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Official Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of Aprepitant Injectable Emulsion in Early Hospitalized Adult Patients With COVID-19
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CLINICAL STUDY PROTOCOL: HTX-019-202

Protocol Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of Aprepitant Injectable Emulsion in Early Hospitalized Adult Patients With COVID-19
Brief Title:	Aprepitant Injectable Emulsion in Patients With COVID-19 (GUARDS-1)
Test Product:	CINVANTI (aprepitant) injectable emulsion
Phase of Development:	2
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 USA 1-858-251-4400
Medical Monitor:	[redacted] MD [redacted]
Medical Project Leader:	[redacted] PhD, MD [redacted]

Protocol Version:	Version 5	11 December 2020
	Version 4	27 August 2020
	Version 3	22 June 2020
	Version 2	16 June 2020
	Version 1	01 June 2020

SPONSOR SIGNATURE

Protocol Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of Aprepitant Injectable Emulsion in Early Hospitalized Adult Patients With COVID-19
Protocol Number:	HTX-019-202

This protocol Version 5 has been reviewed and approved by the Sponsor.

The electronic signature is appended.

[redacted] MD
[redacted]
Heron Therapeutics, Inc.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-019-202

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

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. I will conduct the study as outlined herein.

I will provide copies of the protocol, the Investigator's Brochure, and all other information on the study drugs that are furnished to me by the Sponsor to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the test product and the conduct of the study.

I agree to keep records on all subject information (ie, medical records, source documents, case report forms, and informed consent), study drug shipment and return forms, and all other information collected during the study in accordance with local regulations and national Good Clinical Practice (GCP) regulations and guidelines.

Principal Investigator: _____

Address: _____

Signature: _____

Date (DD Month YYYY): _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	Heron Therapeutics, Inc.
NAME OF TEST PRODUCT:	Aprepitant injectable emulsion (HTX-019)
NAME OF ACTIVE INGREDIENT:	Aprepitant
PROTOCOL NUMBER:	HTX-019-202
PHASE OF DEVELOPMENT:	2

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

STUDY SITES: Approximately 10 sites in the United States (US).

STUDY OBJECTIVES:

Primary:

- 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:

- 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.

BACKGROUND AND RATIONALE FOR THE STUDY:

Aprepitant is a selective high-affinity antagonist of neurokinin-1 (NK_1) receptors. It has been extensively used for almost 20 years for the prevention of chemotherapy-induced nausea and vomiting and for 14 years for the prevention of postoperative nausea and vomiting.

The rationale for the investigation of aprepitant injectable emulsion in COVID-19 is the close association between the binding of substance P (SP) to NK_1 receptors and the resultant induction of inflammatory cytokines, such as interleukin [IL]-6, which are associated with the development of acute respiratory distress syndrome (ARDS). NK_1 receptors are expressed in human central airways, subpleural lung, and postcapillary venules in the upper and lower airways (O'Connor 2004; Quartara 1998). Stimulation of the NK_1 receptors in postcapillary venules leads to capillary leak with extravasation of plasma proteins (Quartara 1998). NK_1 receptors are also expressed on mast cells, neutrophils, eosinophils, monocytes/macrophages, dendritic cells, natural killer cells, B and T cells, microglia, and astrocytes (Mashaghi 2016; Suvas 2017). Expression of NK_1 receptors is markedly increased during infection, especially on lymphocytes and macrophages. Through the binding to NK_1 receptors, SP leads to the production of cytokines with proinflammatory (eg, IL-1), immunomodulatory (eg, IL-10), and chemotactic properties (eg, IL-8) (Mashaghi 2016) contributing to the cytokine storm. Exposure of a human bronchial epithelial cell line to SP resulted in release of IL-6, IL-8, and tumor necrosis factor alpha (TNF-α) (O'Connor 2004).

The role of SP and inflammatory cytokines (such as IL-6) on lung injury, including ARDS, was demonstrated in animal models and in humans (Bhatia 2004; Espiritu 1992; Mao 2016; Puneet 2005;

Sio 2010; Wong 2004). In patients with COVID-19, a significant association of increased concentrations of IL-6 with more severe disease, ARDS, the need for mechanical ventilation, and death was observed (Coomes 2020; Herold 2020).

The antagonism of NK_1 receptors with aprepitant is expected to prevent the cytokine release mediated by the binding of SP to NK_1 receptors. Reduced concentrations of cytokines following treatment with aprepitant were observed in clinical studies in adults infected with HIV (Spitsin 2017; Tebas 2015). It is hypothesized that early decrease of cytokine release should limit cytokine overactivation/dysregulation potentially preventing or reducing the severity of ARDS. Heron hypothesizes that aprepitant injectable emulsion would best be positioned to decrease the dysregulation/overactivation of cytokines/chemokines elicited by SP early in the disease process. Once the lungs are overwhelmed with the inflammatory response, other mechanisms may increase the dysregulation, making NK_1 receptor antagonist treatment less effective. Therefore, it would be proposed to start treatment with an NK_1 receptor antagonist before patients require mechanical ventilation.

In addition, based on published literature, aprepitant may provide direct antiviral activity and could reduce cough severity. Using a computational screening approach, aprepitant was found to have the ability to form 3 hydrogen bonds to key residues within the binding pocket of the main protease (M^{pro}) of SARS-CoV-2, which is a key enzyme required for replication (Liu 2020). Of note, cough is a common symptom of COVID-19 and a recent study has demonstrated that administration of oral aprepitant resulted in significantly decreased severity of cough in patients with advanced lung cancer (Noronha 2020).

Aprepitant injectable emulsion is approved in the US as CINVANTI® (aprepitant) injectable emulsion, for intravenous (IV) use in combination with other antiemetic agents in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) or moderately emetogenic cancer chemotherapy (MEC) as a single-dose regimen or as part of a 3-day regimen on the first day of each chemotherapy cycle. CINVANTI is approved for IV administration either by injection over a 2-minute period or by infusion over a 30-minute period.

METHODOLOGY: In this randomized, double-blind, placebo-controlled study, 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 130 mg or saline placebo administered once daily 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. Detailed information regarding laboratory assessments, including sample collection procedures for PK and cytokines, will be provided in the laboratory manual. 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. Assessments will include the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale of clinical status, respiratory status, COVID-19 symptoms, and adverse events (AEs).

An interim review committee (IRC) composed of Sponsor and external representatives 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.

NUMBER OF PLANNED SUBJECTS: Approximately 100 subjects will be randomized.

STUDY POPULATION:

Inclusion Criteria

Each subject must meet all of the following criteria to be randomized in this study:

1. Is willing and able to, or has a legally authorized representative who is willing and able to, provide written informed consent to participate, and to cooperate with all aspects of the protocol.
2. Is ≥18 years of age at screening.
3. Is hospitalized for ≤48 hours with SARS-CoV-2 infection prior to randomization.
4. Has documented SARS-CoV-2 infection diagnostic test (polymerase chain reaction [PCR], antigen, or immunoglobulin M [IgM] antibody) prior to randomization.
5. Has at least 1 of the following:
    a. Radiographic infiltrates by imaging (eg, chest X-ray, computed tomography [CT] scan), OR
    b. Oxygen saturation (SpO_2) ≤94% by pulse oximetry on room air, OR
    c. Requiring supplemental oxygen.
6. Is not anticipated to require mechanical ventilation within 48 hours after randomization.

Exclusion Criteria

A subject who meets any of the following criteria prior to randomization will be excluded from the study:

1. Is taking high-dose hydroxychloroquine (eg, ≥400 mg twice daily [BID]) or chloroquine (eg, ≥500 mg BID) and unwilling to reduce the dose to hydroxychloroquine <400 mg BID or chloroquine <500 mg BID prior to receiving study treatment.
2. Has taken aprepitant or fosaprepitant <24 hours prior to randomization.
3. Is taking pimozide.
4. Is taking strong or moderate cytochrome P450 (CYP)3A4 inhibitors (eg, ketoconazole, itraconazole, nefazodone, troleandromycin, clarithromycin, ritonavir, nelfinavir, diltiazem) or strong CYP3A4 inducers (eg, rifampin, carbamazepine, phenytoin).
5. Is currently receiving treatment with any of the following:
    a. Janus kinase (JAK) inhibitors, biologic therapies, potent immunosuppressants (including azathioprine and cyclosporine) administered with the intent to modify immune response to COVID-19 (exception: dexamethasone, methylprednisolone, or equivalent are allowed at a 50% reduction of standard dose after the start of study drug dosing), or intravenous immunoglobulin (IVIg; including convalescent plasma) at the time of consent.
    b. Chemotherapy.
    c. Hemodialysis or peritoneal dialysis.
6. Has known hypersensitivity to any components of aprepitant injectable emulsion.
7. Has evidence of ARDS.
8. Has bilirubin >1.5 × the upper limit of normal (ULN), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × ULN.

9. Has a history of long QT syndrome or a QT interval corrected using Fridericia's formula (QTcF) >500 ms at Screening.
10. Has a medical condition or clinically significant laboratory abnormality that, in the opinion of the Investigator, would prevent participation in this clinical study.
11. Is currently participating in another study of an investigational drug or therapeutic medical device at the time of consent. Emergency Use Authorization of an investigational drug is permitted.
12. Has an expected survival <7 days.
13. Is using mechanical ventilation via tracheostomy or endotracheal intubation.
14. Is being treated with oxygen delivered by high-flow nasal cannula (>20 L/minute), nonrebreather mask, noninvasive positive pressure ventilation, or extracorporeal membrane oxygenation (ECMO).
15. Is receiving treatment with a vasopressor(s).
16. Has multiple organ failure.
17. Has current confirmed Influenza A or B infection.
18. Has a history of any of the following:
    a. Organ or hematologic transplant.
    b. HIV.
    c. Active hepatitis B or hepatitis C infection.
19. Female subjects are eligible only if all the following apply:
    a. Not pregnant (female subjects of child-bearing potential must have a negative serum pregnancy test at Screening).
    b. Not lactating.
    c. Not planning to become pregnant while participating in the study.
    d. Females must either practice abstinence from heterosexual contact or agree to use an acceptable form of birth control from the time of Screening, during the study, and for 28 days after the last dose of study drug. Acceptable forms of contraception include being in a monogamous relationship with a partner who is surgically sterile; practicing abstinence; or agreeing to use double-barrier contraception or a nonhormonal intrauterine device (eg, copper) in the event of sexual activity. Note: Female subjects in only a same-sex relationship do not need to meet this criterion. Hormonal contraceptives are not an acceptable form of birth control since the efficacy of hormonal contraceptives may be reduced with aprepitant.

STUDY DRUG: Study drug is defined as aprepitant injectable emulsion (test product) and saline placebo (control product).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION: Aprepitant injectable emulsion is a lipid emulsion formulation of aprepitant for IV use.

Aprepitant injectable emulsion will be supplied by Sponsor in a single-dose, 130-mg vial. (Note: aprepitant injectable emulsion to be supplied as the marketed product CINVANTI in the commercial container and carton with an additional flag label indicating investigational use.) The pharmacist will prepare the product for administration, which includes providing a covering for the syringe and infusion line to blind the contents.

Aprepitant injectable emulsion 130 mg (18 mL) will be administered once daily as a 2-minute IV injection.

CONTROL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

United States Pharmacopeia (USP)-grade normal saline solution (0.9% sodium chloride) will be supplied by study sites. Normal saline 18 mL will be administered once daily as a 2-minute IV injection. The pharmacist will prepare the product for administration, which includes providing a covering for the syringe and infusion line to blind the contents.

OTHER PROTOCOL-SPECIFIED MEDICATION(S):

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

DURATION OF TREATMENT: All subjects will receive treatment for 14 days, or until discharge or death, whichever occurs first, and will be followed through Day 56. The maximum duration of study participation for each subject from Screening through the last study visit will be approximately 62 days.

The overall duration of the study is anticipated to be approximately 12 months.

STUDY ASSESSMENTS:

PK, safety, and efficacy assessments will be performed.

Pharmacokinetic Assessments

Time 0 will be the start of study drug administration on Day 4 for PK assessments.

Blood samples will be collected for measurement of plasma concentrations of aprepitant. Plasma samples may also be used to measure concentrations of hydroxychloroquine and chloroquine in subjects who experience an adverse event of special interest (AESI) of QTcF prolongation >500 ms that may be considered related to hydroxychloroquine or chloroquine use.

Safety Assessments

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).

- AEs, serious adverse events (SAEs), and AESIs.
- Clinical laboratory values (hematology and serum chemistry).
- Vital signs, including SBP and DBP, resting heart rate, and temperature.
- Electrocardiograms (ECGs).

Efficacy Assessments

- The NIAID 8-point ordinal scale of clinical status:
    1. Death.
    2. Hospitalized, on invasive mechanical ventilation or 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: (SpO_2 or partial pressure of oxygen [PaO_2]).
  - Chest X-ray or 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.

STUDY ENDPOINTS:

Primary Endpoint

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

Secondary Endpoints

- Time to death or respiratory failure 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.
- Change from Baseline in IL-6 at each specified timepoint.

PK Endpoints

- PK parameters of aprepitant: maximum concentration (C_{max}), and for subjects in whom all optional PK samples are collected, area under the concentration-time curve from Time 0 to the time of the last quantifiable concentration (AUC_{last}) may be assessed.

[redacted]

[redacted]

STATISTICAL METHODS:

Determination of Sample Size

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

Efficacy Analyses

The proportion of subjects alive and discharged from the hospital at Day 14 will be analyzed using the Fisher's exact test 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.

Safety Analyses

All safety data will be listed and summarized by treatment group; no statistical hypothesis testing will be performed. Incidence of AEs, SAEs, adverse reactions, and AESIs will be coded and tabulated by System Organ Class and Preferred Term. AESIs are events of anaphylaxis and of QTcF prolongation (>500 ms). Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. Individual subject values will be listed and values outside of the standard reference range will be flagged. Changes in vital sign parameters and ECG parameters will be summarized.

Pharmacokinetic Analysis

Plasma PK parameters of aprepitant will be calculated using noncompartmental analysis.

Interim Analysis

No formal interim analyses are planned. An IRC will review the data from the study on an ongoing basis to enhance subject safety without adapting the study design.

SCHEDULE OF EVENTS

Assessment	Screening	Treatment Period													Post-Treatment Evaluation Period						D/C[b]	ET[c]
		Baseline/ D1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	D12 and D13	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56		
Obtain informed consent	X																					
Pregnancy test (WOCBP only)[d]	X																					
Assess/confirm eligibility	X																					
Comorbidities	X																					
Demographics	X																					
Physical examination[e]	X																					
Randomization		X																				
Record min/max vital sign values over 24-hour period[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG for subjects not taking hydroxychloroquine/chloroquine[g]	X		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→		
12-Lead ECG for subjects taking hydroxychloroquine/chloroquine[h]	X		X	X	X	X	X	X	X	X	X	X	X	X								
SARS-CoV-2 diagnostic test[i]	X																					
SARS-CoV-2 viral RNA load test[j]		X		X		X		X			X			X	X						X	X
COVID-19 symptoms average severity over 24-hour period[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record worst hematology and serum chemistry results[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record results for D-dimer, troponin, BNP, ESR, and CK performed for standard of care	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record worst respiratory status over 24-hour period[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment	Screening	Treatment Period													Post-Treatment Evaluation Period						D/C[b]	ET[c]
		Baseline/ D1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	D12 and D13	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56		
Record worst clinical status over 24-hour period on the 8-point ordinal scale[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sample					X	*See table of PK blood sample collection for timepoints on Day 4*																
Cytokine storm panel sample collection		X						X						X		X				X	X	X
Substance P[o]		X						X						X		X				X	X	X
Cytokine limited panel sample collection					X					X		X										
CRP sample collection					X					X		X										
Study drug dosing[p]		X	X	X	X	X	X	X	X	X	X	X	X	X								
Concomitant medications[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CK, creatine kinase; COVID-19, coronavirus disease; CRP, c-reactive protein; CT, computed tomography; D, Day; DBP, diastolic blood pressure; D/C, discharge; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; eCRF, electronic case report form; ESR, erythrocyte sedimentation rate; ET, early termination; ICF, informed consent form; IgM, immunoglobulin M; PCR, polymerase chain reaction; PaO_2, partial pressure of oxygen; PK, pharmacokinetic(s); qPCR, quantitative PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBP, systolic blood pressure; SpO_2, oxygen saturation; WOCBP, women of childbearing potential.

[a] Assessments need not be repeated if performed the same day as the screening procedures.

[b] Subjects who are discharged alive at any time before Day 56 need to complete only the evaluations identified for discharge. Discharged subjects will be followed until Day 56 for assessments listed in the SCHEDULE OF EVENTS POST-DISCHARGE.

[c] If a subject is withdrawn from the study, the ET evaluations will be completed. After study drug discontinuation, every attempt should be made to complete the remaining study assessments listed in the SCHEDULE OF EVENTS POST-DISCHARGE and follow the subject through Day 56. Assessments do not need to be repeated if performed earlier on the same day.

[d] Either serum or urine pregnancy test is acceptable.

[e] A symptom-directed physical examination should be performed at Screening and when appropriate to evaluate an AE. Body weight to be collected at Screening, on Day 1, and if available for other days.

[f] Include SBP, DBP, resting heart rate, and body temperature performed for standard of care. The minimum and maximum values for the daily 24-hour period (from 00:00 to 23:59 hours) should be recorded.

[g] Standard digital 12-lead ECGs will be performed in triplicate at Screening only. The mean of the 3 ECG recordings will be used as the Baseline result. For all subjects, whether or not on continuous ECG monitoring, record the results of a standard-of-care ECG if performed.

Assessment	Screening	Treatment Period													Post-Treatment Evaluation Period						D/C[b]	ET[c]
		Baseline/ D1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	D12 and D13	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56		

[h] For subjects taking hydroxychloroquine/chloroquine, standard digital 12-lead ECGs will be performed in triplicate at Screening only. The mean of the 3 ECG recordings will be used as the Baseline result. Subsequently, for subjects not on continuous ECG monitoring, daily single ECGs will be performed. For subjects on continuous ECG monitoring, record the results of a standard-of-care ECG if performed.

[i] The SARS-CoV-2 infection diagnostic test will be performed by a local laboratory before the subject is hospitalized or at the admitting hospital, or both. The preferred diagnostic test is PCR; if not possible, perform antigen test; if not possible, perform IgM antibody test. The type of test performed will also be recorded.

[j] The SARS-CoV-2 viral RNA load qPCR test will be analyzed by the central laboratory. The method(s) for collecting samples will be described in the Laboratory Manual.

[k] For subjects who are not receiving mechanical ventilation, record each COVID-19 symptom (Section 6.3.5) as none, mild, moderate, or severe. For the Baseline status on Day 1, record the status at randomization and the symptoms onset time(s). For all other assessment days, record the symptoms based on the average severity per subject report during the assessment day's 24-hour period (from 00:00 to 23:59 hours).

[l] The following analyte results from local laboratories will be provided: hematocrit, platelet count, white blood cell count (with automated differential), absolute neutrophils, absolute lymphocytes, hemoglobin, ALT, AST, creatinine, glucose, total bilirubin, sodium, potassium, bicarbonate, total protein, and albumin. For all clinical laboratory tests (except those for Day 1), when more than 1 result is available in the daily 24-hour period (from 00:00 to 23:59 hours), the highest result should be reported in the eCRF. Exceptions include analytes for which a low result is considered clinically significant (eg, hypokalemia, hyponatremia). For Day 1, the most recent result before dosing should be used.

[m] Record the worst respiratory status. For the Baseline status on Day 1, record the status at randomization. For all other assessment days, record the worst status for that assessment day's 24-hour period (from 00:00 to 23:59 hours). For example, for Day 14, record the worst status that occurred on Day 14 from 00:00 to 23:59 hours. Assessments include respiratory rate, oxygen supplementation (room air, nasal cannula, face mask, noninvasive ventilation or high-flow oxygen devices, mechanical ventilation, or ECMO), oxygenation (lowest SpO_2 at rest or PaO_2), and chest X-ray or CT scan findings (to be recorded if performed within 5 days prior to randomization, if available).

[n] For the Baseline score on Day 1, record the clinical status score at randomization. For all other assessment days except for discharge, record the worst (ie, lowest ordinal) score for that assessment day's 24-hour period (from 00:00 to 23:59 hours). For example, for Day 14, record the worst (ie, lowest ordinal) score that occurred on Day 14 from 00:00 to 23:59 hours.

[o] Performed by a central laboratory if possible.

[p] If a subject is discharged alive prior to Day 14, dosing with study drug will be discontinued and the discharge assessments will be completed.

[q] All medications taken by subjects from ICF signing through the last day of study drug administration will be recorded. Medications taken for the treatment of COVID-19 will be recorded through discharge.

[r] All AEs will be recorded from the time the subject signs the ICF through Day 56.

SCHEDULE OF EVENTS POST-DISCHARGE

Assessment[a,b]	D14 ±2 days	D21 ±2 days	D28 ±2 days	D56 +4 days
Record COVID-19 symptoms average severity over 24-hour period[c]	X	X	X	X
Record worst respiratory status over the 24-hour period[d]	X	X	X	X
Record worst clinical status over the 24-hour period on the 8-point ordinal scale[e]	X	X	X	X
AEs[f]	X	X	X	X

Abbreviations: AE, adverse event; COVID-19, coronavirus disease; D, Day.

[a] **The subject will be contacted on Days 15, 22, 29, and 57 to collect the information for the Days 14, 21, 28, and 56 assessments, respectively**.

[b] Subjects should complete the first post-discharge visit following the actual day they were discharged. For example, a subject discharged on Day 22 should start with post-discharge Day 28.

[c] Record each COVID-19 symptom (Appendix B) as none, mild, moderate, or severe based on the average severity per subject report during the assessment day's 24-hour period (from 00:00 to 23:59 hours).

[d] Record the worst respiratory status regarding oxygen supplementation for that assessment day's 24-hour period (from 00:00 to 23:59 hours): room air, nasal cannula, face mask, noninvasive ventilation or high-flow oxygen devices, ECMO, or mechanical ventilation. For example, for Day 21, record the worst status that occurred on Day 21 from 00:00 to 23:59 hours.

[e] Record the worst (ie, lowest ordinal) clinical status score for that assessment day's 24-hour period (from 00:00 to 23:59 hours). For example, for Day 21, record the worst (ie, lowest ordinal) score that occurred on Day 21 from 00:00 to 23:59 hours.

[f] All AEs will be recorded through Day 56.

SCHEDULE OF PK BLOOD SAMPLE COLLECTION

		Day 4				
	Time	Predose[a]	5 min	1 h (Optional)	6 h (Optional)	24 h[b] (Optional)
Assessment	Window	-30 to -1 min	±2 min	±5 min	±5 min	-30 to -1 min
PK blood sample collection		X	X	X	X	X

Abbreviations: PK, pharmacokinetic.

Note: PK sample collection starts on Day 4 after steady state has been reached. Time 0 will be the start of study drug administration on Day 4.

[a] Predose is prior to first dosing on Day 4.

[b] Collect sample prior to subject receiving the next dose of study drug.

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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
BA	Bioanalytical
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
ICF	Informed consent form
ICH	International Council for Harmonisation
IgM	Immunoglobulin M
IL	Interleukin
INR	International Normalized Ratio
IRC	Interim review committee
ITT	Intent-to-Treat
IV	Intravenous(ly)
IVIg	Intravenous immunoglobulin
JAK	Janus kinase
NIAID	National Institute of Allergy and Infectious Diseases

Abbreviation	Definition
NK_1	Neurokinin-1
PK	Pharmacokinetic(s)
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. INTRODUCTION

1.1. Background Information and Study Rationale

Heron is investigating the use of aprepitant injectable emulsion for the treatment of adult patients with early symptomatic coronavirus disease (COVID-19). COVID-19 is caused by infection with the virus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There is currently no approved treatment available for COVID-19. The symptoms of COVID-19 vary from asymptomatic disease to pneumonia, acute respiratory distress syndrome (ARDS), multisystem organ failure, and death (Rodriguez-Morales 2020; Weiss 2020; Wu 2020). Severe complications are more frequent in older patients and patients with preexisting respiratory or cardiovascular conditions (Weiss 2020; Wu 2020). Current management of the disease consists of supportive care, including invasive and noninvasive oxygen support and treatment with antibiotics (Onder 2020; Poston 2020).

Aprepitant is a selective high-affinity antagonist of human neurokinin-1 (NK_1) receptors. It has been extensively used for almost 20 years for the prevention of chemotherapy-induced nausea and vomiting (CINV) and for 14 years for the prevention of postoperative nausea and vomiting (PONV).

The rationale for the investigation of aprepitant injectable emulsion in COVID-19 is the close association between the binding of substance P (SP) to NK_1 receptors and the resultant induction of inflammatory cytokines, such as interleukin [IL]-6, which are associated with the development of ARDS. NK_1 receptors are expressed in human central airways, subpleural lung, and postcapillary venules in the upper and lower airways (O'Connor 2004; Quartara 1998). Stimulation of the NK_1 receptors in postcapillary venules leads to capillary leak with extravasation of plasma proteins (Quartara 1998). NK_1 receptors are also expressed on mast cells, neutrophils, eosinophils, monocytes/macrophages, dendritic cells, natural killer cells, B and T cells, microglia, and astrocytes (Mashaghi 2016; Suvas 2017). Expression of NK_1 receptors is markedly increased during infection, especially on lymphocytes and macrophages. Through the binding to NK_1 receptors, SP leads to the production of cytokines with proinflammatory (eg, IL-1), immunomodulatory (eg, IL-10), and chemotactic properties (eg, IL-8) (Mashaghi 2016) contributing to the cytokine storm. Exposure of a human bronchial epithelial cell line to SP resulted in release of IL-6, IL-8, and tumor necrosis factor alpha (TNF-α) (O'Connor 2004).

The role of SP and inflammatory cytokines (such as IL-6) on lung injury, including ARDS, was demonstrated in animal models and in humans (Bhatia 2004; Espiritu 1992; Mao 2016; Puneet 2005; Sio 2010; Wong 2004). In patients with COVID-19, a significant association of increased concentrations of IL-6 with more severe disease, ARDS, the need for mechanical ventilation, and death was observed (Coomes 2020; Herold 2020).

The antagonism of NK_1 receptors with aprepitant is expected to prevent the cytokine release mediated by the binding of SP to NK_1 receptors. Reduced concentrations of cytokines following treatment with aprepitant were observed in clinical studies in adults infected with HIV (Spitsin 2017; Tebas 2015). It is hypothesized that early decrease of cytokine release should limit cytokine overactivation/dysregulation potentially preventing or reducing the severity of ARDS. Heron hypothesizes that aprepitant injectable emulsion would best be positioned to decrease the dysregulation/overactivation of cytokines/chemokines elicited by SP early in the disease process. Once the lungs are overwhelmed with the inflammatory response, other mechanisms may

increase the dysregulation, making NK_1 receptor antagonist treatment less effective. Therefore, treatment with an NK_1 receptor antagonist before patients require mechanical ventilation is proposed.

In addition, based on published literature, aprepitant may provide direct antiviral activity and could reduce cough severity. Using a computational screening approach, aprepitant was found to have the ability to form 3 hydrogen bonds to key residues within the binding pocket of the main protease (M^{pro}) of SARS-CoV-2, which is a key enzyme required for replication (Liu 2020). Of note, cough is a common symptom of COVID-19 and a recent study has demonstrated that administration of oral aprepitant resulted in significantly decreased severity of cough in patients with advanced lung cancer (Noronha 2020).

1.2. Rationale for Study Design, Doses, and Control Groups

This Phase 2 study was designed to compare the efficacy and safety of aprepitant injectable emulsion with normal saline placebo control in adult patients with early symptomatic COVID-19 who are also receiving standard of care for treatment for COVID-19. Pharmacokinetic (PK) assessments of aprepitant following daily administration of aprepitant injectable emulsion will be performed. The study will employ a randomized and double-blind design to provide the highest quality of evidence, and to minimize potential bias in subject selection as well as efficacy and safety assessments.

Aprepitant injectable emulsion is approved in the United States (US) as CINVANTI® (aprepitant) injectable emulsion, for intravenous (IV) use in combination with other antiemetic agents in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) or moderately emetogenic cancer chemotherapy (MEC) as a single-dose regimen (130 mg) or as part of a 3-day regimen (100 mg) on the first day of each chemotherapy cycle. CINVANTI is approved for administration IV either by injection over a 2-minute period or by infusion over a 30-minute period (CINVANTI USPI October 2019).

This study will evaluate a regimen of 130 mg once daily (QD) aprepitant injectable emulsion, administered for 14 days, compared to saline placebo control. An interim review committee (IRC) will review the unblinded PK, safety, and efficacy data. The available nonclinical and clinical data and marketing experience for aprepitant injectable emulsion support its safe use in adult patients with COVID-19 at a dose level of 130 mg administered as a 2-minute IV injection QD for 14 days.

The nonclinical safety of aprepitant injectable emulsion was adequately characterized at appropriate exposures to support its daily administration for up to 28 days. The results of a repeated-dose toxicity study of aprepitant injectable emulsion following its QD administration for 28 days as a slow IV bolus revealed no safety concerns. The results of a local tolerance study of aprepitant injectable emulsion indicated low risk of toxicity due to its accidental extravasation. Clinically, the administration of aprepitant injectable emulsion 130 mg as a 2-minute IV injection is supported by the results of a Phase 1 study in healthy volunteers (Study 108) and from marketing experience with CINVANTI. Administration QD for 14 days is supported by reports in the literature regarding the safety of high doses of aprepitant. Refer to the Investigator's Brochure (IB) of Aprepitant Injectable Emulsion for Treatment of Patients With COVID-19 for a detailed account of the clinical and nonclinical studies and literature.

To measure the effect of aprepitant injectable emulsion on disease progression, the primary endpoint will be the proportion of subjects alive and discharged from the hospital at Day 14. This endpoint is timed to assess clinically meaningful changes in patient status, treatment, and COVID-19 progression.

To further evaluate disease progression, a secondary endpoint will be time to death or respiratory failure, 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; or extracorporeal membrane oxygenation (ECMO). Other secondary endpoints include the time to discharge from hospital; measures of safety; and the effect of study drug on IL-6, a key cytokine. In patients with COVID-19, a significant association was observed between increased concentrations of IL-6 and more severe disease, ARDS, the need for mechanical ventilation, and death (Coomes 2020; Herold 2020). The incidence of adverse events (AEs) and the change from Baseline in IL-6 at each timepoint will be assessed.

[redacted]

1.3. Potential Risks and Benefits

Aprepitant is a highly selective NK_1 receptor antagonist first approved in 2003. It is indicated for the prevention of CINV and for the prevention of PONV in an oral formulation (EMEND Oral USPI November 2019) and for prevention of CINV as an IV formulation of its prodrug, fosaprepitant (EMEND IV USPI November 2019). Aprepitant injectable emulsion for IV use was US Food and Drug Administration (FDA) approved in November 2017 and has been marketed in the US under the brand name CINVANTI for over 2 years. It is approved for the prevention of CINV for administration either by injection over a 2-minute period or by infusion over a 30-minute period on the first day of each chemotherapy cycle (CINVANTI USPI October 2019). Aprepitant has not been approved for the treatment of COVID-19.

1.3.1. Safety

The potential risks associated with the daily administration of aprepitant injectable emulsion in patients with COVID-19 are not known. It is expected that AEs following administration of aprepitant injectable emulsion to patients with COVID-19 will be similar to those in patients with CINV.

The safety information for aprepitant injectable emulsion presented is based on clinical studies in 304 healthy volunteers and the cumulative patient marketing experience from CINVANTI in cancer patients for prevention of CINV as well as the experience with oral aprepitant and IV fosaprepitant. As of 08 November 2019, the cumulative patient exposure to aprepitant injectable emulsion was estimated to be 152,323.5 patient-years. The majority of patients exposed to aprepitant injectable emulsion received 6 cycles of chemotherapy per year, and aprepitant injectable emulsion was administered once per cycle at a dose of 130 mg for most patients (see

Section 5.4 of the IB for Aprepitant Injectable Emulsion for Treatment of Patients With COVID-19).

The safety profile of aprepitant injectable emulsion in healthy volunteers was similar when administered as either a single 2-minute injection or a 30-minute infusion. Adverse reactions (ie, AEs considered by the Investigator to be possibly related to study drug) reported in >2.0% of 304 healthy subjects who received aprepitant injectable emulsion 130 mg (n=292) or 100 mg (n=12) administered IV over 2 to 30 minutes included headache (3.3%) and fatigue (3.0%).

The most common adverse reactions (≥3%) in adult subjects given oral aprepitant as a 3-day regimen for prevention of CINV (125 mg on Day 1 and 80 mg on Days 2 and 3) included fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, white blood cell count decreased, dehydration, and alanine aminotransaminase (ALT) increased. Stevens-Johnson Syndrome has been reported in a patient receiving the oral aprepitant regimen with cancer chemotherapy. Serious adverse reactions (SARs) reported in non-CINV studies of aprepitant (EMEND IV USPI November 2019) include single cases of angioedema and urticaria, constipation, and subileus.

Hypersensitivity reactions (including anaphylaxis) have been reported in patients receiving aprepitant injectable emulsion. Should it occur, discontinue aprepitant injectable emulsion immediately, and administer appropriate medical therapy and do not reinitiate treatment with aprepitant injectable emulsion.

Aprepitant is a weak-to-moderate (dose dependent) inhibitor and inducer of cytochrome P450 (CYP)3A4. Drugs that are substrates of CYP3A4 should be used with caution. Examples include hydroxychloroquine/chloroquine, which can possibly increase in toxicity, including prolonged QT; dexamethasone, methylprednisolone, or equivalent require a 50% reduction of standard dose; pimozide is contraindicated. Strong or moderate CYP3A4 inhibitors (eg, ketoconazole, diltiazem) may increase the levels of aprepitant, and strong CYP3A4 inducers (eg, rifampin) may decrease its levels; both should be avoided.

Coadministration with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the international normalized ratio (INR) of prothrombin time; therefore, it is important to monitor the INR in patients on chronic warfarin therapy.

Upon coadministration with aprepitant injectable emulsion, the efficacy of hormonal contraceptives may be reduced during administration of and for 28 days following the last dose of aprepitant injectable emulsion. Patients should be advised to use effective alternative or back-up methods of non-hormonal contraception for 1 month following the last administration of aprepitant injectable emulsion.

1.3.2. Efficacy

The efficacy of aprepitant injectable emulsion in the treatment of patients with COVID-19 has not been evaluated.

For more information on aprepitant injectable emulsion, refer to the IB for Aprepitant Injectable Emulsion for Treatment of Patients With COVID-19 and the CINVANTI prescribing information (CINVANTI USPI October 2019).

2. STUDY OBJECTIVES

2.1. Primary Objective

- To assess the effect of aprepitant injectable emulsion on the clinical status of COVID-19 in hospitalized patients with confirmed SARS-CoV-2 infection.

2.2. Secondary Objectives

The secondary objectives are as follows:

- To evaluate the safety and tolerability of daily administration of aprepitant injectable emulsion in hospitalized patients with COVID-19.
- To assess the 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.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

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 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 (Section 6.5), safety (Section 6.4), and efficacy (Section 6.3) assessments. Safety assessments will include 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 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 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.

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

3.2.2. Secondary Endpoints

- Time to death or respiratory failure 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.

3.2.3. Pharmacokinetic Endpoints

- PK parameters of aprepitant: maximum concentration (C_{max}), and for subjects in whom all optional PK samples are collected, area under the concentration-time curve from Time 0 to the time of the last quantifiable concentration (AUC_{last}) may be assessed.

[redacted]

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 12 months.

All subjects will receive treatment for 14 days, or until discharge or death, whichever occurs first, and will be followed through Day 56. The maximum duration of study participation for each subject from Screening through the last study visit will be approximately 62 days.

For regulatory reporting purposes, the end of the study is defined as the date of the last subject's last visit.

3.4. Suspension of the Study

Enrollment will be halted when the Sponsor becomes aware of any of the following:

- If an AE of special interest (AESI) of anaphylaxis (see Section 6.4.2) occurs in at least 2 more subjects treated with aprepitant injectable emulsion compared to the number of subjects administered saline placebo.
- If an AESI of prolongation (>500 ms) of QT interval corrected using Fridericia's formula (QTcF) occurs in at least 2 more subjects treated with aprepitant injectable emulsion compared to the number of subjects administered saline placebo.
- If study drug-related mortality occurs in at least 2 more subjects treated with aprepitant injectable emulsion compared to the number of subjects administered saline placebo.

Following review of the data, a recommendation will be made by the IRC within 24 hours on whether to stop the study, stop future enrollment but continue dosing in subjects where the Investigator believes the observed benefit outweighs the potential risk, or modify the protocol to enhance subject safety without adapting the study design.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 100 subjects will be randomized at approximately 10 study sites in the US.

4.1.1. Inclusion Criteria

Each subject must meet all of the following criteria to be randomized in this study:

1. Is willing and able to, or has a legally authorized representative who is willing and able to, provide written informed consent to participate, and to cooperate with all aspects of the protocol.
2. Is ≥18 years of age at Screening.
3. Is hospitalized for ≤48 hours with SARS-CoV-2 infection prior to randomization.
4. Has documented SARS-CoV-2 infection diagnostic test (polymerase chain reaction [PCR], antigen, or immunoglobulin M [IgM] antibody) prior to randomization.
5. Has at least 1 of the following:
    a. Radiographic infiltrates by imaging (eg, chest X-ray, CT scan), OR
    b. SpO_2 ≤94% by pulse oximetry on room air, OR
    c. Requiring supplemental oxygen.
6. Is not anticipated to require mechanical ventilation within 48 hours after randomization.

4.1.2. Exclusion Criteria

A subject who meets any of the following criteria prior to randomization will be excluded from the study:

1. Is taking high-dose hydroxychloroquine (eg, ≥400 mg twice daily [BID]) or chloroquine (eg, ≥500 mg BID) and unwilling to reduce the dose to hydroxychloroquine <400 mg BID or chloroquine <500 mg BID prior to receiving study treatment.
2. Has taken aprepitant or fosaprepitant <24 hours prior to randomization.
3. Is taking pimozide.
4. Is taking strong or moderate CYP3A4 inhibitors (eg, ketoconazole, itraconazole, nefazodone, troleandromycin, clarithromycin, ritonavir, nelfinavir, diltiazem) or strong CYP3A4 inducers (eg, rifampin, carbamazepine, phenytoin).
5. Is currently receiving treatment with any of the following:
    a. Janus kinase (JAK) inhibitors, biologic therapies, potent immunosuppressants (including azathioprine and cyclosporine) administered with the intent to modify immune response to COVID-19 (exception: dexamethasone, methylprednisolone, or equivalent are allowed at a 50% reduction of standard dose after the start of study drug dosing), or intravenous immunoglobulin (IVIg; including convalescent plasma) at the time of consent.
    b. Chemotherapy.

c. Hemodialysis or peritoneal dialysis.

6. Has known hypersensitivity to any components of aprepitant injectable emulsion.
7. Has evidence of ARDS.
8. Has bilirubin >1.5 × the upper limit of normal (ULN), or aspartate aminotransferase (AST) or ALT >3 × ULN.
9. Has a history of long QT syndrome or a QTcF >500 ms at Screening.
10. Has a medical condition or clinically significant laboratory abnormality that, in the opinion of the Investigator, would prevent participation in this clinical study.
11. Is currently participating in another study of an investigational drug or therapeutic medical device at the time of consent. Emergency Use Authorization of an investigational drug is permitted.
12. Has an expected survival <7 days.
13. Is using mechanical ventilation via tracheostomy or endotracheal intubation.
14. Is being treated with oxygen delivered by high-flow nasal cannula (>20 L/minute), nonrebreather mask, noninvasive positive pressure ventilation, or ECMO.
15. Is receiving treatment with a vasopressor(s).
16. Has multiple organ failure.
17. Has current confirmed Influenza A or B infection.
18. Has a history of any of the following:
    a. Organ or hematologic transplant.
    b. HIV.
    c. Active hepatitis B or hepatitis C infection.
19. Female subjects are eligible only if all the following apply:
    a. Not pregnant (female subjects of child-bearing potential must have a negative serum pregnancy test at Screening).
    b. Not lactating.
    c. Not planning to become pregnant while participating in the study.
    d. Females must either practice abstinence from heterosexual contact or agree to use an acceptable form of birth control from the time of Screening, during the study, and for 28 days after the last dose of study drug. Acceptable forms of contraception include being in a monogamous relationship with a partner who is surgically sterile; practicing abstinence; or agreeing to use double-barrier contraception or a nonhormonal intrauterine device (eg, copper) in the event of sexual activity.
    Note: Female subjects in only a same-sex relationship do not need to meet this criterion. Hormonal contraceptives are not an acceptable form of birth control since the efficacy of hormonal contraceptives may be reduced with aprepitant.

4.2. Method of Assigning Subjects to Treatment Groups

Subjects who meet the Screening eligibility criteria will be randomized. 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.

4.2.1. Procedures for Handling Randomized Subjects Who Do Not Meet the Study Eligibility Criteria

Subjects who fail to meet the eligibility criteria should not, under any circumstances, receive study drug.

In the event a subject does not meet the eligibility criteria, but is randomized and receives study drug, the Investigator should inform the Sponsor immediately. The Sponsor's Medical Monitor and the Investigator will discuss whether to allow the subject to continue on study drug. If the subject does not continue on study drug, the discharge date will be recorded and the subject will undergo study assessments at Days 14, 28, and 56.

4.3. Blinding

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 (Section 5.4). The Sponsor's study team will also be blinded to the treatment assignments with the exception of the clinical trial material (CTM) staff, the clinical research associate (CRA) performing study drug accountability, the Clinical Operations manager for review of unblinded monitoring reports, the bioanalytical (BA) and PK vendors, and the unblinded external statistician who will perform the randomization and interim analysis data review, but will otherwise not be involved in the conduct of the study. The BA vendor will be unblinded to treatment assignment to facilitate generation of BA concentration data from the PK samples, and the PK vendor will be unblinded to analyze the BA concentration data.

The 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. The Product Safety and Risk Management Committee (PSRMC) will monitor blinded safety data on a periodic basis throughout the study.

Additional information will be provided in the Study Blinding Plan.

4.3.1. Breaking the Blind

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. An attempt should be made to contact the Sponsor before breaking the blind. If the Sponsor cannot be

reached and the blind is broken by the Investigator, the reason for unblinding must be documented and the Sponsor must be contacted within 24 hours.

If a study site becomes aware of a potential or actual unblinding event, the site must notify the Sponsor within 24 hours of becoming aware of the event.

All circumstances leading to the premature unblinding will be clearly documented.

4.4. Study Drug Discontinuation and Subject Withdrawal From Study

4.4.1. Study Drug Discontinuation

Study drug may be discontinued for any of the following reasons:

- AE.
- Request by subject.
- Pregnancy.
- Investigator's decision.
- Disease progression.
- Sponsor's decision.
- Other, specify.

The date and primary reason for study drug discontinuation will be recorded on the electronic case report form (eCRF).

After study drug discontinuation, every attempt should be made to complete the remaining study assessments and follow the subject through Day 56.

4.4.2. Subject Withdrawal From Study and Subject Replacement

Subjects are free to withdraw from the study at any time without prejudice to further treatment.

The date and the primary reason for early withdrawal (consent withdrawn or lost to follow-up) will be recorded on the eCRF. At the time of withdrawal from the study, complete the Early Termination assessments.

Randomized subjects who withdraw from study will not be replaced. To account for withdrawal of subjects who were randomized but not dosed, enrollment will continue until at least 100 subjects have been randomized and dosed.

4.5. Subject Rehospitalization After Discharge

For discharged subjects who are readmitted to the hospital prior to Day 56, assessments in the Schedule of Events Post-Discharge will be completed.

5. STUDY DRUG

Study drug is defined as aprepitant injectable emulsion (test product) and saline placebo (control product).

5.1. Description of Study Drug

5.1.1. Test Product

Aprepitant injectable emulsion is supplied as an opaque, off-white to amber emulsion in a single-dose glass vial containing 130 mg/18 mL aprepitant:

NDC 47426-201-01 1 single-dose vial per carton.

Aprepitant injectable emulsion will be supplied by the Sponsor.

5.1.2. Control Product

United States Pharmacopeia (USP)-grade normal saline solution (0.9% sodium chloride) will be supplied by study sites.

5.2. Packaging and Labeling

Aprepitant injectable emulsion will be packaged and labeled by the Sponsor or designee as the marketed product CINVANTI in the commercial container and carton with an additional flag label indicating investigational use, and will be packed and dispatched to comply with shipping and storage conditions. Aprepitant injectable emulsion for investigational use will be labeled so as to not obscure commercial text. Study drug labeling will comply with all applicable national and local laws and regulations.

5.3. Storage

Aprepitant injectable emulsion vials must be refrigerated; store at 2°C to 8°C (36°F to 46°F). Aprepitant injectable emulsion vials can remain at room temperature up to 60 days. Do not freeze.

5.4. Preparation

Aprepitant injectable emulsion will be prepared at the study site. For IV injection over a period of 2 minutes, aseptically withdraw 18 mL from the vial for the 130 mg dose. Do not dilute. The infusion line should be flushed with normal saline before and after administration of aprepitant injectable emulsion. Aprepitant injectable emulsion should not be mixed with solutions for which physical and chemical compatibility have not been established.

The pharmacist will prepare test product and control product for administration, which includes providing a covering for the syringe and infusion line to blind the contents. Refer to the Pharmacy Manual for details on study drug preparation.

5.5. Study Drug Administration

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.

The start and stop times of study drug dosing will be recorded in the eCRF.

5.6. Study Drug Compliance

All study drug must be administered in accordance with the treatment assignment. Subject compliance monitoring is not necessary because study drug will be administered by trained site staff.

5.7. Study Drug Accountability

Aprepitant injectable emulsion provided for this study will be used only as directed in the study protocol. In accordance with Good Clinical Practice (GCP), Investigators are required to maintain accurate and up-to-date records of all aprepitant injectable emulsion to permit reconciliation. The Investigator or designee must maintain adequate records of distribution, including the date received, number and units received, lot numbers, dispensing, and return or destruction of all study drug (ie, accountability or dispensing logs).

All study drug records must be readily available for inspection by the site's Clinical Monitor and/or auditor. The Clinical Monitor is responsible for verifying the accuracy of the aprepitant injectable emulsion records at the study site. All returns, disposal, or destruction must be approved by the Sponsor in writing.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. The timing of procedures and assessments is provided in the SCHEDULE OF EVENTS, the SCHEDULE OF EVENTS POST-DISCHARGE, and the SCHEDULE OF PK BLOOD SAMPLE COLLECTION tables. The assessments to be performed post-discharge are described in Appendix B.

6.1. Comorbidities and Demographics

6.1.1. Comorbidities

Comorbidities will be obtained to ensure that subjects qualify for the study.

6.1.2. Demographics

Demographic information collected will include age, sex, race, and ethnicity.

6.2. Prior and Concomitant Therapy

All medications taken by subjects from informed consent form (ICF) signing through the last day of study drug administration will be recorded. Medications taken for the treatment of COVID-19 will be recorded through discharge.

6.2.1. Allowed Concomitant Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the standard of medical care, except for prohibited medications while on study.

Coadministration of aprepitant injectable emulsion with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the INR of prothrombin time. Monitor the INR in subjects on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following initiation of aprepitant injectable emulsion (CINVANTI USPI October 2019).

If dexamethasone, methylprednisolone, or equivalent, CYP3A4 substrates, are used, the dose should be reduced by approximately 50% (CINVANTI USPI October 2019).

6.2.2. Prohibited Medications and Treatments

Per the exclusion criteria (Section 4.1.2), prohibited medications include high-dose hydroxychloroquine (eg, ≥400 mg BID) or chloroquine (eg, ≥500 mg BID), pimozide, JAK inhibitors, biologic therapies, potent immunosuppressants (including azathioprine and cyclosporine) administered with the intent to modify immune response to COVID-19 (exception: dexamethasone, methylprednisolone, or equivalent are allowed at a 50% reduction of standard dose after the start of study drug dosing), or IVIg, and chemotherapy. Other forms of aprepitant and fosaprepitant are prohibited from 24 hours prior to randomization to Day 14.

Additionally, strong or moderate CYP3A4 inhibitors (eg, ketoconazole, itraconazole, nefazodone, troleandromycin, clarithromycin, ritonavir, nelfinavir, diltiazem,) or strong CYP3A4

inducers (eg, rifampin, carbamazepine, phenytoin) are prohibited during the dosing with study drug and 1 day after the last dose of study drug.

Subjects are prohibited from participating in a concurrent study of an investigational drug or therapeutic medical device.

6.3. Efficacy Assessments

6.3.1. 8-Point Ordinal Scale of Clinical Status

The NIAID 8-point ordinal scale is an assessment of the clinical status (Table 1). For the Baseline score on Day 1, record the score at randomization. For all other assessment days, record the worst (ie, lowest ordinal) score for that assessment day's 24-hour period (from 00:00 to 23:59 hours). For example, for Day 14, record the worst (ie, lowest ordinal) score that occurred on Day 14 from 00:00 to 23:59 hours.

For subjects discharged from hospital before Day 56, clinical status will be followed by telehealth visits or other methods. For each day, record the worst (ie, lowest ordinal) score for that assessment day's 24-hour period (from 00:00 to 23:59 hours). For example, for Day 21, record the worst (ie, lowest ordinal) score that occurred on Day 21 from 00:00 to 23:59 hours.

The status of subjects lost to follow up will be assessed by a vital records search.

Table 1: NIAID 8-Point Ordinal Scale of Clinical Status

Score	Description
1	Death
2	Hospitalized, on invasive mechanical ventilation or 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

Abbreviations: COVID-19, coronavirus disease; ECMO, extracorporeal membrane oxygenation.

6.3.2. Respiratory Status

Respiratory status will be documented by recording the worst results for the 24-hour period (from 00:00 to 23:59 hours) on each assessment day while in the hospital. For the Baseline score on Day 1, record the status at randomization. For all other assessment days, record the worst status for that assessment day's 24-hour period. For example, for Day 14, record the worst status that occurred on Day 14 from 00:00 to 23:59 hours.

For subjects discharged from hospital before Day 56, respiratory status will be followed by telehealth visits or other methods. Record the worst respiratory status regarding oxygen

supplementation for that assessment day's 24-hour period (from 00:00 to 23:59 hours). For example, for Day 21, record the worst status that occurred on Day 21 from 00:00 to 23:59 hours.

Respiratory Status assessments will include the following:

- Respiratory rate (record highest).
- Oxygen supplementation (record highest, listed from lowest to highest).
  - Room air.
  - Nasal cannula.
  - Face mask.
  - Noninvasive ventilation or high-flow oxygen devices.
  - ECMO.
  - Mechanical ventilation.
- Oxygenation: (record lowest SpO_2 at rest or partial pressure of oxygen [PaO_2]).
- Chest X-ray or CT scan findings (if available).

6.3.3. Cytokine Panel and Other Laboratory Parameters

The markers included in the cytokine storm panel and the cytokine limited panel are presented in Appendix A. CRP will be collected independent of the cytokine storm panel per the SCHEDULE OF EVENTS. The cytokine storm panel, the cytokine limited panel, CRP, and, if possible, Substance P will be performed by a central laboratory.

Information from the following standard-of-care laboratory tests will be provided to the Sponsor and recorded in the eCRF, for the following analytes, if available:

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

Detailed instructions on sample collection, processing, and storage are provided in the Laboratory Manual.

6.3.4. Viral Load

SARS-CoV-2 viral RNA load qPCR test will be analyzed by the central laboratory. Heron will retain the viral load samples for potential future retrospective analyses.

The method(s) for collecting samples will be described in the Laboratory Manual.

6.3.5. COVID-19 Symptoms

For subjects who are not receiving mechanical ventilation, record each COVID-19 symptom from the list below as none, mild, moderate, or severe. For the Baseline status on Day 1, record the status at randomization and the symptoms onset time(s). For all other assessment days, record the symptoms based on the average severity per subject report during the assessment day's 24-hour period (from 00:00 to 23:59 hours).

None: Symptom not present.

Mild: Event is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.

Moderate: Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

- 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.

6.4. Safety Assessments

6.4.1. Adverse Events

All AEs, regardless of causality or seriousness, will be recorded from the time the subject or legally authorized representative signs the ICF through Day 56. Additional safety monitoring and reporting information is provided in Section 8.

An abnormal finding from any safety assessment that meets the definition of an AE or requires medical intervention (eg, medication, intravenous fluids) should be deemed clinically significant by the Investigator and must be recorded as AE.

Any abnormal finding from a safety assessment that is not considered clinically significant should not be recorded as an AE.

6.4.2. Prospective Assessment of Anaphylaxis

Anaphylaxis events will be prospectively assessed after each study drug administration using Sampson's criteria (Sampson 2006) modified for the COVID-19 study population.

Anaphylaxis is highly likely when the following criteria are fulfilled:

- Acute onset of an illness (within minutes to several hours of study drug administration) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

  AND AT LEAST ONE OF THE FOLLOWING

  a. New or worsening respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia).
  b. New or worsening reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

If present, anaphylaxis will be recorded as an AE (Section 8.1).

6.4.3. Physical Examinations

A symptom-directed physical examination should be performed at Screening and when appropriate to evaluate an AE.

Baseline height and weight measurements will be conducted at Screening.

6.4.4. Vital Signs

Information from standard-of-care vital signs will be provided to the Sponsor and recorded in the eCRF. Vital sign measurements will be documented by recording the minimum and maximum values during each assessment day's 24-hour period (from 00:00 to 23:59 hours) for SBP, DBP, resting heart rate, and body temperature.

6.4.5. 12-Lead Electrocardiograms

Standard digital 12-lead ECGs will be performed in triplicate at Screening only. The mean of the 3 ECG recordings will be used as the Baseline result. Subsequently, for subjects receiving hydroxychloroquine/chloroquine, if they are not on continuous ECG monitoring, daily single ECGs will be performed. For subjects not receiving hydroxychloroquine/chloroquine, record the results of a standard-of-care ECG if performed. For all subjects on continuous ECG monitoring, record the results of a standard-of-care ECG if performed.

Any abnormal ECG result deemed clinically significant by the Investigator must be recorded as an AE, and the abnormal ECG result must be recorded on an eCRF (scheduled or unscheduled assessment eCRF, as applicable).

6.4.6. Clinical Laboratory Tests

Information from standard-of-care diagnostic and safety laboratory tests will be provided to the Sponsor and recorded in the eCRF.

Blood samples will be collected for diagnostic screening tests and for safety laboratory tests (hematology and serum chemistry) at the study site.

Clinical laboratory assessments at other days may be conducted if required by clinical need or local practice. All laboratory testing will be completed by local laboratories. From Day 1 through Day 56 or discharge, whichever occurs first, the Sponsor will be provided with results for the analytes listed in Table 2.

For Day 1 tests, the most recent result before dosing should be used. After Day 1, when more than 1 result is available in the daily 24-hour period (from 00:00 to 23:59 hours), the highest result should be reported in the eCRF. Exceptions include analytes for which a low result is considered clinically significant (eg, hypokalemia, hyponatremia).

Laboratory results will be reviewed by the Investigator. Laboratory values outside of the normal reference range will be evaluated for clinical significance. An abnormal laboratory result deemed clinically significant by the Investigator must be recorded as an AE.

Table 2: Clinical Laboratory Analytes

Diagnostic Screening Tests (Local Laboratory):	
Pregnancy test: Human chorionic gonadotropin test (female subjects of childbearing potential only) SARS-CoV-2 diagnostic test: PCR, antigen, IgM antibody. If a PCR is not performed as the diagnostic test at Screening, the PCR viral load at Baseline will be the confirmatory test for diagnosis of SARS-CoV-2.	
Diagnostic and Safety Laboratory Tests (Local Laboratory):	
Hematology	**Serum Chemistry**
Hematocrit Hemoglobin Platelet count White blood cell count (with automated differential) Absolute neutrophils Absolute lymphocytes	Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Creatinine Glucose Total bilirubin Sodium Potassium Bicarbonate Total protein Albumin

Abbreviations: PCR, polymerase chain reaction

6.5. Pharmacokinetic Assessments

Blood samples for aprepitant PK analysis will be collected from subjects per the SCHEDULE OF PK BLOOD SAMPLE COLLECTION. Blood samples may be collected using a properly maintained indwelling cannula. Samples will be sent to a bioanalytical laboratory for analysis.

Detailed instructions on sample collection, processing, storage, and shipping procedures are provided in the Laboratory Manual.

Plasma samples may also be used to measure concentrations of hydroxychloroquine and chloroquine in subjects who experience a serious AESI of QTcF prolongation >500 ms that may be considered related to hydroxychloroquine or chloroquine use.

7. GUIDANCE FOR COMPLETING PROCEDURES AND ASSESSMENTS

Study procedures and assessments are described in Section 6. The timing of procedures and assessments is provided in the SCHEDULE OF EVENTS, SCHEDULE OF EVENTS POST-DISCHARGE, and SCHEDULE OF PK BLOOD SAMPLE COLLECTION tables. Time 0 will be the start of study drug administration on Day 4 for PK assessments. Unless there is a safety concern, every effort should be made to avoid protocol deviations by completing procedures and assessments according to the protocol guidance.

During the Screening period, serum or urine pregnancy tests (female subjects of childbearing potential only) should be performed and confirmed as negative prior to performing any additional assessments. The definition of childbearing potential is provided in Section 9.1.

When assessments that involve direct interaction with the subject are scheduled at the same timepoint, perform the assessments in the order of least invasive (eg, assessing clinical status) to most invasive (eg, blood sample collection), as appropriate.

Unscheduled assessments should be performed if clinically indicated in the opinion of the Investigator to investigate an AE (for example, blood samples to assess drug concentrations or for clinical laboratory tests). The results of any unscheduled assessments should be recorded on the eCRF.

8. SAFETY MONITORING AND REPORTING

Investigators are responsible for the detection, assessment, and documentation of AEs, including serious adverse events (SAEs), unanticipated problems, and pregnancies, as detailed in this protocol.

Investigators must review the IB to be aware of the safety-related events that may be anticipated with its use.

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

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 physical examination finding, laboratory value, vital sign result, or ECG finding deemed clinically significant by the Investigator must be reported as an AE. A clinical diagnosis, rather than a change in a laboratory analyte or other assessment, should be recorded (eg, anemia rather than low hemoglobin value).

Examples of AEs include the following:

- Significant or unexpected worsening or exacerbation of the condition or indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition (eg, abnormal physical examination finding).
- Signs, symptoms, or clinical sequelae of a suspected interaction.
- Signs, symptoms, or clinical sequelae of a suspected overdose of the study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur).
- The following abnormal laboratory results:
  - Any laboratory abnormality suggestive of a new disease/organ toxicity or a worsening of a pre-existing condition.
  - Any laboratory abnormality that required the subject to have study drug interrupted or discontinued.
  - Any laboratory abnormality that required the subject to receive specific treatment for the laboratory abnormality.
  - Any laboratory abnormality that required further diagnostic investigation and/or follow-up visits (excluding repeat testing to confirm the abnormality).

The following examples are not considered AEs:

- Medical or surgical procedure (eg, endoscopy, appendectomy), although the condition that leads to the procedure is an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen.
- The disease or disorder being studied; or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition.
- Transient paresthesia that is considered to be clinically normal (would be expected to occur as a long-acting local anesthetic wears off).

8.1.2. Definition of a Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE (ie, an AE that presented an immediate risk of death from the event as it occurred. This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following events do not meet the definition of an SAE:

- Hospitalization for the following:
  - Elective treatment of a pre-existing condition that does not worsen from baseline.
  - A standard procedure for study drug administration and routine monitoring of the studied indication not associated with any deterioration in condition.
- Social or convenience admission to a hospital.
- Prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE.

- Hospitalization or an emergency room visit that lasts less than 24 hours and does not meet the criteria of an important medical or a life-threatening event.

8.1.3. Adverse Events of Special Interest

AESIs are events of anaphylaxis (Section 6.4.2) and of QTcF prolongation (>500 ms). The Investigator is responsible for reporting all AESIs within 24 hours of becoming aware of the event.

8.1.4. Definition of Unanticipated Problems

Unanticipated problems are incidents, experiences, or outcomes that meet all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the research protocol and informed consent document approved by the Ethics Committee (EC; includes Institutional Review Boards [IRBs], Independent Ethics Committees [IECs], and Research Ethics Boards [REBs]) and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

The Investigator will assess the severity of each AE based on his/her clinical judgment using one of the following categories:

- **Mild:** Event is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate:** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2. Relationship to Study Drug

The Investigator will assess the relationship of each AE to study drug (aprepitant injectable emulsion and saline placebo) based on his/her clinical judgment. The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in

determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

Relationship to study drug will be assessed according to the following guidelines:

- **Possibly related:** The AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between the study drug and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.
- **Unlikely related:** There is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.

An SAE, including a serious AESI, considered by the Investigator to be possibly related to the study drug is a SAR. Even in situations in which minimal information is available for initially reporting an SAE, it is important that the Investigator always make an assessment of causality for every event when entering the information into the eCRF or completing the SAE reporting form, in the event electronic data capture (EDC) is not available. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his or her opinion of causality in light of follow-up information and amend the SAE information accordingly in the eCRF or the SAE reporting form, as applicable.

8.3. Time Period and Frequency for Event Assessment and Follow Up

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All AEs will be recorded from the time the subject or legally authorized representative signs the ICF through Day 56.

For subjects who received study drug, if an Investigator becomes aware of an SAE that occurs after the subject's participation in the study ends and the Investigator considers the event to be possibly related to the study drug, the Investigator needs to report the SAR to the Sponsor as described in Section 8.4.1.

8.3.2. Follow-Up of Events

After the occurrence of an AE, the Investigator is required to follow each subject proactively and provide further information on the subject's condition. All AEs documented at a previous visit or contact and designated as ongoing will be reviewed at subsequent visits or contacts.

Nonserious AEs will be followed after the last scheduled study visit until the event resolves, the condition stabilizes, or until the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the subject is lost to follow-up or withdraws consent).

The Investigator will assess the outcome of each AE using the following categories:

- **Recovered/Resolved:** The event resolved or the subject recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.

- **Recovered/Resolved with sequelae:** The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
- **Recovering/Resolving**: The event is improving.
- **Not recovered/Not resolved:** At the end of the study, a nonserious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown:** The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown.
- **Fatal**

SAEs will be followed until the event resolves (ie, when the event no longer meets any of the seriousness criteria), the condition stabilizes, or the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the subject is lost to follow-up or withdraws consent). The Investigator will ensure that follow-up information provided to the Sponsor includes results of any additional laboratory tests or investigations, histopathologic examinations, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both. New or updated information will be recorded as outlined in Section 8.4.1.

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

If the Investigator determines that an event that occurs during the course of this study meets the protocol definition of an SAE (see Section 8.1.2) due to any cause, regardless of relationship to study drug, he/she must notify the Sponsor by entering the SAE information into the eCRF **within 24 hours of the Investigator becoming aware of the SAE**.

If EDC is not available, the Investigator must complete an SAE reporting form and email it to the Sponsor **within 24 hours of the Investigator becoming aware of the SAE**. The Investigator must also enter the SAE information into the eCRF as soon as possible thereafter.

Email Address: Heron_PV@ubc.com

The following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE.

EDC is the primary method for notification of SAE information. In rare circumstances and in the absence of email capacity, notification by fax or telephone is acceptable, with a copy of the SAE reporting form sent by overnight mail. Initial notification via telephone does not replace the need for the Investigator to complete the SAE information in the eCRF within the time frames outlined.

If the Investigator does not have all information regarding an SAE, he/she must not wait to receive additional information before notifying the Sponsor of the event. The SAE must be updated when additional information is received using the same process and timelines as for the initial report.

8.4.2. Reporting Unanticipated Problems to the Sponsor

If the Investigator determines that an event meets the protocol definition of an unanticipated problem (see Section 8.1.4), he/she must notify the Sponsor by completing an Unanticipated Problem Form and emailing it to the Sponsor **within 24 hours of the Investigator becoming aware of the problem**.

Email Address: Heron_PV@ubc.com

The following information will be included with unanticipated problem reporting:

- Protocol identifying information: protocol title, protocol number, and Investigator's name.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem.

It is the Investigator's responsibility to report any unanticipated problem to the Sponsor and their EC, as required by local regulations.

8.4.3. Regulatory Reporting Requirements

The Investigator must promptly report all SAEs to the Sponsor in accordance with the procedures detailed in Section 8.4.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that serious suspected adverse reactions that are either unexpected or observed with increasing occurrence and all serious AESIs be reported and legal obligations and ethical responsibilities regarding the safety of other subjects are met.

Mortality or progression to mechanical ventilation or ECMO will not be collected unless considered drug-related, because these events are collected and reported as part of the efficacy endpoints. The following events will not be notified to regulatory authorities as an expedited report: SAEs relating to mortality or mechanical ventilation except when there is evidence suggesting a causal relationship between study drug and the event, or an aggregate analysis identifies a safety concern.

The Investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the EC.

The Sponsor is responsible for informing ECs, Investigators, and regulatory authorities of any finding that could adversely affect the safety of subjects or affect the conduct of the study. Events will be reported to regulatory authorities in accordance with expedited and periodic

reporting requirements. Serious AESIs will be reported to regulatory authorities as an expedited report.

Investigator letters are prepared according to Sponsor policy and are forwarded to the Investigators as necessary. An Investigator letter is prepared for any suspected adverse reaction that is attributable to study drug, serious, and unexpected. The purpose of the Investigator letter is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

8.4.4. Pregnancy Reporting

Pregnancy is not considered to be an AE; however, study drug must be discontinued immediately for any subject who becomes pregnant during the study. Female subjects who become pregnant within 28 days after receiving study drug should also notify the Investigator. The Investigator must attempt to follow the pregnancy to term or termination in order to report on outcome and health status of mother and child.

The Investigator must notify the Sponsor of any pregnancy by completing a Pregnancy Form and emailing it to the Sponsor **within 24 hours after the Investigator becomes aware of the pregnancy**.

Email Address: Heron_PV@ubc.com

8.5. Safety Oversight

Safety oversight will be provided by an IRC, as described in Section 13.2. In addition, the PSRMC will monitor blinded safety data on a periodic basis throughout the study. A detailed description of safety oversight is provided in the Safety Monitoring Plan for this study.

The criteria for suspending enrollment for safety issues are provided in Section 3.4 and for terminating the study or closing a study site for safety issues in Section 13.6.

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are not in a relationship; and women whose partners have been vasectomized or have received or are utilizing mechanical contraceptive devices.

Females must either practice abstinence from heterosexual contact or agree to use an acceptable form of birth control from the time of Screening, during the study, and for 28 days after the last dose of study drug. Acceptable forms of contraception include being in a monogamous relationship with a partner who is surgically sterile; practicing abstinence; or agreeing to use double-barrier contraception or a nonhormonal intrauterine device (eg, copper) in the event of sexual activity. Note: Female subjects in only a same-sex relationship do not need to meet this criterion. Hormonal contraceptives are not an acceptable form of birth control since the efficacy of hormonal contraceptives may be reduced with aprepitant injectable emulsion.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

All efficacy and safety data will be listed by subject. Unless otherwise specified, Baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to first dose of study drug. All safety and efficacy endpoints will be summarized by treatment group. Continuous variables will be summarized using the number of subjects with data (n), mean, SD, median, minimum, and maximum. Selected continuous variable summaries will also include the SE. Categorical variables will be summarized using frequency and percentages. For time to event analyses, follow-up time starts when subjects are randomized. Additional statistical details will be described in the statistical analysis plan (SAP).

10.2. Determination of Sample Size

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

10.3. 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.

PK Population: All subjects who receive 1 dose of study drug on Day 4 and have sufficient data to calculate PK parameters and do not have protocol deviations thought to significantly affect the PK of aprepitant will be included in the PK population.

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

The number and percentage of subjects in each analysis population will be summarized. Subject disposition, including the number of subjects screened, randomized, dosed, completing the 14-day treatment period, completing the Day 56 Visit, and not completing the Day 56 Visit by reason for withdrawal will be summarized. Subject demographics and baseline characteristics will be summarized for the ITT Population and the Safety Population and will include age, age category, sex, race, ethnicity, height, weight, and BMI.

10.4.2. Efficacy Analyses

10.4.2.1. Primary Efficacy Analysis

The proportion of subjects alive and discharged from the hospital at Day 14 will be analyzed using Fisher's exact test 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.

10.4.2.2. Secondary Efficacy Analyses

Time to death or respiratory failure will be analyzed using Kaplan-Meier methods. Kaplan-Meier plots will be presented by treatment arm and the log-rank test will be used to make pairwise comparisons between treatment arms. Median time to death or respiratory failure, 95% CIs, and p-values will be summarized. 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.

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

Individual and group changes from Baseline in 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.

[redacted]

[redacted]

[redacted]

10.4.3. Handling of Missing Data

The SAP will describe the handling of missing data for the various study endpoints.

10.4.4. Study-Wise Type I Error Control

Unless otherwise specified, all statistical hypothesis testing will be 2-sided using α level= 0.05. Analyses of pairwise comparisons will not be adjusted for multiple comparisons. Details will be provided in the SAP.

10.4.5. Safety Analyses

Safety data will be presented both separately and pooled.

All safety data will be listed and summarized by treatment group; no statistical hypothesis testing will be performed. Incidence of AEs, SAEs, adverse reactions, and AESIs will be coded and tabulated by System Organ Class (SOC) and Preferred Term (PT). AESIs are events of anaphylaxis and of QTcF prolongation (>500 ms).

AEs that occur between the time the subject or legally authorized representative signs the ICF and the start of study drug administration will be considered as non-treatment emergent AEs. AEs that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered TEAEs.

Incidence of TEAEs will be summarized by SOC and PT across treatment arms.

TEAEs leading to study drug discontinuation, if any, will be listed separately.

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. Individual subject values will be listed and values outside of the standard reference range will be flagged. 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. Changes in vital sign parameters and ECG parameters will be summarized.

10.4.6. Pharmacokinetic Analysis

Plasma aprepitant concentrations will be determined using a validated liquid chromatography tandem-mass spectrometry assay. Concentrations will be calculated by interpolation from a calibration curve. PK parameters will be calculated using noncompartmental analysis.

Concentrations of hydroxychloroquine and chloroquine may also be determined using a validated liquid chromatography tandem-mass spectrometry assay. Concentrations will be calculated by interpolation from a calibration curve.

Additional details will be provided in the PK Analysis Plan.

10.5. 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. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and quality control systems will be implemented and maintained by the Sponsor and its designee(s), as appropriate, following Standard Operating Procedures to ensure that the clinical study is conducted and the data are generated, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) E6 GCP guidelines, and applicable regulatory requirements. The accuracy, completeness, and reliability of the study data presented to the Sponsor, however, are the responsibility of the Investigator. The Investigator or designee must record all required data using the prespecified data collection method defined by the Sponsor or its designee.

The study will be monitored regularly by the Sponsor (Section 13.1) and may be audited by the Sponsor (or designee) or inspected by a regulatory authority at any time during the study or after study completion. In the event of an audit or inspection, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the competent authority, or other regulatory authority direct access to all study records. The Investigator will immediately notify the Sponsor of all audits or inspections scheduled by any regulatory authority and promptly forward to the Sponsor copies of any inspection reports received.

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before any site may initiate the study in that country.

12.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol and all applicable regulatory requirements in accordance with ICH/GCP and in general conformity with the most recent version of the Declaration of Helsinki.

12.3. Ethics Committee Approval

The Investigator or the Sponsor is responsible for submitting the following documents to the ECs for review and, if applicable, approval: study protocol, ICF(s), IB, recruitment materials, information about study compensation to subjects, and any information for presentation to potential subjects.

The Investigator is responsible for providing the Sponsor with the written EC approval prior to commencing the study (ie, before shipment of study drug to the site). All amendments to the protocol require review and approval by the EC before the changes to the study are implemented. All changes to the ICF will be approved by the EC; a determination will be made regarding whether previously consented participants need to be re-consented. If any other information previously approved by the EC for presentation to potential subjects is amended during the study, the Investigator is also responsible for ensuring EC review and re-approval.

Study sites must adhere to all requirements stipulated by their respective ECs. This may include, but not be limited to, notifying the EC of serious and unexpected AEs or other local safety reporting requirements, submitting a final status report, or providing a synopsis of the study report upon study completion.

12.4. Informed Consent Process

Note: All references to “subject” in this section refer to the study subject or his/her legally authorized representative.

The Sponsor (or its designee) will provide Investigators with an ICF for this study. Investigators may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 Code of Federal Regulations [CFR] Part 50.25). The final ICF must be accepted by the Sponsor and approved by the EC. Investigators must provide the Sponsor with an unsigned copy of the final ICF before and after it is approved by the EC. If any new information becomes available that might affect subjects’ willingness to participate in the study, or if any amendments to the protocol require changes to the ICF, the Sponsor will provide Investigators with a revised ICF.

Prior to participating in any study-related procedure, each subject must sign and date an EC-approved ICF written in a language the subject can understand. The ICF should be as

nontechnical as practical and understandable to the subject. The ICF must provide the subject with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, possible risks, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF details the requirements of the participant and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to his/her further medical care. The ICF should also include a statement educating subjects about the continued scientific importance of their data if they discontinue study treatment early or withdraw from the study. Before informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject.

Once signed, the original ICF will be stored in the Investigator's site file and made available for review by the Sponsor. Documentation of the informed consent discussion must be noted in the subject's case history. All subjects will receive a copy of their signed and dated ICF.

If the ICF is revised during the study and requires the subject to be re-consented, informed consent will be obtained in the same manner as for the original ICF.

12.5. Confidentiality

All information provided by Heron Therapeutics, Inc. and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the Investigator and site staff. This information and data will not be used by the Investigator or other site personnel for any purpose other than conducting the study and will not be released to any unauthorized third party without prior written approval of the Sponsor. These restrictions do not apply to the following: 1) information that becomes publicly available through no fault of the Investigator or site staff, 2) information that must be disclosed in confidence to an EC solely for the evaluation of the study results, 3) information that must be disclosed in order to provide appropriate medical care to a study subject, or 4) study results that may be published as described in Section 13.7. If a written contract for the conduct of the study is executed and that contract includes confidentiality provisions inconsistent with this statement, that contract's confidentiality provisions shall apply rather than this statement; provided, however, that the confidentiality provisions in any written contract shall not be less restrictive than this statement.

The Investigator agrees to comply with all applicable national, state, and local laws and regulations relating to the privacy of a subject's health information. The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act (HIPAA) and in a form satisfactory to the Sponsor.

The subject's contact information will be securely stored at each clinical site for internal use during the study. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected in the subject's eCRF). At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the EC and institutional regulations.

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the Sponsor requires that the Investigator permit its monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate ECs to review the subject's original medical records (source data or documents), including, but not limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization by the subject as part of the informed consent process (Section 12.4).

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

The Sponsor (or its designee) is responsible for ensuring the proper conduct of the study. This includes ensuring the subjects' rights and well-being are protected, the conduct of the study is within compliance of an approved protocol and GCPs, and the integrity of the data are accurate, complete, and verifiable from source documentation. During the study, the Sponsor's study monitors will contact the study site via site visits or remote monitoring (eg, telephone calls, emails, and letters) in order to review study progress and the eCRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: subjects' informed consent process and documents, the site's essential documents, subject recruitment procedures, subjects' compliance with the study procedures, source-data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and the quality of data.

13.2. Data Monitoring Committees

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 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.

13.3. Source Documents and Record Retention

Each study site will maintain study documents and records as specified in *ICH E6, Section 8 (Essential Documents for the Conduct of a Clinical Trial)* and as required by regulatory authorities and institutional requirements. These include, but are not limited to the following: the study protocol, eCRF, delegation of authority log, pharmacy dispensing records, drug accountability logs, AE reports, subject source data (original or certified copies), correspondence with regulatory authorities and ECs, ICFs, monitoring visit logs and records, laboratory certification or quality control procedures, and laboratory reference ranges and reports. Access to study documents and records will be strictly controlled (Section 12.5).

Study documents and records must be retained for at least 2 years after the last approval of a marketing application in the US and until there are no pending or contemplated marketing applications in the US or until at least 2 years have elapsed since the formal discontinuation of clinical development of the test product. However, these documents must be retained for a longer period if required by applicable regulatory requirements or if agreed to in the Clinical Trial Agreement. It is the responsibility of the Sponsor to inform the site as to when these documents no longer need to be retained.

13.4. Management of Protocol Amendments and Deviations

13.4.1. Protocol Amendments

The protocol cannot be modified except in a formal protocol amendment by the Sponsor.

13.4.2. Protocol Deviations

A protocol deviation is a change, divergence, or departure from the study design or procedures defined in this protocol. The Investigator will notify the EC of any protocol deviations as required by EC guidelines and site requirements. Protocol deviations will be documented at the site and in the Sponsor files.

13.5. Financial Disclosure

The Sponsor will determine whether the study is a Covered Clinical Study and is subject to 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

For a Covered Clinical Study, Investigators are required to inform the Sponsor of all disclosable financial interests or arrangements (including those of their spouse and dependent children), prior to study initiation at the site, at study completion, and any changes after 1 year after study completion in accordance with 21 CFR Part 54. In addition, the Investigator or subinvestigators must promptly notify the Sponsor if there are any reportable changes that occur during the above described period.

Disclosable financial interests or arrangements, or the absence thereof will be recorded on the Financial Disclosure for Clinical Investigators Form.

Any Investigator(s) added as investigational staff to the FDA 1572 form must complete the Financial Disclosure for Clinical Investigators Form at the start of his/her participation in the study.

13.6. Termination of the Study or Closure of a Study Site

If the Sponsor, Investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Investigator(s).

13.6.1. Study Termination

If the study is terminated early by the Sponsor, written notification documenting the reason for study termination will be provided to the Investigator and regulatory authorities. The Investigator will promptly inform the EC and provide the reason(s) for study termination.

13.6.2. Closure of a Study Site

If the Sponsor, Investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Investigator(s). Reasons for closing a site include, but are not limited to, the following:

- Failure of the Principal Investigator to comply with the protocol, GCP regulations and guidelines, or local requirements.
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data.
- Insufficiently complete and/or evaluable data.

- Inadequate recruitment of subjects by the Investigator.
- Sponsor decision.

If a study site is closed by the Sponsor, written notification documenting the reason for study site closure will be provided to the Investigator and regulatory authorities. The Investigator will promptly inform the EC and provide the reason(s) for study site closure.

13.7. Publication and Information Disclosure Policy

All information provided by the Sponsor and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of Heron Therapeutics, Inc.

For clinical interventional studies in patients, Heron will post study results on websites such as https://clinicaltrials.gov/ and https://eudract.ema.europa.eu/ in accordance with FDA and European Union reporting rules. Regardless of study outcome, Heron commits to submit for publication results of its interventional clinical studies according to the prespecified plans for data analysis. Wherever possible, Heron also plans to submit for publication the results of any nonclinical or technology studies while protecting any proprietary information.

Any publication or presentation of the results of this study may only be made in compliance with the provisions outlined in the executed Clinical Trial Agreement. Heron has developed a policy for the publication of scientific and clinical data that follows the recommendations of the International Committee of Medical Journal Editors (ICMJE), the Consolidated Standards of Reporting Trials (CONSORT) group, and Good Publication Practice (GPP). A copy of this policy will be made available to the Investigator upon request.

When the study is completed or prematurely terminated, the Sponsor or designee will ensure a Clinical Study Report is written in compliance with ICH E3 (Structure and Content of Clinical Study Reports) and submitted to the regulatory authorities, as required by the applicable regulatory requirement(s). Where required by applicable regulatory requirements, the Investigator signatory will be identified for the approval of the Clinical Study Report. The Investigator will be provided reasonable access to statistical tables, listings, and figures, as well as relevant reports, and will have the opportunity to review the complete study results.

14. REFERENCE LIST

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APPENDIX A. CYTOKINE PANELS

Table 3: Cytokine Storm Testing for SARS-CoV-2/COVID-19

Test/Abbreviation	Full name
A2Macro	Alpha-2-macroglobulin
AAT	α1-antitrypsin
Adiponectin	Adiponectin
B2M	β2 microglobulin
BDNF	Brain-derived neurotrophic factor
C3	Complement component 3
CRP	C-reactive protein
EN-RAGE	Extracellular newly identified RAGE binding protein
Eotaxin-1	Eotaxin-1
Ferritin	Ferritin
Fibrinogen	Fibrinogen
Gm-CSF	Granulocyte-macrophage colony-stimulating factor
Haptoglobin	Haptoglobin
ICAM-1	Intercellular adhesion molecule 1
IFN-gamma	Interferon
IgA	Immunoglobulin A
IgM	Immunoglobulin M
IL-1 alpha	Interleukin 1 alpha
IL-1 beta	Interleukin -1 beta
IL-10	Interleukin -10
IL-12p40	Interleukin -12p40
IL-12p70	Interleukin -12p70
IL-18	Interleukin -18
IL-18	Interleukin -18
IL-1ra	Interleukin -1ra
IL-2	Interleukin -2
IL-23	Interleukin -23
IL-3	Interleukin -3
IL-4	Interleukin -4
IL-5	Interleukin -5
IL-6	Interleukin -6
IL-7	Interleukin -7

Test/Abbreviation	Full name
IL-8	Interleukin -8
Lp(a)	Lipoprotein (a)
MCP-1	Monocyte chemoattractant protein-1
MIP-1 alpha	Macrophage inflammatory protein-1
MIP-1 beta	Macrophage inflammatory protein-1
MMP-3	Matrix metalloproteinase 3
MMP-9	Matrix metalloproteinase 3
Myoglobin	Myoglobin
PAI-1	Plasminogen activator inhibitor 1
PARC	Pulmonary and activation-regulated chemokine
RANTES	Regulated on activation normal T cell expressed and secreted
SAP	SLAM-associated protein
SCF	Stem cell factor
TBG	Thyroxine-binding globulin
TIMP-1	Metallopeptidase inhibitor 1
TNF-alpha	Tumor necrosis factor alpha
TNF-beta	Tumor necrosis factor beta
TNFRS	Tumor necrosis factor receptors
VCAM-1	Vascular cell adhesion molecule-1
VDBP	Vitamin D-binding protein
VEGF	Vascular endothelial growth factor
vWF	von Willebrand factor

Table 4: Cytokine Limited Panel

Test Abbreviation	Full name
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IFN-gamma	Interferon gamma
IL-2	Interleukin 2
IL-3	Interleukin -3
IL-4	Interleukin -4
IL-5	Interleukin -5
IL-6	Interleukin -6
IL-7	Interleukin -7
IL-8	Interleukin -8
IL-10	Interleukin -10
IL-18	Interleukin -18
MIP-1 alpha	Macrophage inflammatory protein-1 alpha
bMIP-1 beta	Biotinylated MIP beta
MCP-1	Monocyte chemoattractant protein-1
TNF-alpha	Tumor necrosis factor alpha
TNF-beta	Tumor necrosis factor beta

APPENDIX B. POST-DISCHARGE ASSESSMENTS

The subject will be contacted on Days 15, 22, 29, and 57 to collect information for the Days 14, 21, 28, and 56 assessments, respectively.

NIAID 8-Point Ordinal Scale of Clinical Status

Record the worst (ie, lowest ordinal) score for that assessment day's 24-hour period (from 00:00 to 23:59 hours). For example, for Day 21, record the worst (ie, lowest ordinal) score that occurred on Day 21 from 00:00 to 23:59 hours.

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

Record the worst respiratory status regarding oxygen supplementation (listed from lowest to highest, or worst, oxygen supplementation status) for that assessment day's 24-hour period (from 00:00 to 23:59 hours). For example, for Day 21, record the worst status that occurred on Day 21 from 00:00 to 23:59 hours.

- Room air.
- Nasal cannula.
- Face mask.
- Noninvasive ventilation or high-flow oxygen devices.
- ECMO.
- Mechanical ventilation.

COVID-19 Symptoms

Record each COVID-19 symptom from the list below as none, mild, moderate, or severe based on the average severity per subject report during the assessment day's 24-hour period (from 00:00 to 23:59 hours).

None:	Symptom not present.
Mild:	Event is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
Moderate:	Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe:	Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

- 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.

Adverse Events

Record any AEs since the last assessment.

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Approval	[redacted] 14-Dec-2020 18:25:52 GMT+0000

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