16.1.9 Documentation of Statistical Methods

Version	Date
Statistical Analysis Plan, Version 2.0	23 September 2019
Statistical Analysis Plan, Version 1.0	08 September 2016

Statistical Analysis Plan
for
Final Analysis

Version 2.0

Study:	A Phase 2 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Use as a Vascular Prosthesis for Femoro-Popliteal Bypass in Patients with Peripheral Arterial Disease
Study-ID:	CLN-PRO-V004
Sponsor / Contact:	Humacyte, Inc. 2525 East NC Highway 54 Durham, NC 27713 919-313-9633
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Version:	Version 2.0

Revision History

Version	Author	Date	Reason for Revision
1.0	CY	08SEP2016	Final version 1.0
2.0	EN/ME	23SEP2019	The original SAP was based on Protocol V2.0. Incorporate protocol V3.0 16 July 2018 revisions ● Primary safety endpoint revised ○ Incidence of ***HAV*** aneurysm formation ***(true or pseudo)***, anastomotic bleeding or ***spontaneous*** rupture ~~of HAV~~, HAV infection, HAV removal, and ~~irritation~~ significant ***local*** inflammation at the HAV implantation site. ● Long term endpoints revised ○ HAV ~~survival and~~ interventions ○ Evidence of aneurysmal dilatation or stenosis of the HAV on routine clinical ***duplex*** US ○ ***New endpoint***: *Primary, primary assisted, and secondary patency at 18, 24, 30, 36, 42, 48, 54 and 60 months* ○ ***New endpoint:*** Limb salvage/amputation at 18, 24, 36, 48, and 60 months, for all subjects who have not died, withdrawn, or been lost to follow-up. ○ ***New endpoint:*** Incidence of surgical revascularization of the implanted limb, at the level of the HAV or distal to HAV, for all patients who have not died, withdrawn, or been lost to follow-up. ○ ***New endpoint:*** The VascuQol PAD symptom assessment consists of 25 questions. The total score and the 5 domain scores (Activity, Symptom, Pain, Emotional, and Social) will be recorded in the clinical database, at 18, 24, 36, 48 and 60 months, for all patients who have not died, withdrawn, or been lost to follow-up. Interim analyses clarified ● DMC review during study. ● Primary analysis occurs after patients reach 12 months post-implant Clarified patency definitions and algorithm.

			Clarified stenosis analysis: ● Time to first stenosis added. ● Stenosis development by time period added. Clarified laboratory display of standardized units (Conventional will be used). General formatting and consistency changes throughout.

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List of Abbreviations

In the following abbreviations are listed as used within this statistical analysis plan or which might occur within the tables, listings and graphs outputs:

ABI	Ankle-brachial index
AE	Adverse event
aPTT	Activated Partial Thromboplastin Time
ATC	Anatomical therapeutic chemical classification
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CM	Concomitant medication
CRF	Case report form
CT	Computed tomography
eCRF	Electronic case report form
CS	Clinically significant
DMC	Data Monitoring Committee
DRM	Data review meeting
EC	Exclusion criteria
ECG	Electrocardiogram
ET	Early termination
HAV	Human Acellular Vessel
IC	Inclusion criteria
INR	International normalized ratio
K-M	Kaplan Meier
MedDRA	Medical dictionary for regulatory activities
NCS	Not clinically significant
OS	Overall survival
PAD	Peripheral arterial disease
PRA	Panel reactive antibodies
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SOC	System organ class
TLG	Tables, listings, graphs
US	Ultrasound
WHO	World Health Organization
WHO-DRL	WHO Drug Reference List

No abbreviations of standard laboratory tests are included in this list.

1 General

This Statistical Analysis Plan (SAP) was defined by the Sponsor and the responsible Statistician. It is based upon the Study Protocol (version 4.0 of 15 Sep 2020) and contains detailed description of the statistical methods described therein.

The SAP prospectively describes the analyses to be performed on study data. This SAP was finalized prior to the final database lock.

1.1 Phase and Design of the Clinical Study

This is a prospective, multicenter, single arm, non-randomized Phase 2 study to evaluate safety and efficacy of Humacyte's Human Acellular Vessel (HAV) for use as a vascular prosthesis for femoro-popliteal bypass in patients with peripheral arterial disease (PAD).

1.2 Investigator(s) and Study Center(s)

Up to 8 sites in the USA.

1.3 Visit Terminology

Notation used in eCRF and protocol	Notation used for table, listing and graph presentation	Notification for treatment phases
Visit 1 (Screening, Day -35 to -1)	Screening	Screening
Visit 2 (Day 1)	Day 1	HAV implantation
	Baseline[1]	
Visit 3 (Day 5)	Day 5	Follow-up
Visit 4 (Day 29), ± 4 days	Day 29	
Visit 5 (Month 3), ± 14 days	Month 3	
Visit 6 (Month 6), ± 14 days	Month 6	
Visit 7 (Month 9), ± 14 days	Month 9	
Visit 8 (Month 12/ET), ± 14 days	Month 12	
Unscheduled	Unscheduled	
Every 6 - 12 months through Month 60 (± 30 days) at "standard of care" clinic visits	SOC Visit 1 to 10	Additional follow up

[1] The closest non-missing value prior to surgery on Day 1 will be used as baseline value.
ET = Early Termination

1.4 Objectives

1.4.1 Primary Objectives:

This is an open label Phase 2 study. There is no formal hypothesis testing.

Safety:

- To evaluate the safety and tolerability of the Humacyte HAV in PAD patients undergoing femoro-popliteal bypass surgery

Efficacy:

- To determine the patency (primary, primary assisted and secondary) rate of the Humacyte HAV at Month 12
- To determine the incidence of hemodynamically significant stenosis (>70%) defined by duplex ultrasound, and the time to stenosis development

1.4.2 Secondary Objectives:

Safety:

- To assess changes in the panel reactive antibodies (PRA) response after HAV implantation
- To determine mechanical stability of the HAV based on freedom from aneurysmal degeneration on duplex ultrasound and computed tomography (CT) imaging
- To determine HAV durability in terms of freedom from need for HAV explanation or replacement due to infection, bleeding or conduit degeneration

Efficacy:

- To determine the patency of the HAV (primary, primary assisted and secondary) at Months 3, 6 and 9
- To determine the rates of interventions needed to maintain / restore patency in the HAV through Month 12
- To assess effect of HAV implantation on symptoms of PAD using the VascuQol instrument
- To assess effect of the HAV on ankle-brachial index (ABI)
- To assess effect of the HAV on 6 minute walk test

1.5 Sample Size Estimation

Up to 25 patients were planned, and 15 patients were recruited into the study. As this Phase 2 study is one of the first studies of the HAV in humans with PAD, the number of patients was chosen in order to provide preliminary evidence of safety and efficacy of the HAV to allow the initiation of further trials in larger numbers of patients.

The study is not powered to assess the efficacy of the HAV.

2 Efficacy and Safety Variables

2.1 Primary Safety Endpoints

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- Incidence of HAV aneurysm formation (true or pseudo)
- Anastomotic bleeding or spontaneous rupture
- HAV infection
- HAV removal
- Significant local inflammation at the HAV implantation site
- Frequency and severity of adverse events (AEs)

2.2 Secondary Safety Endpoints

- Change from baseline in PRA
- Change from baseline in hematology, coagulation, and clinical chemistry parameters

2.3 Primary Efficacy Endpoints

- HAV patency rates (primary, primary assisted, and secondary patency)
- Hemodynamically significant stenosis (>70% by duplex ultrasound criteria)

2.4 Secondary Efficacy Endpoints

- HAV interventions
- Patient reported PAD symptoms (VascuQol)
- ABI
- 6 minute walk test
- HAV remodeling at Months 1 (Day 29), 6 and 12 by CT angiography and ultrasound (US)

2.5 Long Term Endpoints (Post Month 12 through Month 60)

- HAV interventions
- Evidence of aneurysmal dilatation or stenosis of the HAV on routine clinical duplex US
- Primary, primary assisted, and secondary patency at 18, 24, 30, 36, 42, 48, 54 and 60 months
- Limb salvage/amputation at 18, 24, 36, 48, and 60 months, for all subjects who have not died, withdrawn, or been lost to follow-up.
- Incidence of surgical revascularization of the implanted limb, at the level of the HAV or distal to HAV, for all patients who have not died, withdrawn, or been lost to follow-up.

- VascuQol PAD symptom assessment consists of 25 questions. The total score and the 5 domain scores (Activity, Symptom, Pain, Emotional, and Social) will be recorded in the clinical database, at 18, 24, 36, 48 and 60 months, for all patients who have not died, withdrawn, or been lost to follow-up.

2.6 Other Efficacy Variables

- Doppler ultrasound and high resolution ultrasound
- Time to loss of patency

2.7 Other Relevant Variables

- Medical history
- Smoking history
- 12-lead electrocardiogram (ECG)
- Pregnancy test
- Prior and concomitant medication
- HAV implantation and angiography/intraop ultrasound
- Documentation of surgery
- Study termination and premature discontinuation

3 Statistical Analysis Set

One analysis population set will be analyzed.

3.1 Safety Analysis Set

The safety analysis set (SAF) consists of all enrolled patients who received an HAV when the final patient enrolled reaches 12 months post-implant. For discontinued or withdrawn patients, all available data will be included in the safety analyses.

3.2 Additional Subgroup Analysis

Where appropriate, subgroup analysis may be performed for the main efficacy parameters if enough patients within the subgroups allow further insight to the data.

3.3 Assignment of Analysis Set to Analysis

All analyses will be based on SAF.

3.4 Interim Analysis

Data Monitoring Committee (DMC) reports will be provided during the course of the study.

Endpoints will be assessed over a period of up to 60 months after HAV implantation.

- The **primary analysis** of the study will be based conducted on the earlier of a) when the final patient enrolled reaches 12 months post-implant or b) all subjects enrolled in the initial 36 month accrual period have reached 12 months post-implant. The SAP will call this the 1-year analysis.

- The **final analysis** will occur at the end of the study, when all patients have completed or exited the study.

The database extraction for the **1-year analysis** will include all study data collected at the time of the database extraction. The by-visit tables and figures will display all time points present in the data, including visits after the Month 12 visit (where applicable). Event tables (such as concomitant medications, AEs), will include all events during the study. Listings will display all study data available, including data collected after the Month 12 visit.

The database for the final analysis will include all study data and by-visit tables will display all study timepoints.

4 Statistical Evaluation

All tables, figures and listings will be produced using SAS (v9.4 or a more recent version).

Unless otherwise stated, categorical data will be presented using counts and percentages, whilst continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation [SD], median, minimum, maximum, 25th percentile, and 75th percentile). Minima and maxima will be quoted to the number of decimal places as recorded in the case report form (CRF); means, SDs and medians will be quoted to one further decimal place. Percentages will be rounded to one decimal place.

The closest non-missing values prior to implantation on Day 1 will be used as baseline values.

Unless otherwise stated, all confidence intervals will be presented as 95% two-sided intervals. For categorical endpoints, if all values are either success or failure, the exact CI will be presented.

As no sample size assessment has been undertaken, all analysis results are considered to be exploratory.

Details on the specification, definition, calculation and analysis of the efficacy and safety endpoint variables are given in Section 2 and the following sections.

4.1 Dispositions of Subjects and Analysis Set

Summaries based on all screened patients will include disposition of patients (eligibility), analysis set inclusion (yes/no), patient status (completed or discontinued), and the main reason for study discontinuation. Summaries based on the SAF will include number of patients per center and number of patients per visit. These results will also be provided in listings.

Violated inclusion and exclusion criteria (eligibility) will be noted in a listing.

A patient has completed the study when the end of study CRF indicates that the patient "Study completed". A discontinuation of screen failure is defined as the patient was screened but did not pass the study procedure criteria.

Please note, a patient is assessed for inclusion and exclusion criteria at the preoperative screening visit. On day of the surgery (Day 1), eligibility is re-assessed against the inclusion/exclusion criteria. If the patient does not pass eligibility, then the site will update the inclusion/exclusion violation. The patient will become a screen failure.

The date of visit (if available; yes/no) will be used to indicate if a patient was expected for the visit, whether the respective visit was conducted

4.2 Protocol Deviations

All major protocol deviations will be documented throughout the study and will be provided in a listing.

4.3 Demographics and Other Baseline Variables

Demographic and other baseline variables will be descriptively analyzed for the SAF.

Demographic data

Demographic data (age, gender, ethnicity, race, body height [cm], body weight [kg], body mass index [BMI; kg/m^2]) will be summarized and listed. Demographic data will be summarized and listed for screen failure patients as well.

Medical History

Medical history will be coded by Medical dictionary for regulatory activities (MedDRA). Patients with significant previous or existing concomitant diseases (medical history) will be listed.

PAD surgical/interventional history will be listed.

Smoking History

Count and percentage of current / past / never smokers will be tabled. Pack years (combined current and past smokers) will be summarized. Smoking history data will also be listed.

- Pack years will be calculated for current smokers and former smokers. Pack years will be interpreted as the number of cigarette packs used over the course of their smoking history.

  Pack years were calculated as: Number of Packs per Day * 365.25 * smoking years

  Notes: For patients reporting "< ½ pack", ½ was used in the calculation.

Pre-study Angiography/CT Angio and Vein Mapping

Angiography data will be tabulated and listed.

ECG at Screening

Result of 12-lead ECG at screening will be presented with frequency tabulations.

Documentation of Surgery and Any Complications

Implantation of HAV and documentation of surgical procedure, any complications (e.g., prolonged oozing at anastomoses), and interventions will be listed.

Pregnancy Test

Pregnancy test results will be summarized and listed.

4.4 Efficacy Analysis

4.4.1 Analysis of Primary Efficacy Parameters

Efficacy Objective 1:

Primary, primary assisted, and secondary patency rates of the HAV at Month 12 with evaluation of patency will be described.

Primary patency is defined as the functional patency until any type of intervention.

Primary assisted patency is defined as an HAV still working without thrombosis.

Secondary patency is defined as the functional patency, with or without preceding successful interventional or surgical procedures to maintain or reestablish patency, until either final failure or the HAV is abandoned.

All patients start out in primary patency. A patient is not expected to flow from primary, to assisted, to secondary patency directly. For example, an abandonment can occur after the HAV implant, that ends the primary patency and the patient never went into an assisted or secondary status.

Primary patency	● Start: HAV implantation date ● End: earliest start date from assisted, secondary, or abandonment status
Primary assisted patency	● Start: any type of intervention to HAV ● End: earliest start date from secondary or abandonment status
Secondary patency	● Start: earliest thrombosis AE start date; ● End: abandonment date

Many parts are used to derive patency:

Abandonment	● Source: AE eCRF ● Terms: “Anastomotic stenosis", "Arterial bypass stenosis" ,"Arterial bypass thrombosis", and "Arterial bypass occlusion" ● And action taken is recorded as "Patient withdrawn from study", or "None”

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Stenosis	● Source: AE eCRF ● Terms of "Anastomotic stenosis" "Arterial bypass stenosis"
Thrombosis	● Source: AE eCRF ● Terms of "Arterial bypass thrombosis" "Arterial bypass occlusion"
Interventions for stenosis	● Source: Interventions eCRF ● Intervention to treat stenosis: Intervention type on eCRF as "Intervention to treat anastomotic or mid-HAV stenosis but **without** HAV thrombosis.
Interventions for thrombosis	● Source: Interventions eCRF ● Intervention to treat thrombosis: Intervention type on eCRF as "Intervention to treat anastomotic or mid-HAV stenosis and **with HAV thrombosis**.
End of study	● Source: End of study eCRF

Data handling for this rate will be as followed

The assignment to a patency (yes/no) (primary, primary assisted, secondary patency) will be verified during the Data Review Meeting (DRM) using all data of CRF sections referring to HAV patency, clinical examination of the HAV site, doppler ultrasound assessment of HAV patency, HAV intervention, premature discontinuation, and AEs.

Patency rates will be presented with frequency tabulations showing patient numbers and patency rates for Month 12.

Clopper-Pearson confidence intervals (CI) will be presented for frequency counts of patency rates.

Kaplan-Meier (K-M) curves for primary, primary assisted, and secondary patency will be created at the 1-year report and for all subsequent reports. K-M curves will be provided using two censoring methods:

a. Patients who die, withdraw from the study, or are lost to follow-up are censored at the day of the respective event.

b. Patients who die, withdraw from the study, or are lost to follow-up are considered as having suffered failure of secondary patency at the day of the respective event.

Efficacy Objective #2:

Hemodynamically significant stenosis (>70% by duplex ultrasound criteria): The duplex ultrasound parameters will be summarized by planned visit up to Month 12.

- Frequency of stenosis occurrence, location of stenosis, and presence of aneurysm.
- Numeric summary of volumetric flow rate and inner diameter of HAV mid bypass.

A stenosis event can occur between planned study visits (i.e. Unscheduled Visits). A “by visit”

summary will represent the stenosis event/information that occurred before or on the planned visit. For example, the summary at Day 5 will denote the number of patients who had stenosis occur up to Day 5 or on the Day 5 visit. Similarly, the Day 29 summary will denote the number of patients with stenosis events that occurred after Day 5, and up to Day 29 (inclusive of Day 29).

The time of first stenosis (in days) will be summarized and calculated as number of days from HAV implantation to date of first stenosis event: Date of Stenosis – Date of Day 1 + 1. Patients who did not have a stenosis event will not contribute a value for this summary.

Please note, the clinical duplex will be recorded for all visits. Results after Month 12 **will not** be summarized in tables and will be provided in the listings.

4.4.2 Analysis of Secondary Efficacy Parameters

Patency of the HAV (primary, primary assisted, secondary) rates will be presented for Months 3, 6 and 9.

Clopper-Pearson CIs will be presented for frequency counts of patency rates.

The HAV interventions and type of interventions needed to maintain / restore patency in the HAV through Month 12 will be descriptively summarized. Interventions will be recorded at each study visit and interventions occurring after the Month 12 visit will be provided in a listing.

Number of patients, who needed any intervention to maintain / restore patency throughout the study will be tabulated by counts and frequencies. The cumulative number of patients with any intervention needed will be presented stratified by visit and the number of patients having 1, 2, 3, etc. interventions will be presented.

Due to the nature of the study, an intervention can occur between planned study visits and will be recorded in the EDC as an unscheduled visit. A “by visit” summary will represent the intervention information that occurred before and on the scheduled visit. For example, the summary at Day 5 will denote the information from all interventions that occurred up to Day 5 visit and on the Day 5 visit. Similarly, the Day 29 summary will denote the information from all interventions that occurred after Day 5, and up to Day 29 (inclusive of Day 29).

VascuQol PAD symptom assessment data

The VascuQol PAD symptom assessment consists of 25 questions. The total score and the 5 domain scores (Activity, Symptom, Pain, Emotional, and Social) will be recorded in the clinical database. Total score and each domain score will be presented by descriptive measures for each visit as well as for the absolute change from baseline. Individual data, domain score and total score will also be listed.

The 1-year analysis will provide the table summary by planned visit up to Month 12. The final analysis will only display results in a listing.

ABI and 6 minute walk test

ABI and 6 minute walk test will be presented by descriptive measures for each visit as well as for the absolute change from baseline. Data will also be listed.

The 1-year analysis will provide the table summary by planned visit up to Month 12. The final analysis will only display results in a listing.

HAV Remodeling by CT angiography and US at Months 1 (Day 29), 6, 12, and 60 will be presented descriptively. Data will also be listed.

4.4.3 Analysis of Long Term Efficacy Parameters

Patient overall survival at 60 months

Patients overall survival (OS) status of alive or death, as well as the date of death and date of last known alive will be collected at the Month 60 visit.

OS is defined as: Date of Death or date of last known alive – Date of Surgery + 1

Patients who are still alive will be censored at the 60 month visit date or last known date alive, whichever occurs last. Median OS will be tabulated and Kaplan Meier (K-M) graph will also be included.

HAV interventions

HAV interventions will be listed.

Evidence of aneurysmal dilatation or stenosis of the HAV

Evidence of aneurysmal dilatation or stenosis of the HAV will be listed.

Patency of the HAV (primary, primary assisted, secondary)

Patency of the HAV (primary, primary assisted, secondary patency rates) will be presented for Months 18, 24, 30, 36, 42, 48, 54 and 60. Clopper-Pearson CIs will be presented for frequency counts of patency rates.

Limb salvage/amputation

Limb salvage/amputation at 18, 24, 30, 36, 42, 48, 54 and 60 months will be listed for all subjects who have not died, withdrawn, or been lost to follow-up.

Surgical Revascularization

Incidence of surgical revascularization of the implanted limb, at the level of the HAV or distal to HAV, will be listed for all patients who have not died, withdrawn, or been lost to follow-up.

VascuQol Quality of Life Questionnaire

VascuQol PAD symptom assessment consists of 25 questions. The total score and the 5 domain scores (Activity, Symptom, Pain, Emotional, and Social) will be recorded in the clinical database at 18, 24, 30, 36, 42, 48, 54 and 60 months. VascuQol results will be listed and summarized for all patients who have not died, withdrawn, or been lost to follow-up.

4.4.4 Other Efficacy Variables

High Resolution Ultrasound

Doppler ultrasound (HAV patency) high resolution ultrasound data will be listed.

Time to loss of patency

Time after first implantation of HAV until loss of patency (primary, primary assisted and secondary) will be separately presented in tables using descriptive statistics. The time to loss of patency will be verified during the DRM using all data from the CRF including the information used for patency rates at each visit and information on any AEs and consequent interventions.

Patients discontinued early with the HAV still patent, will be censored at that timepoint.

The median times (or the lower quartile – in case the median is unable to be estimated) will be presented together with the respective 95% CIs using Kaplan-Meier estimates. In case of small numbers of events these analyses may be skipped.

For the 1-year interim analysis, time to loss of patency will be reviewed for the first 12 months, and rates of 3, 6, and 12 months will be presented. For the final analysis, time to loss of patency will be reviewed for the entire study and rates of 3, 6, 12, 24, 36, 48, and 60 months will be presented.

Focused vascular assessment exam will be listed.

Angiography and Endothelium-dependent, flow-mediated vasodilation data will be listed.

5 Safety Analysis

5.1 Vital signs (blood pressure, heart rate, body temperature)

Blood pressure (systolic and diastolic [mmHg]), heart rate (bpm) and body temperature (C) will be presented by descriptive measures for each visit as well as for the absolute change from baseline. Vital signs will be collected up to the Month 12 visit.

5.2 Physical examinations

Physical examinations are collected for each study visit.

- For the 1-year analysis: Results of physical examination will be presented by frequency tabulations for each visit.
- For the final analysis: A shift from baseline to final study visit will be provided.

5.3 Prior and Concomitant medication

Medications will be coded by World Health Organization Drug Reference List (WHO-DRL).

Medications will be tabulated by Anatomic Group (Anatomical therapeutic chemical classification [ATC] level 1), ATC level 4, and WHO-DRL preferred term. The number of entries,

as well as the number and percentage of affected patients will be reported.

Previous and concomitant medications will be separately described. A medication can only be categorized as previous or concomitant.

- Previous medications: are defined as those taken within 7 days prior to day 1 and stopped **before** date of first HAV implantation: Stop Date < Day 1

- Concomitant medications are defined as any used within 7 days prior to Day 1 and stopped **on or after** date of first HAV implantation (≥ Day 1), or which are ongoing from Day 1, or which are taken after date of HAV implantation. If the start or stop date is incomplete and the allocation to previous or concomitant is not clear the medication will be considered to be concomitant.

5.4 Safety Laboratory Parameters

Clinical laboratory variables will be described using summary statistics for the actual values at each visit, as well as for the absolute change from baseline to each visit. The standard error of the mean (SEM) will be included in these tables.

The following laboratory parameters were determined and will be described for the corresponding visits:

Hematology (measured at screening and Month 6)

- Hemoglobin
- Hematocrit
- Red Blood Cells (RBC)
- Absolute Lymphocytes
- Absolute Monocytes
- Absolute Eosinophil
- Absolute Basophil
- White Blood Cells (WBC)
- Absolute Neutrophil Count

Clinical Blood Chemistry (measured at screening and Month 6)

- Sodium
- Potassium
- Calcium

- Blood Urea Nitrogen (BUN)
- Total Bilirubin
- Creatinine
- Glucose (non-fasting)
- Albumin

Coagulation (measured at screening and Month 6)

- International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (aPTT)

Immunology (measured at screening and Month 6)

- PRA sample collection date will be listed.

Hematology, chemistry and coagulation values are quantitative. The findings (normal, abnormal clinically significant [CS], abnormal not clinically significant [NCS]) are available for each test and will be provided in the listings.

The laboratory values were provided by local laboratories and unit values are not consistent across sites. The values used for the table summary will be **conventional units** and will be calculated by a conversion method.

6 Adverse Events (AEs)

Adverse events that started before HAV implantation are collected and documented in the EDC as medical history.

Adverse events will be coded by MedDRA. Presentation of adverse events will be the number of entries, as well as the number and percentage of affected patients. Tabulations will show numbers of adverse events by system organ class (SOC), preferred term (PT), and severity.

Each documented adverse event per patient will be considered, i.e. if a patient experienced the same adverse event (identical adverse event description) more than once during study duration, all events will be counted.

To give an overview of all adverse events a frequency table will be prepared showing the following information (displaying number of patients, percentage of patients and number of events).

Overview table:

- any AEs
- any serious AEs (SAEs)

- any AEs leading to death as outcome

Additionally, the following tables (grouped by MedDRA terms [SOC and PT]) will be presented:

- AEs
- SAEs
- AEs by severity
- Deaths
- Leading to premature discontinuation

HAV Complications

AE relationship is recorded on the AE eCRF. For purpose of the DMC summary, any AE that is related to the HAV will be considered as a HAV complication.

The incidence of HAV complications (aneurysm formation, pseudoaneurysm formation, anastomotic bleeding or spontaneous rupture, HAV removal, HAV infection and significant local inflammation at the HAV implantation site will be identified during DRM and will be separately tabulated. HAV complications will also be listed in terms of incidence, severity, and (where appropriate) time to onset and duration.

7 Analysis of Other Variables

7.1 Other Long-Term Follow-Up Variables

Study duration will be evaluated calculating the number of days being in the trial:

Total Study Duration = Date of Last Visit Available – Date of Day 1 + 1

Descriptive measures will be presented for the total study duration. Individual patient's study duration will be listed.

7.2 Missing Values

Imputations of partial dates are used for the following: determination of study day/time of onset and duration of an AE; definitions of prior and concomitant medications; time to loss of patency; time to first stenosis; day/time of onset and duration of HAV complications. Imputations are made using a conservative approach, which aims to maximize the duration of AEs and HAV complications and minimize the time to loss of patency and time to first stenosis.

Date imputation method for AEs, prior/concomitant medications, and HAV complications

- Partial start dates
    - Missing time – the minimum possible onset time will be calculated and presented

in DD:HH:MM format

- Missing day – impute the 1st of the month. For AEs and HAV complications, if the month is the same month as the HAV implantation, then impute the day of the implant
- Missing day and month – impute as January 1st. For AEs and HAV complications, if the year is the same year as the HAV implantation, then impute as the day of the implant

- Partial end dates
  - Missing time – the maximum possible onset time will be calculated and presented in DD:HH:MM format
  - Missing day – impute the last day of the month
  - Missing day and month – impute as December 31st

Date imputation method for calculating time to loss of patency and time to first stenosis

- Partial patency status or stenosis status dates
  - Missing time – the minimum possible onset time will be calculated and presented in DD:HH:MM format
  - Missing day – impute the 1st of the month. If the month is the same month as the HAV implantation, then impute the day of the implant
  - Missing day and month – impute as January 1st. If the year is the same year as the HAV implantation, then impute as the day of the implant

8 Data Base Closure and Data Review

A data base closure (soft lock) will be performed prior to the DRM and to the analysis. All parameters will be checked, as specified in the data validation plan, and all queries resolved before data base closure and analysis.

The data review will be conducted prior to final data base closure and can be done via a telephone conference or in writing. During the DRM it is to review and define patient's primary, primary assisted and secondary patency outcome (yes/no) and patient's time to loss of patency (primary, primary assisted and secondary). Additionally, adverse events of graft complications (aneurysm formation, anastomotic bleeding or rupture, graft infection and irritation/inflammation at the graft implantation site) will be identified.

For the data review meeting, ARG will provide patient data listings to the Sponsor, containing following information:

- Any data on patient patency (primary, primary assisted, secondary) response classification (yes/ no) concerning the primary efficacy parameter and the secondary efficacy parameter on patency, as well as any data needed to define patients date of HAV failure and date of loss of patency

- Adverse event data (HAV complications)

The final decision regarding the patency outcomes and date of HAV failure/ loss of patency will be documented within a meeting minutes document. The Sponsor will review the document and verify the decision by signing the document.

The final data base closure (hard lock) will be performed afterwards.

9 Miscellaneous

Appendix A contains the table of contents for the tables, listings, and figures.

The listings are always sorted by center and patient. If a different sorting order should be used for some listings this will be noted separately. The variables for the special listings are explicitly given in the description of listings. All listings will be presented for the safety analysis set, if not stated differently.

Enrolled but not treated patients (e.g. withdrawal before treatment) will be considered in tables and listings describing disposition of patients, analysis set and discontinuation as well as listings for patients demographics, time schedules and comments.

10 Changes from Protocol

n/a

11 Literature

n/a

12 Signatures

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Date (DDMMMYYYY)	Signature

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Statistical Analysis Plan
for
Final Analysis

Version 1.0

Study:	A Phase 2 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Use as a Vascular Prosthesis for Femoro-Popliteal Bypass in Patients with Peripheral Arterial Disease
Study-ID:	CLN-PRO-V004
Sponsor / Contact:	Humacyte, Inc 7020 Kit Creek Road PO Box 12698 Research Triangle Park, NC 27560 919-33-9633
CRO:	Atlantic Research Group, Inc. 2421 Ivy Road, Suite 200 Charlottesville, VA 22903
Version:	1.0

Revision History

Version	Author	Date	Reason for Revision
1.0	CY	08SEP2016	Final version 1.0

Statistical Analysis Plan
CLN-PRO-004

Final Analysis
3/19

REVIEW AND APPROVAL

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List of Abbreviations

In the following abbreviations are listed as used within this statistical analysis plan or which might occur within the tables, listings and graphs outputs:

AE	Adverse event
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical classification
AV	Arteriovenous
BP	Blood pressure
CI	Confidence interval
CM	Concomitant medication
CRF	Case report form
eCRF	Electronic case report form
CS	Clinically significant
DRM	Data review meeting
e.g.	Exempli gratia, for example
EC	Exclusion criteria
ECG	Electrocardiogram
ET	Early termination
Gamma-GT (GGT)	Gamma Glutamyl Transpeptidase
HAV	Human acellular vessel
IC	Inclusion criteria
MedDRA	Medical dictionary for regulatory activities
NCS	Not clinically significant
PRA	Panel reactive antibodies
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SOC	System organ class
TLG	Tables, listings, graphs
US	Ultrasound
WHO	World Health Organization
WHO-DRL	WHO Drug Reference List

No abbreviations of standard laboratory tests are included in this list.

1 General

This Statistical Analysis Plan (SAP) was defined by the Sponsor and the responsible Statistician. It is based upon the Study Protocol (version 2.0 of 11 March 2016), Data collection Tool (DCT V1.0) and Annotated eCRF (V 01Jul2016), and contains detailed description of the statistical methods described therein.

The SAP describes prospectively the analyses to be performed on study data. This SAP was finalized prior to the final database lock.

1.1 Phase and Design of the Clinical Study

This is a prospective, multicenter, single arm, non-randomized phase 2 study to evaluate safety and efficacy of Humacyte's human acellular vessel for use as a vascular prosthesis for femoro-popliteal bypass in patients with peripheral arterial disease.

1.2 Investigator(s) and Study Center(s)

Up to 4 sites in the USA.

1.3 Visit Terminology

Notation used in eCRF and protocol	Notation used for table, listing and graph presentation	Notification for treatment phases
Visit 1 (Screening, Day -35 to -1)	Screening	Screening
Visit 2 (Day 1)	Day 1	HAV implantation
	Baseline[1]	
Visit 3 (Day 5)	Day 5	Follow-up
Visit 4 (Day 29), ± 4 days	Day 29	
Visit 5 (Month 3), ± 14 days	Month 3	
Visit 6 (Month 6), ± 14 days	Month 6	
Visit 7 (Month 9), ± 14 days	Month 9	
Visit 8 (Month 12/ET), ± 14 days	Month 12	
Unscheduled	Unscheduled	
Every 6 - 12 months through Month 60 (+/- 30 days) at "standard of care" clinic visits	SOC Visit 1 to 10	Additional follow up

[1] The closest non-missing value prior to surgery on Day 1 will be used as baseline value.

1.4 Objectives

1.4.1 Primary Objectives:

This is an open label phase 2 study. There is no formal hypothesis testing.

Safety:

- To evaluate the safety and tolerability of the Humacyte HAV in PAD patients undergoing femoro-popliteal bypass surgery

Efficacy:

- To determine the patency (primary, primary assisted and secondary) rate of the Humacyte HAV at Month 12
- To determine the incidence of hemodynamically significant stenosis (>70%) defined by duplex ultrasound, and the time to stenosis development

1.4.2 Secondary Objectives:

Safety:

- To assess changes in the PRA response after HAV implantation
- To determine mechanical stability of the HAV based on freedom from aneurysmal degeneration on duplex ultrasound and CT imaging
- To determine HAV durability in terms of freedom from need for HAV explanation or replacement due to infection, bleeding or conduit degeneration

Efficacy:

- To determine the patency of the HAV (primary, primary assisted and secondary) at Months 3, 6 and 9
- To determine the rates of interventions needed to maintain / restore patency in the HAV through Month 12
- To assess effect of HAV implantation on symptoms of PAD using the VascuQol instrument
- To assess effect of the HAV on ankle-brachial index (ABI)
- To assess effect of the HAV on 6 minute walk test

1.5 Sample Size Estimation

Up to 20 patients will be recruited into the study. As this phase 2 study is one of the first studies of the HAV in humans with PAD, the number of patients was chosen in order to provide sufficient safety information on the HAV to allow the initiation of further trials in larger numbers of patients.

The study is not powered to assess the efficacy of the HAV.

2 Efficacy and Safety Variables

2.1 Primary Safety Endpoints

- Incidence of aneurysm formation, anastomotic bleeding or rupture, HAV infection, HAV removal and irritation/inflammation at the HAV implantation site
- Frequency and severity of adverse events

2.2 Secondary Safety Endpoints

- Change in PRA from baseline
- Change from baseline in hematology, coagulation, and clinical chemistry parameters

2.3 Primary Efficacy Endpoints

- Primary patency rate
- Primary assisted patency rate
- Secondary patency rate
- Hemodynamically significant stenosis (>70% by duplex ultrasound criteria)

2.4 Secondary Efficacy Endpoints

- HAV interventions
- Patient reported PAD symptoms (VascuQol)
- ABI
- 6 minute walk test
- HAV remodeling at Months 1 (Day 29), 6 and 12 by CT angiography and US

2.5 Long Term Endpoints (Months 18 through 60)

- Patient survival
- HAV survival and interventions
- Evidence of aneurysmal dilatation or stenosis of the HAV on routine clinical US

2.6 Other Efficacy Variables

- Doppler ultrasound and high resolution ultrasound
- Time to loss of patency

2.7 Other Relevant Variables

- Medical history
- Smoking history
- 12 lead ECG
- Pregnancy test
- Prior and concomitant medication
- HAV implantation and angiography/intraop ultrasound
- Documentation of surgery
- Study termination and premature discontinuation

3 Statistical Analysis Set

One analysis population set will be analyzed.

3.1 Safety Analysis Set

The safety analysis set (SAF) consists of all enrolled patients who received an HAV. For discontinued or withdrawn patients, all available data will be included in the safety analyses.

3.2 Additional Subgroup Analysis

Where appropriate, subgroup analysis may be performed for the main efficacy parameter if

enough patients within the subgroups allow further insight to the data.

3.3 Assignment of Analysis Set To Analysis

All analyses will be based on SAF.

3.4 Interim Analysis

No interim analyses are planned.

4 Statistical Evaluation

All parameters will be analyzed using descriptive methods. Continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation (SD), median, minimum, maximum, 25th percentile, and 75th percentile). Summary statistics for categorical variables will include frequency counts and percentages. All patients within the respective analysis set will be tabulated.

The closest non-missing values prior to implantation on day 1 will be used as baseline values.

As no sample size assessment has been undertaken all analysis results are considered to be exploratory.

Details on the specification, definition, calculation and analysis of the efficacy and safety endpoint variables are given in section 2 and the following sections.

4.1 Dispositions of Subjects and Analysis Set

The disposition of patients (eligibility), analysis set, number of patients per center, inclusion and exclusion criteria, and the status at study termination will be summarized and listed.

4.2 Protocol Deviations

All protocol deviations will be documented throughout the study and will be provided in a listing.

4.3 Demographics and Other Baseline Variables

Demographic and other baseline variables will be descriptively analyzed.

Demographic data

Demographic data (age, gender, ethnicity, race, body height, body weight, BMI) will be summarized and listed.

Medical History

Patients with significant previous or existing concomitant diseases (medical history) will be listed.

Smoking History

Count and percentage of current / past / never smokers will be tabled. Pack years (combined current and past smokers) will be summarized. Smoking history data will also be listed.

Pre-study Angiography/CT Angio and Vein Mapping

Angiography data will be tabulated and listed.

Eligibility (inclusion/exclusion criteria)

Eligibility data will be listed.

ECG at Screening

Result of 12-lead ECG at screening will be presented with frequency tabulations.

Documentation of Surgery and Any Complications

Implantation of HAV and documentation of surgical procedure, any complications (e.g., prolonged oozing at anastomoses), and interventions will be listed.

Pregnancy Test

Pregnancy test result will be summarized and listed.

4.4 Efficacy Analysis

4.4.1 Analysis of Primary Efficacy Parameters

Primary, primary assisted, and secondary patency rates of the HAV at Month 12 month and at all other post-surgery visits with evaluation of patency will be described.

Patency is defined as the functional patency until any type of intervention;

Primary patency is defined as the access patency until any type of intervention.

Primary assisted patency is defined as an HAV still working without thrombosis.

Secondary patency is defined as the functional patency, with or without preceding successful interventional or surgical procedures to maintain or reestablish patency, until either final failure or the access is abandoned.

Early discontinued patients prior to the visit of interest will be determined as being non-patent irrespective of the reason for discontinuation.

The assignment to a patency (yes/ no) (primary, primary assisted, secondary patency) will be verified during the DRM using all data of case report form (CRF) sections referring to HAV

patency, clinical examination of the HAV site, doppler ultrasound assessment of HAV patency, HAV intervention, premature discontinuation, and adverse events.

Patency rates will be presented with frequency tabulations showing patient numbers and patency rates for month 12.

Clopper-Pearson confidence limits will be presented for frequency counts of patency rates.

Hemodynamically significant stenosis (>70% by duplex ultrasound criteria): the absolute change from baseline (Day 1) values to all post-surgery visits of duplex ultrasound parameters will be summarized. Summary statistics will also be provided at each time point.

4.4.2 Analysis of Secondary Efficacy Parameters

Patency of the HAV (primary, primary assisted, secondary) rates will be presented for months 3, 6 and 9.

Clopper-Pearson confidence limits will be presented for frequency counts of patency rates.

The HAV interventions and type of interventions needed to maintain / restore patency in the HAV through Month 12 will be descriptively summarized.

Number of patients, who needed any intervention to maintain/ restore patency throughout the study will be tabulated by counts and frequencies. The cumulative number of subjects with any intervention needed will be presented stratified by visit and the number of subjects having 1, 2, 3, etc. interventions will be presented.

VascuQOL PAD symptom assessment data

Total score and each domain score will be presented by descriptive measures for each visit as well as for the absolute change from baseline. Individual data, domain score and total score will also be listed.

Ankle-brachial index (ABI) and 6 minute walk test

Ankle-brachial index (ABI) and 6 minute walk test will be presented by descriptive measures for each visit as well as for the absolute change from baseline. Data will also be listed.

CT angiography at Months 1 (Day 29), 6 and 12 will be listed.

4.4.3 Analysis of Long Term Efficacy Parameters

Patient overall survival at 60 month

Patients overall survival (OS) status of alive or death, as well as the date of death and date of last know alive will be collected at month 60 visit.

OS is defined as date of death or date of last know alive – date of surgery.

Patients who are still alive will be censored at 60 month visit date. Median OS will be tabulated and KM graph will also be included.

HAV survival and interventions

HAV survival will be analyzed similar to the overall survival. HAV interventions will be listed.

Evidence of aneurysmal dilatation or stenosis of the HAV

Evidence of aneurysmal dilatation or stenosis of the HAV will be listed.

4.4.4 Other Efficacy Variables

High Resolution Ultrasound

Doppler ultrasound (HAV patency) high resolution ultrasound data will be listed;

Time to loss of patency

Time after first implantation of HAV until loss of patency (primary, primary assisted and secondary) will be separately presented in tables using descriptive statistics. The time to loss of patency will be verified during the DRM using all data from the case report form (CRF) including the information used for patency rates at each visit and information on any AEs and consequent interventions.

Patients discontinued early with the HAV still patent, will be censored at that timepoint.

The median times (or the lower quartile – in case the median is not estimable) will be presented together with the respective 95% confidence intervals using Kaplan-Meier estimates. In case of small numbers of events these analyses may be skipped.

Focused vascular assessment exam will be listed.

Angiography and Endothelium-dependent, flow-mediated vasodilation data will be listed.

4.5 Safety Analysis

4.4.1 Vital signs (blood pressure, heart rate, body temperature)

Blood pressure (systolic and diastolic), heart rate (bpm) and body temperature will be presented by descriptive measures for each visit as well as for the absolute change from baseline.

4.4.2 Physical examinations

Results of physical examination will be presented by frequency tabulations for each visit.

4.4.3 Prior and Concomitant medication

Medications will be coded by WHO-DRL.

Medications will be tabulated by Anatomic Group (ATC level 1), ATC level 4, and WHO-DRL preferred term. The number of entries, as well as the number and percentage of affected patients will be reported.

Previous and concomitant medications will be separately described.

- Previous medications: are defined as those taken within 7 days prior to day 1 and stopped before date of first HAV implantation: stop date < day 1.
- Concomitant medications are defined as any used within 7 days prior to day 1 and stopped after date of first study medication implantation (≥ day 1), or which are ongoing from day 1, or which are taken after date of HAV implantation. If the start or stop date is incomplete and the allocation to previous or concomitant is not clear the medication will be considered to be concomitant.

4.4.4 Safety Laboratory Parameters

Clinical laboratory variables will be described using summary statistics for the actual values at each visit, as well as for the absolute change from baseline to each visit. The standard error of the mean (SEM) will be included to these tables.

The following laboratory parameters were determined and will be described for the corresponding visits:

Hematology (measured at screening and Month 6)

Type of all variables is quantitative and finding (normal, abnormal CS, abnormal NCS) are available for all variables.

- Hemoglobin,
- Hematocrit,
- Absolute Lymphocytes,
- Absolute Monocytes,
- Absolute Eosinophil,
- Absolute Basophil,
- White Blood Cells (WBC),
- Absolute Neutrophil Count,
- HbA1c

Clinical Blood Chemistry (measured at screening and Month 6)

Type of all variables is quantitative and findings (normal, abnormal CS, abnormal NCS) are available for all variables.

- Sodium,
- Potassium,
- Calcium,
- BUN,
- Aspartate Aminotransferase (AST),
- Alanine Aminotransferase (ALT),
- Total Bilirubin,
- Creatinine,
- Glucose (non-fasting),
- Albumin,
- Alkaline Phosphatase,
- Gamma-GT (GGT)

Coagulation (measured at screening and Month 6)

Type of all variables is quantitative and findings (normal, abnormal CS, abnormal NCS) are available for all variables.

- INR
- aPTT

Immunology (measured at screening and Month 6)

- PRA sample collection date will be listed.

4.4.5 Adverse Events (AEs)

The incidence of HAV complications (aneurysm formation, anastomotic bleeding or rupture, HAV removal, HAV infection and irritation/inflammation at the HAV implantation site) will be identified during DRM and will be separately tabulated. HAV complications will also be listed in terms of incidence, severity, and (where appropriate) time to onset and duration.

Adverse events will be coded by MedDRA. Presentation of adverse events will be number of entries, as well as the number and percentage of affected patients. Tabulations will show numbers of adverse events by symptom organ class (SOC), preferred term (PT), and severity.

Each documented adverse event per patient will be considered, i.e. if a patient experienced the same adverse event (identical adverse event description) more than once during study duration, all events will be counted.

To give an overview of all adverse events a frequency table will be prepared showing the following information (displaying number of patients, percentage of patients and number of events).

Overview table:

- any AEs
- any serious AEs
- any AEs leading to death as outcome

Additionally the following tables (grouped by MedDRA terms (SOC and PT) will be presented:

- AEs
- Serious AEs
- AEs by intensity
- Deaths

Any premature discontinuations due to adverse events and deaths will be listed and summarized.

4.6 Analysis of Other Variables

4.4.1 Other Long-Term Follow-Up Variables

Study duration will be evaluated calculating the number of days being in the trial (total study duration=date of last visit available – date of day 1+1). Descriptive measures will be presented for the total study duration. Individual patient's study duration will be listed.

4.7 Missing Values

No missing value imputation methods will be applied, e.g. the analyses are based on a valid case basis.

4.8 Data Base Closure and Data Review

A data base closure (soft lock) will be performed prior to the DRM and to the analysis. All parameters will be checked, as specified in the data validation plan, and all queries resolved before data base closure and analysis.

The data review will be conducted prior to final data base closure, and can be done via a telephone conference or in writing. During the DRM it is to review and define patient's primary, primary assisted and secondary patency outcome (yes/no) and patient's time to loss of patency (primary, primary assisted and secondary). Additionally adverse events of graft complications (aneurysm formation, anastomotic bleeding or rupture, graft infection and irritation/inflammation at the graft implantation site) will be identified.

For the data review meeting, ARG will provide patient data listings to the sponsor, containing following information:

- Any data on patient patency (primary, primary assisted, secondary) response classification (yes/ no) concerning the primary efficacy parameter and the secondary efficacy parameter on patency, as well as any data needed to define patients date of HAV failure and date of loss of patency
- Adverse event data (HAV complications)

The final decision regarding the patency outcomes and date of HAV failure/ loss of patency will

be documented within a meeting minutes document. The Sponsor will review the document and verify the decision by signing the document.

The final data base closure (hard lock) will performed afterwards.

4.9 Miscellaneous

For qualitative variables the frequencies (absolute and relative) are calculated. If no further remark is given in the description of the tables following format will be used for all tables with qualitative variables:

	Y-variable(s)	
X-variable(s)	N	%
category 1		
category 2		
Missing		
Total		100.0

For this standard format the description of the tables in Appendix A determines only the X- and Y-variables. If another format of table is described in the details to the tables, the real design will be determined by the technical possibilities within SAS and may not look identical to the provided example. However, all information as displayed will be included.

Quantitative parameters will be described by declaring the mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum. In the description of the tables this will be denoted by"basic statistics". Wherever noted in the SAP, the SEM will be presented, too.

The listings are always sorted by center and patient. If a different sorting order should be used for some listings this will be noted separately. The variables for the special listings are explicitly given in the description of listings. All listings will be presented for the safety analysis set, if not stated differently.

Enrolled but not treated subjects (e.g. withdrawal before treatment) will be considered in tables and listings describing disposition of patients, analysis set and discontinuation as well as listings for subject demographics, time schedules and comments.

The following title will be used for all generated tables, listings, and graphs:

Humacyte Inc.: CLN-PRO-V004 Page # of #
Date of Data Cut: DDMMMYY

<Table/Listing/Graph NNN: Description of contents>

<Subtitle for description of contents - if applicable>

<Analysis set>

The numbering NNN of the tables/listings/graphs will be stated in the detailed description (Appendix A).

Following footnote will be used for all generated tables, listings, and graphs:

ARG, DDMMMYY Confidential Program: <name of program>

The statistical evaluation will be performed using SAS version 9.3 or higher.

5 Changes from Protocol

n/a

6 Literature

n/a

7 Signatures

Statistician	
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