

Our STN: 125678/0

**MID-CYCLE COMMUNICATION
SUMMARY**

DATE: MARCH 14, 2019

BAVARIAN NORDIC A/S
Attention: Dr. Renee Boerner
3025, Carrington Mill Boulevard,
Morrisville, NC 27560.

Dear Dr. Boerner,

Attached is a copy of the summary of your February 14, 2019 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 125678/0 in your future submissions related to JYNNEOS.

If you have any questions, please contact RPM's Sudhakar Agnihothram, Ph.D. and Josephine Resnick, Ph.D. at 301-796-2640.

Sincerely,

Loris McVittie, Ph.D.
Deputy Director (Regulatory)
Division of Vaccines and Related
Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation
and Research

Mid-Cycle Communication Summary

Application type and number: BL 125678/0
Product name: Smallpox (Modified Vaccinia Ankara) Vaccine, Live, Non-replicating.
Proposed indication: For active immunization against smallpox in adults aged 18 years and older
Sponsor: Bavarian Nordic A/S
Meeting date & time: February 14, 2019, 10:00AM– 11:30 AM EST
Meeting Chair: Bharat Khurana, DVM, Ph.D., MBA
RPM(s) Sudhakar Agnihothram, Ph.D.
Josephine Resnick Ph.D.

CBER Attendees:

Bharat Khurana, Sudhakar Agnihothram, Josephine Resnick, John Trefry, Sixun Yang, Alexandra Yonts, Ihid Leao Carneiro, Afolabi Meseda, Nabil Al-Humadi, Martin Green, Alonzo Garcia, Silvia Wanis, Haecin Chun, Salil Ghosh, Most Nahid Parvin, Pankaj Amin, Anissa Cheung, Ruoxuan Xiang, Lei Huang, Kerry Welsh, Rakesh Pandey, Timothy Fritz, Andrea Hulse, Martin (Dave) Green, Tsai-Lien Lin, Keith Peden, Anthony Lorenzo, Qiao Bobo, Dennis Cato, Manette Niu, Loris McVittie, Doran Fink, Carmen Collazo, Jerry Weir, Deepa Arya, Philip Krause, Marion Gruber, Nicolette Devore, David Rouse.

Bavarian Nordic Attendees:

Barbara Petzold, Heinz Weidenthaler, (b) (4), (b) (6), Jane Maclellann, Liddy Chen, Renee Boerner, Britt Christensen, Andrea Knappe, Julia Buschmann, Ariane Volkmann, Darja Schmidt, Thomas Meyer, Cindy Handelsman.

Discussion Summary

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date:
 - Indications beyond prevention of smallpox: CBER stated that they have received inquiries from external stakeholders in the US government regarding the use of licensed vaccines for prevention of monkeypox infection due to recent monkeypox outbreaks in several places. CBER is currently considering whether the data submitted to the JYNNEOS BLA (STN 125678) could support a general indication for active immunization for the prevention of monkeypox infection in adults 18 years and older, and an indication for active immunization for the prevention of orthopoxvirus infection in laboratory workers with occupational exposure to replication-competent orthopoxviruses.

CBER asked Bavarian Nordic (BN) whether they have any additional data (not already submitted to the BLA) to support either of these indications, and if BN has considered seeking an indication for the prevention of monkeypox infection. BN responded that no additional data beyond what

was submitted to the BLA are available, and therefore, they did not consider requesting this indication under the current BLA. However, BN would be open to including an expanded indication supported by the currently available data.

CBER asked BN about their plans for submitting any clinical data from ongoing studies sponsored by the Center for Disease Control and Prevention (CDC) in the Democratic Republic of the Congo (DRC), to support an indication for the prevention of monkeypox infection. BN responded that they are in contact with CDC and are aware that almost one thousand people in DRC have been vaccinated so far with JYNNEOS. However, there is no control group in this study, and CDC is planning to compare the data generated from vaccinated individuals with historical data.

BN added that the data supporting the protective efficacy of JYNNEOS against other orthopoxviruses have also been submitted to the BLA.

CBER confirmed that the non-clinical data related to the efficacy of JYNNEOS against monkeypox and other orthopoxviruses included in the BLA will be reviewed for a potential expanded indication (which should not affect the review timeline), and that CBER will communicate their decision to BN.

- CBER commented that they are expecting to receive BN's responses to items 5-10 in the Information Request (IR) #10, dated January 14, 2019, by February 21, 2019, and added that additional requests for information were recently communicated to BN on February 8, 2019, and February 12, 2019. CBER may consider BN's responses to any existing or future IRs as a major amendment if BN's submission contains a substantial amount of new data or a new analysis of studies not previously submitted to, or reviewed by, the Agency, and this will add an additional three months to the time by which CBER should complete their review. If a decision to issue a major amendment is made, BN will be notified. BN acknowledged CBER's comments and indicated that they plan to submit the responses to all the outstanding IRs as planned.

2. Information regarding major safety concerns:

CBER indicated that they do not have any major safety concerns at this time. However, this opinion may change based on CBER's review of narratives and tabulation analyses of numbers and proportion of subjects reporting SAEs and AESIs for MVA-BN treated subjects in the pooled ISS population (items #5-10 of IR#10, sent on January 14, 2019). BN acknowledged CBER's statement.

3. Preliminary Review Committee thinking regarding risk management:

CBER stated that they recommend additional risk minimization measures beyond routine pharmacovigilance and labeling for important potential risks, including cardiac and neurologic events after vaccination. CBER mentioned that a request for additional information will soon be forwarded to BN regarding the proposed post-authorization safety and efficacy study (included in the pharmacovigilance plan submitted in amendment 19) in the event the product is used in the context of mass vaccination. In response, BN suggested considering a global pharmacovigilance approach and committed to providing the post-authorization pharmacovigilance protocol with which the European Medicines Agency (EMA) has agreed. CBER acknowledged BN's response and stated that they will forward their IR comments only after reviewing that post-authorization pharmacovigilance protocol. BN also confirmed that they will submit the Patient Package Insert (PPI) based on CBER's comments on the pharmacovigilance plan.

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

CBER noted the following IRs for which the response is pending:

IR # 10, sent on January 14, 2019, items# 5-10 for ISS requesting narratives and tabulation analyses of numbers and proportion of subjects reporting SAEs and AESIs:

- By treatment group, health status, and previous smallpox vaccination status
- By System Organ Class (SOC), Preferred Term (PT) stratified by health status and treatment group
- Stratified by age, ethnicity, race and sex as well as treatment group

IR #12, sent on February 8, 2019

IR#13, sent on February 12, 2019

BN acknowledged CBER's statement.

5. Any new information requests to be communicated:

CBER stated that additional IRs (including the one related to PVP) may be communicated in the future.

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

CBER noted that the LCM between BN and the Review Committee is currently scheduled for April 25, 2019, 9:30 AM – 11:00 AM EST, and that BN could choose to have a teleconference or face-to-face meeting.

CBER intends to send the LCM meeting materials to BN approximately 2 calendar days in advance of the LCM. If these timelines change, BN will be notified by CBER accordingly.

7. Updates regarding plans for the Advisory Committee (AC) meeting:

CBER noted that an AC meeting won't be needed for this BLA. BN acknowledged CBER's statement.

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

CBER confirmed the following milestones with BN and noted that these dates may change if a major amendment notification is issued, and BN will be notified of any updates.

Labeling Comments to Applicant:	May 24, 2019
Finalize Lot Release Protocol:	May 24, 2019
PMC/PMR Determination:	May 24, 2019
ADD:	June 25, 2019

The meeting concluded around 10:45 AM EST.