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Division / Office	DVRPA/OVRR
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Priority Review	Yes
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Applicant	Bavarian Nordic
Established Name	Modified Vaccinia Ankara - Bavarian Nordic (MVA-BN)
(Proposed) Trade Name	JYNNEOS
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Live attenuated Vaccinia Virus, strain MVA-BN
Dosage Form(s) and Route(s) of Administration	Suspension for subcutaneous injection. Each dose (0.5mL) is supplied in a single-dose vial
Dosing Regimen	Administer two doses (0.5 mL each) 4 weeks apart
Indication(s) and Intended Population(s)	For prevention of smallpox and monkeypox disease in adults aged 18 years and older determined to be at high risk for smallpox or monkeypox infection

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## 1. EXECUTIVE SUMMARY

### 1.1 Introduction

Bavarian Nordic (BN) submitted the original Biologics License Application (BLA) STN 125678/0 for the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) smallpox vaccine (liquid-frozen formulation) on October 25, 2018. The vaccine is indicated for prevention of smallpox and monkeypox disease in adults aged 18 years and older determined to be at high risk for smallpox or monkeypox infection.

### 1.2 Brief Overview of BLA Submission

The efficacy and immunogenicity of MVA-BN is demonstrated from 9 clinical trials evaluating the same formulation and dose regimen of MVA-BN (POX-MVA-006, POX-MVA-005, POX-MVA-008, POX-MVA-011, POX-MVA-013, POX-MVA-023, POX-MVA-024, POX-MVA-027 and POX-MVA-037; Table 1). The primary efficacy results for smallpox vaccine-naïve individuals are derived exclusively from POX-MVA-006.

The supporting trials are classified and presented per the following categories:

- smallpox vaccine-naïve population (POX-MVA-013, POX-MVA-027)
- smallpox vaccine-experienced population (POX-MVA-005, POX-MVA-023, POX-MVA-024)
- at-risk populations (POX-MVA-008, POX-MVA-011, POX-MVA-037)

### 1.3 Summary Results

1. In the pivotal Phase 3 Study POX-MVA-006, the median maximum lesion areas (MLAs) in the MVA-BN group (Group 1) and the ACAM2000 group (Group 2) were 0.0 mm<sup>2</sup> (95% CI: 0.0, 2.0) and 76.0 mm<sup>2</sup> (95% CI: 70.0, 87.0), respectively. A significant relative reduction in MLA of more than 40% was shown for subjects who received MVA-BN priming prior to ACAM2000 scarification compared to those who did not. The Area Attenuation Rate (AAR) for MLA was 97.9%, with the Hodges-Lehmann (HL) based 95% CI of (96.6%, 98.3%).

2. In the pivotal Phase 3 Study POX-MVA-006, PRNT GMTs at Peak Visits were significantly higher for Group 1 compared to Group 2 (Group 1: 153.5; Group 2: 79.3; Ratio: 1.935 [95% CI: 1.562, 2.397]), demonstrating non-inferiority of MVA-BN compared to ACAM2000. The revised GMTs based on a higher lower limit of quantitation (LLOQ) and different imputation method for <LLOQ values were 152.8 (95% CI: 133.3, 175.0) and 84.4 (95% CI: 73.4, 97.0) for Group 1 and Group 2, respectively. The ratio of the GMTs for Groups 1 and 2 is 1.810 (95% CI: 1.491, 2.198). The non-inferiority conclusion remains unchanged.

3. In the MVA-BN group in Study POX-MVA-006, after ACAM2000 scarification, subjects with a full take showed substantial increase in PRNT antibody titers following ACAM2000 vaccination (before ACAM2000: 117.2; after: 198.3), while subjects without a take showed substantially lower PRNT antibody titers than their pre-ACAM2000

vaccination titers (before ACAM2000: 122.9; after: 55.3), suggesting possible ACAM2000 vaccination failures and thus raising uncertainty about the MLA reduction data.

4. In the pivotal Phase 3 lot consistency Study POX-MVA-013, the ratio of GMTs ranged from 0.8577 (95% CI: 0.7753, 0.9488) to 1.1012 (95% CI: 0.9992, 1.2136) for all three pairs of MVA-BN lots. The confidence intervals were all within the pre-specified equivalence margins of 0.5 and 2. Therefore, the three MVA-BN lots were found to be equivalent per the PRNT equivalence analysis of GMTs.

5. Safety and tolerability were assessed in 12 main integrated summary of safety (ISS) studies, which includes 5110 vaccinia-naïve subjects (4381 healthy subjects and 729 at-risk subjects) and 409 vaccinia-experienced subjects. In the pooled population, overall 37 SAEs were reported in 33/5519 (0.6%) subjects during the vaccination period and 45 SAEs were reported in 35/5519 (0.6%) subjects during the follow-up period. During the vaccination period, 2 SAEs in 2 (0.04%) subjects were considered to be causally-related to the MVA-BN vaccination. During the follow-up period, 1 SAE in 1 (0.02%) subject was considered related.

#### 1.4 Major Statistical Issues and Conclusions

1. The clinical reviewer noticed that the binary take data for Study POX-MVA-006, ordered either by unique subject ID or by the administration time of ACAM2000, was not randomly distributed in the MVA-BN group. I performed a Wald-Wolfowitz runs test and confirmed the non-random pattern. The Bioresearch monitoring (BIMO) team was unable to obtain sufficient data from the study sites to explain this pattern. Because binary take attenuation was not a required endpoint in the clinical study, the clinical reviewer recommended excluding the data and references to take attenuation from the package insert. I agree with the clinical reviewer's recommendation.

2. In two of the phase 2 studies, POX-MVA-008 and POX-MVA-011, both the applicant's and my analyses show post-vaccination troponin elevations detected by the "(b) (4)" assay "(b) (4)" assay (referred to as "high sensitivity assay" hereafter). However, this troponin elevation was not observed in other studies in which a regular troponin assay was used. In addition, in the IR response submitted on January 23, 2019, BN looked into a potential correlation between abnormal Troponin I values measured throughout the clinical trial program and the actual presence of cardiac adverse events, and presented a list of subjects with increased Troponin values or cardiac adverse events. BN claimed that there was no case indicating towards inflammatory cardiac disorders in conjunction with an increase in Troponin I, and that isolated Troponin I increases themselves should not be considered an important medical risk. I defer to the clinical reviewer regarding the acceptability of BN's response.

## 1.5 Conclusion/Recommendation

Overall, the primary immunogenicity/efficacy objectives were met in both pivotal studies. Regarding safety, MVA-BN was in general safe and well tolerated across all clinical trials except that the majority of adverse events of special interest (AESI) in the two Phase 2 studies were related to increases of troponin levels, which were detected by a high sensitive troponin assay. I defer to the clinical reviewer regarding the significance of this finding and potential association between cardiac adverse events and increases of troponin levels and the overall benefit-risk assessment of this vaccine.

## 2. CLINICAL AND REGULATORY BACKGROUND

CBER granted priority review designation for the BLA, and the original action due date (ADD) was June 25, 2019. On March 4, 2019, CBER identified BLA amendment 125678/0.18 as a major amendment due to a substantial amount of new safety data not previously submitted or reviewed by CBER and extended the review clock by three months. The new ADD is September 24, 2019.

The current smallpox vaccine stockpiles are mainly based on replicating vaccines (e.g. Dryvax or ACAM2000) that carry the risk of considerable side effects and are contraindicated in immune compromised individuals. MVA-BN is derived from the highly-attenuated Modified Vaccinia Ankara (MVA) virus and does not replicate in human cells. Traditionally, successful vaccination with a smallpox vaccine was assessed based on the formation of a vesicle (“take”) at the inoculation site seven to nine days after vaccination. Since MVA-BN does not induce a take due to its high attenuation, inability to replicate in human cells, and route of administration, demonstration of the protective efficacy of MVA-BN needs to be based on alternative strategies. BN has focused on comparability of immunological response (neutralizing antibodies measured by plaque reduction neutralization test [PRNT] and total antibodies measured by enzyme-linked immunosorbent assay [ELISA]). An additional component in demonstrating the protective efficacy of MVA-BN was to evaluate the absence and/or attenuation of the take in subjects immunized with MVA-BN after subsequent scarification with a replicating smallpox vaccine.

The path to licensure for MVA-BN was agreed to be based on demonstration of non-inferiority of MVA-BN to ACAM2000 in Study POX-MVA-006. This pivotal phase 3 study evaluated efficacy of MVA-BN by comparing neutralizing antibodies measured by PRNT and attenuation of take in terms of MLA to those after scarification with ACAM2000. The MLA was defined as the maximum of the lesion area measured on day 6-8 and day 13-15 after scarification. Another pivotal Phase 3 study, POX-MVA-013, was designed to demonstrate lot consistency of the manufacturing process for MVA-BN. The primary efficacy/immunogenicity endpoints were met in both clinical trials POX-MVA-006 and POX-MVA-013.

### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

#### 3.1 Submission Quality and Completeness

The quality of the submission was sufficient to perform a statistical evaluation.

#### 3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues in the pivotal studies were noted.

### 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Deferred to reviewers from other disciplines.

### 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

#### 5.1 Review Strategy

The statistical review of this BLA comprises of two parts: I reviewed the clinical (efficacy/immunogenicity and safety) data; Dr. Lei Huang reviewed the bioassay data.

#### 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following submissions were reviewed:

- 125678/0.0 Module 2.5 Clinical Overview
- 125678/0.0 Module 2.7 Clinical Summary
- 125678/0.0 Module 5 Clinical Study Reports
- 125678/0.13 Module 1.11.3 Clinical Information Amendment
- 125678/0.21 Module 1.11.3 Clinical Information Amendment
- 125678/0.29 Module 1.11.3 Clinical Information Amendment

#### 5.3 Table of Studies/Clinical Trials

Table 1 provides an overview of the clinical trials providing efficacy and/or immunogenicity data for this application.

**Table 1. Overview of All Trials Providing Efficacy/Immunogenicity Data**

<b>Trial Identification</b>	<b>Trial Start / Trial End Total Enrollment</b>	<b>Design Control Type</b>	<b>Trial Drug / Control</b>	<b>Primary Trial Objectives</b>

POX-MVA-006	02 March 2015 (first subject screened) / 14 August 2017 (last subject completed) Total enrollment (randomized): Total: 440 Group 1: 221 Group 2: 219 Enrollment target: 440 (220 subjects per group)	Randomized, open-label, Phase 3 trial Active control: ACAM2000	MVA-BN: Dose: $1 \times 10^8$ TCID <sub>50</sub> Route: SC injection  ACAM2000: Dose: $2.5-12.5 \times 10^5$ pfu Route: Scarification  Regimen: Group 1: 2 SC injections of MVA-BN, 1 each at Weeks 0 and 4; followed by 1 dose of ACAM2000 via scarification, 4 weeks later (Week 8) Group 2: 1 dose of ACAM2000 via scarification, at Week 0	To demonstrate the efficacy of MVA-BN by assessing non-inferiority of MVA-BN compared to ACAM2000 in terms of vaccinia-specific PRNT antibody response at the Peak Visits (Week 6 for Group 1 and Week 4 for Group 2) and by showing that vaccination with MVA-BN prior to scarification with ACAM2000 results in an attenuation of take in terms of MLA
POX-MVA-013	18 March 2013 (First subject screened) / 23 May 2014 (Last Follow-up Visit) Total enrollment (enrolled and randomized): Total: 4005 Group 1: 999 Group 2: 1005 Group 3: 999 Group 4: 1002	Randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial Placebo Control	Regimen: Groups 1-3 (LF Lots 1-3): 1 injection of $1 \times 10^8$ TCID <sub>50</sub> at Week 0 and 1 injection of $1 \times 10^8$ TCID <sub>50</sub> at Week 4  Group 4: 1 injection of placebo at Week 0 and 1 injection of placebo at Week 4	To assess the consistency of three consecutively produced MVA-BN lots
POX-MVA-027	29 April 2013 (first screening) / 19 June 2014 (last FU visit) Enrollment (enrolled and randomized): Total: 652 Group 1 (LF): 327 Group 2 (b) (4): 325	Randomized, double-blind, multicentre, Phase 2 study	Group 1: MVA-BN LF Dose: $1 \times 10^8$ TCID <sub>50</sub> Regimen: 1 injection of $1 \times 10^8$ TCID <sub>50</sub> MVA-BN at Week 0 and Week 4, respectively  Group 2: MVA-BN (b) (4) Dose: $1 \times 10^8$ TCID <sub>50</sub> Regimen: $1 \times 10^8$ TCID <sub>50</sub> MVA-BN at Week 0 and Week 4	To assess non-inferiority of immune responses induced by MVA-BN (b) (4) formulation compared to immune responses induced by MVA-BN LF formulation using antibodies titers measured by vaccinia-specific ELISA

**Table 1. Overview of All Trials Providing Efficacy/Immunogenicity Data (Cont'd)**



<b>Trial Identification</b>	<b>Trial Start / Trial End Total Enrollment</b>	<b>Design Control Type</b>	<b>Trial Drug / Control</b>	<b>Primary Trial Objectives</b>
POX-MVA-005	27 April 2006 (first enrollment)/ 27 August 2007 (last subject FU visit)  Total enrollment (enrolled and randomized): 753  Total enrollment (enrolled and at least 1 dose of study vaccine): 745	Partially randomized, partially double-blind, placebo controlled, Phase 2, non-inferiority study  Placebo control	Vaccinia-naïve subjects Groups 1-3: $1 \times 10^8$ TCID <sub>50</sub> at Week 0 and Week 4  Vaccinia-experienced subjects Group 4: $1 \times 10^8$ TCID <sub>50</sub> at Week 0 and Week 4,	To demonstrate a single booster vaccination of MVA-BN in vaccinia-experienced subjects is non-inferior to the primary immune response in vaccinia-naïve subjects who received 2 vaccinations of MVA-BN  To compare the four study groups with regard to ECG changes and cardiac symptoms
POX-MVA-023	18 August 2008 (first subject screened)/ 05 June 2009 (last subject FU visit)  Total Enrollment: Group 1 (formerly Group 1 in POX-MVA-005): 75 Group 2 (formerly Group 2 in POX-MVA-005): 77 Persistence Set (formerly Groups 1, 2 and 4 in POX-MVA-005): 304	Open-label, Phase 2 study	MVA-BN / No Control  Both Groups: $1 \times 10^8$ TCID <sub>50</sub> at Week 0	To assess the immune response in healthy subjects induced by a booster vaccination of MVA-BN ( $1 \times 10^8$ TCID <sub>50</sub> ) 2 years post last MVA-BN vaccination (priming vaccination with 1 or 2 doses of MVA-BN at $1 \times 10^8$ TCID <sub>50</sub> in POX-MVA-005)
POX-MVA-024	01 July 2009 (First screening visit) / 23 March 2010 (Last subject completed visit 5) Total Enrollment: Group 1: 62 Group 2: 58	Randomized, double-blind, placebo-controlled, Phase 2 study Placebo Control	MVA-BN / Placebo (Tris Buffer)  Group 1: $1 \times 10^8$ TCID <sub>50</sub> at Week 0 and Week 4 Group 2: placebo at Week 0 and $1 \times 10^8$ TCID <sub>50</sub> at Week 4	To expand the MVA-BN data base on safety in a vaccinia-experienced population 56 to 80 years of age after administration of either one or two doses of MVA-BN

**Table 1. Overview of All Trials Providing Efficacy/Immunogenicity Data (Cont'd)**

<b>Trial Identification</b>	<b>Trial Start / Trial End Total Enrollment</b>	<b>Design Control Type</b>	<b>Trial Drug / Control</b>	<b>Primary Trial Objectives</b>
POX-MVA-008	16 August 2006 / 22 October 2009  Actual Enrollment (received at least 1 dose of study vaccine): Overall: 632 Group 1: 282 Group 2: 350 (History of AD: 128 and Active AD: 222)	Open-label, controlled, multicenter, Phase 2 study  Subject control Group 1: Healthy vaccinia-naïve subjects Group 2: vaccinia-naïve subjects with diagnosed atopic dermatitis	MVA-BN/ Subject Control (healthy)  All Groups: Dose: $1 \times 10^8$ TCID <sub>50</sub> at Week 0 and Week 4	To assess the humoral immune response (ELISA) induced by MVA-BN in subjects diagnosed with AD compared to healthy subjects
POX-MVA-011	13 June 2006 / 25 March 2009  Actual Enrollment: Overall: 581	Open-label, controlled, multicenter, Phase 2 study Healthy Control	MVA-BN / Subject Control (healthy)  All Groups: Regimen: $1 \times 10^8$ TCID <sub>50</sub> at Week 0 and Week 4	To investigate the safety of MVA-BN in HIV-1 infected subjects with CD4 counts $\geq 200 - 750$ cells/ $\mu$ L, compared to healthy subjects
POX-MVA-037	28 April 2014 (First screening visit)/ 10 May 2017 (Last follow-up visit)  Actual enrollment: Overall: 87 Group 1: 27 Group 2: 29 Group 3: 31	Randomized, open-label, Phase 2 study	MVA-BN/ No control  Each 0.5 mL dose of vaccine had a virus titer of at least $5 \times 10^7$ TCID <sub>50</sub> MVA-BN  Group 1: 2 SC injections on Weeks 0 and 4  Group 2: 4 SC injections on Weeks 0 and 4, 2 at each time point  Group 3: 3 SC injections, each given at Weeks 0, 4, and 12	To assess the safety of MVA-BN when increasing the dose or number of injections compared to the standard two-dose regimen in immunocompromised subjects with HIV infection

SC: Subcutaneous.

Source: Adapted from Table 3 in Module 2.7.3 Summary of Clinical Efficacy.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1: POX-MVA-006

A randomized, open-label Phase 3 non-inferiority trial to compare indicators of efficacy for MVA-BN smallpox vaccine to ACAM2000 in 18-42 year old healthy vaccinia naïve subjects.

#### *6.1.1 Objectives*

Co-Primary Objectives:

To demonstrate the efficacy of MVA-BN by assessing non-inferiority of MVA-BN compared to ACAM2000 in terms of vaccinia-specific PRNT antibody response at the Peak Visits (Day 42 for Group 1 and Day 28 for Group 2) and by showing that vaccination with MVA-BN prior to scarification with ACAM2000 resulted in an attenuation of take in terms of MLA.

Secondary objectives:

- To assess non-inferiority of MVA-BN compared to ACAM2000 in terms of vaccinia-specific ELISA antibody response at the Peak Visits.
- To assess seroconversion rates of MVA-BN compared to ACAM2000 at the Peak Visits. Seroconversion rate at Peak Visits was defined as the percentage of initially seronegative subjects with appearance of antibody titers equal or greater than the Assay Cut-off Value (ACV).
- To assess immune response dynamics in terms of antibody responses.
- To assess the effect on the ACAM2000 vaccination take following MVA-BN priming.
- To assess and compare safety and reactogenicity of vaccinations with MVA-BN and ACAM2000 given alone, or ACAM2000 given after MVA-BN priming.

#### *6.1.2 Design Overview*

This was a randomized, open-label Phase 3 non-inferiority trial to compare indicators of efficacy for MVA-BN smallpox vaccine to ACAM2000 in 18-42 year old healthy vaccinia-naïve subjects. A total of at least 440 vaccinia-naïve subjects were planned for enrollment and assigned randomly to two parallel treatment groups in a 1:1 ratio in order to obtain at least 175 subjects who qualified for the per protocol set (PPS) in each of Groups 1 and 2.

#### *6.1.3 Population*

Please refer to Section 6.1.2 and clinical reviewer's memo for the inclusion and exclusion criteria.

#### *6.1.4 Study Treatments or Agents Mandated by the Protocol*

Investigational Product: One 0.5 milliliter (mL) standard dose of MVA-BN liquid-frozen vaccine containing a nominal titer of  $1 \times 10^8$  tissue culture infectious dose 50% (TCID<sub>50</sub>)

MVA-BN. MVA-BN vaccine was administered as a SC injection preferably in the non-dominant upper arm.

Comparator: One dose of reconstituted ACAM2000 vaccine consisted of  $2.5\text{--}12.5 \times 10^5$  plaque forming units (PFU) of vaccinia virus (VV). A droplet (0.0025 mL) vaccine was picked up with a bifurcated needle and administered by the percutaneous route (scarification) using 15 jabs of a bifurcated needle.

#### *6.1.5 Directions for Use*

Please refer to clinical reviewer's memo.

#### *6.1.6 Sites and Centers*

One clinical trial site (CTS; with two locations) participated in this clinical trial.

#### *6.1.7 Surveillance/Monitoring*

Please refer to clinical reviewer's memo.

#### *6.1.8 Endpoints and Criteria for Study Success*

Co-Primary Endpoints:

- PRNT GMT at the Peak Visits
- MLA in mm<sup>2</sup> after scarification with ACAM2000

Criteria for Study Success: see Section 6.1.9.

#### *6.1.9 Statistical Considerations & Statistical Analysis Plan*

Analysis of Immunogenicity:

Endpoint: vaccinia specific PRNT antibody response at the Peak Visits (Day 42 for Group 1 [MVA-BN] and Day 28 for Group 2 [ACAM2000]).

Statistical Hypothesis:  $H_0: m_1 - m_2 \leq -\Delta$  versus  $H_1: m_1 - m_2 > -\Delta$  where  $m_1$  is the mean PRNT log<sub>10</sub> titer in Group 1 and  $m_2$  is the mean PRNT log<sub>10</sub> titer in Group 2, and  $\Delta$  is the non-inferiority margin ( $\log_{10}(2) = 0.301$ ).

Statistical Method: The hypothesis was tested for the PRNT using a t-test on the difference of the two means based on the assumption that the log<sub>10</sub> titers are normally distributed. The corresponding CI was presented on the original scale by taking antilog of the CI limits calculated on the log<sub>10</sub> scale.

Analysis of Efficacy:

Endpoint: MLA in mm<sup>2</sup> after scarification with ACAM2000.

Statistical Hypothesis:  $H_0: AAR \leq \lambda$  versus  $H_1: AAR > \lambda$ , where AAR is the area attenuation rate (defined as  $1 - x_1/x_2$ ,  $x_1$  and  $x_2$  are the medians of the observed MLAs for Group 1 and Group 2, respectively), and  $\lambda$  is the pre-specified margin of 0.4.

Statistical Method: Hodges-Lehmann (HL) method for calculating the non-parametric CI and implemented using the HL option in the SAS procedure (b) (4). In addition, the median MLA for each group is calculated along with the 95% non-parametric CIs by using the SAS (b) (4) procedure with the option (b) (4).

#### 6.1.10 Study Population and Disposition

##### 6.1.10.1 Populations Enrolled/Analyzed

Up to 750 subjects (military personnel only) were planned to be screened in order to vaccinate 440 eligible vaccinia-naïve subjects (220 per group), aiming to achieve at least 175 subjects per group in the per protocol set (PPS). A total of 637 subjects were screened, of which 440 subjects were randomized, and 433 subjects were vaccinated. Table 2 provides a summary of population disposition for Study POX-MVA-006. The PPS, which is the primary efficacy analysis population, is the subset of subjects in the FAS who received all vaccinations, completed all visits up until Visit 10 for Group 1 and Visit 4 for Group 2, and had no major protocol deviations, which include:

1. Missing lesion area data on Day 6-8 or Day 13-15 after ACAM2000 vaccination;
2. Missing ELISA or PRNT titers at trial Day 0 (both groups) or Day 42 for subjects in Group 1, or Day 28 post ACAM2000 vaccination (Groups 1 and 2).

**Table 2. Population Disposition for Study POX-MVA-006**

	Group 1 N	Group 2 N	Total N
Subjects screened	-	-	637
Subjects randomized	221	219	440
Subjects vaccinated	220	213	433
Full analysis set (FAS)	220	213	433
Per protocol set (PPS)	165	161	326
PPS for Immunogenicity	185	186	371
Initially seronegative subset (ISS)	176	176	352

Source: Table 8 in the CSR for Study POX-MVA-006.

##### 6.1.11 Efficacy and Immunogenicity Analyses

The primary analysis was performed on the PPS for efficacy endpoints and on the PPS for Immunogenicity for immunogenicity endpoints. Specifically, the confirmatory testing of the co-primary endpoint for efficacy (MLA) was based on the PPS, and the confirmatory testing of the co-primary endpoint for immunogenicity (GMT at Peak Visits) was based on the PPS for Immunogenicity. For further descriptive purposes, the same statistical analyses were performed on the FAS. The ISS population was used as an additional analysis set for assessing the robustness of the immunogenicity analyses.

##### 6.1.11.1 Analyses of Primary Endpoint(s)

##### *Lesion Area – Co-Primary Endpoint*

The MLA was defined as the maximum of two measurements: the lesion area measured on Day 6-8 (after scarification) or the lesion area measured on Day 13-15 (after scarification). The success criterion is an area attenuation ratio (AAR) above  $\lambda=0.4$ . This corresponds to a 40% reduction in Group 1 compared to Group 2, which was considered clinically meaningful..

The median MLAs in Groups 1 and 2 were 0.0 mm<sup>2</sup> (95% CI: 0.0, 2.0) and 76.0 mm<sup>2</sup> (95% CI: 70.0, 87.0), respectively. A significant relative reduction in MLA of more than 40% was shown for subjects who received MVA-BN priming prior to ACAM2000 scarification compared to those who did not (AAR for MLA: 97.9%; HL-based 95% CI: 96.6, 98.3). Table 3 presents the MLA results on Day 6-8 (after scarification) and on Day 13-15 (after scarification).

**Table 3. Statistics of (b) (4) Camera Lesion Area after ACAM2000 Vaccination in Study POX-MVA-006-PPS**

	Group 1 (MVA-BN) (N=165) Median (Min, Max)	Group 2 (ACAM2000) (N=161) Median (Min, Max)	AAR	HL 95% CI
Day 6-8	0.0 (0.0, 96.0)	37.0 (0.0, 133.0)	95.2%	(93.8, 96.2)
Day 13-15	0.0 (0.0, 99.0)	75.0 (0.0, 368.0)	98.2%	(97.7, 98.4)
Maximum	0.0 (0.0, 99.0)	76.0 (0.0, 368.0)	97.9%	(96.6, 98.3)

AAR=area attenuation ratio, HL=Hodges-Lehmann, Max=maximum, Min=minimum, N=number of subjects

Source: Table 12 in the CSR for Study POX-MVA-006.

#### *PRNT Geometric Mean Titers – Co-Primary Endpoint*

Non-inferiority of MVA-BN to ACAM2000 in terms of PRNT GMT at the peak visits is concluded if the lower confidence limit of the GMT ratio lies above ½. The PRNT GMTs at Peak Visits were significantly higher for Group 1 compared to Group 2 (Group 1/Group 2 ratio of 1.935; 95% CI: 1.562, 2.397), demonstrating non-inferiority of MVA-BN compared to ACAM2000 (meeting the success criterion). Groups 1 and 2 were comparable at Baseline, with GMTs of 1.0 for both groups (Tables 4 and 5).

**Table 4. Plaque Reduction Neutralization Test Geometric Mean Titers at all Sampling Points – PPS for Immunogenicity**

	Group 1 (MVA-BN) (N=185)		Group 2 (ACAM2000) (N=186)		Ratio of GMTs Group 1/Group 2
Visit Week	n	GMT (95% CI)	n	GMT (95% CI)	Ratio (95% CI)
Week 0	185	1.0 (1.0, 1.1)	186	1.0 (1.0, 1.1)	1.008 (0.968, 1.050)
Week 1	183	1.1 (1.0, 1.3)	184	1.0 (1.0, 1.1)	1.124 (1.020, 1.239)
Week 2	184	16.2 (13.0, 20.1)	184	16.2 (13.1, 20.0)	0.997 (0.738, 1.348)
Week 4	185	16.9 (13.7, 20.8)	186	79.3 (67.1, 93.8)	0.213 (0.163, 0.278)
Week 6	185	153.5 (134.3, 175.6)	181	64.7 (54.9, 76.2)	2.372 (1.922, 2.928)
Week 8	179	118.2 (102.9, 135.8)	183	67.1 (56.9, 79.0)	1.763 (1.422, 2.185)
Week 12	172	96.5 (80.1, 116.2)	-		-

“-” = not applicable. N is the number of subjects in the specified group, and n is the number of subjects with data available.

Source: Table 15 in the CSR for Study POX-MVA-006.

**Table 5. Plaque Reduction Neutralization Test Non-Inferiority at Peak Visit – PPS for Immunogenicity**

	Group 1 (MVA-BN) (N=185)		Group 2 (ACAM2000) (N=186)		Ratio of GMTs Group 1 / Group 2
Visit Week	n	GMT (95% CI)	n	GMT (95% CI)	Ratio (95% CI)
Peak Visit	185	153.5 (134.3, 175.6)	186	79.3 (67.1, 93.8)	1.935 (1.562, 2.397)
Individual Peak	185	246.2 (217.3, 279.0)	186	117.8 (102.3, 135.7)	2.090 (1.732, 2.522)

Peak visit was Day 42 for Group 1 and Day 28 for Group 2. Individual Peak was the maximum titer per subject from Visit 1 to Visit 7 in Group 1 and maximum titer from Visit 1 to Visit 6 in Group 2.

Source: Table 16 in the CSR for Study POX-MVA-006.

**Reviewer's Comment:**

The GMTs in Tables 4 and 5 were applicant's original analyses which imputed all values below limit of detection (LOD) to  $\frac{1}{2} \times \text{LOD}$  and imputed all values between LOD and LLOQ to LOD. The applicant applied this imputation method for all PRNT analyses in all studies. In the original analyses, the LOD and LLOQ for the PRNT assay version used in Study POX-MVA-006 were (b) (4), respectively. Due to the change of LLOQ from (b) (4) to 20 (refer to Dr. Lei Huang's memo) and the change of the imputation method recommended by CBER, which replaces all "<LLOQ" values with  $\frac{1}{2} \times \text{LLOQ}$ , the PRNT analyses in Study POX-MVA-006 were revised and presented in Tables 6 and 7 below. The revised GMTs at the peak visit, generated by me, were 152.8 (95% CI: 133.3, 175.0) and 84.4 (95% CI: 73.4, 97.0) for Group 1 and Group 2, respectively. The ratio of the GMTs for Groups 1 and 2 is 1.810 (95% CI: 1.491, 2.198). The non-inferiority conclusion remains unchanged.

**Table 6. Plaque Reduction Neutralization Test Geometric Mean Titers at all Sampling Points – PPS for Immunogenicity (Revised from Table 4)\***

	Group 1 (MVA-BN) (N=185)		Group 2 (ACAM2000) (N=186)		Ratio of GMTs Group 1/Group 2
Visit Week	n	GMT (95% CI)	n	GMT (95% CI)	Ratio (95% CI)
Week 0	185	10.1 (9.9, 10.2)	186	10 (10, 10)	1.007 (0.994, 1.020)
Week 1	183	10.3 (9.8, 10.9)	184	10 (10, 10)	1.032 (0.978, 1.088)
Week 2	184	23.4 (20.5, 26.7)	184	23.7 (20.9, 26.8)	0.986 (0.823, 1.182)
Week 4	185	23.5 (20.6, 26.9)	186	84.4 (73.4, 97.0)	0.279 (0.230, 0.338)
Week 6	185	152.8 (133.3, 175.0)	181	68.2 (59.5, 78.2)	2.239 (1.847, 2.714)
Week 8	179	118.6 (103.5, 135.9)	183	72.3 (63.7, 82.1)	1.640 (1.361, 1.974)
Week 12	172	100.5 (84.9, 118.9)	-		-

\*All <LLOQ values are imputed with ½ LLOQ. LLOQ=20.

Source: Statistical reviewer's analysis based on analysis dataset (ADEFF.xpt) of POX-MVA-006 submitted to STN 125678/0.

**Table 7. Plaque Reduction Neutralization Test Non-Inferiority at Peak Visit – PPS for Immunogenicity (Revised from Table 5)\***

	Group 1 (MVA-BN) (N=185)		Group 2 (ACAM2000) (N=186)		Ratio of GMTs Group 1 / Group 2
Visit Week	n	GMT (95% CI)	n	GMT (95% CI)	Ratio (95% CI)
Peak Visit	185	152.8 (133.3, 175.0)	186	84.4 (73.4, 97.0)	1.810 (1.491, 2.198)
Individual Peak	185	246.2 (217.3, 279.0)	186	123.8 (110.7, 138.3)	1.990 (1.684, 2.351)

\*All <LLOQ values are imputed with ½ LLOQ. LLOQ=20

Source: Statistical reviewer's analysis based on analysis dataset (ADEFF.xpt) of POX-MVA-006 submitted to STN 125678/0.

#### 6.1.11.2 Analyses of Secondary Endpoints

The analyses of all the secondary endpoints are presented below.

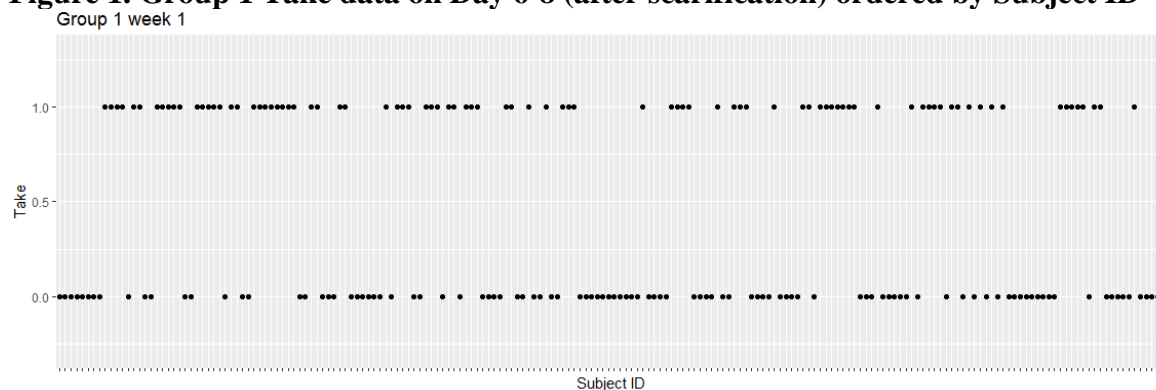
- The median Investigator-measured maximum lesion diameters (MLDs) after scarification with ACAM2000 in Groups 1 and 2 were 0.0 mm and 11.0 mm, respectively. The relative reduction in MLD was 87.5% for subjects that received MVA-BN priming prior to ACAM2000 scarification compared to those who did not (diameter attenuation ratio (DAR)=87.5%; HL-based 95% CI: 83.3, 88.9).
- The observed relative reduction for the Investigator-measured lesion diameter at Day 6-8 after scarification with ACAM2000 was 80.0% (medians: 0.0 mm [Group 1] and 8.0 mm [Group 2]; DAR=80.0%; HL-based 95% CI: 77.8, 85.7).
- The observed relative reduction for the Investigator-measured lesion diameter at Day 13-15 after scarification with ACAM2000 was 88.9% (medians: 0.0 mm [Group 1] and 10.0 mm [Group 2]; DAR=88.9%, HL-based 95% CI: 87.5, 90.0).
- A majority of subjects who were primed with MVA-BN prior to ACAM2000 vaccination had absent takes (89/165 subjects [53.9%]), while the remainder had partial or full takes (38/165 subjects [23.0%] each). Group 1 had far fewer full takes (69.5% less), and more partial and absent takes (18.7% more and 52.1% more, respectively) than Group 2.



- The observed relative reduction for the lesion area at Day 6-8 after scarification with ACAM2000 was 95.2% (medians: 0.0 mm<sup>2</sup> [Group 1] and 37.0 mm<sup>2</sup> [Group 2]; AAR=95.2%; HL-based 95% CI: 93.8, 96.2).
- The observed relative reduction for the lesion area at Day 13-15 after scarification with ACAM2000 was 98.2% (medians: 0.0 mm<sup>2</sup> [Group 1] and 75.0 mm<sup>2</sup> [Group 2]; AAR=98.2%, HL-based 95% CI: 97.7, 98.4).
- The ELISA GMT ratio Group 1/Group 2 at Peak Visit was 5.534 (95% CI: 4.464, 6.859); the ELISA GMT ratio Group 1/Group 2 at individual peak was 5.766 (95% CI: 4.646, 7.156).
- The PRNT GMT ratio Group 1/Group 2 at individual peak was 2.090 (95% CI: 1.732, 2.522).
- Group 1 had higher PRNT GMTs at Weeks 1, 6, and 8 (Group 1/Group 2 ratios between 1.124 and 2.372), and higher ELISA GMTs at Weeks 1, 2, 6, and 8 (Group 1/Group 2 ratios between 1.398 and 7.218). The only time point at which Group 2 had a higher GMT than Group 1 was at Week 4 (Group 1/Group 2 ratios of 0.213, and 0.667 for PRNT and ELISA, respectively).
- Seroconversion rates at Peak Visits were 100.0% (by PRNT or ELISA) for Group 1, and 97.3% (by PRNT) and 96.8% (by ELISA) for Group 2.

The clinical reviewer noted that the distribution of take among Group 1 subjects reported in Listing 16.2.2.1 in the CSR appears to be clustered in terms of the unique subject IDs and requested the statistical reviewer to perform a statistical test on the take data. Figure 1 below shows the Group 1 take data on Day 6-8 (after scarification) ordered by the subject IDs. In the figure, “1” represents take and “0” represents absent take. The Wald–Wolfowitz runs test, which tests the randomness for a sequence of binary data, showed a p-value of 0.0001 and indicated that the binary data were not mutually independent. The p-value for Group 1 take data on Day 13-15 (after scarification) was 0.007. The p-values for Group 1 take data on Day 6-8 (after scarification) for sites 1 and 2 were both 0.009.

**Figure 1. Group 1 Take data on Day 6-8 (after scarification) ordered by Subject ID**



Source: Statistical reviewer’s analysis based on analysis dataset (ADFA.xpt) of POX-MVA-006 submitted to STN 125678/0.

At the request of the clinical reviewer, I calculated the antibody titers prior to and post ACAM2000 vaccination among Group 1 subjects stratified by take type (Table 8). It appears that after the ACAM2000 vaccination, subjects without a take showed lower

PRNT antibody titers than their pre-ACAM2000 vaccination titers, while subjects with full or partial takes showed increases in PRNT antibody titers following ACAM2000 vaccination.

**Table 8. Comparison of Vaccinia Specific Antibody Titers Prior to and Post ACAM2000 Vaccination Among Group 1 Subjects Stratified by Take Type (PPS for Take)**

Subjects and Time Point	N	PRNT GMT (95% CI)	ELISA GMT (95% CI)
All Group 1 Subjects			
Prior to ACAM2000 (Week 8)	165	120.2 (104.0, 139.0)	676.3 (596.3, 766.9)
Post ACAM2000 (Week 12)	162	99.9 (82.6, 120.9)	556.0 (483.8, 639.0)
Subjects with a Full Take			
Prior to ACAM2000 (Week 8)	38	112.5 (85.5, 148.0)	541.8 (414.6, 707.8)
Post ACAM2000 (Week 12)	38	276.6 (193.2, 396.2)	1096.6 (869.3, 1383.3)
Subjects with a Partial Take			
Prior to ACAM2000 (Week 8)	38	122.0 (88.9, 167.4)	813.3 (596.4, 1109.0)
Post ACAM2000 (Week 12)	37	140.8 (105.6, 187.8)	742.0 (589.6, 933.9)
Subjects with any Take			
Prior to ACAM2000 (Week 8)	76	117.2 (95.5, 143.8)	663.8 (540.6, 815.1)
Post ACAM2000 (Week 12)	75	198.3 (156.2, 251.7)	904.4 (766.2, 1067.6)
Subjects without a Take			
Prior to ACAM2000 (Week 8)	89	122.9 (99.8, 151.4)	687.1 (587.0, 804.3)
Post ACAM2000 (Week 12)	87	55.3 (44.1, 69.4)	365.5 (306.8, 435.5)

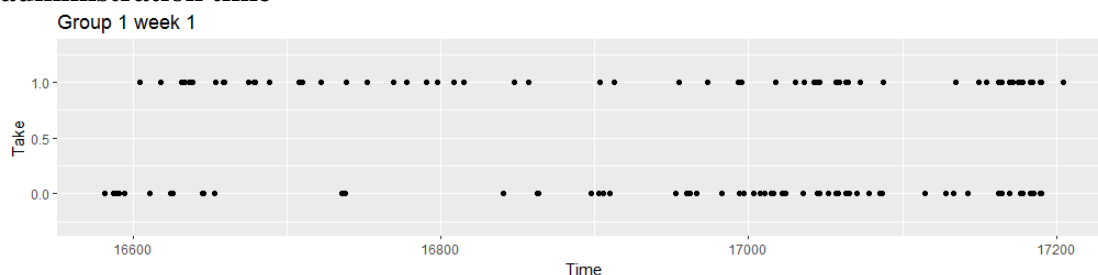
Source: Statistical reviewer's analysis based on analysis dataset (ADFA2.xpt, ADEFF2.xpt) of POX-MVA-006 submitted to STN 125678/0.

The review team sent an IR (IR #13, item #2C) on February 12, 2019 regarding these findings among Group 1 subjects. BN submitted the response to 125678/0.21 on February 26, 2019. In the response, BN clarified that the unique subject IDs have been attributed to the subjects at the time of enrollment, which was at least 8 weeks prior to ACAM2000 administration in Group 1, and therefore ACAM2000 vaccinations in Group 1 subjects were not performed strictly in the order of their subject IDs. BN concluded that the clustering in the distribution of take in terms of the unique subject ID was a “random effect”, and the pattern was less clustered in terms of ACAM2000 administration dates.

Statistical analysis showed that takes were less clustered in terms of ACAM2000 administration dates for Group 1 data. Figures 2 and 3 below show the Day 6-8 (after scarification) take data in Group 1 and the take data from Group 1 Site 1, respectively,

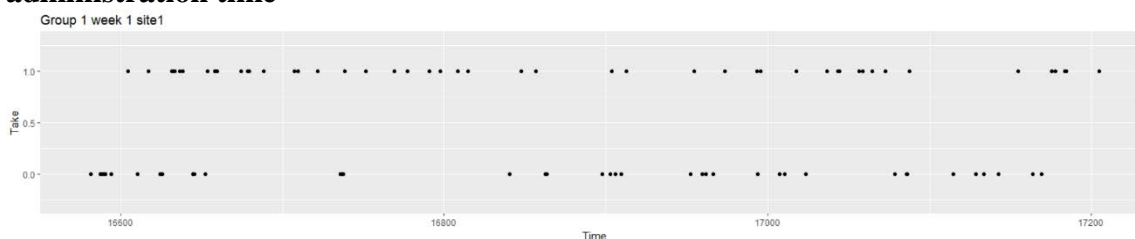
ordered by ACAM2000 administration time. The Wald–Wolfowitz runs test shows a p-value of 0.028. However, the p-value for Group 1 take data on Day 13-15 is 0.104. The p-values of Group 1 take data on Day 6-8 (after scarification) for sites 1 and 2 are 0.003, 0.173, respectively. It can be observed from Figures 2 and 3 that more takes tended to be observed during the first half of the administration period while takes and absent takes tended to be balanced during the second half of the administration period. The clustering pattern of takes in Group 1 is likely driven by the imbalance of Site 1 take data during the first half of the administration period.

**Figure 2. Group 1 Take data (Sites 1 & 2) on Day 6-8 ordered by ACAM2000 administration time**



Source: Statistical reviewer's analysis based on analysis dataset (ADFA.xpt) of POX-MVA-006 submitted to STN 125678/0.

**Figure 3. Group 1 Site 1 Take data on Day 6-8 ordered by ACAM2000 administration time**



Source: Statistical reviewer's analysis based on analysis dataset (ADFA.xpt) of POX-MVA-006 submitted to STN 125678/0.

At the request of the clinical reviewer, I calculated the take rates among Group 1 subjects by study sites (Table 9). Site 2 has a higher absent take rates than Site 1 numerically.

**Table 9. Take Rates among Group 1 Subjects by Study Sites (PPS, FAS, and Modified FAS)**

Populations	Site 1	Site 2
PPS	N=77	N=88
Percentage of subjects with full take (95% CI)	24.7 (15.6, 35.8)	21.6 (13.5, 31.6)
Percentage of subjects with partial take (95% CI)	32.5 (22.2, 44.1)	14.8 (8.1, 23.9)
Percentage of subjects with no take (95% CI)	42.9 (31.6, 54.6)	63.6 (52.7, 73.6)
FAS	N=100	N=120
Percentage of subjects with full take (95% CI)	22.0 (14.3, 31.4)	18.3 (11.9, 26.4)
Percentage of subjects with partial take (95% CI)	27.0 (18.6, 36.8)	13.3 (7.8, 20.7)
Percentage of subjects with no take (95% CI)	43.0 (33.1, 53.3)	54.2 (44.8, 63.3)
Modified FAS	N=92	N=103
Percentage of subjects with full take (95% CI)	23.9 (15.6, 33.9)	21.4 (13.9, 30.5)
Percentage of subjects with partial take (95% CI)	29.3 (20.3, 39.8)	15.5 (9.1, 24.0)
Percentage of subjects with no take (95% CI)	46.7 (36.3, 57.4)	63.1 (53.0, 72.4)

Note: Modified FAS is defined as subjects in FAS who had take assessment data. N=number of subjects in the specified population.

Source: Statistical reviewer's analysis based on analysis dataset (ADFA2.xpt) of POX-MVA-006 submitted to STN 125678/0.

The review team sent another IR (IR #21, item 1) on March 27, 2019 regarding this issue. In the response, BN acknowledged the clustering pattern in the distribution. BN were assured by the principal investigator that all ACAM2000 vaccinations were administered by the US Department of Defense (DoD) staff trained according to Defense Health Agency (DHA) guidelines, ensuring compliance with vaccination processes. Although the clustering pattern seems more obvious in 2015 (first half of the administration period), it cannot be explained by any potential "learning curve" because ACAM2000 administration was not new to any of the DoD staff who were responsible for the vaccine administration. No potential operational issue was identified by the sites.

To assess robustness of the data related to this co-primary endpoint, BN has performed further sensitivity analyses. The primary endpoint, maximum lesion area by the (b) (4) camera, is assessed for each of the following subgroups: periods of ACAM2000 administration (first and second half of 2015, 2016 and 2017) and study sites (Site 01 and Site 02). Regardless of the small group sizes in some of the subgroups, the

differences between Group 1 and Group 2 were substantial, and the lower bounds of the Hodges-Lehmann 95% CIs of the AAR were well above 40% (pre-specified success criterion) in all subgroups.

BN also acknowledged the difference between the sites identified by CBER. Because the two sites are officially considered as one site (e.g., nurses rotated between the two study sites, immune samples were processed in one location) and vaccines were administered by staff who had the same training, site was not pre-specified as a significant subgroup factor, and there was no pre-planned subgroup analysis by site. BN claimed that it is well recognized that many apparent subgroup effects have been shown to be spurious. BN believed that the same precaution should apply when interpreting the difference between the sites and the related clustering pattern by the administration time of ACAM2000.

BIMO has completed their inspections and was unable to obtain sufficient data from the sites to explain the identified issues. Because binary take assessment was not a required endpoint to be assessed in the clinical study, the clinical reviewer intends to not to draw any firm conclusion regarding take attenuation. I agree with the clinical reviewer's approach.

#### *6.1.11.3 Subpopulation Analyses*

N/A

#### *6.1.11.5 Exploratory and Post Hoc Analyses*

N/A

#### *6.1.12 Safety Analyses*

An overview of Adverse Events (AE) is provided in Table 10. All subjects (N=433) received at least one vaccination were included in the safety analysis (FAS). Most subjects had at least one AE documented during the clinical trial (209 subjects [95.0%] in Group 1, and 209 subjects [98.1%] in Group 2). Most of the subjects experienced non-serious AEs within 29 days of vaccination (208 subjects [94.5%] in Group 1, 209 subjects [98.1%] in Group 2). Most of the subjects who experienced non-serious AEs in Group 1 experienced AEs after receiving the ACAM2000 vaccination (Vaccination Period 3): 168 subjects (76.4%) after MVA-BN vaccination 1; 135 subjects (64.9%) after MVA-BN vaccination 2; and 181 subjects (92.3%) after the ACAM2000 vaccination.

During the clinical trial, 8 subjects experienced Serious Adverse Event (SAE) (5 subjects [2.3%] in Group 1, and 3 subjects [1.4%] in Group 2). Two SAEs were within the 29-day follow-up period (both in Group 1) and were considered unrelated to the vaccination. An additional SAE in Group 2 occurred outside of the 29-day follow-up period, but within the active trial phase because the subject's Visit 4 was conducted 15 days out-of-window. Five SAEs occurred outside of the 29-day follow-up period (3 SAEs in Group 1, ranging from 72-157 days after vaccination with ACAM2000; and 2 SAEs in Group 2, ranging from 90-206 days after vaccination with ACAM2000). A total of 11 subjects experienced

Adverse Event of Special Interest (AESI) (7 subjects [3.2%] in Group 1, and 4 subjects [1.9%] in Group 2).

The majority of subjects experienced AEs were considered to be related with the vaccine within 29 days after vaccination by the investigator, with a greater proportion in Group 2 (142 subjects [64.5%] in Group 1 and 158 subjects [74.2%] in Group 2).

More subjects who experienced grade  $\geq 3$  AEs were in the ACAM2000 vaccination group (24 subjects [10.9%] in Group 1, and 64 subjects [30.0%] in Group 2). Approximately one third of these were considered related and within 29 days after vaccination (7 subjects [3.2%] in Group 1, and 22 subjects [10.3%] in Group 2).

**Table 10. Overview of Pooled Solicited and Unsolicited Adverse Events during the Clinical Trial – FAS**

	Group 1 MVA-BN (N =220)		Group 2 ACAM2000 (N=213)	
	n (%)	E	n (%)	E
At least one AE documented	209 (95.0)	1883	209 (98.1)	1674
At least one				
Non-serious AE	208 (94.5)	1877	209 (98.1)	1671
Non-serious AE within 29 days after vaccination	208 (94.5)	1874	209 (98.1)	1670
Serious AE	5 (2.3)	5	3 (1.4)	3
AE of Special Interest	7 (3.2)	7	4 (1.9)	4
Related AE within 29 days after vaccination	142 (64.5)	595	158 (74.2)	531
AE graded $\geq 3$ within 29 days after vaccination	24 (10.9)	45	64 (30.0)	113
Related AE graded $\geq 3$	7 (3.2)	18	22 (10.3)	44
Related AE graded $\geq 3$ within 29 days	7 (3.2)	18	22 (10.3)	44
AE leading to withdrawal from trial	2 (0.9)	2	0	0
AE leading to withdrawal from vaccination	2 (0.9)	2	0	0
Number (%) of deaths	0	0	0	0

E=number of events, N is the number of subjects, and n is the number of subjects with at least one report of one particular kind of AE.

Source: Table 22 in the CSR for Study POX-MVA-006.

## 6.2 Trial #2: POX-MVA-013

A randomized, double-blind, placebo-controlled Phase III trial to evaluate immunogenicity and safety of three consecutive production lots of IMVAMUNE (MVA-BN) smallpox vaccine in healthy, vaccinia-naïve subjects.

### 6.2.1 Objectives

Primary Objective:

To assess the consistency of 3 consecutively produced IMVAMUNE lots.

Secondary Objectives:

- To assess uncommon adverse reactions, in particular any cardiac sign and symptom indicating a case of myo-/pericarditis, and to compare the frequency of those reactions against Placebo.
- To collect vaccinia-specific humoral immune response data.

*6.2.2 Design Overview*

This was a randomized, double-blind, placebo-controlled Phase III trial to evaluate immunogenicity and safety of three consecutive production lots of IMVAMUNE (MVA-BN) smallpox vaccine in healthy, vaccinia-naïve subjects. In total, 4000 vaccinia-naïve subjects were planned for inclusion in this trial. All subjects were randomly assigned (1:1:1:1) to one of the three IMVAMUNE groups (Groups 1, 2 or 3) or the Placebo group (Group 4) to receive 2 subcutaneous vaccinations with IMVAMUNE or Placebo administered in a double-blind manner.

*6.2.3 Population*

In total, 4000 healthy, vaccinia-naïve subjects were planned for inclusion in this trial. Overall, the mean subject age was 27.7 years (range was 18 to 40 years old). Please refer to clinical reviewer's memo for the inclusion and exclusion criteria.

*6.2.4 Study Treatments or Agents Mandated by the Protocol*

Subjects received a single vaccination (0.5 mL) subcutaneously in the deltoid region of the upper arm (preferably the non-dominant arm) at Visits 1 (Day 0) and 3 (Visit 1 + 28 to 35 days). Vaccines were administered after required assessments were performed. Each 0.5 mL dose of liquid frozen (LF) IMVAMUNE had a nominal virus titer of  $1 \times 10^8$  TCID<sub>50</sub> MVA- BN drug product. The IMVAMUNE lots used in POX-MVA-013, LF lots # C00001, C00002, C00003, have been part of a long-term real time stability study.

Placebo consisted of the IMVAMUNE formulation buffer, Tris-buffered Saline (TBS), was provided in liquid aliquots. One dose of 0.5 mL Placebo contained 0.605 mg tris(hydroxymethyl)-amino methane and 4.09 mg sodium chloride.

Note: IMVAMUNE is the same vaccine product as JYNNEOS. It was the name used during the clinical development of MVA-BN.

*6.2.5 Directions for Use*

Please refer to the clinical reviewer's memo.

*6.2.6 Sites and Centers*

A total of 34 clinical trial sites in the USA participated in this trial.

### 6.2.7 Surveillance/Monitoring

Please refer to the clinical reviewer's memo.

### 6.2.8 Endpoints and Criteria for Study Success

The primary endpoint is vaccinia-specific neutralizing GMTs after 2 IMVAMUNE vaccinations measured by PRNT at Visit 4.

Criteria for Study Success: see Section 6.2.9.

### 6.2.9 Statistical Considerations & Statistical Analysis Plan

Endpoint: vaccinia specific PRNT antibody response two weeks after the second vaccination.

Statistical Hypothesis:

$H_0: m_1 - m_2 < -\Delta \text{ OR } m_1 - m_2 > \Delta \text{ OR } m_1 - m_3 < -\Delta \text{ OR } m_1 - m_3 > \Delta \text{ OR } m_2 - m_3 < -\Delta \text{ OR } m_2 - m_3 > \Delta$

versus

$H_1: m_1 - m_2 > -\Delta \text{ AND } m_1 - m_2 < \Delta \text{ AND } m_1 - m_3 > -\Delta \text{ AND } m_1 - m_3 < \Delta \text{ AND } m_2 - m_3 > -\Delta \text{ AND } m_2 - m_3 < \Delta,$

where  $m_1$ ,  $m_2$  and  $m_3$  are the means of the  $\log_{10}$  titers in Groups 1, 2 and 3, respectively, and  $\Delta$  is the equivalence margin of 0.301 for the  $\log_{10}$  titers of the PRNT (equivalent to a factor of 2 for GMT).

Statistical Method: The hypothesis was tested using t-tests on the differences of the two means based on the assumption that the  $\log_{10}$  titers are normally distributed. The corresponding CIs were presented on the original scale by taking antilog of the CI limits calculated on the  $\log_{10}$  scale.

Success Criteria: The means of the  $\log_{10}$  PRNT titers were equivalent within the margin of equivalence ( $\Delta$ ) 0.301.

### 6.2.10 Study Population and Disposition

#### 6.2.10.1 Populations Enrolled/Analyzed

Four thousand subjects (1000 subjects per group) were planned to be vaccinated in the study. A total of 5357 subjects were screened, of which 4005 subjects were randomized and received at least 1 vaccination. Table 11 provides a summary of population disposition for Study POX-MVA-013.



	Group 1 Lot 1 N = 999	Group 2 Lot 2 N = 1005	Group 3 Lot 3 N = 999	Group 4 Placebo N = 1002	All subjects N = 5357
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects randomized	999	1005	999	1002	4005
Subjects vaccinated	999	1005	999	1002	4005
Full analysis set (FAS)	999(100.0)	1005(100.0)	999(100.0)	1002(100.0)	4005(100.0)
Immunogenicity Analysis Set (IAS)	710 (71.1)	703 (70.0)	706 (70.7)	710 (70.9)	2829 (70.6)
Per protocol set (PPS)	637 (63.8)	628 (62.5)	641 (64.2)	643 (64.2)	2549 (63.6)

**Table 11. Population Disposition for Study POX-MVA-013**

Source: Table 5 in the CSR for Study POX-MVA-013.

#### 6.2.11 Immunogenicity Analyses

The primary objective of Study POX-MVA-013 is to assess the consistency of 3 consecutively produced IMVAMUNE lots. The primary immunogenicity analyses were conducted using the PPS, which consisted of all subjects in the IAS who received both vaccinations, completed Visits 1, 3 and 4, and had no major protocol deviations.

##### 6.2.11.1 Analyses of Primary Endpoint(s)

The PRNT GMTs at Visit 1 and Visit 4 for the PPS are provided in Table 12, and the lot consistency results based on the PPS are provided in Table 13. The GMTs were 1.0 at baseline for all treatment groups, i.e., there were no significant differences in baseline GMTs among groups. At Visit 4, the GMT was 110.7 for Group 1, 100.5 for Group 2, and 117.2 for Group 3, compared to 1.0 for Placebo. The ratio of GMTs between any two IMVAMUNE groups ranged between 0.8577 and 1.1012, with the CIs meeting the study success criteria. Therefore, the primary endpoint of this clinical trial was met. Results of the additional analysis based on the IAS were similar.

**Table 12. PRNT GMTs at Visits 1 and 4 in Study POX-MVA-013 (PPS)**

Group	Visit 1 (Day 0)		Visit 4 (Day 42)	
	GMT	95% CI [LCL, UCL]	GMT	95% CI [LCL, UCL]
Group 1 (Lot 1) [N = 637]	1.0	[1.0, 1.1]	110.7	[103.4, 118.4]
Group 2 (Lot 2) [N = 628]	1.0	[1.0, 1.1]	100.5	[93.7, 107.8]
Group 3 (Lot 3) [N = 641]	1.0	[1.0, 1.1]	117.2	[109.0, 126.0]
Group 4 (Placebo) [N = 643]	1.0	[1.0, 1.1]	1.0	[1.0, 1.1]

Source: Table 9 in the CSR for Study POX-MVA-013.

**Table 13. PRNT Equivalence Analysis of Visit 4 GMTs in Study POX-MVA-013 (PPS)**

Group	Ratio of GMTs [95% CI]	Equivalence Met (Yes/No)
Group 1 / Group 2	1.1012 [0.9992, 1.2136]	Yes
Group 1 / Group 3	0.9444 [0.8554, 1.0427]	Yes
Group 2 / Group 3	0.8577 [0.7753, 0.9488]	Yes

- Equivalence is passed if the LCL > 1/Delta and the UCL < Delta. For the PRNT, delta is 2, i.e., CI must be within [1/2, 2].

Source: Table 10 in the CSR for Study POX-MVA-013.

#### 6.2.11.2 Analyses of Secondary Endpoints

Results for secondary immunogenicity endpoints were as follows (all conclusions were based on the PPS and results in the IAS were similar):

- GMTs measured 2 weeks after the second vaccination using a vaccinia-specific ELISA for IMVAMUNE Groups 1, 2 and 3 were 901.0, 794.4 and 946.7 respectively, compared to 1.2 for the Placebo group.
- Seroconversion rates 2 weeks after the second vaccination were determined using the vaccinia-specific PRNT and ELISA with similar results between the assays: seroconversion rates were 99.5 to 100.0% for IMVAMUNE Groups by both assays, while the seroconversion rate for Placebo (Group 4) was 1.4% by PRNT and 2.0% by ELISA.

The PRNT and ELISA titers at Visit 4 appear correlated in all treatment groups, with Pearson correlation coefficient  $r$  between 0.581 and 0.620 for Group 1, 2 and 3 (0.486 for Placebo group).

#### 6.2.11.3 Subpopulation Analyses

N/A

#### 6.2.11.5 Exploratory and Post Hoc Analyses

N/A

#### 6.2.12 Safety Analyses

Table 14 summarizes the overall safety profile by treatment group. More subjects receiving IMVAMUNE experienced at least 1 treatment-emergent adverse events (TEAE; 2716/3003 subjects [90.4%]) compared to subjects receiving Placebo (581/1002 subjects [58.0%]).

A total of 1700 (56.6%) subjects in the combined IMVAMUNE group and 349 (34.8%) subjects in the Placebo group experienced AEs that were considered related to the investigational products. Grade 3 or higher AEs were observed in ~15% subjects vaccinated with IMVAMUNE and in ~5% subjects vaccinated with Placebo.

One subject in IMVAMUNE Group 1 died (suicide) during the trial. The death was considered not related to IMVAMUNE. A small proportion of subjects (< 1%) experienced SAEs (IMVAMUNE combined groups 1 to 3: 25/3003 [0.8%]; Placebo: 8/1002 [0.8%]) and treatment-emergent AESIs (IMVAMUNE combined groups 1-3: 8/3003 [0.3%]; Placebo: 1/1002 [0.1%]) during the study.

A total of 19 (0.6%) subjects vaccinated with IMVAMUNE and 3 (0.3%) subjects vaccinated with Placebo were withdrawn from vaccination due to an AE.

**Table 14. Overview of Solicited and Unsolicited Adverse Events in Study POX-MVA-013 (Full Analysis Set)**

Number of Subjects with at least 1	Group 1 (Lot 1) (N = 999)	Group 2 (Lot 2) (N = 1005)	Group 3 (Lot 3) (N = 999)	Combined Groups 1-3 (N = 3003)	Group 4 (Placebo) (N = 1002)
	n (%)	n (%)	n (%)	n (%)	n (%)
AE	917 (91.8)	906 (90.1)	908 (90.9)	2731 (90.9)	601 (60.0)
TEAE	913 (91.4)	903 (89.9)	900 (90.1)	2716 (90.4)	581 (58.0)
SAE	11 (1.1)	7 (0.7)	7 (0.7)	25 (0.8)	8 (0.8)
TE AESI	2 (0.2)	5 (0.5)	1 (0.1)	8 (0.3)	1 (0.1)
Related TEAE	565 (56.6)	559 (55.6)	576 (57.7)	1700 (56.6)	349 (34.8)
Related SAE	0	0	0	0	1 (0.1)
TEAE Grade $\geq 3$	155 (15.5)	142 (14.1)	132 (13.2)	429 (14.3)	53 (5.3)
Related TEAE Grade $\geq 3$	58 (5.8)	57 (5.7)	53 (5.3)	168 (5.6)	27 (2.7)
Related TE AESI	0	1 (0.1)	1 (0.1)	2 (0.1)	0
AE leading to withdrawal from trial	5 (0.5)	9 (0.9)	4 (0.4)	18 (0.6)	3 (0.3)
AE leading to withdrawal from vaccination	6 (0.6)	8 (0.8)	5 (0.5)	19 (0.6)	3 (0.3)
Deaths	1 (0.1)	0	0	1 (0.0)	0

N = Number of subjects in the specified group; n = Number of subjects with at least 1 report of 1 particular symptom;  
NC = Not Calculated

Source: Table 18 in the CSR for Study POX-MVA-013.

## 6.3 Supportive Studies

### 6.3.1 General Information

Three out of the nine trials providing efficacy data for MVA-BN were conducted in populations considered at high risk of experiencing severe adverse reactions attributable to the replicating nature of traditional smallpox vaccines. Trial POX-MVA-008 evaluated safety and immunogenicity of MVA-BN in subjects diagnosed with atopic dermatitis (AD). Clinical trials POX-MVA-011 and POX-MVA-037 assessed safety and immunogenicity of MVA-BN in HIV-infected subjects. POX-MVA-008 and POX-MVA-011 also included a control group of healthy subjects in addition to the groups of subjects diagnosed with AD or HIV-infected subjects. During the review process, some post-vaccination troponin elevations in the high-risk populations were detected by the high-sensitivity assay used in trials POX-MVA-008 and POX-MVA-011. In both trials, the regular troponin assay was replaced by the high-sensitivity assay. The upper limits of

normal range (ULN) for the regular assay and the high-sensitivity assay are  $< 0.08 \mu\text{g/L}$  and  $< 0.04 \mu\text{g/L}$ , respectively, both of which are determined as the limit of quantification (LoQ). This section focuses on the review of the troponin elevation issue. A brief description of Studies POX-MVA-008 and POX-MVA-011 is provided in Table 1, Section 5.3 of this review memo.

### 6.3.2 POX-MVA-008

#### *Title:*

A multicenter, open-label, controlled phase II study to evaluate safety immunogenicity of MVA-BN (IMVAMUNE) smallpox vaccine in 18-40 year old subjects with diagnosed atopic dermatitis.

#### *Study design:*

The study was a multicenter, open-label, controlled, phase II study enrolling healthy subjects and subjects with diagnosed AD. The study consisted of a screening period of up to 28 days prior to Visit 1 (first vaccination), an active study period of up to 10 weeks and a follow-up (FU) period of at least 26 weeks after the last vaccination.

Table 15 provides a brief summary of the safety and reactogenicity results based on the Safety analysis set.

**Table 15. Overview of safety results for Study POX-MVA-008 (Safety Analysis Set)**

Safety Endpoint	Healthy Subjects (N = 282) n (%)	Subjects with diagnosed AD (N = 350) n (%)
At least one AE	268 (95.0)	331 (94.6)
$\geq$ Grade 3 AEs related to study vaccine (Day 0-28 after vaccination)	16 (5.7)	27 (7.7)
SAE	2 (0.7) in active study period 1 in FU period	1 (0.3) in active study period 2 in FU period
Any solicited AE	260 (92.2)	313 (90.7)
Solicited local AE	248 (87.9)	301 (87.2)
Solicited general AEs (Day 0-7 after vaccination)	159 (56.4)	242 (70.1)
Unsolicited AEs	182 (64.5)	240 (68.6)
AE of special interest	38 (13.5)	58 (16.6)
AE leading to withdrawal from study	1 (0.4)	0

AE = adverse event, n = number of subjects with at least one respective AE, SAE= serious adverse event

Source: the Safety and Reactogenicity table in the synopsis section in the CSR for Study POX-MVA-008.

Overall, eight SAEs occurred in six subjects (three subjects in each group). All SAEs were assessed as not related to the study vaccine with the exception of one SAE. For 38 healthy subjects (13.5%) and 58 subjects diagnosed with AD (16.6%) at least one AE of special interest (AESI) was recorded during the study. The vast majority of AESIs in study groups was “troponin I increased”. Table 16 below summarizes the post vaccination troponin elevations ( $\geq 2$  ULN) in the study. In summary, 0.94% and 5.67% subjects had clinically significant post-vaccination troponin elevations in the healthy population and AD population, respectively.

**Table 16. Clinically Significant Post-Vaccination Troponin Elevations ( $\geq 2$  ULN) in Study POX-MVA-008**

		Healthy subjects	AD subjects
Regular assay <sup>a</sup>	# of Events	0	0
	Missing, m	0	1
	Subjects, n/ N	0/94	0/67
	Incidence % (95% CI)	0 (0, 3.85)	0 (0, 5.36)
High sensitivity assay <sup>b</sup>	# of Events	2	27
	Missing, m	0	1
	Subjects, n/ N	2/212	17/300
	Incidence % (95% CI)	0.94 (0.11, 3.37)	5.67 (3.34, 8.92)

n = number of subjects with events (imputed), N = total subjects in the safety population, m = number of subjects with missing post-vaccination troponin values. They are imputed to normal.

a. Excluded subjects only have post-vaccination high sensitivity troponin I test. A total of 40 subjects from study POX-MVA-008 had both post-vaccination regular and high sensitivity troponin I tests. They were included in both incidence rate calculation.

b. Excluded subjects with no high sensitivity troponin I test.

Source: Adapted from Table 7.2.2 in the integrated summary of safety submitted to 125678.0 Section 5.3.5.3.

Table 17 provides the results of my analysis of the categorical shifts from the screening troponin level to the post-vaccination level, as measured by the high-sensitivity assay. Since the screening troponin values were missing for some subjects, the Ns for the high-sensitivity assay in Table 16 above and Table 17 below are different. In summary, the percentages of subjects who had troponin values shifted above the ULN in the healthy and AD populations are 22.4% and 17.7%, respectively. In addition, the percentages of subjects who had troponin values shifted above  $2 \times \text{ULN}$  from below the ULN at screening in the healthy and AD populations are 1.2% and 4.9%, respectively.

**Table 17. Troponin elevations in Study POX-MVA-008 (Categorical shift)**

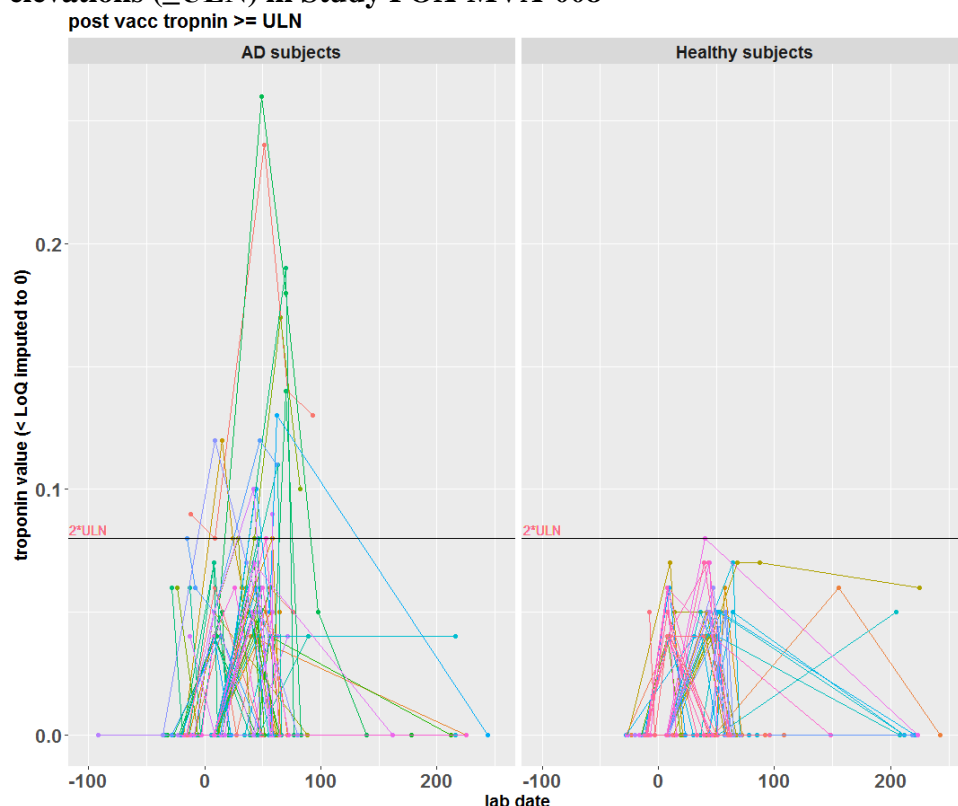
	Healthy subjects, N=177 Screening (highest value)			AD subjects, N=278 Screening (highest value)		
Post vaccination (highest value)	<ULN (n=170)	$\geq \text{ULN}$ (n=7)	$\geq 2\text{ULN}$ (n=0)	<ULN (n=266)	$\geq \text{ULN}$ (n=12)	$\geq 2\text{ULN}$ (n=2)
<ULN	132 (77.6%)	6	0	219 (82.3%)	6	0
$\geq \text{ULN}$	38 (22.4%)	1	0	47 (17.7%)	6	2
$\geq 2\text{ULN}$	2 (1.2%)	0	0	13 (4.9%)	4	2

Counts of  $\geq \text{ULN}$  include subjects with troponin level  $\geq 2\text{ULN}$ .

Source: Reviewer's analysis based on Dataset axtrop.xpt submitted to 125678.0 Section 5.3.5.3

Figure 4 below provides a graphical presentation of the troponin values for each subject with post-vaccination Troponin elevations (determined by high-sensitivity assay) in the study. Three (two from AD population, one from healthy population) extreme observations with troponin values above 0.5 were excluded from the figure. It appears that troponin elevations occurred after Day 0, when the first MVA-BN was given, and after Day 28, when the second MVA-BN was given. More elevation was observed in the AD subjects compared to the healthy subjects. All elevations in the healthy subjects were below the clinically significant threshold of  $2 \times \text{ULN}$ .

**Figure 4. Troponin values for each subject with post-vaccination Troponin elevations ( $\geq$ ULN) in Study POX-MVA-008**



Source:

Reviewer's analysis based on Dataset *axtrop.xpt* submitted to 125678.0 Section 5.3.5.3

I fitted a linear mixed model with Subjects as a random effect, Group (AD vs. healthy) and vaccination period (post-vaccination 1 or PV1, post-vaccination 2 or PV2, and FU) as fixed effects. The response variable is troponin values, excluding the aforementioned three (two from AD population, one from healthy population) extreme observations. For the analysis, 90.9% of the troponin values are  $<$ LoQ and imputed by  $\frac{1}{2} \times$  LoQ. The results are presented in Table 18. Applying the Z-test for contrast in R, it is estimated that mean troponin increases (95% CI) post vaccination 1 and post vaccination 2 in the AD group are 0.0016 (95% CI: -0.0007, 0.0038) and 0.0065 (95% CI: 0.0043, 0.0086), respectively. The troponin elevation post vaccination 2 appears to be larger compared to baseline in the AD population, with its 95% CI excluding 0.

**Table 18. Continuous analysis (Linear mixed model) of troponin values in Study POX-MVA-008**

	Estimate	Std. Error	95% CI
PV1 vs. baseline	1.377e-03	1.430e-03	(-0.0014, 0.0042)
PV2 vs. baseline	2.188e-03	1.354e-03	(-0.0005, 0.0048)

Follow-up vs. baseline	2.021e-03	2.485e-03	(-0.0028, 0.0069)
AD vs. healthy	3.308e-04	1.489e-03	(-0.0026, 0.0032)
PV1 × AD	1.736e-04	1.842e-03	(-0.0034, 0.0038)
PV2 × AD	4.282e-03	1.748e-03	(0.0009, 0.0077)
Follow-up × AD	-2.391e-03	3.325e-03	(-0.0089, 0.0041)

Number of subjects: 512; Number of observations: 1673.

Source: Reviewer's analysis based on Dataset *axtrop.xpt* submitted to 125678.0 Section 5.3.5.3

### 6.3.3 POX-MVA-011

#### Title:

A multicenter, open-label, phase II study to evaluate safety and immunogenicity of MVA-BN (IMVAMUNE) smallpox vaccine in 18-55 year old naïve and previously vaccinated HIV infected subjects with CD4 counts  $\geq 200$ -750 cells/ $\mu$ l.

#### Study design:

The four groups in this study are listed in Table 19. The study consisted of a screening period of up to four weeks, a treatment period (in general, the treatment period was the period from the first vaccination to the 4-week visit after the last vaccination) of up to 10 weeks, and a follow-up period of at least 26 weeks after the last vaccination.

Table 19 provides a brief summary of the Adverse Events of Special Interest during the treatment period. Among the 8 subjects with related AESI in the healthy population, 6 were related to elevated troponin I levels (5 assessed as possible and 1 assessed as definite). Among the 8 subjects with related AESI in the HIV infected population, 7 were related to elevated troponin I levels (6 assessed as possible and 1 assessed as definite).

**Table 19. Adverse Events of Special Interest (FAS, N = 579) in Study POX-MVA-011**

Subject based	Healthy			HIV infected		
	N*	All AESIs n (%)	Related AESIs n (%)	N*	All AESIs n (%)	Related AESIs n (%)
Vaccinia-naïve	88	14 (15.9)	8 (9.1)	351	43 (12.3)	8 (2.3)
Vaccinia-experienced	9	0 (0.0)	0 (0.0)	131	9 (6.9)	2 (1.5)

N = number of subjects, N\* = number of subjects in the specified group, n = number of subjects with at least one AESI

Source: Table 54 in the CSR for Study POX-MVA-011.

Table 20 below presents clinically significant troponin elevations ( $\geq 2$  ULN) post vaccination in the study.



**Table 20. Clinically Significant Post-Vaccination Troponin Elevations ( $\geq 2$  ULN) in Study POX-MVA-011**

		Healthy subjects	HIV subjects
Regular assay <sup>a</sup>	# of Events	0	0
	Missing, m	0	2
	Subjects, n/ N	0/19	0/8
	Incidence % (95% CI)	0 (0, 17.65)	0 (0, 36.94)
High sensitivity assay <sup>b</sup>	# of Events	3	10
	Missing, m	0	2
	Subjects, n/ N	1/73	7/349
	Incidence % (95% CI)	1.37 (0.03, 7.40)	2.01 (0.81, 4.09)

n = number of subjects with events (imputed), N = total subjects in the safety population, m = number of subjects with missing post-vaccination troponin values. They are imputed to normal.

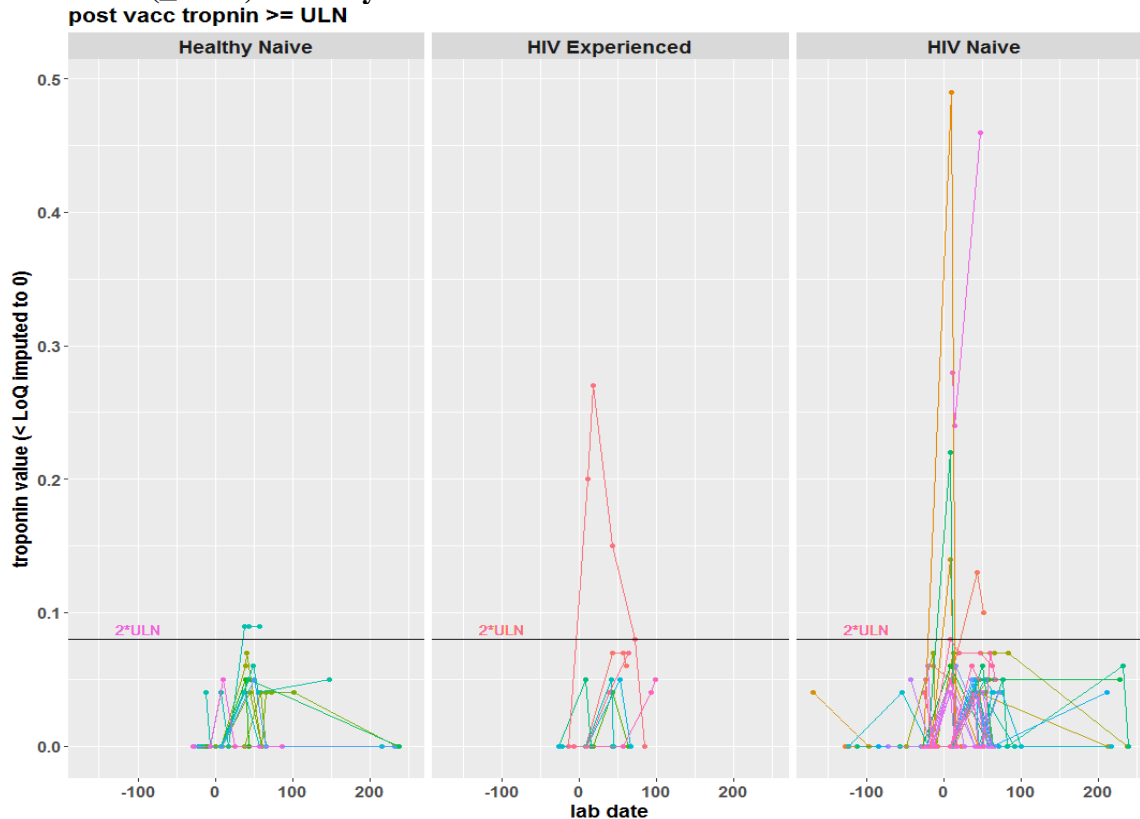
a. Excluded subjects only have post-vaccination high sensitivity troponin I test. A total of 8 subjects from study POX-MVA-011 had both post-vaccination regular and high sensitivity troponin I tests. They were included in both incidence rate calculation.

b. Excluded subjects with no high sensitivity troponin I test.

Source: Adapted from Table 7.2.2 in the integrated summary of safety submitted to 125678.0 Section 5.3.5.3.

Figure 5 below is a graphical presentation of the troponin values for each subject with post-vaccination Troponin elevations (determined by high-sensitivity assay) by group and prior vaccinia exposure in the study. Two (from HIV naïve population) extreme observations with troponin values above 0.5 were excluded from the figure. There were no subjects with post-vaccination troponin elevations in the healthy vaccinia-experienced group. The HIV naïve group appears to have greater post vaccination troponin elevations; however, the seemingly smaller troponin elevations in the other two groups could possibly be due to small sample sizes.

**Figure 5. Troponin values for each subject with post-vaccination Troponin elevations ( $\geq$ ULN) in Study POX-MVA-011**



Source: Reviewer's analysis based on Dataset axtrop.xpt submitted to 125678.0 Section 5.3.5.3

I fitted a linear mixed model with Subjects as a random effect, Group (Healthy naïve vs. Healthy experienced, HIV naïve vs. Healthy experienced and HIV experienced vs. Healthy experienced) and vaccination period (PV1, PV2 and FU) as fixed effects. The response variable is troponin value, excluding three (two from AD population, one from healthy population) aforementioned extreme observations. For the analysis, 93.8% of the values are < LoQ and imputed by  $\frac{1}{2} \times \text{LoQ}$ . The results are presented in Table 21. The group by vaccination period interaction was not included in the mixed model since there was no evidence suggesting interaction based on the full model. The estimated mean troponin increases (95% CI) post vaccination 1 and post vaccination 2 are 0.0021 (95% CI: 0.0003, 0.0040) and 0.0023 (95% CI: 0.0005, 0.0041), respectively.

**Table 21. Continuous analysis (Linear mixed model) of the troponin values in Study POX-MVA-011**

	Estimate	Std. Error	95% CI
PV1 vs. baseline	2.144e-03	9.531e-04	(0.0003, 0.0040)
PV2 vs. baseline	2.326e-03	9.256e-04	(0.0005, 0.0041)
Follow-up vs. baseline	1.987e-03	1.755e-03	(-0.0014, 0.0054)
Healthy naïve vs. Healthy experienced	2.140e-03	6.672e-03	(-0.0109, 0.0152)
HIV naïve vs. Healthy experienced	3.236e-03	6.466e-03	(-0.0094, 0.0159)
HIV experienced vs. Healthy experienced	2.037e-03	6.566e-03	(-0.0108, 0.0149)

Number of subjects: 553; Number of observations: 1927.

Source: Reviewer's analysis based on Dataset axtrop.xpt submitted to 125678.0 Section 5.3.5.3

Please refer to Section 8. Integrated overview of safety for additional investigation on troponin elevations.

## 7. INTEGRATED OVERVIEW OF EFFICACY

Efficacy of MVA-BN has been demonstrated by direct comparison to a US licensed replicating smallpox vaccine ACAM2000 in the pivotal Phase 3 clinical trial POX-MVA-006. As agreed upon with the FDA during the Type C Meeting on June 29, 2017 and the pre-BLA meeting on May 30, 2018, primary efficacy data for smallpox vaccine-naïve individuals are derived exclusively from POX-MVA-006. Hence, efficacy of MVA-BN cannot be assessed across trials. Immunogenicity data from eight additional clinical trials of the MVA-BN development program are considered supportive for demonstration of efficacy based on considerations of vaccine formulation and dosing schedule. Assessment of immunogenicity data across clinical trials is not interpretable since the ELISA and PRNT methods underwent modifications in critical reagent lots and assay parameters as the clinical development progress. The immunogenicity data were therefore distributed differently across studies, making it difficult to perform a pooled immunogenicity analysis. The definition of seroconversion based on ELISA and PRNT also differed from trial to trial. Assay detection limits and quantitation limits also varied as a result of changing critical reagents. The supporting trials are classified and presented per the following categories:

- smallpox vaccine-naïve population (POX-MVA-013, POX-MVA-027)
- smallpox vaccine-experienced population (POX-MVA-005, POX-MVA-023, POX-MVA-024)
- at-risk populations (POX-MVA-008, POX-MVA-011, POX-MVA-037)

The PRNT GMT values at peak visits for all supporting trials in smallpox vaccine-naïve subjects are provided in Table 22.

**Table 22. GMTs (PRNT, ELISA) at Peak Visits in Healthy, Smallpox Vaccine-Naïve Subjects**

Study (Data Set)	Regimen	MVA-BN Dose	Peak Visit (GMT)	Peak Visit PRNT GMT (95% CI)
POX-MVA-006, PPS for Immunogenicity, N = 371				
Group 1	MMA	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	153.5 (134.3, 175.6)
Group 2	A	N/A	Week 4	79.3 (67.1, 93.8)
POX-MVA-013, PPS, N = 1906 (Groups 1-3)				
Group 1 (Lot 1)	MM	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	110.7 (103.4, 118.4)
Group 2 (Lot 2)	MM	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	100.5 (93.7, 107.8)
Group 3 (Lot 3)	MM	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	117.2 (109.0, 126.0)
Combined Groups 1–3	MM	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	109.3 (104.9, 113.8)
POX-MVA-027, PPS, N = 297 (Group 1)				
Group 1 (LF)	MM	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	81.8 (73.0, 91.6)

N = Total number of subjects for the specified dataset; M = MVA-BN; A = ACAM2000; N/A = Not applicable; LF = Liquid frozen formulation of MVA-BN; TCID<sub>50</sub> = Tissue Culture Infectious Dose 50%

Source: Adapted from Tables 12 and 13 in the summary of clinical efficacy submitted to 125678.0 Section 2.7.3

The PRNT GMT values at peak visits for all trials supporting efficacy in smallpox vaccine-experienced subjects are provided in Table 23.

**Table 23. GMT (PRNT) at Peak Visits in Studies with Healthy, Smallpox Vaccine-Experienced Subjects**

Study (Data Set)	Regimen	MVA-BN Dose	Peak Visit	Peak PRNT GMT (95% CI)	Peak ELISA GMT (95% CI)
POX-MVA-005, FAS, N = 745, 18 – 55 year old					
Group 1, Smallpox vaccine-naïve	MM	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	45.6 (35.1, 59.3)	495.8 (431.8, 569.4)
Group 2, Smallpox vaccine-naïve	MP	$1 \times 10^8$ TCID <sub>50</sub>	Week 4	7.2 (5.5, 9.4)	60.3 (47.6, 76.5)
Group 4, Smallpox vaccine-experienced	M	$1 \times 10^8$ TCID <sub>50</sub>	Week 2	175.1 (140.0, 219.1)	568.8 (473.3, 683.6)
POX-MVA-023, Booster FAS, N = 152					
Group 1, MVA-BN-experienced	MM/M	$1 \times 10^8$ TCID <sub>50</sub>	Week 2	125.3 (89.5, 175.3)	1688.2 (1381.5, 2062.9)
Group 2, MVA-BN-experienced	MP/M	$1 \times 10^8$ TCID <sub>50</sub>	Week 2	80.7 (54.4, 119.7)	1608.9 (1285.9, 2013.0)

POX-MVA-024, FAS, N = 119, 56 – 80 year old					
Group 1, Smallpox vaccine-experienced	MM	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	210.3 (146.1, 302.7)	804.1 (636.3, 1016.0)
Group 2, Smallpox vaccine-experienced	PM	$1 \times 10^8$ TCID <sub>50</sub>	Week 6	126.7 (82.4, 194.8)	605.8 (479.6, 765.2)

FAS=Full Analysis Set; M=MVA-BN; P=Placebo; N/A=Not applicable

The overall MVA-BN regimen administered to subjects in POX-MVA-023 for Group 1 was MM (POX-MVA-005)/M (POX-MVA-023), and for Group 2 was MP (POX-MVA-005)/M (POX-MVA-023).

POX-MVA-005: The FAS is defined as the total number of randomized healthy subjects who received at least one vaccination.

POX-MVA-023 and POX-MVA-024: The FAS consists of all subjects for whom baseline and any post-vaccination immunogenicity data were available.

Source: Adapted from Tables 22 and 23 in the summary of clinical efficacy submitted to 125678.0 Section 2.7.3

The PRNT GMT values at peak visits for all trials supporting efficacy in subjects at risks are provided in Table 24.

**Table 24. GMT (PRNT) at Peak Visits in At-Risk Subjects**

Study (Data Set)	Regimen	MVA-BN Dose	Peak Visit (Week)	Peak PRNT GMT (95% CI)
POX-MVA-008, PPS, N = 451				
Group 1, Smallpox vaccine-naïve, Healthy	MM	$1 \times 10^8$ TCID <sub>50</sub>	6	34.6 (26.4, 45.3)
Group 2, Smallpox vaccine-naïve, Diagnosed AD	MM	$1 \times 10^8$ TCID <sub>50</sub>	6	47.7 (38.1, 59.8)
POX-MVA-011, PPS, N = 394				
Group 1, Healthy, smallpox vaccine-naïve	MM	$1 \times 10^8$ TCID <sub>50</sub>	6	20.8 (12.3, 35.3)
Group 2, HIV, Overall, Smallpox vaccine- naïve	MM	$1 \times 10^8$ TCID <sub>50</sub>	6	13.0 (9.6, 17.5)
Group 2, HIV, CD4 $\geq$ 501–750, Smallpox vaccine-naïve	MM	$1 \times 10^8$ TCID <sub>50</sub>	6	12.8 (7.3, 22.4)
Group 2, HIV, CD4 $\geq$ 350–500, Smallpox vaccine-naïve	MM	$1 \times 10^8$ TCID <sub>50</sub>	6	12.0 (7.6, 19.0)

Group 2, HIV, CD4 $\geq$ 200–349, Smallpox vaccine-naïve	MM	$1 \times 10^8$ TCID <sub>50</sub>	6	15.5 (8.5, 28.3)
Group 3, Healthy, Smallpox vaccine-experienced	MM	$1 \times 10^8$ TCID <sub>50</sub>	4	100.2 (2.7, 3721.7)
Group 4, HIV, Overall, Smallpox vaccine-experienced	MM	$1 \times 10^8$ TCID <sub>50</sub>	4	42.3 (26.9, 66.4)
Group 4, HIV, CD4 $\geq$ 501–750, Smallpox vaccine-experienced	MM	$1 \times 10^8$ TCID <sub>50</sub>	4	36.9 (19.1, 71.6)
Group 4, HIV, CD4 $\geq$ 350–500, Smallpox vaccine-experienced	MM	$1 \times 10^8$ TCID <sub>50</sub>	4	76.2 (38.3, 151.6)
Group 4, HIV, CD4 $\geq$ 200–349, Smallpox vaccine-experienced	MM	$1 \times 10^8$ TCID <sub>50</sub>	4	11.9 (3.7, 37.7)
POX-MVA-037, PPS, N = 69				
Group 1	MM	$1 \times 10^8$ TCID <sub>50</sub>	6	78.9 (49.9, 124.8)
Group 2	MM	Two injections of $1 \times 10^8$ TCID <sub>50</sub> per time point	6	100.3 (59.8, 168.4)
Group 3	MMM	$1 \times 10^8$ TCID <sub>50</sub>	14	281.1 (166.6, 474.1)
Group 1 and 3 combined	MM/ MMM	$1 \times 10^8$ TCID <sub>50</sub>	6	88.1 (61.3, 126.6)

Source: Adapted from Tables 22 and 23 in the summary of clinical efficacy submitted to 125678.0 Section 2.7.3

Based on the tables above, it appears that either one or two doses of MVA-BN administered to healthy, vaccine-naïve or healthy, vaccine-experienced or at-risk adults elicit antibody responses as measured by PRNT. However, as of the completion time of this review memo, there are still some unresolved issues for the validation of an earlier version of the PRNT assay which was used to test samples from Studies POX-MVA-011 and POX-MVA-005. Please refer to Dr. Lei Huang's assay review.

## 8. INTEGRATED OVERVIEW OF SAFETY

The safety and tolerability characteristics of the MVA-BN non-replicating smallpox vaccine were pooled for 12 of the studies (main ISS studies) from the MVA-BN clinical development program to include all subjects (healthy and at-risk, vaccinia-naïve and vaccinia-experienced) who were exposed to the standard dose and regimen of the (to be licensed) LF formulation, and subjects who were in the controlled group (ACAM2000 or Placebo) in comparator controlled studies.

The main pooled safety population includes 5110 vaccinia-naïve subjects (4381 healthy subjects and 729 at-risk subjects) and 409 vaccinia-experienced subjects. In the pooled population, overall 37 SAEs were reported in 33/5519 (0.6%) subjects during the vaccination period and a further 45 SAEs were reported in 35/5519 (0.6%) subjects during the follow-up period. During the vaccination period, 2 SAEs in 2 (0.04%) separate subjects were considered to be causally-related to the MVA-BN vaccination. During the follow-up period, 1 SAE in 1 (0.02%) subject was considered related.

Table 25 provides a summary of the adverse events during the vaccination period for all 12 studies. A total of 4381 healthy, vaccinia-naïve subjects received at least 1 standard dose of MVA-BN. Of these, 23 (0.5%) subjects had SAEs. Table 26 presents the comparator-controlled analysis only (studies POX-MVA-006 [ACAM2000 controlled] and POX-MVA-013 and POX-MVA-005 [both placebo controlled]), with a total of 3406 healthy vaccinia-naïve subjects received at least 1 standard dose of MVA-BN, 213 subjects received ACAM2000, and 1183 healthy, vaccinia-naïve subjects received at least 1 dose of placebo. Of these, 18 (0.5%) and 3 (0.3%) subjects had SAEs infor the MVA-BN and placebo groups, respectively. Among the total of 213 subjects who received a single-dose scheduled vaccination of ACAM2000, and there was no subject experiencing SAE in this group.

**Table 25. Overview of Solicited and Unsolicited Adverse Events During the Vaccination Period – vaccinia-naïve and vaccinia-experienced**

analysis groups

		Vaccinia-Naïve Subject Analysis Group						Vaccinia-Healthy Subjects Experienced
		Comparator Controlled Studies, Healthy subjects N=3406	Noncomparator Controlled Studies, Healthy subjects N=975	All Studies, Healthy subjects N=4381	AD Subjects N=350	HIV Subjects N=379	All Subjects N=5110	Subject Analysis Group N=409
All adverse events	Events, n	22077	7199	29276	2388	2238	33902	1980
	Subjects, n (%)	3083 (90.5)	936 (96.0)	4019 (91.7)	329 (94.0)	336 (88.7)	4684 (91.7)	398 (97.3)
Serious adverse events	Events, n	19	6	25	1	10	36	1
	Subjects, n (%)	18 (0.5)	5 (0.5)	23 (0.5)	1 (0.3)	8 (2.1)	32 (0.6)	1 (0.2)
Related adverse events	Events, n	20307	6336	26643	1912	1611	30166	1817
	Subjects, n (%)	3010 (88.4)	918 (94.2)	3928 (89.7)	313 (89.4)	307 (81.0)	4548 (89.0)	391 (95.6)
Adverse events leading to discontinuation from 2nd vaccination	Events, n	32	11	43	0	1	44	N/A
	Subjects, n (%)	20 (0.6)	1 (0.1)	21 (0.5)	0 (0.0)	1 (0.3)	22 (0.4)	N/A
Fatal adverse events	Events, n	1	0	1	0	0	1	0
	Subjects, n (%)	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Cardiac events	Events, n	19	14	33	24	15	72	6
	Subjects, n (%)	18 (0.5)	11 (1.1)	29 (0.7)	22 (6.3)	12 (3.2)	63 (1.2)	5 (1.2)
Serious cardiac events	Events, n	1	0	1	0	2	3	0
	Subjects, n (%)	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.3)	2 (0.0)	0 (0.0)

Source: Table 2.1.2 in the integrated summary of safety submitted to 125678.0 Section 5.3.5.3

**Table 26. Overview of Solicited and Unsolicited Adverse Events During the Vaccination Period – comparator controlled analysis group**

	Vaccinia-Naïve, Healthy Subjects
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		Placebo (N=1183)	ACAM2000 (N=213)	MVA-BN (N=3406)
All adverse events	Events, n	2447	1676	22077
	Subjects, n (%)	717 (60.6)	209 (98.1)	3083 (90.5)
Serious adverse events	Events, n	3	0	19
	Subjects, n (%)	3 (0.3)	0 (0.0)	18 (0.5)
Related adverse events	Events, n	1869	1524	20307
	Subjects, n (%)	599 (50.6)	207 (97.2)	3010 (88.4)
Adverse events leading to discontinuation from 2nd vaccination	Events, n	3	N/A	32
	Subjects, n (%)	3 (0.3)	N/A	20 (0.6)
Fatal adverse events	Events, n	0	0	1
	Subjects, n (%)	0 (0.0)	0 (0.0)	1 (0.0)
Cardiac events	Events, n	5	1	19
	Subjects, n (%)	4 (0.3)	1 (0.5)	18 (0.5)
Serious cardiac events	Events, n	0	0	1
	Subjects, n (%)	0 (0.0)	0 (0.0)	1 (0.0)

Source: Table 2.1.1 in the integrated summary of safety submitted to 125678.0 Section 5.3.5.3

Table 27 summarizes post-vaccination troponin elevations (>1x ULN) by treatment group in all smallpox vaccine naïve subjects. This analysis included 5698 vaccinia-naïve subjects who received any dose or formulation of MVA-BN and had post-vaccination evaluation of troponin. A total of 1201 vaccinia-naïve subjects receiving placebo and 213 vaccinia-naïve subjects receiving ACAM2000 were also included. In summary, the regular assay detected only 0.12% subjects with post-vaccination troponin elevations while the high sensitivity assay detected 15.42% subjects with troponin elevations.

**Table 27. Post-Vaccination Troponin Elevations (>1x ULN) by Treatment Group – All Smallpox Vaccine Naïve Subjects**

		MVA-BN LF	MVA-BN (b) (4)	Placebo	ACAM2000
All Studies <sup>a</sup>	# of Events	7	0	0	1
	Missing, m	93	4	24	4
	Subjects, n/ N	5/4288	0/524	0/1201	1/213
	Incidence % (95% CI)	0.12 (0.04, 0.27)	0 (0, 0.70)	0 (0, 0.31)	0.47 (0.01, 2.59)
All Studies (high sensitivity) <sup>b</sup>	# of Events	218	NA	NA	NA
	Missing, m	3			
	Subjects, n/ N	144/934			
	Incidence % (95% CI)	15.42 (13.16, 17.90)			

n = number of subjects with events (imputed), m = number of subjects with missing post-vaccination troponin values. They are imputed to normal. N = total subjects in the safety population, LF = liquid frozen formulation, (b) (4) formulation

a. Excluded subjects only have post-vaccination high sensitivity troponin I test from studies POX-MVA-008 and POX-MVA-011.

b. Excluded subjects with no high sensitivity troponin I test from studies POX-MVA-008 and POX-MVA-011.

Source: Adapted from table 7.1.1 in the integrated summary of safety submitted to 125678.0 Section 5.3.5.3

**Reviewer's Comment:**

*The finding of post vaccination troponin elevation determined by the high sensitivity assay is inconclusive and difficult to interpret. There are several limitations for this observation, which include inconsistency of the troponin findings revealed by the regular and by high sensitivity assay (Table 27 above), and that Studies POX-MVA-008 and POX-MVA-011 are not controlled. Since no severe clinical manifestations were associated with the elevated troponin levels reported, the clinical team concluded that this finding does not raise major safety concerns. In addition, the applicant proposed an observational post-marketing outbreak study (MVA-POX-039) that will capture clinically indicated cardiac assessments, including troponin I measurements and ECGs, or new onset cardiac symptoms during a 6-month period after vaccination in a post-marketing outbreak setting.*

*In the IR response submitted on January 23, 2019, BN looked into a potential correlation between abnormal Troponin I values measured throughout the clinical trial program and the actual presence of cardiac adverse events, and presented a list of subjects with increased troponin values or cardiac adverse events. BN identified only 4 subjects (all in Study POX-MVA-011; 3 in the HIV group and 1 in the healthy group) showing both Troponin I increase and presence of a cardiac symptom. BN claimed that there was no case indicating inflammatory cardiac disorders in conjunction with an increase in Troponin I in all 7871 MVA-BN recipients, and isolated Troponin I increases themselves should not be considered an important medical risk. I defer to the clinical reviewer regarding the acceptability of BN's response.*

**9. ADDITIONAL STATISTICAL ISSUES**

NA

## 10. CONCLUSIONS

Statistical analyses support the efficacy and immunogenicity of the MVA-BN vaccine. The primary efficacy/immunogenicity endpoints of clinical trials POX-MVA-006 and POX-MVA-013 were both met. Regarding safety, MVA-BN was generally safe and well tolerated across all clinical trials except that the majority of AESIs in the two Phase 2 studies were related to increases in troponin levels, which were detected by a high sensitivity troponin assay. I defer to the clinical reviewer regarding the significance of this finding and potential association between cardiac adverse events and increases of troponin levels, and the overall benefit-risk assessment of this vaccine.