CANGENE

Statistical Analysis Plan

Vaccinia Vaccination (ACAM2000®) of Plasma Donors for the Production of Vaccinia Immune Globulin Intravenous (VIGIV)

Protocol: VA-008

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[redacted]

Author:

[redacted]

Name	Position	Signature	YYYY/MMM/DD

Reviewed and Approved:

[redacted]

Name	Position	Signature	YYYY/MMM/DD

[redacted]

Name	Position	Signature	YYYY/MMM/DD

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1 INTRODUCTION

Smallpox vaccine is made from a virus called vaccinia, which is a "pox"-type virus related to smallpox but causes milder disease. ACAM2000®, (Smallpox (Vaccinia) Vaccine, Live) is a live, attenuated vaccinia virus derived from ACAM1000, a similar smallpox vaccine produced in cell culture by plaque-purification cloning from Dryvax® (Wyeth Laboratories, Marietta, PA). Dryvax® was prepared from calf lymph, which was purified, concentrated and dried by lyophilization. It was prepared with a seed virus derived from the New York City Board of Health (NYCBOH) strain of vaccinia.

In a previous plasma collection program study (VA-001) Dryvax® vaccine was used to induce anti-vaccinia immune globulin titers in subjects and then plasma was collected to produce VIGIV. In a follow up study (VA-006), subjects were vaccinated using ACAM2000® smallpox vaccine, and their plasma was collected to compare the VIGIV manufactured from plasma collected from donors vaccinated with ACAM2000® to VIGIV manufactured from plasma previously collected from donors vaccinated with Dryvax® smallpox vaccine. ACAM2000® vaccinated donors produced plasma titres that were sufficient for pooling to manufacture VIGIV. In general, the key quality attributes of VIGIV manufactured from plasma donors vaccinated with ACAM2000® fell within the range of results seen for VIGIV manufactured from plasma donors vaccinated with Dryvax® .

Study VA-008 is an open-label, single arm, multicenter vaccination study. In this study, healthy adult male and female volunteers 18-65 years of age, who meet the requirements for source plasma donation and study entry criteria will be vaccinated with ACAM2000® smallpox vaccine for collection of plasma to be used in the manufacture of VIGIV. There are possible risks associated with ACAM2000® vaccination. To ensure the safety of plasma donors, risk factor screening procedures and collection of post-vaccination safety data will be assessed throughout the study. Approximately 750 to 3000 donors will be enrolled in this study.

ACAM2000® must be administered only by a qualified medical practitioner who has received training by Cangene Corporation to safely and effectively administer the vaccine by the percutaneous route (scarification) at baseline (Day 0), as required by FDA. All subjects will be followed to Day 35 post-vaccination, with a final safety assessment conducted on Day 90. Extended follow-up visits will be conducted for any unresolved serious adverse events and non-serious related adverse events, weekly or until resolution. Subjects with vaccination sites that have not healed will also be assessed at extended follow-up weekly visits until the vaccination site has completely healed.

2 STUDY OBJECTIVE

The objectives of study VA-008 are:

- To vaccinate plasma donors with the ACAM2000® smallpox vaccine thereby inducing an immune response resulting in high anti-vaccinia antibody titers. The collection of donor plasma will be used in the manufacturing of Vaccinia Immune Globulin Intravenous (VIGIV).

- To ensure the safety of plasma donors vaccinated with ACAM2000® through the implementation of risk factor screening procedures and the collection of post-vaccination safety data.

Donors are vaccinated under a clinical trial protocol to ensure adequate screening of risk factors and monitoring of potential reactions. This statistical analysis plan will only address the second objective of study VA-008: the assessment of safety data collected from plasma donors vaccinated with ACAM2000®.

3 STUDY ENDPOINTS

3.1 Safety Endpoints

Safety endpoints include adverse events and the assessment of peri/myocarditis symptoms at each study visit. Additional endpoints related to subject safety which were captured during the study include vaccination site inspection, laboratory results (hematology, blood chemistry, pregnancy tests and EKG (see protocol for details)), physical exams, concomitant medications and vital signs.

Anticipated vaccination reactions (as defined in the study protocol), which are typically mild and do not interfere with daily function, will not be characterized as adverse events and are not captured on the case report forms. However, any vaccination reaction which is of greater intensity or duration than expected (i.e., moderate or severe pain, requires medication or interferes with daily life) will be categorized as an adverse event. In addition, any vaccination scab that has not separated by 28 days after vaccination will be categorized as an adverse event.

4 ANALYSIS POPULATION

Safety analyses will be performed on the safety population, which includes all subjects who were vaccinated with ACAM2000® smallpox vaccine per protocol during the study.

5 MISSING VALUES

Missing data are assumed to occur at random and to be minimal, thus no imputation methods will be used.

All summary statistics will be calculated with missing values omitted from analysis. The sample size for summary statistics will be provided in all summary tables.

6 ANALYSIS METHODS

Adverse events will be coded by the MedDRA coding dictionary. The incidence, intensity and relationship of events to ACAM2000® will be evaluated through the use of frequency tables, by MedDRA system organ class and preferred term.

The adverse events causality will be reported by the principle investigator from the sites, and reviewed by the medical monitor on a monthly basis. The company assessed causality for the adverse events will be documented as part of the standard process of medical review. The

summary of adverse events by relatedness will be based on the final company causality assessment.

In order to calculate the incidence of adverse events, each subject will be counted only once within each system organ class and preferred term category. The total number of events will also be provided for each system organ class and preferred term. When intensity or relationship to ACAM2000® is considered, the subject will be counted once, within each system organ class and preferred term category, for each intensity or relatedness category.

The incidence of most common reported Adverse Events, defined as those reported by at least 5% of subjects, will be tabulated by system organ class and preferred term as described above.

All adverse events reported during the study will be listed individually by subject. The time to onset of each adverse event relative (in number of days) to the day of ACAM2000® administration (Day 0) will be provided.

Serious Adverse Events (SAEs) will be listed and summarized in the same fashion as for all adverse events, if applicable.

The assessment of peri/myocarditis symptoms will be listed individually over time, including Day 90 safety assessment.

To reduce the potential risk of adverse events associated with ACAM2000®, including pericarditis and/or myocarditis, the VA-008 protocol inclusion and exclusion criteria have been developed to exclude subjects with cardiac risk factors, consistent with ACAM2000® labeling. To mitigate the risk of enrolling at risk subjects and potentially jeopardizing subject safety it is suggested that an EKG be performed prior to vaccination with ACAM2000® smallpox vaccine in all potential subjects ≥ 50 years old and for all subjects < 50 with two cardiac risk factors including; severely or morbidly obese or higher obesity classification (BMI ≥36); high blood pressure diagnosed by a doctor; high blood cholesterol diagnosed by a doctor and; diabetes or high blood sugar diagnosed by a doctor. Only these subjects that have successfully passed initial screening and inclusion/exclusion criteria will be required to have an EKG assessment during the screening visit. Clinical trial site personnel must be appropriately trained by a site investigator or sub-investigator who is a licensed physician, to recognize the symptoms of pericarditis and/or myocarditis. The clinical trial site will also be appropriately trained to administer the EKG. EKG results will be reviewed and interrupted by a Board-Certified Cardiologist offsite. The assessment of the EKG will be communicated from the offsite cardiologist to the PI at the clinical trial site and the sponsor team within 24 hours. The incidence of abnormal EKG results will be calculated for all the subjects with EKG results tested.

Concomitant medications will be coded and classified by the WHO drug dictionary. Concomitant medications will be listed individually, in full, using the WHO code.

Hematology, blood chemistry and vital signs will be listed and summarized for each visit. The incidence of abnormal laboratory results will also be summarized by visit. The EKG results will be listed and summarized as well.

Listings of pregnancy test results together with the screening assessment of the childbearing potential will be provided. A summary of pregnancy test results over time will be provided to identify any pregnant subjects during the study.

The abnormal results for physical exam will be included in the medical history results and listed.

All summary statistics for continuous variables will include the mean, standard deviation, median, minimum, maximum and sample size. Count and percentages will be provided for categorical variables.

7 RULES FOR INTERPRETATION OF ANALYSIS

No formal statistical analyses are planned; therefore there is no rule for the interpretation of results for this study.

The ongoing data listings included in Appendix III will be prepared by the statistical team at Cangene Corporation, and provided to the medical monitor every month for ongoing safety monitoring. Additional ongoing listings and summary tables may be required for the centralized monitoring purpose.

Statistical team at Cangene Corporation will also provide support on the centralize monitoring. The following aspects may be reviewed remotely for each site:

- Timeliness and completeness of entering initial subject data
- Enrollment status
- Days since last entering of data into EDC vs. expected entered data
- Missing data
- Number of queries
- Query Status
- Data error rates
- Protocol deviations/violations
- Number of AEs/SAEs
- Percentage of Screen Failures

Any concerns raised by monitoring requires additional subjects or additional percentage of information to be monitored at the site, the additional subjects will be randomly selected by Biostatistician at Cangene Corporation.

An independent DSMB will review the study data on a regular basis. The first DSMB meeting following the DSMB organizational meeting will be held after the initial fifty (50) subjects have reached Day 28 and this milestone will mark the commencement of the DSMB annual meetings thereafter. The whole safety data package predefined in the appendices will be provided to the DSMB meeting for review. This data package will include all information available as of the cut-off date. If at any point in the study, there are any signals indicative of potential safety concerns, additional data package will be provided to the DSMB for an ad-

hoc meeting as required. An ad-hoc meeting will occur if the one of the following situations has occurred:

1. In the event that either one related SAE is reported and/or two subjects with related unexpected (assessed as severe as per section 7.5 of the protocol) AEs occur.
    - Complete information on the known AE profile of ACAM2000 is documented in the Investigator's Brochure.
2. As described in Investigator's Brochure: In the ACAM2000 clinical studies 92% of previously vaccinated subjects, experienced one or more adverse event. Common events included injection site reactions (erythema, pruritus, pain and swelling) and constitutional symptoms (fatigue, malaise, feeling hot, rigors and exercise tolerance decreased). Across all ACAM2000 studies 3% of previously vaccinated subjects experienced at least one severe adverse event (defined as interfering with normal daily activities). In the event that 6% of vaccinated subjects report related expected AEs assessed as severe as per section 7.5 of the protocol an ad hoc DSMB meeting will occur.
3. If two pregnancies occur during the study.
    - ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal vaccinia and/or fetal death.
    - Note: One pregnancy will result in a Cangene Corporation directed investigation, corrective actions and a Dear Investigator Letter to all study sites as noted in the VA-008 Medical Monitoring Plan.
4. If two secondary transmissions occur during the study.
    - ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those stated for vaccinees.

APPENDIX I SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered according to ICH E3. The following is a list of table numbers and titles that will be included as summary tables in the clinical study report section 14. Additional tables may be added to section 14 at the request of the clinical study report authors.

14.1 Demographic Data

14.1.1 Summary of baseline demographic and other characteristics

14.2 Efficacy Data N/A

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.1.1 Adverse events by system organ class and preferred term

14.3.1.2 Adverse events by system organ class, preferred term and relatedness

14.3.1.3 Adverse events by system organ class, preferred term and intensity

14.3.1.4 Adverse events by system organ class and preferred term with incidence ≥5%[1]

14.3.1.5 Serious adverse events by system organ class and preferred term[2]

14.3.1.6 Serious adverse events by system organ class, preferred term and relatedness[2]

14.3.1.7 Serious adverse events by system organ class, preferred term and intensity[2]

14.3.1.8 Serious adverse events by system organ class and preferred term with incidence rate ≥ 5%[2]

14.3.1.9 Related adverse events by system organ class, preferred term and intensity

14.3.2 Listing of deaths and other serious adverse events

14.3.3 Narratives of death and other serious adverse events

14.3.4 Summary of laboratory values

14.3.4.1 Summary of blood chemistry results

14.3.4.2 Summary of hematology results

14.3.4.3 Summary of out-of-range blood chemistry test results

[1] This table will be generated if at least one adverse event is experienced by at least 5% of subjects.
[2] This table will only be generated if a sufficient number of SAEs are recorded.

14.3.4.4 Summary of out-of-range hematology test results

14.3.4.5 Summary of incidence of abnormal EKG results

14.3.4.6 Summary of vital signs over time

14.3.4.7 Summary of pregnancy test results

APPENDIX II SAS OUTPUTS

As there are no efficacy analyses described in the statistical analysis plan, no statistical methods were used in the analysis of data. Section 16.1.9 Documentation of Statistical Methods of the Clinical Study Report will contain the Statistical Analysis Plan but will not contain any SAS output.

APPENDIX III DATA LISTINGS

The following listings are to be included in the clinical study report section 16.2 Patient Data Listings. Additional listings may be added to section 16.2 at the request of the clinical study report authors. Data listings are numbered in accordance with ICH E3.

16.2.1 Discontinued subjects

16.2.1.1 Listing of discontinued subjects

16.2.2 Protocol deviations

16.2.3 Patients excluded from the efficacy analysis N/A

16.2.4 Demographic Data

16.2.4.1 Listing of demographic and other baseline characteristics

16.2.4.2 Listing of medical history

16.2.4.3 Listing of smallpox vaccination history

16.2.5 Compliance and/or drug concentration data

16.2.5.1 Listing of screening failures

16.2.5.2 Listing of inclusion/exclusion criteria

16.2.5.3 Listing of vaccine administration

16.2.6 Individual efficacy response data N/A

16.2.7 Adverse event listing

16.2.7.1 Listing of adverse events

16.2.7.2 Listing of related adverse events

16.2.7.3 Listing of peri/myocarditis assessments

16.2.7.4 Listing of vaccination site inspection

16.2.8 Listing of individual laboratory measurements by subject

16.2.8.1 Listing of blood chemistry test results

16.2.8.2 Listing of hematology test results

16.2.8.3 Listing of assessment of childbearing potential and pregnancy test results

16.2.8.4 Listing of immunologic assessments

16.2.8.5 Listing of EKG results

16.2.8.6 Listing of HIV serology results

16.2.9 Additional Data Listings

16.2.9.1 Listing of concomitant medications

16.2.9.2 Listing of vital signs

16.2.9.3 Listing of comment log

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Note to File

Protocol No. / Title: VA-008 / Vaccinia Vaccination (ACAM2000®) of Plasma Donors for the Production of Vaccinia Immune Globulin Intravenous (VIGIV), Amendment 2.5

Site Code: N/A **Investigator:** N/A

TMF Section/Artifact Name: 1.7.7 Statistical Analysis Plan

Date: 2019Jul24

Details:

Protocol Amendment 2.5 dated 2019-Feb-08 permitted re-enrollment of study subjects as detailed in Section 4.3.4, below.

> **4.3.4 Subject Re-Entry into the Study**
>
> Subjects who have been previously vaccinated with ACAM2000 in VA-008 may be eligible to re-enter the study after three years providing that subjects meet all eligibility and screening requirements.

The statistical analysis plan (SAP) version 1.0 dated 2015Jun10 and the associated table and listing shells version draft 0.2 dated 2015May15 did not provide for subjects to enroll in the study more than once. For example, the demographic table counts each subject once in descriptive statistics of age, gender, race, ethnicity, height, weight and body mass index. In order to avoid double counting of the same subject, the subsequent enrollment record for a re-enrolled subject would need to be subtracted from the dataset. Rules would need to be established, such as whether the age summary should count the subject's age at first enrollment, at second enrollment or both.

As another example, adverse event (AE) incidence counts each subject only once within each system organ class and preferred term category as is standard in clinical trials. Additional programming would be required to link AE records from first enrollment and second enrollment for a re-enrolled subject in order to count him/her only once within each system organ class and preferred term.

Additional programming would be required also to link records for laboratory results and vital signs for re-enrolled subjects. All data listings would need reprogramming to link re-enrolled subjects as well.

A further complication is that several subjects re-enrolled in the study without the knowledge of the sponsor or study staff by visiting a different site and failing to disclose their prior participation in the VA-008 study. Such subjects may not have met the minimum 3-year interval between subsequent enrollments mandated in the protocol amendment.

Assessment:

Regarding a decision to amend the SAP, redesign the table and listing shells and reprogram the outputs, the following points were considered:

1. The primary objective of the VA-008 study is to ensure the safety of plasma donors vaccinated with ACAM2000 through implementation of risk factor screening procedures and collection of post-vaccination safety data. The reporting of study data in the clinical study report (CSR) does not impact subject safety, whether or not the outputs are modified for subject re-enrollment.
2. Scientifically, an argument can be made for treating re-enrolled subjects as independent subjects, particularly in the case of at least 3 years between vaccinations. Entry criteria for the study already require prior smallpox immunization. The protocol focuses on safety data surrounding each separate vaccination event from screening and vaccination through scab separation (by Day 35) and resolution/ stabilization of any related AEs (through Day 90).
3. The study is ending this year and all tables and listings have already been programmed. The rework involved in modification of the outputs at this stage is considerable and the benefit minimal.