calculation for rVE greatly magnifies very small numerical differences in assay results and to refer to the 13 February 2020 Type C meeting (CRMTS# 12264) under INDs 11561 and 14605. GSK added this was also followed by CBER's acceptance of the clinical study V72_72 protocol and the SAP.

CBER responded that these points will be taken into consideration. GSK asked if CBER's current concerns pertained to approvability of the vaccine or if these concerns are about how to reflect the findings in the MenABCWY USPI. CBER responded that because the BLA review is still ongoing, we cannot provide GSK with an answer at this time;

nonetheless, CBER encouraged GSK to submit their points as an Amendment to the BLA for CBER's further consideration.

b. CMC:

Information request (IR) sent July 8, 2024 (to IND 14605), requesting additional information regarding GSK's emails dated June 12, 2024, and July 5, 2024, concerning the trend over time of (b) (4) Relative Potency (RP) results for Bexsero (b) (4). GSK's response is still pending.

Meeting Discussion:

There was no additional discussion of this item during the telecon.

c. CMC Statistics:

We may have CMC statistical comments concerning your response to our IR#16 (responses received August 12, 2024), regarding the (b) (4) assays for serogroup A and serogroup C polysaccharides. Your response is still under review, and written correspondence will be communicated to you as soon as the information is reviewed.

Meeting Discussion:

There was no additional discussion of this item during the telecon.

2. Information regarding major safety concerns.

There are no major safety concerns identified at this time.

Meeting Discussion:

There was no additional discussion of this item during the telecon.

3. Preliminary Review Committee thinking regarding a) risk management, b) the potential need for any post-marketing requirement(s) (PMRs), and/or safety-related PMCs, and c) the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk.

The review of the Risk Management Plan, including the plan for adverse event reporting and assessment of any need for a PMR, PMC, or postmarketing study in CBER's Sentinel Program, is ongoing. No need for PMRs or PMCs has been identified to date.

Meeting Discussion:

There was no additional discussion of this item during the telecon.

4. Any information requests sent, and responses not received.

a. Device-related IR sent August 13, 2024, with response requested by August 27, 2024.

Meeting Discussion:

There was no additional discussion of this item during the telecon.

5. Any new information requests to be communicated.

There are no new information requests at this time, but we may send additional IRs later based on our review progress.

Meeting Discussion:

There was no additional discussion of this item during the telecon.

6. Proposed date for the Late-Cycle meeting (LCM).

- a. The LCM between you and the Agency will be scheduled no later than October 30, 2024.
- b. We intend to send the LCM materials to you approximately 5 days in advance of the LCM date.
- c. If these timelines change, we will communicate updates to you during the course of the review.

Meeting Discussion:

There was no additional discussion of these items during the telecon.

7. Update regarding plans for the Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting.

A discussion of this application at a VRBPAC is not anticipated at this time.

Meeting Discussion:

There was no additional discussion of this item during the telecon.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

- a. Initial labeling comments will be communicated no later than January 15, 2025.
- b. Any postmarketing requirement requests and postmarketing commitment requests will be communicated no later than December 20, 2024, and January 15, 2025, respectively.
- c. First Action Due Date: February 14, 2025.

Meeting Discussion:

There was no additional discussion of these items during the telecon.

9. Discuss status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval.

We have no issues to report on the status of inspections.

Meeting Discussion:

There was no additional discussion of this item during the telecon.

END