STATISTICAL ANALYSIS PLAN (SAP)

Amendment 1 to Edition 8.0

11 October 2017

FY12-19, HP-12-19, POX-MVA-006

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

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

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1 Rationale for Amendment

The main purpose of this Amendment 1 to the Statistical Analysis Plan (SAP) Edition 8.0 dated 21-Mar-2016 is to describe a modification of the per protocol set (PPS) for the immunogenicity analysis of clinical trial POX-MVA-006.

In SAP Edition 8.0 it is stated that the same PPS is the main analysis set for both the assessment of immunogenicity as well as efficacy of the trial. In particular, the confirmatory testing of the co-primary endpoints is planned to be performed on the PPS.

During the Data Review Meeting, held on 01-August-2017, it was observed that the number of subjects to be excluded from the PPS for the co-primary endpoints in the clinical trial was higher than anticipated. Due to the restricted indication for use of ACAM2000, POX-MVA-006 was performed by the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) in a military-only environment in South Korea in soldiers for whom an ACAM2000 vaccination is ordinarily applicable as part of the US Defense Health Agency (formerly MILVAX Agency) policy. Soldiers that volunteered for this clinical trial were often required to do off-site military training exercises particularly those soldiers recruited at the satellite site at Camp Hovey. This significantly restricted the ability for the soldiers to return for the required clinical trial site visits. Hence there were a relatively very high number of visit window deviations specific to this IMVAMUNE clinical trial. Hence, many observed violations pertain to missing assessments of any of the two co-primary endpoint parameters or major violations of visit windows of visits critical for the assessment of one co-primary endpoint. The number of deviations is equally distributed among the two treatment arms.

Since the two assessments related to the co-primary endpoints i.e. the Plaque Reduction Neutralization Test (PRNT) for immunogenicity and the maximum lesion area (MLA) after scarification for efficacy were scheduled at different time points and are considered independent, it is deemed appropriate from a scientific perspective to define separate PPS for immunogenicity and efficacy, excluding only those subjects that had a protocol violation with a substantial impact on the respective endpoint.

Immunogenicity data remains blinded for this clinical trial. As PRNT testing has not yet been performed and hence this data has not yet begun to be generated, a new analysis set (PPS for immunogenicity) is introduced in this SAP Amendment for the main analysis of all immunogenicity parameters, which replaces the immunogenicity analyses on the PPS as described in SAP Edition 8.0.

In the PPS for immunogenicity, subjects with major protocol deviations for efficacy (MLA) only will not be excluded, which leads to a higher precision of the estimated treatment effect for immunogenicity endpoints.

The efficacy analysis (MLA) on the PPS will remain unchanged as, due to the open-label nature of the study, access to efficacy data and treatment codes would have been possible at the time of finalization of the SAP Ed 8 Amendment.

2 Changes to the Statistical Analysis Plan

Additions to the SAP are shown in **bold** and deletions are displayed in ~~strikethrough mode~~. Comments and instructions for changes are shown in *italics*.

All changes described in this document implicitly apply also to Table and Listing Shells. However, these are not listed in this document.

2.1 Changes to the General Definitions

The definition of MLA is corrected to match the definition in the Clinical Trial Protocol Edition 8.0.

The Maximum Lesion Area (MLA) is 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).

There is only one lesion area measurement performed using the SilhouetteConnect camera system **at each respective visit**.

~~If one of the lesion areas is missing, then the MLA will be calculated as the single lesion area which is present. However, subjects with only one lesion area recorded will be considered a major protocol violation and will be excluded from the per protocol set (and therefore also from the initially seronegative set).~~ **If one of the lesion areas is missing, then the MLA will not be calculated.**

The MLA will be used in the co-primary endpoint analysis. However, the Day 6-8 and Day 13-15 lesion areas will also be reported and included as descriptive secondary endpoints.

2.2 Changes to Section 1.4.1

A new analysis set is introduced, that replaces the PPS as defined in SAP Edition 8.0 for immunogenicity analyses.

[…]

~~Both~~**The analysis of the** co-primary endpoint **for efficacy (MLA)** ~~analyses~~ will be conducted using the Per Protocol Set (PPS)**, whereas the analysis of the co-primary endpoint for immunogenicity will be based on the PPS for immunogenicity**. ~~However, i~~**I**dentical secondary robustness analyses will also be conducted using the Full Analysis Set (FAS) and the Initially Seronegative Subset (ISS), a subset of the PPS **for immunogenicity**.

2.3 Changes to Section 1.4.2

One analysis set is modified for immunogenicity analyses.

[…]

These secondary analyses will be conducted on the PPS **for immunogenicity**, FAS and ISS.

2.4 Addition of Section 1.7

The newly defined analysis set PPS for immunogenicity is described, as well as the derivation of the ISS from this analysis set.

1.7 Changes in the Planned Analyses from the Protocol

- **A new analysis set (PPS for immunogenicity) was introduced for the primary analysis of immunogenicity, which does not exclude subjects having only major protocol violations regarding efficacy.**
- **Consequently, the ISS analysis set is defined as the subset of the PPS for immunogenicity of initially seronegative subjects.**

2.5 Changes to Section 3.2

One analysis set is modified for immunogenicity analyses.

~~Both~~**The** co-primary trial hypothese~~s~~is **for immunogenicity** will be conducted on the PPS **for immunogenicity** as the main analysis set. Similar analyses will also be conducted on the FAS and ISS.

[…]

2.6 Changes to Section 3.7.2

The PPS for immunogenicity is defined and examples of major protocol violations leading to the exclusion of this set are provided. Moreover, it is clarified that the confirmatory testing for immunogenicity will be on that analysis set.

[…]

The Per Protocol Set for immunogenicity (PPS for immunogenicity) is the subset of subjects in the FAS who have received all vaccinations, completed all visits up until Visit 7 for Group 1 and Visit 4 for Group 2, and adhered to all protocol conditions *pertaining to immunogenicity*. Subjects with only minor (not relevant) protocol deviations will be included into this dataset.

Examples of major protocol violation are:

1. **Premature discontinuation of the trial (the question "prematurely terminated the trial?" is answered with "yes" even where no other reason exists to exclude the subject from further participation in accordance with the protocol)**
2. **Subject did not meet all of the inclusion criteria**

3. **Subject met one or more of the exclusion criteria**
4. **Withdrawal from the second vaccination (Group 1)**
5. **Major vaccine preparation and administration deviation from specification as given in the protocol including cases where the subject fulfils at least one of the criteria specified in the protocol for withdrawal from vaccination**
6. **Major deviations of the visit window *pertaining to collection of immunogenicity data* as determined during the DRM**
7. **Unallowed prior or concomitant medication**
8. **Missing ELISA or PRNT titers at trial Day 0 or Day 42 for subjects in Group 1 and at trial Day 0 or Day 28 post ACAM2000® vaccination (Group 2).**

The **co-**primary endpoint dataset **for efficacy (MLA)** will be the PPS**, whereas the confirmatory testing of the co-primary endpoint for immunogenicity will be based on the PPS for immunogenicity.** ~~All confirmatory testing is based on this subgroup.~~ For further descriptive purposes, the same statistical procedures will be applied to the FAS.

2.7 Changes to Section 3.7.3

Resulting from the PPS for immunogenicity, the ISS as defined in SAP Edition 8.0 for immunogenicity analyses is modified.

As seen in supposedly vaccinia-naive populations in previous MVA-BN® trials, some subjects will most likely be initially tested seropositive at Visit 1 prior to vaccination in either the ELISA or PRNT. An additional subgroup analysis based on the subset of the PPS **for immunogenicity** of initially seronegative subjects, the Initially Seronegative Subset (ISS) will therefore be performed which will provide assurances that the results have not been affected by the possible inclusion of some vaccinia-experienced subjects. In doing so it should be noted that some of the initially seropositive values might be false positive values. However, there is no reliable way to determine which seropositive cases are false positive and which are true positive values, and the ISS is therefore a conservative approach to validating the results in a confirmed naïve population.

A subject of the PPS **for immunogenicity** will be part of the ISS, if the subject is seronegative for both ELISA and PRNT at baseline.

The ISS population will be used as an additional robustness analysis set for the immunogenicity and the demographic analyses.

2.8 Changes to Section 3.8.3

The MedDRA dictionary was up-versioned from Version 18.0 to 20.0 during the study.

MedDRA (Medical Dictionary for Regulatory Activities) version ~~18.0~~ **20.0** will be used for coding of AEs.

[…]

2.9 Changes to Section 3.10.3

Summary tables of demographic data are added for additional analysis sets.

[…]

All listings will be based on the screened subjects with screen failures and subjects randomized but not treated considered as two separate trial groups. However tables of the descriptive statistics for the demographics will ~~only~~ be produced for the FAS**,** ~~and~~ **the** PPS**, the PPS for immunogenicity, and the ISS**.

2.10 Changes to Section 3.10.7

One analysis set is modified for immunogenicity analyses.

[…]

All immunogenicity results will be listed. Tables and figures will be prepared for the PPS **for immunogenicity**, ISS and the FAS. All of the following analyzes will be performed for results generated using both the PRNT and ELISA.

[…]

Correlation of ELISA and PRNT results

Pearson's correlation coefficient (with associated CI) for $\log_{10}$ titers measured by ELISA and PRNT at each post baseline sampling visit will be calculated per group with the associated p-values and 95% CIs for the PPS **for immunogenicity**, ISS and FAS. The correlation will also be presented on a scatter plot by group.

[…]

2.11 Changes to Section 5.1

An additional table for demographic data was added based on the additional analysis set, PPS for immunogenicity. Table numbers are adapted as indicated. The main analysis set for immunogenicity tables was modified.

[…]

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[…]

Section 15.2 Efficacy and Immunogenicity

[…]

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15.2.2.2.1 PRNT Seroconversion Rates at all Post Baseline Sampling Points – PPS **for immunogenicity**
15.2.2.2.2 PRNT Seroconversion Rates at all Post Baseline Sampling Points – FAS
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15.2.2.3.2 PRNT Geometric Mean Titers at all Sampling Points – FAS
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15.2.3.1.2 ELISA Seropositivity Rates at all Sampling Points – FAS
15.2.3.1.3 ELISA Seropositivity Rates at all Sampling Points – ISS

15.2.3.2.1 ELISA Seroconversion Rates at all Post Baseline Sampling Points – PPS **for immunogenicity**
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