Summary Basis for Regulatory Action Template

Date: September 24, 2019

From: Bharat Khurana, DVM, PhD, MBA
Chair of the Review Committee
Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

BLA STN#: 125678/0

Applicant Name: Bavarian Nordic A/S

Date of Submission: October 25, 2018

Goal Date: September 24, 2019

Proprietary Name: JYNNEOS

Indication: JYNNEOS is a vaccine indicated for prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority:

Marion F. Gruber, Ph.D.
Director, Office of Vaccines Research and Review/CBER

X I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Office of Compliance and Biologics Quality Signatory Authority:

Mary Malarkey
Director, Office of Compliance and Biologics Quality/CBER

X I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA:

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (OVRR/DVP)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (BN, Denmark)* • *Establishment Inspection Report* ((b) (4)) • *Inspection Waiver Memo* ((b) (4)) • *Applicant's Response to Inspectional Observations*	Alonzo Garcia, PhD – Aug. 23, 2019 Pankaj Amin - Sep. 18, 2019 Pankaj Amin, Anissa Cheung, MS, and Bharat Khurana, DVM, PhD, MBA – Sep. 18, 2019 Pankaj Amin, Hector Carrero – Sep. 18, 2019 Pankaj Amin and Bharat Khurana, DVM, PhD, MBA – Sep. 10, 2019 Anissa Cheung, MS – May 20 & July 23, 2019 Bharat Khurana, DVM, PhD, MBA – July 3, 2019 Pankaj Amin – Sep. 19, 2019
Clinical Review(s) • *Clinical (OVRR/DVRPA)* • *Pharmacovigilance (OBE/DE)* • *BIMO (OCBQ/DIS)*	Sixun Yang, MD, PhD and Alexandra Yonts, MD – Sep. 19, 2019 Kerry Welsh, MD, PhD – Aug. 21, 2019 Haecin Chun, MS – Aug. 15, 2019
Statistical Review(s) • *Clinical data (OBE/DB)* • *Non-clinical data (OBE/DB)*	Ruoxuan Xiang, PhD – Aug. 29, 2019 Lei Huang, PhD – Aug. 29, 2019
Pharmacology/Toxicology Review(s) • *Toxicology (OVRR/DVRPA)* • *Animal pharmacology (OVRR/DVP)*	Nabil Al-Humadi, PhD – Aug. 26, 2019 Afolabi Meseda, PhD – July 22, 2019
Labeling Review(s) • *APLB (OCBQ/APLB)* • *Carton and Container Label Review (OVRR/DVRPA)*	Oluchi Elekwachi, PharmD, MPH – June 19, 2019 Josephine Resnick, PhD – Sep. 24, 2019
Other Review(s) • *Analytical Methods and Product Testing (OCBQ/DBSQC)* • *Priority Review Request (OVRR/DVRPA)*	M. Nahid Parvin, PhD – Aug. 5 & Aug. 9, 2019 Simleen Kaur, MS – Feb. 26, 2019 Salil Ghosh, PhD – June 21, Aug. 20, 2019 Marie Anderson, PhD – Aug. 23, 2019 Hyesuk Kong, PhD, Josephine Wulu, MS & Karla Garcia, MS – May 1, 2019 Bharat Khurana, DVM, PhD, MBA – Aug. 12, 2019

1. INTRODUCTION

Bavarian Nordic A/S (BN) submitted Biologics License Application (BLA) 125678 for licensure of Smallpox and Monkeypox Vaccine, Live, Non-replicating. The proprietary name of the vaccine is JYNNEOS. JYNNEOS is a vaccine indicated for the prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection. The vaccine is administered subcutaneously (SC) in two doses (0.5 mL each) at a four-week interval.

JYNNEOS is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus. MVA-BN is grown in primary Chicken Embryo Fibroblast (CEF) cells suspended in a serum-free medium, harvested from (b) (4) CEF cells, purified and concentrated by several Tangential Flow Filtration (TFF) steps including (b) (4) for removal of residual impurities and digestion of residual DNA by benzonase. The purified and concentrated MVA-BN drug substance (DS) is stored in (b) (4) containers at (b) (4) until formulation and filling. To manufacture the final drug product (DP), the MVA-BN DS is (b) (4) with the formulation buffer and filled into single dose vials.

JYNNEOS is supplied in a single-dose vial containing a 0.5 mL dose. Each 0.5 mL dose is formulated to contain 0.5×10^8 to 3.95×10^8 infectious units of MVA-BN live virus in 10 mM Tris (tromethamine) and 140 mM sodium chloride at pH 7.7. It does not contain any adjuvants or preservatives but may contain trace amounts of residual host cell DNA and protein, benzonase and gentamicin. The expiration date is 36 months (b) (4) from the date of manufacture when stored at -25°C to -15°C (b) (4), respectively. JYNNEOS is administered subcutaneously, preferably into the upper arm (deltoid).

2. BACKGROUND

Smallpox is a serious, highly contagious, and sometimes fatal infectious disease with a mortality rate of 30-40%. Smallpox is considered as a high-priority threat under the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan (2017-2018). In the mid-1980s the World Health Organization declared that smallpox had been eradicated by vaccination efforts using conventional replicating smallpox vaccines such as Dryvax, a smallpox vaccine derived from the New York Board of Health vaccinia strain and originally licensed by FDA in 1944 to Wyeth Laboratories, Inc. of Madison, N.J. Manufacture of Dryvax ceased following the declaration of smallpox eradication, and currently there is only one US-licensed smallpox vaccine: ACAM2000, a replicating vaccinia virus-based smallpox vaccine derived by plaque purification from the Dryvax vaccine that was licensed on August 31, 2007. ACAM2000 is indicated for

active immunization against smallpox disease for persons determined to be at high risk for smallpox (variola) virus infection. ACAM2000 is contraindicated for use in individuals with severe immunodeficiency who are not expected to benefit from the vaccine. The Warnings and Precautions section of the package insert for ACAM2000 describes a number of clinically significant adverse reactions including generalized vaccinia, progressive vaccinia (in immunocompromised individuals), eczema vaccinatum (in individuals with atopic dermatitis), fetal vaccinia (in pregnant women), and inadvertent inoculation of contacts of vaccinees. Thus, there is an unmet need for a smallpox vaccine with an improved safety profile. MVA-BN was previously approved for use as a smallpox vaccine in 2013 by the European Medicines Agency under the "exceptional circumstances" licensure pathway (trade name IMVANEX) and by the Public Health Agency of Canada (trade name IMVAMUNE).

Monkeypox is a rare viral zoonotic disease with symptoms similar to those seen in smallpox patients. Although it is clinically less severe than smallpox, it can be fatal. Typically, case fatality in monkeypox outbreaks has been between 1% and 10%, with most deaths occurring in younger age groups. With the eradication of smallpox in 1980 and subsequent cessation of smallpox vaccination, monkeypox virus has emerged as the most clinically important orthopoxvirus with active transmission to humans. Sporadic cases of monkeypox have been reported from west and central African countries in remote areas near tropical rainforests. In 2003, a monkeypox outbreak was confirmed in the U.S. This was the first time human monkeypox was reported outside of the African continent. Currently, there is no approved treatment or licensed vaccine for monkeypox, although the Advisory Committee on Immunization Practices (ACIP) recommends that ACAM2000 be used for prevention of monkeypox in individuals at high risk of exposure (e.g., lab workers who handle monkeypox virus). Thus, there is an unmet need for a monkeypox vaccine.

During the discussions of the licensure pathway for MVA-BN, FDA and BN agreed that the most appropriate approach to demonstrate vaccine effectiveness of MVA-BN would be an immunogenicity comparison to ACAM2000 using a primary endpoint of non-inferior vaccinia specific geometric mean neutralizing antibody titers evaluated at time points that approximate the peak antibody response to each vaccine. Given that vaccine antigens and replication competence are different for MVA-BN vs. ACAM2000, and that a vaccinia neutralizing antibody response that predicts protection against smallpox has not been established, we considered that demonstrating vaccine efficacy in animal models showing protection against relevant orthopoxvirus challenge (monkeypox virus in NHPs and ectromelia virus in mice) would be critical to support the immunologic non-inferiority comparison.

BN's original proposed indication did not include monkeypox. During the review of this submission, inquiries were received from external stakeholders in the US government asking whether the available data for MVA-BN would support an indication for prevention of monkeypox to make available an effective countermeasure for this disease. FDA determined that immunogenicity data for

MVA-BN obtained in humans together with the non-human primate (NHP) data already submitted to BLA 125678/0 would be sufficient to support the indication for prevention of monkeypox, since the clinical and non-clinical studies provided multiple lines of evidence that the immune response to MVA-BN provided protection against different orthopoxviruses, and specifically monkeypox in the NHP challenge model.

During the BLA review cycle, discussions were held with BN regarding issues with data presentation in the integrated summary of safety (ISS), resulting in the submission of a substantial amount of new data and new analyses on February 21, 2019, that was classified as a major amendment. Consequently, the action due date to complete CBER review was extended by three months to September 24, 2019.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

Document review conclusions; discuss critical issues, notable issues and internal or external disagreements in each section below, including:

a) Product Quality

Product Composition:

JYNNEOS is supplied as a frozen suspension in a 2 mL vial containing 0.5 mL extractable volume of the vaccine. Each 0.5 mL dose is formulated to contain 0.5 x 10^8 to 3.95 x 10^8 infectious units of MVA-BN live virus in 10 mM Tris (tromethamine) and 140 mM sodium chloride at pH 7.7. The composition of the JYNNEOS drug product and the functions of the ingredients are provided in Table 1.

Table 1: Composition of the JYNNEOS Drug Product

Component	Quantity per Dose (0.5 mL)	Function	Quality Demand / Specification
MVA-BN	0.5 x 10^8 to 3.95 x 10^8 Inf. U	Active substance immunizing antigen	In-house specification
Tris (Tris-hydroxymethyl-aminomethane, Trometamol)	(b) (4)	Buffering agent	(b) (4)
Sodium chloride		Saline	(b) (4)
Water for injection	q.s.	Solvent	(b) (4)

Drug Substance:

The DS is MVA-BN, which is derived from the attenuated Modified Vaccinia Ankara (MVA) strain of the parental vaccinia virus by (b) (4)

(b) (4)

Master and Working Seed Virus:

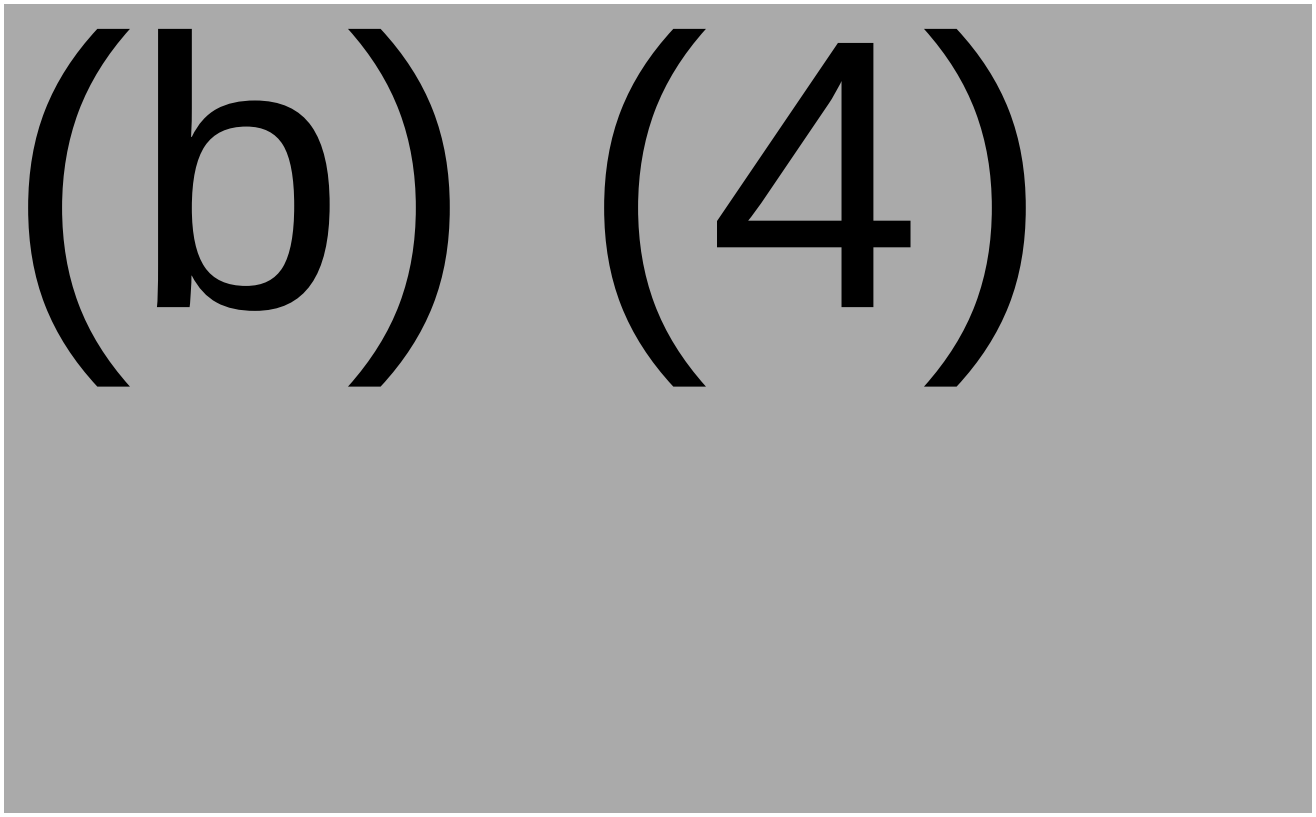
(b) (4)

Manufacturing Overview:

The MVA-BN DS is manufactured at Bavarian Nordic facility in Kvistgaard, Denmark, under aseptic conditions starting with primary CEF cells prepared from embryos that are harvested from eggs of (b) (4) flocks of chicken. The CEF cells, re-suspended in serum-free medium, are infected with MVA-BN (b) (4) serum free medium supplemented with the additives: gentamicin, (b) (4). Following (b) (4), the homogenized virus harvest is purified and concentrated through several TFF steps including (b) (4) for removal of residual impurities and digestion of residual DNA by Benzonase. A full batch size of the purified bulk DS is (b) (4) per

manufacturing process run. Since (b) (4), the purified and concentrated MVA-BN DS is collected in a (b) (4) bag and distributed in (b) (4) containers each containing up to (b) (4). The MVA-BN DS in (b) (4) containers is (b) (4) and then stored at (b) (4) until formulation and filling. Prior to implementation of the (b) (4) container closure system for MVA-BN DS storage at (b) (4) in (b) (4), the DS was stored in (b) (4).

Test parameters, analytical procedures and acceptance criteria established for the release of the MVA-BN DS are shown in Table 2 below.



Stability of DS:

Parameters used to assess stability of the MVA-BN DS include: (b) (4)

Drug Product:

Manufacture of the MVA-BN DP consists of (b) (4) of DS, formulation of final bulk DP (b) (4) formulation buffer (10 mM Tris, 140 mM NaCl, pH 7.7) (b) (4) DS, aseptic filling into single-dose vials, followed by inspection, labeling and packaging of the vials. The entire DP lot is placed into a freezing (b) (4) freezer (b) (4) -20°C (b) (4) for long-term storage.

DP is supplied as a frozen suspension in a 2 mL (b) (4) borosilicate glass vial containing 0.5 mL extractable volume of the vaccine. Critical Process Parameters and Release Tests for Process Intermediates have been established to serve as appropriate tests to monitor the process and assure a consistent performance of the manufacture of the drug product. Test parameters, analytical procedures and acceptance criteria for drug product release testing are summarized in Table 3.

Table 3: Release specification for Drug Product (DP)

Test parameter	Analytical procedure	Acceptance criteria
Appearance	Visual inspection (b) (4)	Transparency/Turbidity: Milky. Color: Light yellow to pale white. State: Suspension. Particles: Free from visible extraneous particles. Closure: Completely closed vial. Caps firmly and evenly attached.
pH	(b) (4)	(b) (4)
Extractable volume	(b) (4)	≥ 0.50 mL
Identity	(b) (4)	Identity confirmed
Sterility	(b) (4)	No growth of bacterial and fungi
Bacterial endotoxins	(b) (4)	(b) (4)
Infectious virus titer	(b) (4)	(b) (4) – 8.9 $\log_{10}$ Inf. U/mL ((b) (4) - 7.9×10^8 Inf. U/mL)
Total protein	(b) (4)	(b) (4)

Packaging and Testing of DP:

The MVA-BN DP is manufactured, labelled and packaged (including primary and secondary packaging) at (b) (4).

Storage and batch release of DP are conducted by Bavarian Nordic at Kvistgaard, Denmark facility. Testing of drug product and intermediates is performed either in-house or by approved subcontractors. Testing sites involved in testing of drug product and intermediates include:

- (b) (4) : DP, (b) (4) and stability testing: sterility, bacterial endotoxins, osmolality, and pH

- Bavarian Nordic, Kvistgaard, Denmark: DP and stability testing: appearance, pH, extractable volume, and total protein
- Bavarian Nordic, (b) (4) : DP and stability testing: identity and infectious virus titer

- (b) (4) : Stability testing: sterility

Stability of DP:

For long-term storage, the MVA-BN DP final container may be stored (b) (4) -20°C (b) (4) . The test parameters, analytical procedures and acceptance criteria for the DP stability testing are summarized in Table 4. The stability data provided in the submission support the expiration date of the MVA-BN DP final container for 36 months when stored at -20°C ± 5°C (b) (4) .

Table 4. Shelf life specifications for DP

Test parameter	Analytical procedure	Acceptance criteria
Appearance	Visual inspection (b) (4)	Transparency/Turbidity: Milky. Color: Light yellow to pale white. State: Suspension. Particles: Free from visible extraneous particles. Closure: Completely closed vial. Caps firmly and evenly attached.
pH	(b) (4)	(b) (4)
Identity	(b) (4)	Identity confirmed
Sterility	(b) (4)	No growth of bacterial and fungi
Bacterial endotoxins	(b) (4)	(b) (4)
Infectious virus titer	(b) (4)	8.0 – 8.9 $\log_{10}$ Inf. U/mL (1.0×10^8 - 7.9×10^8 Inf. U/mL)
Container closure integrity	(b) (4)	None of the vials should (b) (4)

Testing Specifications:

The analytical methods and their validations and/or qualifications reviewed for the MVA-BN Smallpox vaccine DS and DP were found to be adequate for their intended use.

Container Closure System:

The DP is filled into clear, (b) (4), 2 mL borosilicate glass vial ((b) (4)) with a 13 mm latex free butyl rubber stopper ((b) (4)), and 13 mm aluminum cap with flip-off crimp seal ((b) (4)). Bavarian Nordic conducted the container closure integrity testing, employing dye (b) (4) method (test performed at (b) (4) facility), and (b) (4) test method (test performed at (b) (4)); all acceptance criteria were met.

Adventitious Agents Testing:

The entire manufacturing process, from the starting materials, MVB and CEF cell substrate, to MVA-BN, DS and DP, is designed to minimize the risk of microbial and viral contamination by adequate controls and specifications for starting materials, raw materials, and excipients, appropriate in-process controls and specifications for DS and DP, and validation of the relevant process steps.

CMC Review Issues:

The following review issues related to validation of the plaque reduction neutralization test (PRNT) using vaccinia virus of Western Reserve (VV-WR) strain as a reporter virus were encountered and resolved:

A major concern was that BN had determined the lower limit of quantitation (LLOQ) for PRNT versions (b) (4), which were used for testing samples from lot-consistency trial POX-MVA-013 and pivotal trial POX-MVA-006, respectively, based on extrapolation with no supporting data. BN had estimated the lower limit of detection (LLOD) and LLOQ at a titer of (b) (4) for PRNT versions (b) (4), respectively, using an extrapolation method of the dilutional-linearity plot. Although the ICH Q2(R1) guidance document indicates that extrapolation can be used for estimating the LLOD, this practice does not necessarily apply to estimating the LLOQ. The discrepancy of setting the LLOQ based on extrapolation was discussed and BN was recommended to demonstrate adequacy of the provisional LLOQ based on confirmatory experimental data, involving the testing of additional samples with titers (at or near the target range of the LLOQ) to evaluate the relative accuracy and precision at the proposed LLOQ or to adjust the LLOQ accordingly.

BN agreed to extend the linearity study of the PRNT (assay version (b) (4)) down to titers at the provisional LLOQ of (b) (4). After performing linearity testing, BN proposed a hypothetical increase of the LLOQ from (b) (4) 20 and provided selected analyses for

clinical data from Phase 3 Studies POX-MVA-006 and POX-MVA-013 because linearity was not adequate near the provisional LLOQ of (b)(4). BN showed that the results with a LLOQ of 20 are reasonably similar to those provided in the Clinical Studies Reports with a LLOQ of (b)(4) and that the overall conclusion stays the same. CBER advised BN to set the LLOQ value at a titer of ~20 and revise the PRNT immunogenicity data enclosed in the Prescribing Information (PI) accordingly. BN agreed to revising the PRNT immunogenicity data enclosed in the PI to reflect the change of the LLOQ.

Due to expiry and depletion of reagents used in the PRNT assay version (b)(4), the additional testing to extend the linearity of the PRNT assay version (b)(4) down to titers at the LLOQ of (b)(4) could not be performed. However, the assay validation parameters (specificity, precision, linearity, detection and quantitation limit) were comparable between PRNT assay versions (b) (4). So, the dilutional linearity testing that was done for assay version (b)(4) was considered to be representative for assay version (b)(4) as well, and the LLOQ value of 20 was determined to be suitable for PRNT assay version (b)(4).

Version (b)(4) of the PRNT was used in clinical studies POX-MVA-005, POX-MVA-023 and POX-MVA-011, and Version (b)(4) of the PRNT was used in clinical studies POX-MVA-008 and POX-MVA-024. Several issues and/or inconsistencies with the linearity and the precision results were identified for PRNT versions (b) (4), including that linearity was not established down to the LLOQ (20), and the substantial differences in precision results from the pre-validation study and the validation study. Consequently, the review team considered that the PRNT assay versions (b) (4) are likely inadequate and cannot be used to draw conclusions from the clinical studies in which these versions were used.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facilities information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of JYNNEOS are listed in Table 5. In addition, the activities performed, and inspectional histories are noted in Table 5 and are further described in the paragraph that follows.

Table 5: Manufacturing Sites involved in the manufacture of MVA-BN DS and DP

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Results/ Justification
DS manufacture, storage and release testing; DP release testing Bavarian Nordic A/S Hejreskovvej 10A 3490 Kvistgaard, Denmark	3008318564	310209754	Pre-License Inspection	CBER 02/25/2019 - 03/01/2019 VAI
DP manufacture, storage and release testing (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER (b) (4) VAI
Test Laboratory for DP release testing: Identity and Infectious Virus Titer assay Bavarian Nordic (b) (4)	(b) (4)	(b) (4)	Waiver	(b) (4)

** Under FDASIA Section 712, Recognition of Foreign Government Inspections
FEI: Facility Establishment Identifier, DUNS: Data Universal Numbering System, VAI: Voluntary Action Indicated

CBER conducted a pre-license inspection (PLI) of the Bavarian Nordic A/S facility, February 25 - March 1, 2019 for DS manufacturing and QC lab release testing. At the end of the inspection, CBER issued a Form FDA 483. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

CBER conducted a PLI of (b) (4) facility, (b) (4) for DP manufacturing and QC lab release testing activities. At the end of the inspection, CBER issued a Form FDA 483. The firm responded to the observations, and the

corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as this naturally occurring product is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment, and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

General Toxicology:
JYNNEOS was evaluated in four general- and repeat-dose toxicology studies at different doses and intervals in rabbits and rats following intramuscular or subcutaneous administration. Adequate nonclinical toxicology data were included in these studies. The vaccine was well tolerated, and no significant vaccine related systemic or local toxicity was identified.

Developmental and Reproductive Toxicity Studies:
Developmental and reproductive toxicity studies were conducted in female rats and rabbits. In one study, female rabbits were administered a single human dose of JYNNEOS (0.5 mL) by the subcutaneous route on three occasions: prior to mating, and on gestation days 0 and 14. Three studies were conducted in female rats administered a single human dose of JYNNEOS (0.5 mL) by the subcutaneous route on two or three occasions: prior to mating, and on gestation days 0 and 14; or prior to mating, and on gestation day 0; or on gestation days 0 and 6. No vaccine-related fetal malformations or variations and adverse effects on female fertility or pre-weaning development were reported in these studies.

Nonclinical Pharmacology supporting Vaccine Effectiveness
Animal studies in non-human primates (NHP) and mouse models using relevant orthopoxvirus challenge were conducted to support the effectiveness of JYNNEOS against smallpox and monkeypox in humans. These data, combined with the comparative clinical immunogenicity study, POX-MVA-006 described in Section 6 (Summary of Clinical Vaccine Effectiveness), provide the pivotal data demonstrating effectiveness of the vaccine in preventing smallpox and monkeypox in humans.

The efficacy of JYNNEOS to protect cynomolgus macaques (*Macaca fascicularis*) against a monkeypox virus (MPXV) challenge was evaluated in several studies. Animals were administered Tris-Buffered Saline (placebo) or JYNNEOS (1×10^8 $TCID_{50}$) subcutaneously on day 0 and day 28. On day 63, animals were challenged with MPXV delivered by aerosol (3×10^5 pfu), intravenous (5×10^7 pfu) or

intratracheal (5 x 10^6 pfu) route. Across all studies, 80-100% of JYNNEOS-vaccinated animals survived compared to 0-40% of control animals.

The protective efficacy of MVA-BN was also evaluated in several studies conducted with a murine intranasal (i.n.) challenge model using ectromelia virus (ECTV). (b) (4) mice were treated with either placebo (Tris-Buffered Saline) or MVA-BN (1x10^8 TCID50) given subcutaneously on Day 0 and Day 28. On Day 42, the treated mice were challenged with a lethal i.n. dose of ECTV of 58x MLD50. All immunized mice survived the lethal challenge with ECTV and all mice in the placebo groups succumbed to the viral challenge (as shown by signs of sickness on Day 6 and death occurring on Day 7 – 8).

Data from these animal studies indicate that JYNNEOS induces cross-protection against other orthopoxviruses and support the effectiveness of JYNNEOS against both smallpox and monkeypox in humans.

5. CLINICAL PHARMACOLOGY

JYNNEOS is an attenuated, live, non-replicating smallpox and monkeypox vaccine that elicits humoral and cellular immune responses to orthopoxviruses. Vaccinia neutralizing antibody responses in humans were evaluated to establish the effectiveness of JYNNEOS for prevention of smallpox and monkeypox.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

General Description of Clinical Studies

BN proposed a 2-dose primary series for use in smallpox vaccine naïve individuals and a single booster dose for use in individuals previously vaccinated with a smallpox vaccine (replicating smallpox vaccine or MVA-BN primary series). BN submitted 22 clinical trials to support the effectiveness and safety of MVA-BN for licensure. Among these 22 clinical trials, 7 clinical trials were considered essential by the review team to support the proposed indication and usage. Full clinical study reports were submitted to the BLA for these 7 studies:

- POX-MVA-006: A pivotal Phase 3 non-inferiority trial comparing MVA-BN with ACAM2000 to support safety and effectiveness of MVA-BN in vaccinia naïve healthy subjects
- POX-MVA-013: A placebo-controlled Phase 3 lot consistency trial to establish manufacturing consistency of MVA-BN as well as to support safety of MVA-BN
- POX-MVA-008: A Phase 2 trial to support use of MVA-BN in individuals with atopic dermatitis

- POX-MVA-011: A Phase 2 trial to support use of MVA-BN in HIV-infected individuals
- POX-MVA-005 and POX-MVA-023: A Phase 2 trial and its extension trial, respectively, to support use of MVA-BN in vaccinia experienced individuals
- POX-MVA-024: A Phase 2 trial to support use of MVA-BN in individuals 65 years of age and older

In addition to these essential clinical trials, BN submitted an ISS, which pooled serious adverse events (SAEs) and cardiac adverse events of special interest (AESIs) across various study populations throughout the clinical development program. Safety of MVA-BN was assessed in more than 7800 subjects who received at least one dose of MVA-BN in 22 studies under the drug development program. Safety data from individual studies and the ISS are discussed in Section 7.

Summary of Clinical Vaccine Effectiveness

As described previously, demonstration of vaccine effectiveness was based on an immunogenicity non-inferiority comparison to ACAM2000 and was supported by efficacy data from animal models described in Section 4 (Nonclinical Pharmacology Supporting Vaccine Effectiveness) showing protection against relevant orthopoxvirus challenge.

POX-MVA-006 was a two-site, open-label, randomized, immune-analysis blinded Phase 3 trial to assess the effectiveness and safety of MVA-BN compared to ACAM2000 in smallpox vaccine-naïve, healthy US military personnel 18 through 42 years of age. The primary endpoint was vaccinia specific neutralizing antibody titer at Peak Visit (defined as two weeks after the second dose of MVA-BN in Group 1 and four weeks after a single dose of ACMA2000 in Group 2). Solicited adverse reactions were collected via diary card for 14 days after each vaccination, and SAEs and cardiac AESIs were followed up for at least 6 months after the last vaccination. The trial included two groups:

- Group 1: Vaccinia-naïve subjects received two 0.5 mL (1×10^8 Inf. U.) doses of MVA-BN, administered SC four weeks apart followed by one dose of ACAM2000 ($2.5\text{-}12.5 \times 10^5$ plaque forming units) via scarification four weeks after the second MVA-BN vaccination
- Group 2: Vaccinia-naïve subjects received one dose of ACAM2000 ($2.5\text{-}12.5 \times 10^5$ plaque forming units) via scarification

The study enrolled 433 vaccinia-naïve subjects from Department of Defense personnel, 220 in Group 1 and 213 in Group 2.

Vaccinia specific neutralizing antibody was determined by PRNT using the VV-WR as the reporter. Take attenuation was determined by comparing maximal median skin lesion area (MLA) following ACAM2000 scarification in MVA-BN vaccinated

subjects in Group 1 with the MLA following ACAM2000 scarification in Group 2 subjects.

Analyses of antibody responses were performed in the per-protocol immunogenicity (PPI) population, consisting of individuals who received all vaccinations and completed all visits up until the peak visit without major protocol violations pertaining to immunogenicity assessments.

PRNT GMTs at Peak Visits for Group 1 and Group 2 were 152.8 (95%CI: 133.3, 175.0) and 84.4 (95%CI: 73.4, 97.0), respectively. The PRNT GMT ratio of Group 1/Group 2 was 1.81 (97.5% CI: 1.49, 2.20).

The MLA in Group 1 was 0.0 mm^2 (95%CI: 0.0, 1.0), and the MLA in Group 2 was 37.0 mm^2 (95% CI: 33.0, 42.0). The area attenuation ratio (AAR) was defined as 1-(MLA in Group 1/MLA in Group 2). The AAR in MVA-BN immunized subjects was 97.9% with an LB of 95% CI of 96.6%, which met the protocol specified success criterion of LB of 95% CI > 40%.

The applicant submitted data from additional studies that evaluated vaccine effectiveness specifically in HIV-infected individuals, individuals with atopic dermatitis (AD), or individuals previously vaccinated with smallpox vaccine. However, versions of PRNT used in these studies were insufficiently validated and precluded us from making any conclusion regarding vaccine effectiveness in these study populations. However, there is no biological reason to suspect decreased effectiveness of MVA-BN in individuals with AD, and benefit-risk of MVA-BN may still be favorable in HIV-infected individuals. While the assay validation issues precluded inference of effectiveness of a single booster dose of MVA-BN in individuals previously vaccinated with smallpox vaccine, it was reasonable to conclude that the 2-dose regimen of MVA-BN would be as effective in smallpox vaccine-experienced individuals as compared to smallpox vaccine-naïve individuals.

These additional studies are summarized below:

POX-MVA-008 was a Phase 2, multicenter, open-label, healthy control, prospective cohort study to evaluate the safety and immunogenicity of MVA-BN smallpox vaccine in vaccinia-naïve 18-40-year-old subjects with AD. The study enrolled 632 vaccinia-naïve subjects into two groups: 282 healthy subjects as control and 350 subjects with a history of or currently active AD. Both groups of subjects received two doses of MVA-BN at 28 days apart. The primary endpoint was seroconversion rate (SCR) determined by ELISA at 2 weeks after the second dose of MVA-BN.

POX-MVA-011 was a Phase 2, multicenter, open-label, healthy-control, prospective cohort study to evaluate the safety and immunogenicity of MVA-BN smallpox vaccine in vaccinia-naïve as well as vaccinia-experienced HIV-infected subjects with CD4 cell counts 200-750. The study enrolled 581 subjects: 88 vaccinia naïve and 9 vaccinia-experienced healthy subjects, 352 vaccinia-naïve and 132 vaccinia-

experienced HIV-infected subjects. All subjects received two doses of MVA-BN at 28 days apart. The primary objective of this study was to assess the safety of MVA-BN in HIV-infected subjects compared to healthy subjects. Secondary endpoints included ELISA SCR and GMT, and PRNT SCR and GMT.

POX-MVA-005 was a Phase 2 trial to compare immunogenicity of two doses of MVA-BN in vaccinia-naïve healthy subjects and a single dose of MVA-BN in vaccinia-experienced healthy subjects who were vaccinated with the first generation of smallpox vaccines over 25 years ago. The study enrolled 549 vaccinia-naïve subjects and 204 subjects who were previously vaccinated with the first generation of smallpox vaccines. The primary endpoint was vaccinia-specific SCR derived from the ELISA specific antibody titers two weeks after the last vaccination.

POX-MVA-023 was an extension study of POX-MVA-005 to evaluate the safety and immunogenicity of a single dose of MVA-BN in MVA-BN experienced subjects. POX-MVA-023 also evaluated persistence of immune responses following the primary MVA-BN vaccination as well as following a single booster dose vaccination with MVA-BN among MVA-BN primed subjects and subjects who received replicating vaccinia-based smallpox vaccines. The primary endpoint was vaccinia-specific SCR derived from the ELISA specific antibody titers two weeks after the last vaccination.

POX-MVA-024 was a randomized, double-blind, placebo-controlled study to evaluate the safety and immunogenicity of one versus two doses of MVA-BN in 120 vaccinia-experienced subjects 56 – 80 years of age. The primary objective was safety. Immunogenicity endpoints (secondary objective) were proportion of subjects with any immune responses determined by ELISA and PRNT. A response was defined as either the appearance of antibody titers ≥ assay LLOD for seronegative subjects at baseline or an increase of the antibody titer compared to the baseline titer for subjects with a pre-existing vaccinia-specific antibody titer.

In summary, the vaccine effectiveness against smallpox and monkeypox was inferred from the POX-MVA-006 clinical study by comparing the immunogenicity of JYNNEOS to a licensed smallpox vaccine (ACAM2000) based on PRNT using the VV-WR and was supported by efficacy data from animal challenge studies in mouse and NHP models demonstrating protection of animals vaccinated with MVA-BN from relevant orthopoxvirus challenge. The data submitted support the effectiveness of a two-dose regimen of MVA-BN in preventing smallpox and monkeypox in individuals 18 years of age and older.

Lot Consistency

POX-MVA-013 was a randomized, double-blind, placebo-controlled Phase 3 lot consistency and safety study in healthy, vaccinia naïve subjects. A total of 4005 subjects were randomized into four study groups (1:1:1:1 via block randomization) to receive two doses of 1 of 3 MVA-BN lots or placebo 28 days apart. The study

enrolled 999, 1005 and 999 subjects in 3 MVA-BN lot groups respectively, and 1002 subjects in placebo group. The primary objective was to assess the consistency of 3 consecutively produced MVA-BN lots. Lot equivalence was pre-specified as 95% CI of PRNT GMT ratio of each two lots between 0.5 and 2.0.

PRNT GMTs at Peak Visit were similar between the 3 MVA-BN lot groups, 110.5 (95% CI: 103.3, 118.1), 100.7 (95% CI: 94.0,107.9), 117.0 (95% CI: 108.9, 125.8) for MVA-BN lot 1, 2, and 3, respectively. The pairwise ratios of PRNT GMTs between MVA-BN lots were 0.86 (95% CI: 0.78, 0.95) for Lot 2 to 3, 0.94 (95% CI: 0.86, 1.04) for Lot 1 to 3, and 1.1 (95% CI: 1.0, 1.21) for Lot 1 to 2, respectively. These ratios fell in the pre-defined range for equivalence of 0.5-2.0. The study met its primary objective to demonstrate manufacturing consistency for the 3 consecutively produced vaccine lots.

Bioresearch Monitoring

Bioresearch Monitoring (BIMO) inspections were conducted at five clinical investigator study sites that participated in the conduct of Studies POX-MVA-006 or POX-MVA-013. The inspections did not reveal any issues that impact the data submitted in the BLA.

Other Clinical Review Issues

In study POX-MVA-006 BN proposed ACAM2000 take attenuation following MVA-BN vaccination as an additional primary endpoint that provided clinically meaningful evidence that vaccinia virus replication at the ACAM2000 inoculation site was suppressed by the immune response to MVA-BN. While we considered immunologic non-inferiority to ACAM2000 in combination with supportive animal efficacy data to be adequate to demonstrate vaccine effectiveness, we agreed with the applicant's proposal also to evaluate attenuation of ACAM2000 take reaction in individuals previously vaccinated with MVA-BN compared to smallpox vaccine naïve individuals.

Several issues with take assessment were identified in POX-MVA-006 study. Take distribution among Group 1 subjects clustered in terms of study subject identification number as well as ACAM2000 administration date. There was an imbalance in take rate among Group 1 subjects between the two study sites (57% vs. 36%). In addition, among Group 1 subjects who had no take following ACAM2000 vaccination, vaccinia specific antibody titers were lower after ACAM2000 vaccination than prior to ACAM2000, suggesting the possibility of vaccination failure of unknown cause. BN was not able to provide a reasonable or acceptable explanation for these issues. Therefore, we decided the data were not reliable, and since not necessary to demonstrate vaccine effectiveness would not be considered to support licensure or be included in the package insert.

b) Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for a new active ingredient, new dosage form, new dosing regimen, new indication, or new route of administration is submitted, unless the requirement for assessment has been deferred or waived.

BN requested a full-waiver of the pediatric study requirement for JYNNEOS because the necessary studies are impossible or highly impracticable. Smallpox has been eradicated, and there are no pediatric populations currently at risk of smallpox. Pediatric populations at risk of monkeypox are limited to small and dispersed communities living in areas lacking sufficient infrastructure and stability to support clinical trials.

BN's request for waiver of pediatric studies of JYNNEOS was presented to the FDA's Pediatric Review Committee on January 30, 2019 (for smallpox indication) and June 26, 2019 (for monkeypox indication). The committee agreed with the BN's request for waiver of studies for prevention of smallpox and monkeypox disease in pediatric subjects.

7. SAFETY

Safety of MVA-BN was assessed in more than 7800 subjects who received at least one dose of MVA-BN in 22 studies under the drug development program. Solicited adverse reactions were collected via diary card for 7 to 14 days after each vaccination, and SAEs and AESIs were followed from the day of the first study vaccination through at least 6 months after the last study vaccination. Across all 22 clinical trials and in all populations including HIV-infected subjects and AD subjects, the safety profile of MVA-BN was favorable.

In study POX-MVA-013, which evaluated safety of MVA-BN compared to Tris-buffered saline placebo in vaccinia-naïve healthy adults, the most common (>10%) solicited injection site reactions following any dose of MVA-BN and placebo, respectively, were pain (84.9% vs. 19.1%), redness (60.8% vs. 17.7%), swelling (51.6% vs. 5.6%), induration (45.4% vs. 4.6%), and itching (43.1% vs. 11.7%); the most common solicited systemic adverse reactions following any dose of MVA-BN and placebo, respectively, were muscle pain (42.8% vs. 17.6%), headache (34.8% vs. 25.6%), fatigue (30.4% vs. 20.5%), nausea (17.3% vs. 13.1%) and chills (10.4% vs. 5.8%). The vast majority of these adverse reactions were mild to moderate, and in general similar proportions of subjects experienced solicited adverse reactions after Dose 2 of MVA-BN compared with Dose 1, with the exception of injection site pain, which was more commonly reported following Dose 1 (79.3%) than Dose 2

(69.9%). Frequencies of adverse reactions following MVA-BN were generally similar across the integrated study population of smallpox vaccine-naïve healthy adults compared to those reported following MVA-BN in study POX-MVA-013. The most commonly reported adverse reactions following MVA-BN vaccination are comparable to other licensed vaccines administered via the SC route.

In healthy adults previously vaccinated with a smallpox vaccine following vaccination with MVA-BN, the most common (> 10%) solicited injection site reactions were redness (80.9%), pain (79.5%), induration (70.4%), swelling (67.2%), and itching (32.0%); the most common solicited systemic adverse reactions were fatigue (33.5%), headache (27.6%), and muscle pain (21.5%). No clinically relevant difference in the safety and reactogenicity of MVA-BN was observed between vaccinia-naïve and vaccinia-experienced populations. Although there were differences noted in the individual studies, no clear patterns emerged regarding the number and nature of AEs among the different doses and formulations.

In study POX-MVA-011, which evaluated safety of JYNNEOS in HIV-infected vaccine-naïve and vaccine-experienced individuals, solicited local and systemic adverse reactions were reported at similar or lower frequencies in HIV-infected smallpox vaccine-naïve subjects as compared to those seen in non-HIV-infected smallpox vaccine-naive individuals in this study. In HIV-infected subjects with previous smallpox vaccine exposure, fever and chills were reported in 11.5% and 8.4% of subjects respectively. Frequencies of other solicited local and general adverse reactions in this population were similar to those reported in non-HIV-infected subjects who had previously received smallpox vaccination.

The safety of JYNNEOS in smallpox vaccine-naïve subjects with currently active or a history of AD was evaluated in a multicenter, open-label clinical study POX-MVA-008 that included 350 subjects with AD and 282 subjects without AD. In subjects with AD, solicited local and systemic adverse reactions were reported at similar frequencies as those in subjects without AD in this study, with the exception of redness (61.2% with AD vs. 49.3% without AD), swelling (52.2% with AD vs. 40.8% without AD), chills (15.9% with AD vs. 7.8% without AD) and headache (47.2% with AD vs. 34.8% without AD).

Because of the risk of myopericarditis associated with ACAM2000 in smallpox vaccine-naïve individuals, cardiac adverse events of special interest (AESIs) were monitored during clinical development of MVA-BN. Evaluation of cardiac AESIs included any cardiac signs or symptoms, ECG changes determined to be clinically significant, or troponin-I elevated above 2 times the upper limit of normal. In the 22 studies, subjects were monitored for cardiac-related signs or symptoms through at least 6 months after the last vaccination. The numbers of JYNNEOS and placebo recipients, respectively, with troponin-I data were: baseline level (6,376 and 1,203); level two weeks after first dose (6,279 and 1,166); level two weeks after second dose (1,683 and 193); unscheduled visit, including for clinical evaluation of suspected cardiac adverse events (500 and 60).

The cardiac safety profile of MVA-BN also appears to be favorable. Overall, the frequency of AESIs in this clinical development program was relatively low. Cardiac AESIs were reported to occur in 1.3% (95/7,093) of JYNNEOS recipients and 0.2% (3/1,206) of placebo recipients who were smallpox vaccine-naïve. Cardiac AESIs were reported to occur in 2.1% (16/766) of JYNNEOS recipients who were smallpox vaccine-experienced. The higher proportion of JYNNEOS recipients who experienced cardiac AESIs was driven by 28 cases of asymptomatic post-vaccination elevations of troponin-I in two studies: POX-MVA-011, which enrolled 482 HIV-infected subjects and 97 healthy subjects, and POX-MVA-008, which enrolled 350 subjects with atopic dermatitis and 282 healthy subjects. An additional 127 cases of asymptomatic post-vaccination elevation of troponin-I above the ULN but not above 2 times the ULN were documented in JYNNEOS recipients throughout the clinical development program, 124 of which occurred in studies POX-MVA-011 and POX-MVA-008. Proportions of subjects with troponin-I elevations (> ULN) were similar between healthy (13.7%) and HIV-infected (11.5%) subjects in POX-MVA-011 and between healthy (18.9%) and atopic dermatitis (18.0%) subjects in POX-MVA-008. A different troponin assay was used in these two studies compared to the other studies, and these two studies had no placebo controls. None of the asymptomatic troponin-I elevations were associated with ECG findings that substantiated a suspicion of myocarditis or pericarditis. The clinical significance of these asymptomatic post-vaccination elevations of troponin-I is therefore unknown.

Additionally, only one case of clinically apparent suspected pericarditis, and no cases of clinically apparent suspected myocarditis, occurred following MVA-BN in >7000 exposed smallpox vaccine naive subjects. The case of suspected pericarditis was based on clinical symptoms with normal troponin-I, ECG, and echocardiogram and was assessed by the clinical reviewer and by the applicant as unlikely related to MVA-BN and more likely related to documented coxsackie virus infection.

Among all the cardiac AESIs reported, only 6 cases (0.08%) were considered by the clinical reviewer and the applicant to be causally related to JYNNEOS vaccination and included tachycardia, electrocardiogram T wave inversion, electrocardiogram abnormal, electrocardiogram ST segment elevation, electrocardiogram T wave abnormal, and palpitations. None of the cardiac AESIs considered causally related to study vaccination were considered serious.

Across the 22 clinical trials, no trends for unexpected and/or serious adverse events due to the investigational product were detected. In addition, none of the historically reported complications of replicating vaccinia-based smallpox vaccines, such as vaccinia rash, eczema vaccinatum, generalized vaccinia, progressive vaccinia, erythema multiforme or post-vaccinal encephalitis were observed in the clinical development program of MVA-BN.

There were two deaths reported from the 22 clinical trials: one each was reported from POX-MVA-011 (due to overdose of Xanax and benzodiazepine) and POX-

MVA-013 (suicide), respectively. None was deemed related to MVA-BN by the applicant or clinical reviewer.

In summary, the safety profile of MVA-BN, including in HIV-infected subjects and subjects with AD, was favorable. The studies did not observe increased cardiac events among MVA-BN vaccinated individuals compared with placebo recipients. The submitted safety data also support use of MVA-BN in individuals infected with HIV or with AD.

8. ADVISORY COMMITTEE MEETING

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because FDA review of this submission did not identify concerns or issues which would have benefitted from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

Recommendation for granting Priority Review and Material Threat Medical Countermeasure Priority Review Voucher

Priority Review

BN requested priority review for this BLA on the premise that 1. JYNNEOS targets a serious condition (smallpox), and 2. JYNNEOS provides a significant improvement in safety, particularly in multiple subpopulations of individuals for whom the currently licensed vaccine, ACAM2000, is either contraindicated or could have severe and potentially life-threatening clinical consequences.

The serious risks associated with ACAM2000 are directly related to replication of the vaccine virus at and beyond the vaccination site. JYNNEOS is incapable of replication in human cells and tissues, and preliminary review of the safety data accumulated in the JYNNEOS clinical development program support the safety profile. JYNNEOS is intended to prevent a serious condition and, if approved, would provide an effective smallpox vaccine with an improved safety profile as compared to the currently available smallpox vaccine. The BLA was therefore granted priority review.

Material Threat Medical Countermeasure Priority Review Voucher

BN requested that a Priority Review Voucher as a material threat medical countermeasure (MCM) be issued if FDA agrees with their request for priority review designation of the BLA for JYNNEOS. Section 565A of the FD&C Act (21 U.S.C. 360bbb-4a), which was added by the 21st Century Cures Act, authorizes FDA to

award priority review vouchers to sponsors of approved material threat MCM product applications that meet certain criteria upon approval of those applications. We have determined that JYNNEOS meets all the criteria for a material threat MCM Priority Review Voucher described in the FDA's draft guidance, Material Threat Medical Countermeasure Priority Review Voucher Program, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/material-threat-medical-countermeasure-priority-review-vouchers-draft-guidance-industry

Therefore, a material threat MCM Priority Review Voucher was granted to BN.

10. LABELING

The proposed proprietary name, JYNNEOS, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) on November 28, 2018 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on January 23, 2019. APLB found the PI, package, and container labels acceptable from a promotional and comprehension perspective.

The Review Committee negotiated revisions to the PI, including: adding an indication for monkeypox; modifying the proposed proper name from "Smallpox vaccine, live, non-replicating, Modified Vaccinia Virus Ankara" to "Smallpox and Monkeypox vaccine, live, non-replicating"; removing the take attenuation data from the PI due to concerns with the data quality; removing the immunogenicity data for study POX-MVA-005, -023, -008 -011, and -024 because the PRNT used in these studies were not validated and accepted by CBER assay reviewers; removing the proposed single booster dose for use in smallpox vaccine-experienced individuals due to the PRNT assay issues cited above; simplifying the presentation of adverse events by presenting SAE and AESI data of integrated safety summary instead of individual study populations.

The Review Committee also discussed BN's request for listing dual storage conditions on the carton label and PI: (b) (4) storage temperature for stock-piling purposes and -20°C storage temperature for other non-stockpiling purposes. To reduce the possibility of medication errors due to deviations in storage conditions, the review committee recommended listing only the -20°C (-25°C to -15°C) storage condition on the carton label and PI. For stockpiled product to be stored at (b) (4) , the review committee recommended BN to include a separate memorandum with the product detailing the expiration date for that storage condition.

All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of JYNNEOS for the labeled indication and usage.

b) Risk/ Benefit Assessment

Based on the data submitted by BN to support the safety and effectiveness of JYNNEOS that have been presented and discussed in this document, as well as the serious illnesses associated with smallpox and monkeypox diseases, the Review Committee agrees that the risk/benefit profile for JYNNEOS is favorable and supports approval of this BLA.

The vaccinia specific geometric mean neutralizing antibody titer elicited by two doses of MVA-BN administered at 28 days apart in vaccinia-naïve individuals was non-inferior to that elicited by ACAM2000. It is reasonable to expect that this regimen of the vaccine is effective in smallpox vaccinia-naïve as well as in smallpox vaccine experienced individuals.

Non-inferiority comparison of MVA-BN with ACAM2000 was not conducted in populations of AD subjects or HIV-infected subjects because it was not safe to vaccinate these subjects with ACAM2000, nor was it conducted in smallpox-vaccine-experienced subjects. A cross-study comparison of vaccinia specific neutralizing antibody titers is generally not appropriate and in this vaccine development program even more so because great variation exists among the different versions of PRNT including assay LLODs and LLOQs as well as differences among the study populations. These issues preclude a specific inference of effectiveness in HIV-infected subjects or subjects with AD and preclude a determination of whether a single dose of MVA-BN is effective in smallpox vaccine experienced subjects. The safety profile of MVA-BN is favorable in subpopulations for whom ACAM2000 is contraindicated or not recommended outside of high risk of smallpox disease, such as HIV-infected individuals or individuals with atopic dermatitis. Consequently, the benefit/risk balance is likely to be favorable in all adult populations, and there is no reason to exclude any specific subpopulation from a general indication despite assay issues precluding the labeling of immunogenicity data to infer effectiveness in several of these specific subpopulations.

The risks and benefits analysis of MVA-BN applies to both smallpox and monkeypox indications.

c) Recommendation for Postmarketing Activities

BN has proposed a post-licensure observational study in the event of a smallpox event where any collected cardiac data will be used to further assess for a cardiac signal. BN's proposed pharmacovigilance plan adequately reflects the safety concerns based on the clinical trial experience. There are no identified serious risks. The potential risks of severe hypersensitivity reactions, inflammatory cardiac disorders, and immune-mediated neurologic disorders are adequately addressed with labeling, the addition of event-specific questionnaires, and the mass vaccination study. No case of myocarditis or pericarditis suspected to be related to MVA-BN was observed in the clinical trials. The cutaneous AEs seen with replicating smallpox vaccines (e.g., autoinoculation, progressive vaccinia, generalized vaccinia, eczema vaccinatum) were not observed in the clinical studies and are not expected with JYNNEOS, which is a non-replicating vaccine. Additionally, there were no cases of post-vaccinal encephalitis or an imbalance of neurological events in the clinical trials. Missing information on patients exposed during pregnancy is addressed through the pregnancy outcomes questionnaire and the mass vaccination study. The other areas of missing information on pediatric patients, individuals with organ impairment, safety experience in mass vaccination, and interactions with other vaccines and concomitantly administered immunoglobulin is adequately addressed by routine pharmacovigilance, the mass vaccination study, and labeling.

The reviewed safety data does not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS), nor does it suggest a safety concern that needs to be further evaluated in a study in the CBER Sentinel Program, or a post-marketing requirement (PMR) safety study.