



**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Division of Epidemiology (DE)**

**PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

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**Subject:** Review of Pharmacovigilance Plan

**Sponsor:** Bavarian Nordic (b) (4)

**Product:** Jynneos® (Smallpox [Modified Vaccinia Ankara] Vaccine, Live, Non-replicating)

**Application Number:** BLA/ STN 125678/0.0

**Proposed Indication:** Jynneos® is a vaccine indicated for active immunization against smallpox or monkeypox in adults aged 18 years and older determined to be at high risk for smallpox or monkeypox infection.

**Submission Date:** October 25, 2018

**Action Due Date:** September 24, 2019

## 1.0 OBJECTIVE

The purpose of this review is to assess the adequacy of the pharmacovigilance plan based on the safety profile of Jynneos®.

## 2.0 PRODUCT INFORMATION

### 2.1 Product description

Jynneos (Smallpox [Modified Vaccinia Ankara] Vaccine, Live, Non-replicating) is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopox virus. Jynneos is grown in Chicken Embryo Fibroblast cells, harvested, concentrated, and purified. Each 0.5 mL dose is formulated to contain at least  $0.5 \times 10^8$  Infectious Units of MVA-BN live virus in 10 mM Tris (tromethamine), 140 mM sodium chloride at pH 7.7.

Jynneos is a vaccine indicated for active immunization against smallpox or monkeypox in adults aged 18 years and older determined to be at high risk for smallpox or monkeypox infection.

### 2.2 Proposed dosing regimen(s) and formulation

Individuals not previously vaccinated against smallpox:  
Administer two doses (0.5 mL each) four weeks apart.

Individuals previously vaccinated against smallpox:  
Administer as a single 0.5 mL dose.

The product is supplied in a liquid-frozen formulation as a 0.5 mL single-dose vial for subcutaneous injection.

## 3.0 MATERIALS REVIEWED

**Table 1: Materials reviewed in support of this assessment**

Source	Document Type	Document(s) Reviewed
Bavarian Nordic (b) (4)	BLA Sequence 001	Module 1.14, Draft Labeling Text
Bavarian Nordic (b) (4)	BLA Sequence 001	Module 2.2, Introduction
Bavarian Nordic (b) (4)	BLA Sequence 001	Module 2.4, Nonclinical Overview
Bavarian Nordic (b) (4)	BLA Sequence 001	Module 2.5, Clinical Overview

<b>Source</b>	<b>Document Type</b>	<b>Document(s) Reviewed</b>
Bavarian Nordic (b) (4)	BLA Sequence 001	Module 2.73, Summary of Clinical Efficacy
Bavarian Nordic (b) (4)	BLA Sequence 001	Module 2.74, Summary of Clinical Safety
Bavarian Nordic (b) (4)	BLA Sequence 001	Module 5.3.5.3, ISS Section 1-7_Integrated Analysis
Bavarian Nordic (b) (4)	BLA Sequence 002	Module 1.16, Pharmacovigilance Plan
Bavarian Nordic (b) (4)	BLA Sequence 0010	Module 1.16, Pharmacovigilance Plan (Revision submitted January 9, 2019)
Bavarian Nordic (b) (4)	BLA Sequence 0010	Module 1.11.3, Clinical Information Amendment: Response to Information Request
Bavarian Nordic (b) (4)	BLA Sequence 0014	Module 1.11.3, Clinical Information Amendment: Response to Information Request
Bavarian Nordic (b) (4)	BLA Sequence 0017	Module 1.11.3, Clinical Information Amendment: Response to Information Request, Submission of EMA Clinical Study Protocol POX-MVA-039
Bavarian Nordic (b) (4)	BLA Sequence 0019	Module 1.11.3, Clinical Information Amendment: Response to Information Request 10 – Q5 to 10
Bavarian Nordic (b) (4)	BLA Sequence 0028	Module 1.11.3, Clinical Information Amendment: Response to Information Request
Bavarian Nordic (b) (4)	BLA Sequence 0028	Module 1.16, Pharmacovigilance Plan (Revision submitted March 29, 2019)
Bavarian Nordic (b) (4)	BLA Sequence 0030	Module 1.11.3, Clinical Information Amendment: Response to Information Request
Bavarian Nordic (b) (4)	BLA Sequence 0035	Module 1.16, Pharmacovigilance Plan (Revision submitted May 21, 2019)
Bavarian Nordic (b) (4)	BLA Sequence 0035	Module 1.11.3, Clinical Information Amendment: Response to Information Request

Source	Document Type	Document(s) Reviewed
Bavarian Nordic (b) (4)	BLA Sequence 0039	Module 1.11.3, Clinical Information Amendment: Response to Information Request
Bavarian Nordic (b) (4)	BLA Sequence 0039	Module 1.17.1, POX-MVA-039 Clinical Study Protocol

#### 4.0 SUMMARY OF POST-MARKET EXPERIENCE

The sponsor holds a marketing authorization under exceptional circumstances for MVA-BN in Europe for active immunization against smallpox in adults (trade name IMVANEX®) and has licensed MVA-BN in Canada to protect populations with contraindications to receive replicating smallpox vaccines (trade name IMVAMUNE®). The product has an international birth date of July 31, 2013 (European approval). **Table 2** below provides an overview of the worldwide shipments of the vaccine since the international birth date up to January 31, 2019.

**Table 2. Worldwide shipments of MVA-BN from July 31, 2013 – January 31, 2019\***

Destination	Cumulative number of doses shipped
United States	(b) (4)
European Union	(b) (4)
Other	(b) (4)
Total	(b) (4)

\*Adapted from Table 18 (page 23) of the revised *Pharmacovigilance Plan* (STN 125678/0.34, Module 1.16.1)

According to the sponsor, all doses delivered to the U.S. were directed to the Strategic National Stockpile. Less than 4,000 doses were used for vaccinations of laboratory workers, military personnel, and first line responders; four patients reported adverse events (AEs), of which there was one serious adverse event (SAE) of spontaneous abortion in a 40-year old female who was unaware of the pregnancy at the time of vaccination (STN 125678/0.34, Module 1.16.1, Appendix 1, revised *Pharmacovigilance Plan*).

#### 5.0 SAFETY RELATED CONCERNS OF SMALLPOX VACCINES

ACAM2000® is the currently used smallpox vaccine for Department of Defense (DoD) personnel (1). ACAM2000 was licensed by the FDA in August 2007, replacing Dryvax® for smallpox vaccination. Smallpox vaccination with live vaccinia virus has historically been associated with several serious AEs usually involving the skin, eyes, heart or in rare cases the nervous system (2-4). Cutaneous reactions included rash, autoinoculation, ocular vaccinia, generalized vaccinia, progressive

vaccinia, and eczema vaccinatum. Post-vaccinal encephalitis has also been rarely reported. Cardiac adverse events are a well-known complication of smallpox vaccination with live vaccinia vaccines and include pericarditis, myocarditis, dilated cardiomyopathy, and arrhythmias (5, 6). The Phase III prospective study for ACAM2000 identified suspected myopericarditis rates of 5.7 per 1000 (5 of 873) vaccinees within the ACAM2000 group and a rate of 10.4 per 1000 (3 of 289) vaccinees in the Dryvax vaccine group 30 days after vaccination (ACAM2000 package insert). Other studies have confirmed the association of smallpox vaccination with myopericarditis, including subclinical myopericarditis (7).

## 6.0 DESCRIPTION OF JYNNEOS SAFETY DATABASE

### 6.1 Clinical studies

A total of 7871 subjects have been vaccinated in 22 completed clinical trials. Primary efficacy data for the smallpox indication are mainly derived from the Phase 3 non-inferiority study POX-MVA-006. POX-MVA-006 enrolled healthy, smallpox vaccine-naïve military personnel stationed in the Yongsan Garrison in South Korea. Group 1 subjects in POX-MVA-006 received Jynneos on Days 0 and 28 and ACAM2000 on day 56, while Group 2 subjects received one dose of ACAM2000. The primary efficacy endpoints of the POX-MVA-006 study were to demonstrate:

- the non-inferiority of Jynneos compared to ACAM2000 in terms of the vaccinia specific Plaque Reduction Neutralization Test (PRNT) antibody response
- Jynneos vaccination prior to ACAM2000 vaccination (scarification) results in an attenuation of the take (i.e., major cutaneous reaction consisting of crusting and scarring at the site of primary inoculation) based on a comparison of Maximum Lesion Areas in Group 1 versus Group 2 subjects

Efficacy data are further provided in eight additional clinical trials using the same Jynneos formulation and dose regimen as in POX-MVA-006. **Table 3** below provides a summary of the clinical studies supporting the efficacy of Jynneos.

**Table 3. Summary of clinical studies supporting the efficacy of Jynneos\***

Study	N	Description
POX-MVA-005 (supporting)	745	Partially randomized, partially double blind, placebo controlled Phase 2 non-inferiority trial to evaluate immunogenicity and safety of one and two doses of Jynneos in 18 – 55 year old healthy subjects.
POX-MVA-006 (pivotal)	433	Randomized open-label Phase 3 non-inferiority trial to compare indicators of efficacy of Jynneos to ACAM2000, with ACAM2000 given alone or after Jynneos vaccine priming in 18 – 42 year old healthy, vaccinia naïve military subjects.
POX-MVA-008 (supporting)	632	Multicenter, open-label, controlled Phase 2 trial to evaluate safety and immunogenicity of Jynneos in 18 – 40 year old subjects with diagnosed atopic dermatitis compared to healthy subjects.

POX-MVA-011 (supporting)	579	Multicenter, open-label, Phase 2 trial to evaluate safety and immunogenicity of Jynneos in 18 – 55 year old vaccinia-naive and vaccinia-experienced HIV-infected subjects with CD4 counts $\geq 200 - 750$ cells/ $\mu$ L compared to healthy subjects.
POX-MVA-013 (supporting)	4005	Randomized, double-blind, placebo-controlled Phase 3 trial to evaluate immunogenicity and safety of three consecutive production lots of Jynneos in healthy, vaccinia-naive subjects.
POX-MVA-023 (supporting)	152	Open label, Phase 2 study to evaluate and compare the immune responses induced by a single booster dose of Jynneos two years after the last vaccination with one or two doses of Jynneos. This study also assessed the persistence of antibody titers in subjects two years after a single dose or a two-dose priming with Jynneos in study POX-MVA-005, and in vaccinia experienced subjects who had received a single booster dose of Jynneos in POX-MVA-005.
POX-MVA-024 (supporting)	119	Randomized, double-blind, placebo-controlled Phase 2 trial to evaluate safety and immunogenicity of one and two doses of Jynneos in 56 – 80 year old vaccinia-experienced subjects.
POX-MVA-027 (supporting)	651	Randomized, double blind, multicenter Phase 2 trial to compare the immunogenicity and safety of a liquid frozen and a (b) (4) formulation of Jynneos in vaccinia-naive, healthy subjects.*
POX-MVA-037 (supporting)	87	Multicenter randomized, open label, Phase 2 trial to assess the safety and immunogenicity of Jynneos when increasing the number of injections compared to the standard dose regimen in immunocompromised subjects with HIV infection.

\*Adapted from Table 2 (pages 15 - 16) of the *Summary of Clinical Efficacy* document, BLA/STN125678.0, Sequence 001, Module 2.73.

\*Only the liquid frozen formulation is being considered in this application.

## 6.2 AEs

Most of the clinical trials collected data on solicited general (e.g., a pyrexia, headache, chills, myalgia, nausea, fatigue) and local AEs (injection site reactions) likely to occur after vaccination as recorded by subjects on diary cards on Day 0, 4, 7, or 14 post-vaccination (dates specified by study). Additionally, information was collected on all unsolicited AEs (defined by occurrence of any medical event observed by the investigator or reported by the subject at trial visits), AEs leading to withdrawal, serious adverse events (SAE), and AEs of special interest (SIAE). Solicited AEs were defined by each individual study; **Table 4** summarizes AEs that occurred in more than 1% of clinical trial subjects.

**Table 4. Suspected\*\* AEs reported by  $\geq 1\%$  of subjects in the completed Jynneos clinical trials (n=7863\*)**

Preferred Term	Number of Reports by Subjects	Frequency
Injection site pain	6,385	81.2%

Injection site erythema	5,049	64.2%
Injection site swelling	3,804	48.4%
Injection site induration	3,315	42.2%
Injection site pruritus	2,935	37.3%
Myalgia	2,54	32.1%
Fatigue	2,425	30.8%
Headache	2,274	28.9%
Nausea	1,102	14.0%
Rigors/chills	684	8.7%
Body temperature increased	269	3.4%
Appetite disorder	218	2.8%
Arthralgia	206	2.6%
Injection site nodule	195	2.5%
Injection site discolouration	191	2.4%
Pain in extremity	147	1.9%
Injection site haematoma	107	1.4%
Pyrexia	99	1.3%
Axillary pain	91	1.2%
Injection site warmth	85	1.1%

\*Adapted from Table 17 (page 19) of the revised *Pharmacovigilance Plan* (STN125678, sequence 0035, Module 1.16.1).

\*\* Suspected AEs were possibly related to vaccine as determined by the sponsor or Data Safety Monitoring Board

‡ Eight subjects received Jynneos vaccination who were not included in analysis. This included 7 subjects in POX-MVA-009 who received Dryvax either on the same day or within 7 days after Jynneos administration, and one subject in POX-MVA-029 who did not receive vaccine according to randomization.

As noted in Section 5.0 above, smallpox vaccines are associated with cardiovascular, cutaneous, and neurologic AEs. Cardiac AEs are discussed in Section 6.3 below. Cutaneous AEs associated with previous generations of smallpox vaccines (i.e., autoinoculation, progressive vaccinia, generalized vaccinia, eczema vaccinatum, erythema multiforme) were not observed. There was one case of extraocular muscle paresis eight days after the second Jynneos vaccination in a 28 year-old female that resolved. There were no cases of post-vaccinal encephalitis. No imbalance of serious AEs by treatment group in the System Organ Classes (SOC) “Nervous System Disorders” or “Skin and Subcutaneous Tissue Disorders” was observed (STN125678/0.18).

### 6.3 Adverse events of special interest (SIAE)

The SIAE were specifically defined by each clinical study. In general, SIAE included cardiac symptoms (e.g., chest pain or tightness, dyspnea, etc.), clinically significant electrocardiogram (ECG) changes, and in some studies cardiac enzymes elevated

above the upper limit of normal (ULN) or two times above the ULN. There was one case of a “possible case of acute pericarditis” reported in trial POX-MVA-013. This patient was a 32-year-old female subject who developed chest pain that was worse when lying down and improving when sitting in an upright position 23 days after receiving the first dose of Jynneos vaccine; troponin and ECG were normal (STN/BLA 125678/0.0, Module 5.3.5.1 *Clinical Study Report*, POX-MVA-013, p. 99-100). There was also a case of non-ST elevation myocardial infarction four months after Jynneos vaccination in a 30 year-old male with a history of obesity and a family history of cardiovascular disease. Additionally, there were four SIAE cases of cardiac events consisting of three events of dyspnea and one event of chest pain after ACAM2000.

ECG changes were monitored in several studies. In the pooled analysis comparing vaccinated subjects to placebo or ACAM2000 control subjects (Table 6.1, Pooled Safety Data Tables), no subjects had baseline ECGs with clinically significant abnormalities. There were four subjects who developed a clinically significant abnormality after vaccination, which was after administration of the first vaccine for all subjects (generally assessed 1 – 2 weeks after vaccination): one subject in a placebo group (1/1183, 0.1%) and three subjects in a Jynneos vaccination group (3/3406, 0.1%); there were no subjects in the ACAM2000 group that developed a clinically significant ECG abnormality (n = 213).

In response to a DE information request (IR), the sponsor noted that many subjects had troponin-I values between the ULN and 2 x ULN throughout the course of the clinical trials (*Clinical Overview* document, STN/BLA 125678/0, Module 2.5). Additional information on the specific troponin assays used in the clinical studies and analyses comparing post-vaccination troponin values relative to baseline were provided (STN/BLA 125678/0.13, Module 1.11.3). **Table A1** in the **Appendix** shows the categorical shift of post-vaccination troponin-I values from screening (baseline) in the all vaccinia-naïve population using any troponin assay; 96/5593 (1.7%) subjects who received Jynneos had a screening troponin value below the assay limit of quantitation (LoQ) and had a highest post-vaccination troponin value above the LoQ. The majority of shifts of baseline troponin values below the LoQ to above the ULN post-vaccination occurred in studies POX-MVA-008 and POX-MVA-011 (Table A1a and A1b). Specifically, 28/282 (9.9%) of healthy subjects and 38/349 (10.9%) of atopic dermatitis subjects had screening troponin values below the LoQ and a highest post-vaccination troponin value above the ULN (Study POX-MVA-008). In study POX-MVA-011, 23/349 (6.6%) of HIV-positive, vaccinia-naïve subjects and 7/88 (8.0%) healthy, vaccinia-naïve subjects had screening troponin values below the LoQ and post-vaccination troponin values above the ULN. Both Study POX-MVA-008 and POX-MVA-011 had troponin testing performed at the same clinical laboratory. This laboratory switched assays during the period in which the trials were conducted from a (b) (4) , Troponin I-QT assay with a reference cut-off value of 0.08 µg/L to a (b) (4) assay, Troponin I High Sensitivity assay with a reference cut-off value of 0.04 µg/L after November 2006.



The sponsor provided information on the troponin assays used in 17 clinical studies that performed testing (IR responses, STN/BLA 125678/0.13 and STN/BLA 125678/0.29). The complete analyzer name was provided for two laboratories. The sponsor only provided the assay technology type without a specific assay name for five studies. Additionally, the specific laboratory accreditation program was not provided for 12/17 clinical studies that performed testing.

*Reviewer comment: The sponsor attributed the increase in the proportion of subjects with elevated troponin values to a change in the assay from one with an ULN of 0.08 µg/L (b) (4), Troponin I-QT assay) to an assay with an ULN of 0.04 µg/L (b) (4) assay, Troponin I High Sensitivity assay). The sponsor stated the assay with a lower ULN was a “high sensitivity assay” and concluded this more stringent ULN resulted in more cases with elevated troponin. However, troponin assays are neither standardized nor harmonized, thus, each troponin assay will have a different ULN (typically defined as the 99<sup>th</sup> percentile of a healthy reference population) (8). Furthermore, the International Federation of Clinical Chemistry (IFCC) defines a high sensitivity troponin assay as an assay that can measure troponin values in at least 50% of healthy individuals and has a coefficient of variation of <10% at the 99<sup>th</sup> percentile of a healthy reference population (9). The sponsor’s classification of their assay as “high sensitivity” is incorrectly based on a lower ULN instead of as defined above by the IFCC. It is not clear from the information provided in the submission if the assay used by the sponsor meets the specific criteria of the IFCC’s definition of a high-sensitivity assay. Therefore, the sponsor’s explanation of the high proportion of elevated troponin results in studies POX-MVA-008 and POX-MVA-011 is incorrect.*

*Searches of the 510(k) database using the product code “MMI” and applicant name “(b) (4)” on January 30, 2019 did not identify any FDA cleared troponin assays with “QT” or “High Sensitivity” in the proprietary name prior to 2018, when all clinical trials were conducted. No results were identified from a search of the CLIA database on January 30, 2019 using search parameters of manufacturer “(b) (4)” and analyte name “troponin.” Review of (b) (4) assay labels in the CDRH Image database did not identify any assays with a claimed cut-off of 0.08 µg/L. Thus, the sponsor may not have used FDA cleared assays in some of the clinical trials. It is not clear from the information provided if the sponsor performed the full assay validation expected from a laboratory developed test.*

*The sponsor concluded that isolated troponin I values less than 2 x ULN do not correlate with cardiac abnormalities. The clinical significance of transient elevations of troponin values in otherwise healthy subjects is unknown. Several studies have noted that elevated troponin values, and even values within the normal range, may be associated with adverse cardiovascular outcomes when using both conventional and high-sensitivity assays (10, 11). However, increases in troponin values following strenuous exercise are common, although the prevalence, pattern of rise and fall, and absolute increase in troponin values varies considerably across studies (12, 13). While the sponsor’s conclusion that elevated troponin values are clinically*

*insignificant is not correct, the interpretation of transient elevations in the physically active, generally healthy military population cannot be determined at this time. Cardiac SIAEs that occurred in the clinical trials are described in the product labeling.*

## 7.0 SPONSOR'S PHARMACOVIGILANCE PLAN (PVP)

The sponsor proposes routine pharmacovigilance for all AEs. A summary of the sponsor's PVP is provided in **Table 5** below.

**Table 5. PVP\***

Safety Concern	Proposed Action
<i>Important Identified Risks</i>	
• None	Not applicable
<i>Important Potential Risks</i>	
• Severe hypersensitivity reactions	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Observational post-authorization safety and efficacy study in the event of mass vaccination</li> <li>• Labeling</li> </ul>
• Inflammatory cardiac disorders	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Event-specific (targeted) questionnaires</li> <li>• Observational post-authorization safety and efficacy study in the event of mass vaccination</li> <li>• Labeling</li> </ul>
• Immune mediated neurologic disorders	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Event-specific (targeted) questionnaires</li> <li>• Observational post-authorization safety and efficacy study in the event of mass vaccination</li> </ul>
<i>Important Missing Information</i>	
• Pregnant and lactating women	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Documentation and tracking of all pregnancy reports using a dedicated Pregnancy Questionnaire</li> <li>• Observational post-authorization safety and efficacy study in the event of mass vaccination</li> <li>• Labeling</li> </ul>
<ul style="list-style-type: none"> <li>• Children and adolescents (&lt; 18 years)</li> <li>• Individuals with organ impairment</li> <li>• Safety experience in mass vaccination due to smallpox outbreak</li> <li>• Interactions with other vaccines and concomitantly</li> </ul>	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Observational post-authorization safety and efficacy study in the event of mass vaccination</li> <li>• Labeling</li> </ul>

administered immunoglobulins	
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\*Adapted from Table 27 (page 29) and Table 28 (page 35), *Pharmacovigilance Plan* (STN125678/0.34, sequence 0035, Module 1.16.1).

### **Event-specific questionnaires**

The sponsor developed event-specific questionnaires for inflammatory cardiac disorders, immune mediated neurologic disorders, and women who received Jynneos vaccination during pregnancy. MedDRA preferred terms (PTs) triggering the use of these questionnaires are pre-specified. The event-specific questionnaire will be sent to the reporter when the initial AE report contains at least one event matching the pre-specified MedDRA terms. The data capture aids collect patient data, suspect products including administration dates, event terms, clinical description, event-specific key diagnostics, treatments, risk factors, and medical history relevant for the targeted events.

All pregnancy cases will be tracked until the estimated date of delivery, at which time the pregnancy reporter will be contacted to obtain the outcome of the pregnancy. If the outcome is a normal healthy baby, no further follow-up is performed. Outcomes of abortion, stillbirth, abnormal neonate, or a neonate experiencing an AE are followed for results of autopsy if performed, prenatal tests, and other factors such as maternal health problems or complications during delivery. At least three attempts throughout a three-month period to contact the reporter of the pregnancy will be performed to obtain outcome information.

### **Post-authorization safety and efficacy study**

The sponsor proposes a post-market, non-interventional safety and efficacy surveillance study in the event that Jynneos is used in the context of mass vaccination in a post-outbreak scenario. The protocol was developed as a post-authorization study as requested by EMA (STN 125678/0.16 and STN 125678/0.38). The objectives of this study are:

#### Primary objective

- To monitor and characterize incidence of SAEs and/or medically attended AEs in patients exposed to Jynneos in accordance with a national public health vaccination program and/or other real-life use.

#### Secondary objectives:

- To monitor and evaluate cases of potential risks typically associated with traditional smallpox vaccines: myopericarditis, vaccinia rash/eczema vaccinatum, generalized vaccinia, progressive vaccinia, erythema multiforme, postvaccinal encephalitis and incorrect route of drug administration.
- To investigate the protection of vaccinated subjects against the onset of smallpox infection.

The study will consist of all subjects vaccinated with Jynneos who have consented to participate in the study. There are no exclusion criteria. The study will collect information on subject demographics, medical history, and concomitant medications. Subjects will be observed for 30 minutes for immediate AEs after vaccination and will be followed for AEs by phone 4 weeks and then every six months until two years after the last vaccination. Subjects will be queried for solicited general and local AEs, SAEs, and SIAEs (cardiac signs or symptoms, ECG changes, elevated troponin, and cases of smallpox infection).

The sponsor aims to monitor up to 9,000 vaccinees, but the actual sample size may depend on the specific region/country setting of the vaccination program. The sponsor states a target population of at least 9,000 vaccinated subjects will allow the detection of AEs with an incidence of 1/3,000 with a 95% probability.

Safety information during the course of the surveillance study will be continuously monitored to identify signals on a weekly basis. The six-month or annual Period Safety Update Reports (PSUR) falling within the outbreak period will be replaced by monthly PSURs accompanied by a summary of vaccine distribution. Once 9,000 participants have been vaccinated, all data will be analyzed and reported. An interim report will be generated with safety information recorded up to and including follow-up data generated 4 weeks after the last MVA-BN vaccination. The final study report will contain all data including 6-month follow-up data.

## **8.0 ANALYSIS OF SPONSOR'S PVP**

### **8.1 Important Potential Risks**

#### **8.1.1 Severe hypersensitivity reactions**

All vaccines may cause hypersensitivity reactions. For severe hypersensitivity disorders, risk minimization measures include contraindications for individuals with known severe allergy to the vaccine or any of its components as well as the need to ensure appropriate medical treatment for the management of possible anaphylactic reactions following administration of the vaccine. The proposed product labeling includes a contraindication for individuals with known severe allergy to the vaccine or its components.

*Reviewer comment: Hypersensitivity and anaphylaxis are well-recognized potential risks associated with vaccines. No marked imbalance in hypersensitivity cases was observed across the trial groups. The sponsor's plan for routine pharmacovigilance and labeling is adequate.*

#### **8.1.2 Inflammatory cardiac disorders: myopericarditis, including cardiomyopathy as a potential late complication**

Myopericarditis is a known class effect of conventional smallpox vaccines, with a rate of 10.38 events per 1,000 vaccinations following vaccination with Dryvax and 5.73 per 1,000 vaccinations with ACAM2000 (ACAM2000 package insert). Persons with a prior history and/or risk factors for cardiovascular diseases were

excluded from the studies. The sponsor proposes routine pharmacovigilance with the use of event-specific questionnaires that will be used as a targeted follow-up instrument for cardiac AEs. The sponsor will collect further information on cardiac AEs in the event this product is used in a mass vaccination scenario. The sponsor includes cardiac SIAEs in the product labeling.

*Reviewer comment: Only one case of possible acute pericarditis was observed in the clinical trials and there are no reported cases of myopericarditis in the approximately 4,000 subjects vaccinated in the post-marketing database. The combination of routine pharmacovigilance, enhanced surveillance in the form of event-specific questionnaires, the mass vaccination study, and labeling of cardiac SIAEs from the clinical studies is adequate for monitoring the potential risk of inflammatory cardiac disorders. The cardiac event-specific questionnaire will be used to obtain follow-up information for subjects who develop elevated troponin values.*

### **8.1.3 Immune-mediated neurologic disorders: post-vaccinal encephalitis and other immune-mediated neurological disorders**

Encephalitis and encephalomyelitis have occurred following either primary vaccination or revaccination with conventional smallpox vaccines. Persons with a prior history or symptoms of central nervous system disease were excluded from the clinical trials. The sponsor proposes routine pharmacovigilance with enhanced pharmacovigilance in the form of event-specific data capture aids that will be used as a targeted follow-up mechanism for immune-mediated neurologic disorders. The sponsor will collect additional information on neurologic events in the mass vaccination study.

*Reviewer comment: Neurologic AEs are a rare event observed after administration of the currently licensed (vaccinia replicating) smallpox vaccines (ACAM2000, Dryvax). The sponsor's proposed plan of routine pharmacovigilance with event-specific questionnaires and the mass vaccination study is adequate.*

## **8.2 Important missing information**

### **8.2.1 Children and adolescents (<18 years)**

No studies were performed in children and adolescents under 18 years old. Section 8.4 of the product labeling notes that the safety and effectiveness of Jynneos has not been established in individuals less than 18 years of age. The sponsor proposes to collect information on AEs in subjects under age 18 who receive vaccination in the mass vaccination study.

*Reviewer comment: The sponsor has not requested an indication for use in pediatric patients. This product will only be used for stockpiling and vaccination of military, first responders, and at-risk laboratory personnel. Addressing the lack of pediatric data in the labeling is appropriate.*

### **8.2.2 Pregnant and lactating women**

No studies were undertaken in pregnant or lactating women. The sponsor proposes to document and follow-up all pregnancy reports using a data capture aid for obtaining pregnancy information and pregnancy-related outcome information. Section 8.1 of the label notes that available human data on Jynneos administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Section 8.2 of the label states that data are not available to assess the effects of Jynneos in the breastfed infant. The sponsor will also collect information on pregnant women exposed to the product in the mass vaccination study using the pregnancy questionnaire.

*Reviewer comment: The sponsor's plan to address the absence of data in pregnant and lactating women in the labeling and with a pregnancy-specific questionnaire to collect pregnancy outcomes on women exposed to the product during pregnancy is adequate.*

### **8.2.3 Individuals with organ impairment**

Individuals with comorbidities such as clinically significant renal, hepatic, or cardiac impairment were excluded from the clinical studies. The sponsor states that no adverse effect of a non-replicating vaccine is expected, and the medical need would outweigh risk in the case of a smallpox outbreak. The sponsor proposes routine pharmacovigilance for all AEs.

*Reviewer comment: This vaccine is expected to be used in military and at risk-laboratory personnel and first responders, who are expected to be healthy. The sponsor will collect additional information on all patient populations who are exposed in the event the product is used in mass vaccination. The sponsor's proposal of routine pharmacovigilance for all AEs and the mass vaccination study is adequate.*

### **8.2.4 Safety experience in mass vaccination due to smallpox outbreak**

This sponsor proposes a study of safety and efficacy in the event this product is used in a mass vaccination scenario.

*Reviewer comment: The sponsor's proposal to address the lack of data in a mass vaccination scenario in the proposed mass vaccination study is adequate.*

### **8.2.5 Interactions with other vaccines and concomitantly administered immunoglobulins**

No interaction studies with other vaccines or drugs have been performed. The co-administration of vaccine with any immunoglobulin, including anti-vaccinia immunoglobulin, has not been evaluated.

*Reviewer comment: This product is expected for limited use in stockpiling and administration to at risk military and laboratory personnel. Co-administration of anti-vaccinia immunoglobulin may impact vaccine effectiveness; however, this scenario is not likely to occur under routine conditions. The mass vaccination*

*study will collect additional safety and efficacy data in the event this product is used in a mass vaccination scenario, when it is possible that patients could concomitantly receive anti-vaccinia immunoglobulin and smallpox vaccines.*

## **9.0 CONCLUSIONS**

The sponsor's PVP adequately reflects the safety concerns based on the clinical trial experience. There are no identified 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. Only one case of possible acute pericarditis was observed in the clinical trials and there are no reported cases of myopericarditis in the approximately 4,000 subjects vaccinated in the post-marketing database. 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 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 postmarketing requirement (PMR) safety study.

## **10.0 DE RECOMMENDATIONS**

No additional actions recommended prior to approval. The sponsor's proposed pharmacovigilance plan is adequate. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

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**Table A1. Categorical shift of post-vaccination troponin-I values from screen (baseline)****a) All Vaccinia-naïve population, all assays<sup>a</sup>**

	Screening Value							
	JYNNEOS				Placebo			
	< LoQ	LoQ – ULN	> ULN	> 2x ULN	< LoQ	LoQ – ULN	> ULN	> 2x ULN
Highest post-vaccination value	n = 5593				n = 1175			
< LoQ	4823 (86.2%)	164 (2.9%)	5 (0.1%)	0	998 (84.9%)	46 (3.9%)	0	0
LoQ – ULN	289 (5.2%)	199 (3.6%)	2 (0.04%)	0	87 (7.4%)	44 (3.7%)	0	0
> ULN*	96 (1.7%)	3 (0.1%)	6 (0.1%)	2 (0.04%)	0	0	0	0
> 2x ULN	22 (0.4%)	2 (0.04%)	6 (0.1%)	2 (0.04%)	0	0	0	0

**b) Trial POX-MVA-008<sup>b</sup>**

	Screening Value							
	Healthy				Atopic Dermatitis			
	< LoQ	LoQ – ULN	> ULN	> 2x ULN	< LoQ	LoQ – ULN	> ULN	> 2x ULN
Highest post-vaccination value	n = 282				n = 349			
< LoQ	242 (85.8%)	0	0	0	290 (83.1%)	1 (0.3%)	3 (0.9%)	0
LoQ – ULN	12 (4.3%)	0	0	0	12 (3.4%)	0	0	0
> ULN*	28 (9.9%)	0	0	0	38 (10.9%)	1 (0.3%)	2 (0.6%)	1 (0.3%)
> 2x ULN	2 (0.7%)	0	0	0	14 (4.0%)	1 (0.3%)	2 (0.6%)	1 (0.3%)

**c) Trial POX-MVA-011<sup>c</sup>**

	Screening Value							
	Healthy				HIV			
	< LoQ	LoQ – ULN	> ULN	> 2x ULN	< LoQ	LoQ – ULN	> ULN	> 2x ULN

## Appendix

Highest post-vaccination value	n = 349				n = 131			
< LoQ	308 (88.3%)	1 (0.3%)	0	0	123 (93.9%)	0	0	0
LoQ – ULN	15 (4.3%)	0	0	0	1 (0.8%)	0	0	0
> ULN*	23 (6.6%)	0	2 (0.6%)	1 (0.3%)	7 (5.3%)	0	0	0
> 2x ULN	5 (1.4%)	0	2 (0.6%)	1 (0.3%)	1 (0.8%)	0	0	0

<sup>a</sup>Adapted from Table 13.1.1.1, page 19, of the *Clinical Information Amendment: Response to Information Request* (STN/BLA 125678/0.13, Module 1.11.3)

<sup>b</sup>Adapted from Table 13.2.7, page 87, of the *Clinical Information Amendment: Response to Information Request* (STN/BLA 125678/0.13, Module 1.11.3)

<sup>c</sup>Adapted from Table 13.2.9, page 96, of the *Clinical Information Amendment: Response to Information Request* (STN/BLA 125678/0.13, Module 1.11.3)

‡LoQ = Limit of quantitation; ULN = upper limit of normal

\* >ULN includes > 2x ULN