Document Type:	Statistical Analysis Plan
Official Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of Aprepitant Injectable Emulsion in Early Hospitalized Adult Patients With COVID-19
NCT Number:	NCT04470622
Document Date:	22-Jun-2021

STUDY HTX-019-202

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of Aprepitant Injectable Emulsion in Early Hospitalized Adult Patients With COVID-19

22 June 2021

Statistical Analysis Plan

Version 1.0

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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 AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
BID	Twice daily
CFR	Code of Federal regulations
CINV	Chemotherapy-induced nausea and vomiting
COVID-19	Coronavirus disease
CRP	C-reactive protein
CT	Computed tomography
CYP	Cytochrome P450
DBP	Diastolic blood pressure
EC	Ethics committee
ECG	Electrocardiogram/electrocardiographic
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IL	Interleukin
INR	International Normalized Ratio
IRC	Interim review committee
ITT	Intent-to-Treat
IV	Intravenous(ly)
IVIg	Intravenous immunoglobulin
JAK	Janus kinase
KM	Kaplan-Meier
NIAID	National Institute of Allergy and Infectious Diseases
NK_1	Neurokinin-1
PK	Pharmacokinetic(s)

Abbreviation	Definition
PONV	Postoperative nausea and vomiting
PSRMC	Product Safety and Risk Management Committee
PT	Preferred term
QD	Once daily
qPCR	Quantitative polymerase chain reaction
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Severe adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SOC	System Organ Class
SP	Substance P
SpO_2	Oxygen saturation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood cell

Note: Abbreviations defined in the text but not used again in the text are not included in this List of Abbreviations. Abbreviations used only in tables or figures are also excluded from this List of Abbreviations; they are defined in the table or figure footnotes.

1. ADMINISTRATIVE STRUCTURE

1.1. Sponsor and Oversight

This study is being conducted under the sponsorship of Heron Therapeutics, Inc. (Heron). Data management (DM) will be performed by Heron and the statistical analyses will be performed under contract with [redacted], with oversight from Heron. [redacted].

1.2. Data Quality Assurance

The Clinical Operations and Biostatistics departments will collaborate 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 and analysis of efficacy and safety data collected in this Phase 2 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 technical and 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). Methods described in the SAP supersede any methods or analyses described in the study protocol.

3. OBJECTIVES

Primary Objective:

- To assess the effect of aprepitant injectable emulsion on the clinical status of coronavirus disease (COVID-19) in hospitalized patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Secondary Objectives:

- To evaluate the safety and tolerability of daily administration of aprepitant injectable emulsion in hospitalized patients with COVID-19.
- To assess the pharmacokinetics (PK) of aprepitant following daily dosing of aprepitant injectable emulsion to hospitalized patients with COVID-19.
- To evaluate the impact of aprepitant injectable emulsion on the inflammatory response mediated by cytokines.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 2 randomized, double-blind, placebo-controlled study in which approximately 100 subjects will receive their randomized treatment in addition to Investigator standard of care for the treatment of COVID-19.

Subjects will be screened less than 48 hours of hospitalization to determine eligibility to enter the study. Eligible subjects will be randomized in a 1:1 ratio in a parallel manner to receive aprepitant injectable emulsion or saline placebo administered once daily (QD) as a 2-minute IV injection for 14 days.

Standard of care will be at the Investigator's discretion generally following the COVID-19 treatment protocol at the institution.

Subjects will undergo PK, safety, and efficacy assessments. Safety assessments will include adverse events (AEs), clinical laboratory values (hematology and serum chemistry), vital signs, and electrocardiograms (ECGs). Detailed information regarding laboratory assessments, including sample collection procedures for PK and cytokines, will be provided in the laboratory manual. Efficacy assessments will include respiratory status, cytokine panel, SARS-CoV-2 viral load, COVID-19 symptoms, and the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale of clinical status. Subjects will be followed until death or Day 56, whichever occurs first. If discharged, the site will still contact subjects for efficacy and safety follow-up until Day 56.

An interim review committee (IRC) will review the unblinded PK, safety, and efficacy data during the conduct of the study and may interrupt or stop enrollment, or modify the protocol to enhance subject safety without adapting the study design.

4.2. Assessments

Safety and efficacy assessments will be performed.

Safety assessments will include the following:

- AEs, serious adverse events (SAEs), and AEs of special interest (AESIs).

- Clinical laboratory values (hematology and serum chemistry).
- Vital signs, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), resting heart rate (HR), and temperature.
- Electrocardiograms (ECGs).

Information from standard-of-care diagnostic and safety laboratory tests will be provided to the Sponsor and recorded in the electronic case report form (eCRF).

Efficacy assessments will include:

- The NIAID 8-point ordinal scale of clinical status:
    1. Death.
    2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).
    3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices.
    4. Hospitalized, requiring low-flow supplemental oxygen.
    5. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19–related or otherwise).
    6. Hospitalized, not requiring supplemental oxygen, no longer requiring ongoing medical care.
    7. Not hospitalized, limitation on activities and/or requiring home oxygen.
    8. Not hospitalized, no limitations on activities.
- Respiratory status:
    - Respiratory rate.
    - Oxygen supplementation.
        - Room air.
        - Nasal cannula.
        - Face mask.
        - Noninvasive ventilation or high-flow oxygen devices.
        - Mechanical ventilation.
        - ECMO.
    - Oxygenation: (oxygen saturation (SpO_2) at rest or partial pressure of oxygen [PaO_2]).
    - Chest X-ray or computed tomography(CT) scan findings (if available).
- Cytokine panel.

- SARS-CoV-2 viral load by quantitative PCR (qPCR).
- COVID-19 symptom assessment (4-point scale, 0=none, 1=mild, 2=moderate, 3=severe):
  - Cough.
  - Fever.
  - Sore throat.
  - Loss of taste and/or loss of smell.
  - Malaise/fatigue.
  - Headaches.
  - Myalgia.
  - Gastrointestinal symptoms.
  - Shortness of breath on exertion.
  - Shortness of breath at rest.

4.3. Study Endpoints

4.3.1. Primary Endpoint

- Proportion of subjects alive and discharged from the hospital at Day 14.

4.3.2. Secondary Endpoints

- Time to death or respiratory failure, whichever comes first. Respiratory failure is defined as any of the following:
  - Endotracheal intubation and mechanical ventilation.
  - Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min).
  - Noninvasive positive pressure ventilation.
  - ECMO.
- Time to discharge from hospital.
- Incidence of treatment-emergent adverse events (TEAEs).
- Change from Baseline in IL-6 at each specified timepoint.

[redacted]

[redacted]

5. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be presented using descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Descriptive statistics on efficacy measures will also include the standard error (SE). Categorical data will be summarized by the frequency 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 one 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, and median will have one decimal place and SD and SE will have 2 decimal places.
- If the original value has 1 decimal place: mean, and median 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, 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.

All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001, it will be reported as "<0.0001".

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 efficacy and 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.

5.1. Sample Size

The sample size was selected empirically without formal statistical hypotheses or assumptions.

5.2. Randomization, Stratification, and Blinding

Subjects who meet the Screening eligibility criteria will be randomized in a 1:1 ratio in a parallel manner to receive aprepitant injectable emulsion 130 mg or saline placebo administered once daily as a 2-minute IV injection for 14 days. Subjects will be randomized using a centralized computer-generated blocked randomization algorithm and assigned using an interactive response technology (IRT) system. All randomization information will be kept in a secure location accessible only by the randomization personnel, the assigned Pharmacist(s) and his/her verifier, and the unblinded clinical monitor. No subject may receive study drug prior to randomization.

This study will use a double-blind design. Subjects, Investigators, and site staff will be blinded to treatment assignment until after database lock. The site's pharmacy will not be blinded to the treatment assignments because aprepitant injectable emulsion is supplied as an opaque, off-white to amber emulsion, whereas saline placebo is not. The pharmacy will prepare study drug for administration and provide a covering for the syringe and infusion line to blind the contents.

The study blind should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the study drug he/she received.

5.3. Analysis Populations

Intent-to-Treat (ITT) Population: All subjects who are randomized will be included in the ITT Population. This population will be used as the primary analysis population for all efficacy endpoints. The randomized treatment assignment will be used for analysis in this population.

Safety Population: All subjects who receive study drug will be included in the Safety Population. 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. Layout of Summaries

Table 1 displays the planned treatment groups being studied.

Table 1. Layout of Treatment Groups

Study Phase	Treatment Group	Planned Sample Size
2	Aprepitant injectable emulsion 130 mg/18 mL	50
	Saline placebo	50

Unless otherwise specified, efficacy and safety analyses will be summarized by treatment group (Table 2).

Table 2. Layout of Summary

Aprepitant 130 mg (18 mL)	Saline placebo

5.5. Other Important Considerations

5.5.1. 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.

5.5.2. 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:

$P_t = 100*(C_t/M_B)$.

5.5.3. Study Day Calculation for Reporting Purposes

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

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

5.5.4. Visit Windows

Unless otherwise specified, analyses and summaries by visit will use nominal visits. No programmatically defined visit windows will be applied to map unscheduled or early termination visits to nominal scheduled visits.

5.5.5. Handling of Missing and Partial Data

Methods for missing data will be described for each efficacy endpoint in Section 9.

No imputation of missing safety data will be performed except in the case of partial AE and concomitant medication onset dates (Appendix A).

5.5.6. Study-Wise Type I Error Control

Unless otherwise specified, all statistical hypothesis testing will be 2-sided using $\alpha = 0.05$.

6. SUBJECT DISPOSITION

The number and percentage of subjects in each analysis population will be summarized. Subject disposition, including the number of subjects enrolled (signed the Informed Consent Form), subjects who failed screening with reason for screening failure, subjects in the ITT Population, subjects in the Safety Population, subjects completing scheduled treatment prior to discharge, primary reason for discontinuation from study drug, subjects completing the study (completing through Day 56 Visit or death), and subjects not completing the study by reason for withdrawal will be summarized.

7. DEMOGRAPHICS, CHARACTERISTICS, AND MEDICAL HISTORY

7.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized for the ITT Population, and the Safety Population (if different from the ITT Population) and will include age, age category, sex, race, ethnicity, height, weight, and body mass index (BMI). Chest imaging results will also be summarized if available. Baseline height and weight measurements will be conducted at Screening and BMI will be derived based on BMI = (Weight in kilograms [kg])/(height in meters [m])^2. 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. Demographics will also be presented for all subjects enrolled who fail screening.

7.2. Medical History

Medical history comorbidities will be summarized based on confirmation of comorbidity for each comorbidity by frequency and percentage of subjects for the safety population.

7.3. Protocol Deviations

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

- Informed Consent Form procedures.
- Eligibility criteria.
- Prohibited concomitant medication/therapy.
- Study procedures not done.
- Safety reporting.
- Study drug dosing/administration.
- Out of window procedure.
- Other.

Classification of deviations as major protocol deviations will be decided on a case-by-case basis. All protocol deviations and major protocol deviations will be presented in a summary table by protocol deviation category for the ITT Population and the Safety Population (if different from the ITT Population). All protocol deviations will also be listed.

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 Global B3 Format (WHODrug Global B3), March 2020.

Prior and concomitant medications will be summarized separately by drug class and generic drug name. 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. Study Treatment

Eligible subjects will be administered aprepitant injectable emulsion 130 mg (18 mL) or saline placebo (18 mL) once daily as a 2-minute IV injection.

Drug compliance will be calculated for each subject by taking into account whether a subject takes all doses of randomized drug as planned. The overall investigational drug compliance rate will be calculated as (the total number of doses administered/the total number of doses planned) *100. The number of planned doses is defined as the number of days through discharge (-1 day) or Day 14, whichever is less. Basic descriptive statistics will be summarized for drug compliance. In addition, the following summaries will be provided:

- Total number of doses administered (n, mean, med, min, max).
- Total number of doses planned (n, mean, med, min, max).
- Total Number of full doses received (n, mean, med, min, max).
- Subjects with full dose not administered by reason (n (%)).
- Subjects with doses prolonged or interrupted by reason (n (%)).

9. EFFICACY ANALYSIS

For efficacy analyses, the date of randomization is considered as Day 1.

9.1. Primary Endpoint

9.1.1. Proportion of Subjects Alive and Discharged From the Hospital at Day 14

The proportion of subjects alive and discharged from the hospital at Day 14 will be calculated as the number of subjects who are documented as being discharged alive from the

hospital, and have not subsequently died, on or before study Day 14, with day of randomization equal to Day 1, divided by the number of subjects randomized. The numerator is the number of subjects who are discharged alive, and have not subsequently died, on or before study Day 14 and who have a non-missing discharge date that is less than or equal to the date of randomization + 13 days.

Subjects who are rehospitalized due to COVID-19 or COVID-19 sequelae and remain in hospital before Day 14 will not be considered as being discharged at Day 14. For example, if a subject was initially discharged on Day 8 and rehospitalized on Day 10 and was discharged a second time on Day 20, this subject is not considered to have met the primary endpoint criterion of discharged at Day 14. Subjects who are rehospitalized before Day 14 due to non-COVID-19 reasons will retain the original discharge date and will be considered to have met the primary endpoint criterion of discharged at Day 14.

Subjects who are transferred from one hospital to another hospital will be considered as having a single uninterrupted hospitalization. The date of discharge will be from the second hospital.

Fisher's exact test will be used to compare differences in proportions across treatment arms. Summaries will be expressed as the frequency and percentage of subjects meeting the criteria of alive and discharged from hospital at Day 14 by treatment arm. Differences in proportions across treatment arms along with corresponding exact 95% CIs will also be presented.

9.2. Secondary Endpoints

9.2.1. Time to Death or Respiratory Failure

Time to death or respiratory failure will be analyzed using Kaplan-Meier (KM) methods. KM plots will be presented by treatment arm and the log-rank test will be used to make comparisons between treatment arms. Median time to death or respiratory failure (if it can be estimated), 95% CIs, and p-values will be reported. Events will be defined as either time when the subject first meets any of the 4 criteria of respiratory failure or dies, whichever comes first. Subjects who never meet the criteria for respiratory failure and who are alive at the end of the study will be censored at the time of last assessment of respiratory status. Follow-up time starts when subjects are randomized.

Respiratory failure is defined as:

- Having an oxygen supplementation status of "Oxygen delivered by high-flow nasal cannula," "Noninvasive positive pressure ventilation", "ECMO", or "Endotracheal intubation and mechanical ventilation".

For subjects who have an event (respiratory failure or death), the time to event will be calculated as:

- Date of first occurrence of event – date of randomization + 1.

For subjects who are censored, the time to event will be calculated as:

- Date of last assessment of respiratory status – date of randomization + 1.

9.2.2. Time to Discharge From Hospital

The analysis of time to discharge from hospital will be based on KM methods. KM plots will be presented by treatment arm and the log-rank test will be used to make comparisons between treatment arms. Number of events and number at risk will be presented in KM plots. Median time to discharge, 95% CIs, and p-values will be summarized. Subjects who are not discharged and are alive at the end of the study will be censored at the time of last contact. Follow-up time starts when subjects are randomized.

Subjects who are rehospitalized due to COVID-19 or COVID-19 sequelae and remained in hospital will not be considered as being discharged. For example, if a subject was initially discharged on Day 8 and rehospitalized on Day 10 due to COVID-19 or COVID-19 sequelae and stays in the hospital, this subject is not considered to have a discharge event on Day 8. However, if this subject is discharged a second time on Day 20, the subject's discharge date will be updated to Day 20. However, subjects who are rehospitalized due to non-COVID-19 reasons will retain their original discharge date.

Subjects who are transferred from one hospital to another hospital will be considered as having a single uninterrupted hospitalization. The date of discharge will be from the second hospital.

Deaths that occur prior to being discharged alive from the hospital will be censored at the longest observed follow-up time across the 2 arms in the analysis. Censoring time for deaths should be set to the longest follow-up time among all subjects. The follow-up time includes the following 3 types:

- For subjects who are discharged alive, set followup time as from date of randomization to date of discharge.
- For subjects alive but not discharged, set followup time as from date of randomization to the end of study date, if available, or date of their last observation (including scheduled/unscheduled visits as well as log forms, such as AE/CM), if the end of study date is not available.
- For subjects who died prior to being discharged, set followup time as from date of randomization to date of their death.

For subjects who are discharged alive from the hospital, the time to discharge will be calculated as:

- Date of discharge – date of randomization + 1.

For subjects who are censored, the time to event will be calculated as:

- Date of censoring – date of randomization + 1.

9.2.3. Change From Baseline in Interleukin 6 at Each Specified Timepoint

Individual and group changes from Baseline in interleukin (IL)-6 will be assessed across timepoints by treatment arm using both graphical and/or tabular presentations. Change from Baseline and percentage change from Baseline will be presented in graphical profiles across timepoints in spaghetti plots. Tabular summaries of change from Baseline and percentage change from Baseline will include descriptive statistics by post-Baseline timepoints. Tabular

presentations will include summary statistics (mean, median, min, max) presented at each scheduled timepoint, for minimum and maximum post-Baseline values, and for last post-Baseline value. Analysis will be based on observed data.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. SAFETY ANALYSIS

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

For safety analyses, the study day of start of study drug administration is Study Day 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 1 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 it is known that the event resolves before study drug administration on Study Day 1.

AEs will be coded using MedDRA version 23.0. 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. Secondary Endpoint

10.1.1.1. 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 for aprepitant. For tables showing incidence by PT only, the PTs will be sorted in descending order of incidence for aprepitant.

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 TEAE possibly related to study drug.
- Number of subjects with at least 1 severe TEAE:
    - Number of subjects with at least 1 severe TEAE by severity.

- Number of subjects with at least 1 TEAE leading to discontinuation of study drug.
- Number of subjects with at least 1 TEAE leading to study withdrawal.
- Number of subjects with TEAEs that are AESIs.
- Number of treatment-emergent SAEs (TESAEs):
  - Number of subjects with at least 1 TESAE by severity.
- Number of subjects with at least 1 TESAE.
- Number of subjects with fatal TEAEs.
- Number of subjects with at least 1 TESAE possibly related to study drug.

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

10.1.1.1.1. Relationship of Adverse Events to Study Drug

The incidence of TEAEs possibly related to study drug will be presented in a table by SOC and PT.

10.1.1.1.2. Severity of Adverse Event

The incidence of severe TEAEs will be presented in a table by SOC and PT.

10.1.1.1.3. 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.

Incidence of TESAEs will be presented in a table by SOC and PT. All SAEs will also be listed separately.

Incidence of TESAEs related to study drug will also be summarized by SOC and PT.

10.1.1.1.4. 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.

10.1.1.1.5. Adverse Events of Special Interest

Incidence of AESIs will be presented by PT. Prespecified AEs that may be AESIs include the following:

- Anaphylaxis.

- QT prolongation (>500 ms).

AESIs will be ascertained from the Adverse Event Details form on the eCRF. If "Yes" was selected for "Was this an Anaphylaxis event?" or "Is this event a QT prolongation (QTcF) greater than 500 ms?" the AE would be considered an AESI.

10.1.1.1.6. Adverse Events Leading to Study Withdrawal

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

10.1.1.1.7. Adverse Events Leading to Discontinuation of Study drug

All TEAEs reported with "Drug withdrawn" checked on the eCRF will be presented in a listing. The incidence of TEAEs leading to discontinuation of study drug will be presented in a table by SOC and PT.

10.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a local laboratory (hematology, serum chemistry, and urine pregnancy test) and all summaries of local laboratory data will be based on the standard international (SI) units provided by the local lab. Sites will record the worst hematology and serum chemistry results from a daily 24-hour period. 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 at each scheduled visit (Screening, Day 1, Derived Baseline, at each day from Day 2 through Day 14, Day 21, Day 28, Day 35, Day 42, Day 49, Day 56, at Discharge) the highest postdose value, lowest postdose value, and the 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 local laboratory. Shift tables will be produced showing the frequency of shifts from baseline to the minimum and maximum post-Baseline value, last post-Baseline value, and by visit. Laboratory parameters will also be summarized by visit.

Laboratory data collected at unscheduled and early termination (if applicable) 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 or early termination 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 local laboratory normal ranges that indicate how far out of the normal range a value is. For example, a value that is ≥3 ×the upper limit of normal (ULN) but below 4 × ULN 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 out-of-range values for hematology and chemistry will be presented separately in addition to listings of all laboratory values.

10.2.1. Hematology

The following laboratory tests will be included in hematology summary tables: hematocrit, hemoglobin, platelet count, absolute neutrophils, absolute lymphocytes, and total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

In addition, change from Baseline in WBC count and lymphocytes will be analyzed using spaghetti plots showing individual subject data over time. Also, the number and percentage of subjects with a maximum lymphocyte count less than 0.82×10^3/L and greater than or equal to 0.82×10^3/L will be tabulated by treatment group. The maximum value for each subject will be based on all samples taken after the first dose of study drug.

10.2.2. Serum Chemistry

The following laboratory tests will be included in the serum chemistry summary tables: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine, glucose, total bilirubin, sodium, potassium, bicarbonate, total protein, albumin.

Evaluation of drug-induced serious hepatotoxicity (eDISH) scatterplots of the highest postdose ALT within the 24 hour period vs. total bilirubin observed during the same 24 hour period as the highest postdose ALT value, and of the highest postdose AST within the 24 hour period vs. total bilirubin observed during the same 24 hour period as the highest postdose AST value, will be produced.

The incidence of subjects with out-of-range liver function values will be summarized at each visit for the following categories. Subjects with out-of-range liver function values will be presented in data listing as well.

- ALT or AST:
  - >1 × ULN.
  - ≥2 × ULN.
  - ≥3 × ULN.
  - ≥4 × ULN.
  - ≥5 × ULN.
- Total bilirubin ≥2 × ULN.
- ALP:
  - ≥1.5 × ULN.
  - ≥2 × ULN.
- ALT ≥3 × ULN and AST ≥3 × ULN (from same 24 hour period).
- ALT ≥3 × ULN and total bilirubin ≥2 × ULN (from same 24 hour period).
- AST ≥3 × ULN and total bilirubin ≥2 × ULN (from same 24 hour period).

- Potential Hy's Law: (ALT or AST ≥3 × ULN) and ALP <2 × ULN and total bilirubin ≥2 × ULN (from same 24 hour period).

10.2.3. Other Laboratory Parameters

Other standard-of-care central laboratory analytes that will be summarized include:

- D-dimer.
- Troponin.
- Brain natriuretic peptide (BNP).
- Erythrocyte sedimentation rate (ESR).
- Creatine kinase (CK).

Standard-of-care laboratory tests, if available, are collected at Screening, Baseline/Day 1, at each day from Day 2 through Day 14, Day 21, Day 28, Day 35, Day 42, Day 49, Day 56, at Discharge, and at Early Termination (if applicable).

Summaries of standard-of-care laboratory tests will be similar to the analyses described in Section 10.2.

10.3. Vital Sign Measurements

Vital signs including SBP, DBP, resting HR, and body temperature will be collected at Screening, Day 1, Baseline, each day from Day 2 to Day 14, Day 21, Day 28, Day 35, Day 42, Day 49, Day 56, discharge, and early termination (if applicable). Vital sign measurements will be documented by recording the minimum and maximum values from the previous 24 hours for each scheduled visit. The minimum and maximum values from the previous 24 hours will be presented in separate summaries. Summaires of change from Baseline based on maximum and minimum value from previous 24 hours will also be presented.

The number and percentage of subjects with out-of-range vital sign values will be presented using data from any postdose visit (including unscheduled visits). Subjects with out-of-range vital sign values will be presented in a data listing as well. The criteria for out-of-range vital sign values are shown in Table 3.

Table 3: Out-of-Range Vital Signs Values

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

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

10.4. Electrocardiogram

The 12-lead ECGs will be performed at Screening and at each day from Day 2 to Day 14, Day 21, Day 28, Day 35, Day 42, Day 49, and Day 56. ECG parameters include HR (beats/min), PR interval (ms), RR interval (ms), QRS interval (ms), QT interval (ms), and QT interval corrected using Fridericia's formula (QTcF) (ms). Overall interpretations of ECG results are also included.

QTcF will be calculated and used in tabular summaries, according to,

$$QTcF = QT \text{ interval} / (RR \text{ interval})^{1/3}.$$

Site reported ECG parameters and calculated QTcF will be provided in listings.

ECG assessments will be performed in triplicate only at Screening, where the mean value of the observed triplicates will be used for each ECG parameter. Only 12-lead ECGs, if performed, will be summarized. Summary statistics of ECG parameters and change from Baseline in ECG parameters will be presented using descriptive statistics at each scheduled visit by treatment group. Shift from Baseline of overall ECG interpretation at each postoperative timepoint will also be provided.

The frequency and percentage of subjects with the following clinically relevant abnormalities will be presented in summary tables and data listings at each timepoint:

- QTcF values >450 ms, >480 ms, and >500 ms.
- Change from Baseline in QTcF values >30 ms and >60 ms.

Clinically relevant abnormalities will be summarized overall at any timepoint and by timepoint. Reasons for why 12-lead ECGs were not performed will be summarized using frequency and percentages.

10.5. Physical Examination

A symptom-directed physical examination will be performed at Screening and when appropriate to evaluate an AE. Physical examination data will only be listed.

11. INTERIM ANALYSIS

No formal interim analyses are planned. An IRC will review the summary-level unblinded PK, safety, and efficacy data during the conduct of the study and may interrupt or stop enrollment, or modify the protocol to enhance subject safety without adapting the study design. The IRC will be composed of Sponsor representatives from each of the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions, and an external expert in critical care medicine. The IRC will operate under a written, detailed IRC Charter.

11.1. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will not be involved with the conduct of this study. The internal IRC and Product Safety and Risk Management Committee (PSRMC) will monitor safety data on a periodic basis throughout the study, including regular review of AEs (including SAEs), laboratory results, and other safety assessments.

12. REFERENCES

Dong G, Qiu J, Wang D, Vandemeulebroecke M (2018). "The stratified win ratio." Journal of Biopharmaceutical Statistics **28**(4): 778-796.

APPENDIX A. 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

Abbreviation: 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 B. DOCUMENT REVISION HISTORY

Version	Date	Notes/Revisions
Version 1.0	22JUN2021	Version 1.0, based on protocol version 5 (11 December 2020)

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Approval Task	[redacted]tistics 23-Jun-2021 17:38:45 GMT+0000

Approval Task	[redacted] 23-Jun-2021 18:13:37 GMT+0000

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