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STATISTICAL ANALYSIS PLAN

STUDY BUPI-502

A PHASE 4, RANDOMIZED, OPEN-LABEL STUDY OF THE PHARMACOKINETICS AND TOLERAILITY OF BUPIVACAINE HCL FOLLOWING ONE OF TWO ROUTES OF ADMINISTRATION IN SUBJECTS UNDERGOING AUGMENTATION MAMMOPLASTY

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Upon review of this document, the undersigned approves the statistical analysis plan. The analysis methods are acceptable, and the table, listing, and figure shell production can begin.

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List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	Area under the curve
bpm	Beats per minute
BMI	Body mass index
BUN	Blood urea nitrogen
CRO	Contract research organization
CSR	Clinical Study Report
DBP	Diastolic blood pressure
DM	Data management
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDISH	Evaluation of drug-induced serious hepatotoxicity
GGT	Gamma-glutamyltransferase
HCl	Hydrochloride
HR	Heart rate
IM	Intramuscular
IV	Intravenous(ly)
LAST	Local Anesthetic System Toxicity
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MME	Morphine milligram equivalency
NSAID	Nonsteroidal anti-inflammatory drug
ORAE	Opioid-related adverse event
PACU	Postanesthesia Care unit

Abbreviation	Term
PK	Pharmacokinetic(s)
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SDA	Study drug administration
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SI	Standard international
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHODDE	World Health Organization Drug Dictionary Enhanced

1. ADMINISTRATIVE STRUCTURE

1.1. Sponsor and Oversight

This study is being conducted under the sponsorship of Heron Therapeutics, Inc. (Heron). The data management (DM) is being performed under contract with DSG, Inc. (DSG) and the statistical analyses are being performed under contract with Agility Clinical, Inc. (Agility) with oversight from Heron.

1.2. Data Quality Assurance

The Clinical Operations, DM, and Biostatistics departments at the contract research organizations (CROs) will collaborate internally and with the Sponsor to ensure that the data collected and analyzed for this study are of the highest quality possible and meet the data standards set for the study. This will be accomplished in part through programmed edit checks which will be reviewed by the data managers, statisticians, programmers, and other team members on an ongoing basis to evaluate whether any checks need to be added or any existing checks need to be modified. In addition, periodic reviews of listings of accumulating data, assessment of data query trends, and resulting retraining of study site personnel will be performed to further ensure data quality.

2. INTRODUCTION

This statistical analysis plan (SAP) presents a detailed plan of the statistical methods to be used during the reporting of safety data collected in this study. This SAP does not include the planned analysis and reporting of pharmacokinetics (PK) assessments in the study. Planned PK analysis will be presented in a separate PK analysis plan.

This SAP was prepared prior to data analysis to provide full details of analyses to be presented in the clinical study report (CSR), including a detailed elaboration of the statistical analysis methods presented in the protocol. Revisions can be made to this SAP while the study is ongoing; however, it must be finalized prior to database lock. Any deviations from the analysis plan provided in the SAP will be fully documented in the final CSR.

This SAP should be read in conjunction with the study protocol and the electronic Case Report Forms (eCRFs).

3. OBJECTIVES

The primary objective of the study is as follows:

- To characterize the bupivacaine pharmacokinetic (PK) profiles of bupivacaine HCl in this study population.

The secondary objective is as follows:

- To assess the safety and tolerability of bupivacaine HCl in this study population.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 4, randomized, open-label study of bupivacaine HCl administered either by instillation into the surgical site or by injection into the surgical site in approximately 30 subjects undergoing bilateral submuscular augmentation mammoplasty under general anesthesia.

Approximately 30 subjects will be randomized to 1 of the following 2 treatment group in a 1:1 ratio:

- Bupivacaine HCl 150 mg (60 mL) via instillation (15 subjects)
- Bupivacaine HCl 150 mg (60 mL) via injection (15 subjects)

4.2. Assessments

Safety assessments will include the following:

- Adverse event (AE) recording.
- Concomitant medication recording.
- Clinical safety laboratory tests (hematology and serum chemistry).
- 12-lead electrocardiogram (ECG).
- Physical examinations.
- Wound healing assessment.
- Vital signs collections.
- Local Anesthetic Systemic Toxicity (LAST) assessment.

4.3. Endpoints

4.3.1. Safety Endpoints

The safety endpoints are the following:

- Incidence of treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), opioid-related AEs (ORAEs), and potential LAST-related TEAEs through Day 28.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs at each assessed timepoint.
- Rate of potential LAST symptoms based on questionnaire results.
- Wound healing assessment at 72 hours and on Day 10 and Day 28.

5. GENERAL STATISTICAL CONSIDERATIONS

No statistical hypothesis testing will be performed. Continuous data will be presented using descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized by the number and percent of subjects. Data will be displayed in all listings sorted by treatment group, subject number and visit/study day. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise stated. Non-zero percentages will be rounded to 1 decimal place, except 100% will be displayed without any decimal places. Additional rounding rules are as follows:

- If the original value has 0 decimal places: mean, median, and CI will have 1 decimal place and SD and SE will have 2 decimal places.
- If the original value has 1 decimal place: mean, median, and CI will have 2 decimal places and SD and SE will have 3 decimal places.
- If the original value has 2 or more decimal places: mean, median, CI, SD, and SE will all have 3 decimal places.

Minimum and maximum will always have the same decimal places as the original measure, up to a maximum of 3 decimal places. The above rounding rules will not be applied to original measures displayed in listings.

Values that are collected with "<" or ">" signs will be analyzed as the numerical value without the sign in tables and figures. In listings, these data will be reported as collected with the sign.

All safety data will be collected electronically. Datasets will be created using the Study Data Tabulation Model (SDTM) v. 1.4 or higher, conforming to the SDTM Implementation Guide (SDTMIG) v. 3.2 or higher. Datasets, tables, listings, and figures will be programmed using SAS® v. 9.4 or higher. All safety data will be listed via the SDTM datasets and selected safety data will be listed via programmed listings.

5.1. Sample Size

The sample size in this study was selected empirically without a formal statistical assumption.

5.2. Randomization, Stratification, and Blinding

This is an open-label study. Subjects will be randomized to receive bupivacaine HCl 150 mg via instillation or bupivacaine HCl 150 mg via injection. The randomization will not be stratified.

The randomization will be based on a centralized computer-generated blocked randomization algorithm created by Agility.

5.3. Analysis Populations

5.3.1. Safety Population

The Safety Population will consist of all subjects who receive study drug. This population will be used for all summaries of safety data. The actual treatment received will be used for analysis in this population.

5.4. Other Important Considerations

5.4.1. Definition of Baseline

Baseline data are defined as the last observed measurement collected, whether scheduled or unscheduled, prior to the start of study drug administration.

5.4.2. Calculation of Change and Percent Change from Baseline

Change from Baseline to any timepoint t (C_t) is calculated as follows:

$C_t = M_t - M_B$, where:

- M_t is the measurement of interest at timepoint t.
- M_B is the measurement of interest at Baseline.

Percent change from Baseline to any timepoint (P_t) is calculated as follows:

$P_t = 100*(C_t/M_B)$

5.4.3. Study Day Calculation for Reporting Purposes

The following convention will be used to calculate study day for reporting purposes:

- The study day of study drug administration is Study Day 1.
- For measurements that are *on or after* the date of study drug administration:
  - Study Day = date of measurement – date of study drug administration + 1.
- For measurements that are *prior* to the date of study drug administration:
  - Study Day = date of measurement – date of study drug administration.

For all subjects, the day of study drug administration should be the same day as the day of the surgical procedure.

5.4.4. Start date/time of Study Drug Administration (Time 0)

The start date/time of study drug administration is defined as the date and time of the start of instillation or injection with study drug

The start date/time of study drug administration will be Time 0 for all safety assessments.

5.4.5. 72-Hour Postoperative Observation Period

The 72-hour postoperative observation period will be defined as the period of time from the start date/time of study drug administration to the date/time of PK sample collection at the nominal 72-hour postoperative timepoint.

Subjects who have a reported PK sample collection at the nominal 72-hour postoperative timepoint will be considered as completing the 72-hour postoperative observation period.

5.4.6. Visit Windows

No programmatically calculated visit windows are defined for this study.

5.4.7. Handling of Missing and Partial Data

All safety results will be summarized using observed cases with no imputation.

For partial dates involving AE start dates and concomitant medication start dates, the algorithms for imputation will vary depending upon the parameter; the details can be found in Appendix 1. No other partial dates will be imputed.

6. SUBJECT DISPOSITION

A summary of disposition of subjects will include the number and percentage of subjects for the following categories: subjects enrolled (signed the Informed Consent Form), subjects who failed screening with reasons for screen failure, subjects randomized, subjects in the Safety Population, subjects completing the 72-hour postoperative observation period, subjects completing Day 28, and subjects not completing Day 28 by reason for withdrawal. Only 1 reason for study withdrawal will be recorded for each subject.

7. DEMOGRAPHICS, CHARACTERISTICS, AND MEDICAL HISTORY

7.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented in tables using descriptive statistics. Demographics consist of age, age category, sex, race, and ethnicity. Baseline characteristics consist of weight, height, and body mass index (BMI). A subject's age in years is calculated using the integer part of the difference in number of days between the date that informed consent is signed and date of birth divided by 365.25, or is recorded directly on the eCRF. The number and percentage of subjects in the following age categories will be presented: 18-44, 45-54, 55-64, 65-74, 75-84, and ≥ 85.

7.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 19.1. Medical history will be summarized for the Safety Population and will display the number and percentage of subjects with a past and/or concomitant disease or past surgeries by System Organ Class (SOC) and preferred term (PT).

7.3. Protocol Deviations

Deviations and violations from the protocol will be recorded. Protocol deviations will be classified into, but not necessarily limited to, the following categories:

- ICF procedures.
- Eligibility criteria.
- Prohibited concomitant medication/therapy.
- Laboratory assessment.
- Study procedure (eg, vital signs, ECG, PE).
- Safety reporting.
- Randomization
- Study drug dosing/administration
- Visit schedule/windows

Protocol deviations will be presented in a summary table by protocol deviation category and treatment.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

Prior medications are defined as medications with a stop date occurring before Day 1. Concomitant medications are defined as medications that are ongoing on Day 1 or with a start date occurring on or after Day 1. Medications with start and stop dates which bracket Day 1, or for which missing start and/or stop dates make it impossible to determine the prior or concomitant status, will be summarized as concomitant medications.

All medications will be coded with the World Health Organization Drug Dictionary Enhanced (WHODDE), September 1, 2016.

Prior and concomitant medications will be summarized separately by drug class and PT. At each level of summarization, a subject is counted once if that subject reports 1 or more medications at that level. Drug class will correspond to the Anatomical Therapeutic Classification (ATC) Level 2 term.

All prior and concomitant medications will be summarized for the Safety Population.

8.2. Rescue Medication

The following steps will be implemented to identify rescue medication in the study:

1. Select concomitant medications that are coded as an opioid analgesic.
2. Identify rescue medications from Step 1 in which the start date/time of medication is within the 72-hour postoperative observation period (see Section 5.4.5 for details).

Opioid rescue medication in intravenous (IV) morphine milligram equivalency (MME) dose and non-opioid rescue medication dose will be summarized for 0-24 hours, 0-48 hours, and 0-72 hours. In addition, proportions of subjects who received no rescue medication, who received opioid rescue medication only, who received non-opioid rescue medication only, and who received both opioid and non-opioid rescue medication will be summarized through 72 hours.

8.3. Surgery Procedure

The type of implant (silicone or saline), implant size per side, and duration of surgery will be summarized. Duration will be calculated as completion time minus start time, reported in minutes.

8.4. Study Drug

For all subjects, treatment will consist of a single dose of study drug administered by a surgeon. As such, extent of exposure will be reported in the CSR as the number of subjects by treatment received in the Safety Population. A summary of treatment compliance will not be produced, as by definition it will be 100% for the Safety Population.

9. EFFICACY ANALYSIS

Not applicable.

10. SAFETY ANALYSIS

All analyses of safety data will be conducted using the Safety Population. Statistical hypothesis testing will not be performed. No imputation of missing safety data will be performed except in the case of partial AE and concomitant medication onset dates (Appendix 1).

10.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A TEAE is any AE which occurs any time during or after study drug administration, or any AE with an onset prior to study drug administration that worsens during or after study drug administration. An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal laboratory value, vital sign result, or ECG finding deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an AE.

For an event to be a TEAE, it must meet one of the following conditions:

- Begins on Study Day 1, during or after administration of study drug.
- Begins after Study Day 1.

- Begins before Study Day 1 and worsens in severity during or after the Study Day 1 administration of study drug.

AEs with unknown onset dates or unknown end dates will be counted as TEAEs unless the event resolves before Study Day 1.

AEs will be coded using MedDRA version 19.1. Only TEAEs will be presented in AE tables, according to the SOC and PT. Any AEs that occur and resolve prior to Study Day 1 or are ongoing but do not worsen on or after Study Day 1 will be considered pretreatment AEs and will appear in the AE listing but not in TEAE tables.

10.1.1. Incidence of Treatment Emergent Adverse Events

The incidence of TEAEs table will include only 1 occurrence of a PT per subject. If a subject reports the same PT multiple times, then that PT will only be incremented by 1 since subject counts will be presented. As with the PT, if a subject reports multiple TEAEs within the same SOC, then that SOC will only be incremented by 1 since subject counts will be presented. For tables showing incidence by SOC and PT, SOCs will be sorted by the internationally agreed order and PTs will be sorted within SOC in descending order of incidence in the total column. For tables showing incidence by PT only, the PTs will be sorted in descending order of incidence in the total column.

An overall summary of TEAEs will be presented, and will include the following:

- Number of TEAEs.
- Number of subjects with at least 1 TEAE.
- Number of subjects with at least 1 possibly related TEAE.
- Number of subjects with at least 1 severe TEAE.
- Number of subjects with at least 1 TEAE leading to study withdrawal.
- Number of subjects with at least 1 ORAE.
- Number of subjects with at least 1 local inflammatory TEAE.
- Number of subjects with at least 1 potential LAST-related TEAE.
- Number of SAEs.
- Number of subjects with at least 1 SAE.
- Number of subjects with at least 1 possibly related SAE.
- Number of subjects with fatal TEAEs.

The incidence of all TEAEs will be presented by SOC and PT and separately by PT only.

10.1.2. Relationship of Adverse Events to Investigational Drug

The incidence of possibly related TEAEs will be presented in a table by SOC and PT. TEAEs that are missing relationship will be considered “Possibly Related” for the purpose of this incidence table but will be presented in the data listing with a missing relationship.

10.1.3. Severity of Adverse Event

The incidence of severe TEAEs will be presented in a table by SOC and PT. TEAEs that are missing severity will be considered "severe" for the purpose of this incidence table but will be presented in the data listing with a missing severity.

10.1.4. Serious Adverse Events

The seriousness of a TEAE should be assessed by the Investigator independently from the severity of the TEAE. An SAE is an AE occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing inpatient hospitalization, results in persistent or significant disability/incapacity, or is a congenital abnormality/birth defect.

Important medical events that may not be immediately life-threatening or result in death, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed above.

SAEs will be presented in a listing.

10.1.5. Adverse Events Leading to Study Withdrawal

All TEAEs reported with "Withdrawal from Study" checked on the eCRF will be presented in a listing.

10.1.6. Opioid-related Adverse Events

Incidence of TEAEs that are potentially opioid-related, regardless of whether a subject actually received an opioid medication, will be presented by PT. Prespecified PTs that may be opioid-related include the following:

- Nausea
- Vomiting
- Constipation
- Pruritus
- Pruritus generalised
- Somnolence
- Respiratory depression
- Urinary retention

Incidence of ORAEs will be presented separately as follows:

- Incidence of ORAEs.
- Incidence of ORAEs through the 72-hour postoperative observation period.

10.1.7. Local Inflammatory Adverse Events

To enable a broad and comprehensive analysis of TEAEs potentially related to adverse effects on wound healing, local inflammatory TEAEs will be reviewed by searching the safety database using a custom list of PTs created by Heron (Table 1).

Table 1. Local Inflammatory Adverse Events by System Organ Class and Preferred Term

• Blister • Blood blister • Cellulitis • Erythema[a] • Impaired healing • Incision site cellulitis • Incision site complication • Incision site erythema	• Incision site haemorrhage • Incision site infection • Incision site oedema • Incision site rash • Incision site swelling • Incision site vesicles • Infection • Postoperative wound complication	• Postoperative wound infection • Post procedural cellulitis • Purulent discharge • Wound complication • Wound dehiscence • Wound infection • Wound secretion

[a] The Preferred Term of erythema was included in addition to incision site erythema for the most comprehensive review.

Incidence of local inflammatory TEAEs will be presented in a table by PT.

10.1.8. Potential Local Anesthetic Systemic Toxicity (LAST) related Adverse Events

The symptoms that are potentially related to LAST will be reviewed by searching the clinical database using a custom list of PTs created by Heron (Table 2).

Table 2. Potential LAST-Related Adverse Events by System Organ Class and Preferred Term

• Arrhythmia (any preferred term with the string of "Arrhythmia") • Bradycardia (any preferred term with the string of "Bradycardia") • Cardiac arrest • Dizziness • Dysgeusia	• Hypotension • Muscle twitching • Paraesthesia • Paraesthesia oral • Respiratory arrest	• Seizure • Tinnitus • Tremor • Vision blurred • Visual impairment

Incidence of potential LAST-related TEAEs will be presented in a table by PT.

10.1.9. Death

Any subject deaths during this study will be collected and presented in a listing. The information that is presented will include date of death, days on study, cause of death, and relationship of death to study drug.

10.2. Local Anesthetic Systemic Toxicity Assessment

A LAST assessment questionnaire will be provided on a regular basis to monitor for early neurologic and cardiac signs and symptoms potentially associated with LAST. A summary of LAST assessment results will be produced, showing the number and percentage of subjects with any sign of LAST symptom with breakdown of each symptom for overall and by each visit. LAST assessment results will also be listed.

10.3. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory (hematology and serum chemistry) or locally (pregnancy test and drug screen). All summaries of central laboratory data will be based on the standard international (SI) units provided by the central lab. Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together.

Summary tables for hematology and chemistry including actual values and change from Baseline values will be presented for clinical laboratory tests with numeric values. These tables will include each visit (Baseline, Hour 24 [hematology only], Hour 72, and Day 10), highest postdose value, lowest postdose value, and last postdose value.

Laboratory data will also be summarized using shift tables where appropriate. Each subject's hematology and serum chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory.

Laboratory data collected at unscheduled visits will be included in listings and will contribute to tables of shifts from Baseline and in tables showing changes from Baseline to highest value, lowest value, and last value. Unscheduled laboratory results will not be windowed for the purposes of assigning a nominal visit.

Listings of laboratory values will include flags for values outside the central laboratory normal ranges that indicate how far out of the normal range an abnormal value is. For example, a value that is ≥ 3 times the upper limit of normal (ULN) but below 4 times the upper limit of normal will have a "3H" flag. Flag multipliers will show values that are 1, 2, 3, 4, 5, and 10 times relative to the ULN if high. Values that are below the lower limit of normal (LLN) will be flagged simply with "L".

Listings of abnormal values for hematology and chemistry will be presented separately in addition to listings of all laboratory values.

10.4. Hematology

The following laboratory tests will be included in hematology summary tables: hematocrit, hemoglobin, mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, and total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

10.4.1. Blood Chemistry

The following laboratory tests will be included in the blood chemistry summary tables: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate

aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, direct bilirubin, gamma-glutamyltransferase (GGT), glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.

Associated laboratory parameters such as hepatic profile (ALT, albumin, ALP, AST, direct bilirubin, GGT, total bilirubin), electrolytes (bicarbonate, calcium, chloride, magnesium, phosphorus, potassium, sodium), renal profile (BUN, creatinine), and other (glucose, LDH, total protein, uric acid) will be sorted/grouped together in table and listing presentations.

Evaluation of drug-induced serious hepatotoxicity (eDISH) scatterplots of the highest postdose ALT vs. total bilirubin observed at the same draw as the high ALT value, and of the highest postdose AST vs. total bilirubin observed at the same draw as the high AST value, will be produced.

The incidence of subjects with clinically relevant abnormalities in liver function tests will be summarized at each visit for each treatment group for the following categories. Subjects with clinical relevant abnormalities in Liver Function Tests will be presented in data listing as well.

- ALT or AST:
  - $> 1 \times$ ULN
  - $\geq 2 \times$ ULN
  - $\geq 3 \times$ ULN
  - $\geq 4 \times$ ULN
  - $\geq 5 \times$ ULN
- Total bilirubin $\geq 2 \times$ ULN
- ALP:
  - $\geq 1.5 \times$ ULN
  - $\geq 2 \times$ ULN
- ALT $\geq 3 \times$ ULN and AST $\geq 3 \times$ ULN
- ALT ≥ 3 x ULN and total bilirubin $\geq 2 \times$ ULN
- AST ≥ 3 x ULN and total bilirubin $\geq 2 \times$ ULN
- Potential Hy's Law: (ALT or AST $\geq 3 \times$ ULN) and ALP $< 2 \times$ ULN and total bilirubin $\geq 2 \times$ ULN

10.4.2. Urine Pregnancy Test and Urine Drug Screen

Urine pregnancy test results (women of childbearing potential) and urine drug screen results will be listed.

10.5. Vital Sign Measurements

Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate/pulse (HR), body temperature, and respiration rate will be collected at screening, on Day 1 before surgery, and post-treatment at 30 minutes and at 1, 1.5, 2, 4, 8, 12, 18, 24, 36, 48, 60, and 72 hours, and on Day 10.

Summary tables including actual values and changes from Baseline will be presented for vital signs.

The number and percentage of subjects with clinically relevant abnormalities will be presented using data from any postdose visit (including unscheduled visits). Subjects with clinical relevant abnormalities in vital signs will be presented in data listing as well. The criteria for clinically relevant abnormalities are shown in Table 3.

Table 3. Clinically Relevant Vital Signs Abnormalities

Vital Sign	Low	High
HR	≤50 bpm and ≥15 bpm decrease from Baseline	≥120 bpm and ≥15 bpm increase from Baseline
SBP	≤90 mmHg and ≥20 mmHg decrease from Baseline	≥160 mmHg and ≥20 mmHg increase from Baseline
DBP	≤50 mmHg and ≥15 mmHg decrease from Baseline	≥100 mmHg and ≥15 mmHg increase from Baseline

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

10.6. Electrocardiogram

12-lead ECG (triplicate) is performed at screening only. ECG results will be listed.

10.7. Physical Examination

Physical examination is performed at Screening and 72 hours. Physical examination data will be listed only.

10.8. Wound Healing Assessment

Surgical wound healing will be assessed using a wound healing assessment questionnaire at 72 hours and on Day 10 and Day 28. A summary of wound healing assessment results will be produced, showing the number and percentage of subjects with abnormal wound healing symptoms at each visit. Wound healing assessment results will also be listed.

11. INTERIM ANALYSIS

11.1. Interim Analysis

No formal interim analyses are planned.

11.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will not be involved with the conduct of this study. The Sponsor will review tables and listings of accumulating data approximately monthly to check enrollment, adherence to follow-up schedule, and ongoing safety results.

APPENDIX 1. IMPUTATION OF PARTIAL AND MISSING DATES

Incomplete Dates of Adverse Event start

All AE onset dates must be entered on the eCRF as complete dates. In the rare case that all or part of an AE onset date is missing but an AE resolution date is present and after study drug administration then the AE onset date will be imputed as follows:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Date of SDA
year = year of SDA	Missing	Nonmissing	Date of SDA
year = year of SDA	Missing	Missing	Set month and day to those of SDA
year < year of SDA	Missing	Nonmissing	set month to December
year < year of SDA	Missing	Missing	set month and day to December 31
year > year of SDA	Missing	Nonmissing	set month to January
year > year of SDA	Missing	Missing	set month and day to January 1
year = year of SDA	Month = month of SDA	Missing	Set day as day of SDA
year = year of SDA	Month < month of SDA	Missing	Set day as last day of onset month
year = year of SDA	Month > month of SDA	Missing	Set day as first day of onset month
year < year of SDA	Nonmissing	Missing	Set day as last day of onset month
year > year of SDA	Nonmissing	Missing	Set day as first day of onset month

SDA = study drug administration.

If AE resolution date is present and prior to study drug administration, no need to impute incomplete AE start date, as the AE is not treatment emergent and the event should be in the medical history.

Concomitant Medications

- If year and month are present and day is missing then set day to first day of month for start date, and set day to last day of month for end date.
- If year and day are present and month is missing then set month to January for start date, and set month to December for end date.
- If year is present and month and day are missing then set month and day to January 1 for start date, and set month and day to December 31 for end date.
- Completely missing dates will not be imputed.

If start date is completely missing and end date is not prior to study drug administration, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are completely missing will be classified as concomitant.

APPENDIX 2. DOCUMENT REVISION HISTORY

Version	Date	Notes/Revisions
1	20 September 2018	Initial version, based on protocol version 1 (20 August 2018)

Signature Page for VV-TMF-34588 v1.0

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