NCT04784897

CLINICAL PROTOCOL

IPI-BRIc-201

A Phase 2, Randomized, Double-blind, Placebo-controlled,
Multi-center Study to Evaluate the Efficacy and Safety of Brilacidin
in Hospitalized Participants with COVID-19

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AMENDMENT RATIONALE AND REVISIONS

AMENDMENT 2, 24 December 2020

Amendment Rationale

The purpose of this amendment is to address feedback from FDA received with IND approval for this study to proceed, and to fix minor protocol discrepancies that have been identified.

The study has not yet started. This amendment does not alter the patient population eligibility criteria.

Changes to the Protocol

Changes made to the protocol, are summarized as follows:

- Addition of hematology, blood chemistry and coagulation safety laboratory tests on Study Day 2.
- Added dose regimen as covariate (if expanded after DMC recommendation) to the analysis of the primary efficacy endpoint time to sustained recovery through Day 29.
- Text added to emphasize respiratory swab sample collection is to be pre-dose on dosing days; efforts are to be made to allow for swabs to be collected at approximately the same time each collection day throughout the study.
- Dose calculation for a subject's study treatment infusions will be based on actual body weight measured at Screening.
- Text added to clarify that blood samples for PK assessments are to be drawn from an alternate site other than the arm used for the study treatment infusion.

Changes to specific sections of the protocol are shown in the Tracked Changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

AMENDMENT 1, 04 November 2020

Amendment Rationale

The purpose of this amendment was to address feedback from FDA received on the draft protocol during the pre-IND process, and to fix minor protocol discrepancies that had been identified.

Changes to the Protocol

Changes made to the protocol, are summarized as follows:

- Inclusion criterion update: edit made to moderate COVID-19 respiratory rate ≥ 20 to < 30 breaths per minute.
- Exclusion criteria updates: addition of extracorporeal membrane oxygenation (ECMO) at the time of randomization to exclusion criterion #2; addition of moderate hepatic impairment to exclusion criterion #8; specifying male condom use throughout the study and for up to 30 days after stopping treatment.
- Primary endpoint: altered to time to sustained recovery through Day 29; censoring of subjects who die or who are lost to follow-up after/before achieving recovering prior to Day 29 updated.
- Replacement of Study Management Committee by an independent Data Monitoring Committee (DMC). The DMC will review safety data summaries and listings.
- Adverse Events of Special Interest (AESIs): edited to include paresthesias / dysesthesias.
- Individual subject discontinuation details altered, identifying that should study treatment discontinuation occur that scheduled efficacy and safety assessments should continue, unless a subject withdraws consent or is lost to follow-up.
- Study stopping criteria added.
- Additional follow-up visit, by telephone contact, included at Day 60.
- Additional assessment included: an ECG post-infusion on Day 1.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Innovation Pharmaceuticals Inc.
Name of Finished Product: Brilacidin
Name of Active Ingredient: Brilacidin tetrahydrochloride
Study Number: IPI-BRIc-201
Title of Study: A Phase 2, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Brilacidin in Hospitalized Participants with COVID-19
Study Centers: Approximately 15
Number of Subjects Planned: Approximately 120 hospitalized participants with COVID-19
Study Duration per subject: Each subject will complete the study in about 60 days, from screening at Day -1 or 1 to follow-up on Day 60 ±10 days
Phase of Development: Phase 2
Purpose and rationale: The purpose of this study is to evaluate the efficacy and safety of Brilacidin intravenous (IV) treatment in addition to current standard of care (SoC) compared with SoC alone in participants with moderate to severe COVID-19
Primary Objective(s): • To evaluate the clinical efficacy of Brilacidin IV treatment in addition to SoC, compared with SoC alone, in subjects with COVID-19
Secondary Objective(s): • To assess multiple clinical measures of disease severity and disease burden • To assess the safety and tolerability of Brilacidin IV treatment in subjects with COVID-19
Exploratory/ Other Objective(s): • In-hospital outcomes • To measure biological and immunological markers of illness/inflammation • To explore the change in the SARS-CoV-2 viral load • To estimate plasma pharmacokinetics of Brilacidin
Design and Methodology: This Phase 2 study is a randomized, blinded, placebo-controlled, parallel group design. The target population to be treated are patients with moderate to severe COVID-19, SARS-CoV-2 infection confirmed by positive standard polymerase chain reaction (PCR) test (or

equivalent/ other approved diagnostic test) within 4 days prior to starting study treatment, and hospitalized with respiratory distress but not yet requiring high-level respiratory support (as defined in exclusion criterion #2).

The study is comprised of three parts:

Screening/ Baseline visit (Day -1 to 1): Lasts up to 24-48 hours and comprises screening/ baseline assessments. This visit will confirm that study inclusion and exclusion criteria are met by participants prior to randomization.

Treatment period (Day 1-3 with potential to expand to Day 4-5): Randomized subjects will receive blinded study treatment once daily for 3 days by IV infusion, in addition to SoC.

Follow-up period (Day 4-6 through Day 60): Subjects will be assessed daily while hospitalized. Discharged patients will be asked to attend study visits at Days 15 and 29. All subjects will undergo a series of efficacy and safety assessments, including laboratory assays. Blood samples and nasopharyngeal (NP) swabs will be obtained on Days 1, 3, 5, 8, 11 (while hospitalized) and/or on day of discharge; and Days 15 and 29 (by returning to the clinic/ remote visit or if still hospitalized). **Note: NP swabs are to be collected.**

If subjects are discharged from hospital prior to Day 15, or Day 29, and a hospital visit is not possible, then visiting nursing services and mobile phlebotomy may support that visit remotely where these are available in accordance with local guidelines and should include all possible assessments (e.g., oxygen saturation with portable monitors). Every effort should be made to ensure discharged patient follow-up at Days 15 and 29, via a healthcare interaction (minimally by telephone call). A follow-up visit at Day 60(±10), by telephone call, is also included to confirm patient status.

Study Treatments

All subjects receive local SoC, plus allocated study treatment in addition. Two IV study treatment arms are planned:

- SoC + Brilacidin IV 0.6 mg/kg (D1), 0.3 mg/kg (D2 and D3) with potential to expand dosing[a] of 0.3 mg/kg on D4 and D5
- SoC + Saline IV infusion (D1, D2, and D3) with potential to expand dosing[a] on D4 and D5

[a] Note: Dependent on safety review and recommendation by the Data Monitoring Committee (DMC).

D1, D2, and D3 (above) refer to Day 1, Day 2 and Day 3 of study treatment. Similarly, D4 and D5 are Day 4 and Day 5.

Treatment randomization is 1:1 (n=60 per arm). Randomization will also be stratified by (1) Age (≤65 years, >65 years), (2) Severity of disease (moderate, severe), and (3) Country.

Interim Analyses and Data Monitoring Committee Oversight

An independent Data Monitoring Committee (DMC) will be established to conduct periodic safety reviews. An initial safety review is planned to occur after approximately 20 randomized subjects have completed up to Day 15, and a further safety review by the DMC is planned to occur after approximately 50% of subjects have completed up to Day 29. The DMC may

recommend expanding dosing to Days 4 and 5 (at the same doses as on Days 2 and 3), continuation of the Days 1-3 study dosing unchanged, or that the trial be interrupted or stopped for safety reasons. Details of the DMC will be prepared separately from this protocol in a DMC Charter; the charter may supersede the summary details presented here in the protocol.

Inclusion Criteria:

- Signed and dated written Informed Consent Form (ICF) to participate in the clinical study by patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative.
- Male or non-pregnant female adults between 18 and 80 years of age, inclusive, at time of informed consent.
- SARS-CoV-2 infection confirmed by positive standard polymerase chain reaction (PCR) test (or equivalent/ other approved diagnostic test) ≤ 4 days before randomization.
- Currently hospitalized and requiring medical care for COVID-19.
- Moderate OR severe COVID-19, defined by respiratory function at screening, as below:

  Moderate, meets at least one of the following criteria:
  - Peripheral oxygen saturation SpO_2 > 93% on room air;
  - Respiratory rate ≥ 20 to < 30 breaths per minute.

  Severe, meets at least one of the following criteria:
  - Peripheral oxygen saturation SpO_2 ≤ 93% on room air OR arterial oxygen partial pressure (PaO_2) / fraction of inspired oxygen (FiO_2) < 300mmHg (1mmHg=0.133kPa) [corrective formulation should be used for higher altitude regions (over 1000m)];
  - Respiratory rate ≥ 30 breaths per minute.
- Body mass index (BMI) of ≥18 to <40kg/m^2 at screening.
- Agrees to the collection of nasopharyngeal (NP) swabs and venous blood per protocol.
- In the opinion of the investigator, willing and able to comply with the study protocol assessments, and is committed to the study and the study follow up visits.

Exclusion Criteria:

- Participation in any other clinical trial of an experimental agent treatment.
- Requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) at the time of randomization.
- Has explicitly expressed the wish not to receive intensive care support (Do not resuscitate or Do not intubate order) should this become necessary.
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 72 hours, irrespective of the provision of treatment, such as rapidly progressive multiorgan failure.
- Requiring systemic anti-infective therapy for suspected or confirmed active bacterial/fungal/viral systemic infection other than COVID-19.

- Hypertensive urgency (e.g., SBP >220 mmHg or DBP >120 mmHg) or hypertensive emergency within the last 72 hours, as assessed by the investigator following local guidelines.
- If has a history of hypertension in the last 3 months, must have been receiving appropriate anti-hypertensive therapy in accordance with local guidelines.
- Evidence of moderate or severe hepatic impairment (Child-Pugh Class B or C).
- Estimated GFR (eGFR) <30 mL/min/1.73m^2 (based on CKD-EPI formula).
- Prior to a participant's study entry, known allergies or intolerance to Brilacidin or formulation excipients.
- Any serious medical or psychiatric condition or test abnormality(ies) that, in the investigator's judgment, puts the participant at significant risk, could confound the study results, or may interfere significantly with the subject's safe participation in and completion of the study.
- Pregnancy or breast-feeding, or positive urine or serum pregnancy test in a pre-dose assessment.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception as defined below, throughout the study and for up to 30 days after stopping treatment.

  Effective contraception methods include:

  - Total abstinence (if this is the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before start of study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
  - Male partner sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that female subject.
  - Double barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
  - Use of oral*, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. (*In the case of oral contraception, subjects should have been using the same pill on a stable dose for a minimum of 3 months before start of study treatment).
  - Intrauterine device (IUD) or intrauterine system (IUS)

  Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before start of study treatment. In the case of oophorectomy alone, only

when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

In addition, female subjects must also refrain from egg donation and in vitro fertilization during study treatment and for 7 days after stopping study treatment.

- Sexually active males with female partners of childbearing potential unwilling to use a condom when engaging in intercourse of reproductive potential throughout the study and for up to 30 days after stopping treatment.

  In addition, male participants must not donate sperm during study treatment and for 7 days after stopping study treatment.

Test Product, Dose, and Mode of Administration:

Brilacidin for Injection is provided as a sterile frozen solution containing 50 mg/mL of Brilacidin free base and 20% w/v hydroxypropyl-beta-cyclodextrin (Kleptose HPB) in water for injection. Brilacidin sterile concentrated solution is a clear, colorless to yellow to brown solution supplied in 2 mL glass vials with a fill volume ~1.2 mL to ensure 1.0 mL extractable volume per vial. The sterile solution formulation provided requires further dilution with normal saline for subsequent intravenous infusion.

The 2 mL glass vials are labelled as containing "Brilacidin for Injection, 50 mg/mL (free base) for 1.0 mL extractable volume".

For intravenous infusion administration, Brilacidin for Injection is diluted in sterile 0.9% w/v sodium chloride (normal saline) to provide the desired final dose within 8 hours of administration. Diluted Brilacidin drug product is stored at room temperature not above 25°C, 77°F, prior to use and is filtered through a 0.2 μm membrane when administered intravenously over 60 minutes. Placebo IV infusion will be sterile saline.

Brilacidin IV infusion requires unblinded pharmacist (or appropriate designee) preparation at the study site; allows for blinded treatment administration by use of local blinded labelling. A separate pharmacy manual will be provided. Dose calculation for a subject's study treatment infusions will be based on actual body weight measured at Screening.

On Day 1, randomized subjects will be allocated to one of the following two IV study treatment arms in a ratio of 1:1

- SoC + Brilacidin IV 0.6 mg/kg (D1), 0.3 mg/kg (D2 and D3) with potential to expand dosing[a] of 0.3 mg/kg on D4 and D5
- SoC + Saline IV infusion (D1, D2, and D3) with potential to expand dosing[a] on D4 and D5

[a] Note: Dependent on safety review and recommendation by the DMC.

D1, D2, and D3 (above) refer to Day 1, Day 2 and Day 3 of study treatment. Similarly, D4 and D5 are Day 4 and Day 5.

The rationale for looking to expand treatment duration to five days, from the initial dose regimen of three days, is to be able to provide a longer duration of systemic Brilacidin exposure at a level that can strongly suppress SARS-CoV-2 virus activity, and any associated symptoms, and thus provide a more optimal therapy to hospitalized patients with moderate or severe COVID-19. The longer treatment duration is expected to allow for

greater impact of Brilacidin treatment and provide enhanced benefit to the patient, with the 5-day regimen incorporated only following recommendation by the DMC subsequent to DMC review of all available safety data following safety review interim analysis(es).

Endpoint(s):

Efficacy Endpoints

Primary Efficacy endpoint based on the clinical status ordinal scale:

- Time to sustained recovery through Day 29

Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale with response sustained through Day 29:

- Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than for per protocol dosing or assessments, as appropriate);
- Not hospitalized, limitation on activities and/or requiring home oxygen;
- Not hospitalized, no limitations on activities.

Secondary Efficacy:

- Composite endpoints, from the ordinal scale:
  - Achieving recovery status scores (see definition in primary endpoint above) at Day 29
  - Composite endpoint by Day 29, defined as: Death OR Respiratory failure (requires invasive mechanical ventilation)
- Clinical status measures, from the ordinal scale:
  - Achieving at least one-point/ two-point improvement in clinical status at Days 8, 15 and 29
  - Time to at least one-point/ two-point improvement in clinical status
  - Clinical status over time
- National Early Warning Score (NEWS2)
  - Time to a NEWS2 of ≤ 2 and maintained for 24 hours
  - Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS2

Exploratory Efficacy:

- In-hospital outcomes
  - Duration of hospitalization
  - Time to discharge
  - Duration of invasive mechanical ventilation
  - Duration of supplemental oxygen support
  - Duration of ECMO
  - No oxygen therapy (and/or peripheral oxygen saturation $SpO_2 > 93\%$ on room air) at Days 8, 15 and 29
- All-cause mortality
  - 28-day mortality (to Study Day 29)

Safety Endpoints

- Incidence and severity of treatment-emergent Adverse Events (AEs), including Serious Adverse Events (SAEs)
- Clinically significant changes in laboratory measures and vital signs

Other Endpoints

- SARS-CoV-2 viral load
  - Change from baseline in SARS-CoV-2 viral load from NP or OP samples at Days 3, 5, 8, 11 (while hospitalized) and/or on day of discharge; and Days 15 and 29 (by returning to the clinic/ by remote visit or if still hospitalized)
- Biological and immunological markers of illness/inflammation
  - Changes from baseline in biomarkers from blood samples may include, but are not limited to: CRP, ferritin, LDH, D-dimer, troponin T hs, absolute neutrophil count and IL-1β, IL-6, IL-10, total IL-18, TNF-α [at Days 2(local lab tests only), 3, 5, 8, 11 (while hospitalized) and/or on day of discharge; and Days 15 [and 29(local lab tests only)] (by returning to the clinic/ by remote visit or if still hospitalized)]
- Plasma pharmacokinetics of Brilacidin
  - Plasma concentrations of Brilacidin measured from blood samples collected on Days 1 to 4

Statistical Methods:

Full details of the statistical methodology for summary and analyses of the data collected in this study will be prepared separately from the protocol in a Statistical Analysis Plan (SAP).

This Phase 2 Proof of Concept (PoC) study is exploratory in nature and will be initiated with a dose regimen of Brilacidin in addition to SoC, compared to placebo with SoC. Proof of concept will be established by a significant treatment effect on the primary endpoint or a positive direction of effect amongst multiple efficacy endpoints. Comparisons will be performed against placebo plus SoC at a one-sided type I error rate of 0.05 which will not be adjusted for multiple testing.

The selected primary efficacy endpoint is time to sustained recovery, where recovery is defined as the participant being well enough for hospital discharge, meaning the participant either no longer requires supplemental oxygen or ongoing medical care in the hospital, or is no longer hospitalized (with or without some limitation on activities).

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic, and safety parameters. For categorical variables, summary tables with number and percentage of subjects within each category will be presented. For continuous variables, descriptive statistics including the number of subjects, mean, median, standard deviation, minimum, and maximum values will be presented. Kaplan-Meier methods will be used to summarize time to event endpoints, including the 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 90% confidence intervals, as well as percentage of events and censored observations.

Sample Size

This study is exploratory in nature and the sample size (up to 60 per treatment arm) was selected to provide sufficient power under a range of alternative hypotheses to support PoC of Brilacidin versus SoC. The type I error will not be adjusted to account for multiple comparisons.

For the primary efficacy endpoint of time to recovery, assuming a total of 100 subjects (50 per treatment arm included in analysis), if a total of 75 recovery events are observed, the comparison between treatment groups would provide at least 90% power with a one-sided type I error rate of 0.05 and a hazard ratio of 2.0 [equivalent to median time to recovery of 5 days on Brilacidin versus 10 days on SoC]. If instead the hazard ratio is 1.67 (time to recovery on Brilacidin of 6 days versus 10 days on SoC) and 75 recovery events occur, the difference could be detected with at least 70% power. The assumptions for sample estimation are adapted from the median time to recovery data reported for the remdesivir (11 days) treatment group in Beigel et al 2020; remdesivir has Emergency Use Authorization (EUA) in multiple countries and has become SoC where available.

Interim Analyses/ Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to conduct periodic safety reviews. Details of the DMC will be prepared separately from this protocol in a DMC Charter. The charter may supersede the summary details presented here in the protocol.

Safety data summaries and listings will be produced for DMC safety monitoring when needed.

An initial safety review is planned to occur after approximately 20 randomized subjects have completed up to Day 15. This initial interim analysis will focus on review of cardiovascular safety, vital signs and adverse events that have occurred in the approximately 20 subjects to receive Days 1-3 of study treatment. A further safety review by the DMC is planned to occur after approximately 50% of subjects have completed up to Day 29, to allow for unblinded monitoring of safety data around the study mid-point. The DMC may recommend expanding dosing to Days 4 and 5 (at the same doses as on Days 2 and 3), continuation of the Days 1-3 study dosing unchanged, or that the trial be interrupted or stopped for safety reasons. The DMC will be guided by the degree and incidence of hypertensive values/events observed in the ongoing study which should not exceed the number and/or severity of those observed in previous studies with Brilacidin IV treatment for expansion of dosing to occur as planned.

The primary efficacy analysis will occur once all subjects complete the Day 29 visit (or discontinue from study, if before Day 29). Final database lock and updated safety reporting will follow the completion of Day 60 follow-up telephone visits.

Analysis Population

Efficacy analyses performed on the Intent-to-Treat (ITT) population will be considered primary, with the ITT population including all subjects who are randomized and receive at

least one dose of study drug. Subjects in this population will be analyzed according to the treatment group to which they were randomized.

The Safety population includes all subjects in the ITT population. Subjects in this population will be analyzed according to treatment received. All safety analyses will be based on this population.

The Per Protocol (PP) population is a subset of the ITT population and includes subjects who meet particular study completion criteria with no major protocol deviations; these criteria will be described in the SAP and will be approved prior to database lock and study unblinding. Efficacy analyses performed using the PP population will be considered supportive.

All subjects in the ITT population who provide at least one PK sample and have at least one valid concentration measurement will be included in the PK population.

Statistical Analysis

The primary efficacy endpoint is time to sustained recovery which will be analyzed with the log-rank test for treatment difference, stratified by age group, disease severity and country, with dose regimen as covariate (if expanded after DMC recommendation), and summarized using Kaplan-Meier methodology. Secondary and exploratory/ other endpoints will be presented with summary statistics. Between treatment group comparisons for secondary and exploratory/ other endpoints will be performed via logistic regression, including proportional odds logistic regression for changes in the ordinal scale, and analysis of covariance models, stratified by age group, disease severity and country, for categorical and continuous endpoints, respectively. Sensitivity analyses may include longitudinal models and models adjusted for additional covariates.

All safety data, demographic and baseline characteristics will be summarized descriptively through appropriate data tabulations, descriptive statistics, and categorical summaries on the Safety Population.

Table 1: Schedule of Activities

	Screening	Treatment Period[2]			Follow-up period												
		Baseline			*Daily or twice daily assessments are until hospital discharge*[3]												EOS
Study Day +/- window	**-1 to 1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9, 10**	**11**	**12, 13, 14**	**15[4] +/-2**	**16 to 28**	**Successful Discharge[3]**	**29[4] +/-3**	**60 +/-10**
Informed Consent[1]	X																
Inclusion/ Exclusion Criteria	X																
Medical History/ Current Medical Conditions	X																
Demographics	X																
Weight[5]	X								X				X		X		
Height[5]	X																
Physical Examination[6]	X												X		X	X	
12-lead ECG (local)	X	X[16] (post-dose)											X		X		
Vital signs (twice daily)[3,7]	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Respiratory status (twice daily)[3,7]	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Positive SARS-CoV-2 virus by PCR (local lab)[8]	X																
Nasopharyngeal swabs for SARS-CoV-2 quantitation (central lab)[8]		X		X		X			X		X		X		X	X	
Clinical Status Evaluation with 8-category ordinal scale[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NEWS2 (twice daily unless in ICU)[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test (urine/serum), if WOCBP (local lab)[9]	X																
Hematology (local lab)	X	X[2]	X	X		X			X		X		X		X	X	
Blood chemistry (includes CRP, ferritin, LDH, D-dimer, troponin T hs) and Coagulation (local lab)	X	X[2]	X	X		X			X		X		X		X	X	
Blood sample collection for additional biomarkers, may include but not limited to IL-1β, IL-6, IL-10, total IL-18, TNF-α (central lab)		X		X		X			X		X		X		X		
Blood sample collection for Brilacidin plasma concentrations (central lab)[10]		X	X	X	X												
Randomization (IRT)[11]	X	X pre-dose confirmation															
Study Drug IV Infusion[12]		X	X	X	(X)[13]	(X)[13]											
Blood pressure and pulse rate (around study IV infusion; pre-dose, 1h and 3h post start of infusion)[14]		X	X	X	(X)[13]	(X)[13]											
Adverse Event Assessment[15]	X →															►X	X
Prior and Concomitant Medications & Therapies/Procedures	X →															►X	

1 Informed consent must be signed prior to any study-related procedure. EOS = End of Study

2 Study treatment may start once screening/baseline measurements are completed and eligibility confirmed.
Eligibility assessments for vital signs, respiratory status, and local laboratory tests do not need to be performed separately for screening and baseline if participants are randomized and treated on the same day/within 24 hours of commencing screening/signature of informed consent.

During the treatment period, all assessments should be performed in the morning pre-dose.

3 Any subject successfully discharged before Day 29 is to complete all assessments listed on the day of discharge.

Daily or twice daily assessments are until hospital discharge, with the exception of Clinical Status Evaluation, which should be sought by telephone (between 7AM and 12 PM local time) up to Day 15 if a subject is successfully discharged before Day 15.

4 For Day 15/29 assessments: if subject is discharged prior to Day 15/29, visiting nursing services and mobile phlebotomy may support that visit remotely where these are available in accordance with local guidelines and should include all possible assessments. Every effort should be made to ensure discharged patient follow-up via a healthcare interaction. Visit windows for Day 15/29 visits only apply should a patient have been discharged.

5 Height and weight measured without shoes. If not possible to measure, height can be reported by the subject.

6 Complete physical examination to be performed at Screening/Baseline, including review of the following body systems: skin, neck (including thyroid), HEENT (head, eyes, ears, nose and throat), heart, lungs, abdomen, lymph nodes, extremities, vascular and neurologic function. Subsequent examinations may be abbreviated including, at a minimum: HEENT, heart, lungs, abdomen, extremities and examination of any body system where there are symptoms reported by the subject.

7 Vital signs include heart rate, systolic and diastolic blood pressures and body temperature. Respiratory status (respiratory rate, oxygenation and any oxygen supplementation) should be measured at the same time as the vital sign measurements, if possible.

All parameters of the NEWS2 – including the vital sign parameters and oxygen saturation – should be recorded together in the morning, and then between noon and midnight, for the duration of hospitalization if outside of the ICU. Following hospital discharge these parameters should be recorded once at each return visit to the clinic (Days 15 and 29).

8 Results confirming positive SARS-CoV-2 virus by PCR or equivalent/ other approved diagnostic testing within 4 days prior to randomization may be used for eligibility. Nasopharyngeal swabs used from pre-dose assessment for quantitative PCR analysis at central laboratory.

9 Pregnancy test applicable only for females of childbearing potential, serum pregnancy test (serum hCG) will be performed by local laboratory. For enrollment a negative urine test is sufficient.

10 Blood samples (for Brilacidin plasma concentration analysis) will be collected at the following timepoints:

- Day 1: pre-dose, within 30 mins after the end of infusion, and between 8-12 hours from start of the Day 1 infusion.
- Day 2: pre-dose (approximately 24 hours from start of the Day 1 infusion)
- Day 3: pre-dose (approximately 24 hours from the start of the Day 2 infusion)
- Day 4: at approximately 24 hours from the start of the Day 3 infusion.

11 Brilacidin IV infusion requires unblinded pharmacist preparation at the study site. Brilacidin for Injection concentrated solution is diluted in sterile 0.9% w/v sodium chloride (normal saline) to provide the desired final dose within 8 hours of administration; diluted Brilacidin drug product is then stored at room temperature not above 25°C, 77°F, prior to use. Placebo IV infusion will be sterile saline.

Since pharmacist preparation ahead of dosing is required, randomization using IRT may be performed prior of full confirmation of subject eligibility. Full confirmation of eligibility must then be confirmed pre-dose on Day 1.

12 Brilacidin IV infusion is filtered through a 0.2 μm membrane when administered intravenously over 60 minutes. On study treatment days, assessments should be performed pre-dose unless otherwise specified.

13 Brilacidin treatment may be expanding to Day 4 and Day 5 following an initial interim safety analysis; additional assessments then needed on Day 4 and Day 5.

14 Blood pressure and pulse rate measured at additional timepoints during study treatment, around the timing of the study IV infusion; pre-dose, within no more than 30 mins after the end of infusion, and 3 hours (±30 mins) post-start of infusion (i.e., ~2 hours post-end of infusion). Additional assessments to be made as appropriate based on the systolic and diastolic blood pressure values recorded.

15 Adverse events (AEs) with onset after a subject has provided informed consent are to be recorded. At follow-up through Day 29, ongoing AEs assessed as related and all ongoing Serious AEs are to be further followed up to appropriate resolution.

16 Post-dose ECG on Day 1 performed within 2 hours after the end of infusion.

LIST OF ABBREVIATIONS

ABSSSI	acute bacterial skin and skin structures infections
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
cm	centimeter
COVID-19	Coronavirus disease 2019
CRO	clinical research organization
CRP	C-reactive protein
CS	clinically significant
CT	computerized axial tomography
D	Day
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
(e)CRF(s)	(electronic) case report form(s)
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
HDPs	host defense proteins
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IL	interleukin
IN	Investigator Notification
IPI	Innovation Pharmaceuticals Inc.
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous(ly)
ITT	Intent-to-Treat
kg	kilogram
LDH	lactate dehydrogenase
mg	milligram
mL	milliliter

MedDRA	Medical Dictionary for Regulatory Activities
mins	minutes
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	not clinically significant
OM	oral mucositis
PaO_2	arterial oxygen partial pressure
PCR	polymerase chain reaction
PET	positron emission tomography
PK	pharmacokinetic(s)
PoC	Proof of Concept
PP	Per-Protocol
PT	preferred term
RBC	red blood cell
RRT	renal replacement therapy
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SDV	source document verification
SoC	standard of care
SOC	system organ class
SOM	severe oral mucositis
SpO_2	peripheral oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TEAE(s)	treatment-emergent adverse event(s)
TID	three times per day
TNF-α	Tumor necrosis factor alpha
ULN	upper limit of normal
WBC	white blood cell
WFI	Water for Injection
WHO	World Health Organization
WHO-DDE	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

1. INTRODUCTION AND BACKGROUND

1.1. Disease Overview

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified as the cause of an outbreak of respiratory illness due to coronavirus disease 2019 (COVID-19) that was first detected in Wuhan, China, in December 2019. The virus causes respiratory illness in people and can spread from person to person. Common signs of infection include fever, cough, shortness of breath, breathing difficulties, and other respiratory symptoms. Gastrointestinal symptoms (nausea, vomiting, diarrhea) also appear to be common clinical manifestations of COVID-19. In severe cases, SARS-CoV-2 can cause pneumonia, severe acute respiratory syndrome, kidney failure, and death (WHO 2020a). On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern (WHO 2020b). Further to the WHO declaration, on 31 January 2020, Health and Human Services declared a public health emergency in the United States (US) (DHHS 2020).

As of November 3, 2020, over 47.2 million COVID-19 cases have been diagnosed in at least 190 countries, resulting in over 1.2 million reported deaths, including over 9.3 million cases and almost 233,000 fatalities in the United States (Johns Hopkins Coronavirus Resource Center 2020). While COVID-19 mortality rates can vary greatly by geographic region, with differences in how rates are calculated, it is generally accepted that, for COVID-19, the overall mortality rate is many times higher than that seen with seasonal influenza; moreover, it has been observed that up to 15% of COVID-19 patients develop lung injury, including respiratory distress progressing to acute respiratory distress syndrome (ARDS) requiring prolonged ventilator support over weeks (Zhou et al 2020). This can result in intensive care units, hospitals and health care systems becoming overwhelmed. Presently, there are no approved vaccines and few minimally effective therapies to treat COVID-19. According to a May 1, 2020, Congressional Research Service report, worldwide economic growth could be reduced by 2 percent per month if current pandemic conditions persist, with global trade falling by 13 percent to 32 percent, with the economic downturn attributable to the COVID-19 crisis could vastly exceed that of the Great Recession (2007-2009) (Congressional Research Service 2020). The Congressional Budget Office estimates the novel coronavirus pandemic will cost the U.S. economy $8 trillion through 2030 (Stein 2020).

ARDS is characterized by pro-inflammatory cytokine release, inflammatory cellular infiltration and cell death, resulting in severe pulmonary damage and the development of respiratory failure that requires mechanical ventilation with high positive end-expiratory pressures (PEEP) to maintain life. In patients with a prior history of hypertension, diabetes and cardiovascular disease (common comorbid conditions), poor health outcomes have been reported that may be a result of poor underlying cardiac reserve—meaning that patients develop cardiac failure in response to ventilation, with pulmonary edema further exacerbating respiratory failure (Zhou et al 2020).

ARDS is an important contributor to the morbidity and mortality associated with COVID-19. ARDS manifestation is connected to heightened inflammatory responses resulting from

SARS-CoV-2 infection, adversely impacting normal lung function. A therapeutic intervention that exhibits immunomodulatory properties might help control this inflammatory response as characterized by ARDS. An intervention that also exerts antiviral activity would provide an even more complete solution to the SARS-CoV-2 infection associated ARDS challenge.

1.2. Background of Brilacidin

Brilacidin is a fully synthetic, non-peptidic, host defense protein mimetic. Brilacidin is a small molecule, new chemical entity, created so as to mimic the amphiphilic structure of host defense proteins (HDPs), having one surface with positively charged groups (cationic) and the opposite surface consisting of hydrophobic groups. With this general synthetic form, there is no need for an agent to be of the size or composition of naturally-occurring proteins to effectively function as a HDP, as the ability to act as a HDP is retained by the much smaller synthetic amphiphilic molecule.

Brilacidin has anti-inflammatory activity – the mechanism of which is proposed to be based largely on inhibition of phosphodiesterases (PDE4 and PDE3) and subsequent down-regulation of pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6, IL-8). Like natural HDPs, Brilacidin has antibacterial activity (with a predominantly gram-positive spectrum).

New *in vitro* research has demonstrated robust and consistent antiviral activity of Brilacidin against SARS-CoV-2, as summarized below.

1.2.1. Proposed Therapeutic Properties in COVID-19

Brilacidin has three complementary anti-COVID-19 therapeutic properties combined in a single drug: antiviral; immunomodulatory/anti-inflammatory; and antimicrobial (Figure 1).

Brilacidin has demonstrated antiviral activity against SARs-CoV-2 in cell-based assays (see Section 1.3.1.3), and the mechanisms for this activity are postulated as being:

1) Membrane Disruption: disrupting the viral envelope (virucidal)
2) Entry Inhibition: by competing with the virus for the ACE2 receptor, preventing ACE2 receptor binding and viral entry
3) Intracellular Targets: inhibiting viral replication intracellularly, by binding to SARS-CoV-2 main protease (M^{pro})
4) Anti-inflammatory: suppressing IL-6 and other pro-inflammatory mediators implicated in the “cytokine storm”, through inhibition of phosphodiesterase

The main proposed mechanism of action of Brilacidin involves the disruption of viral membrane integrity. Other direct antiviral mechanisms of action of Brilacidin may include blocking viral entry and interrupting viral replication intracellularly. An *in silico* quantum mechanical molecular screening study of 11,522 compounds (both FDA-approved and those in testing) identified Brilacidin as one of the most promising potential inhibitors of the novel coronavirus based on the potential of its physico-chemical properties to interfere with the

intracellular replication of SARS-CoV-2's main protease (M^{pro}) (Cavasotto and Filippo 2020). An article detailing *in vitro* results and proposed mechanisms of action is being submitted for peer review publication, with a pre-print (Bakovic et al 2020) made available.

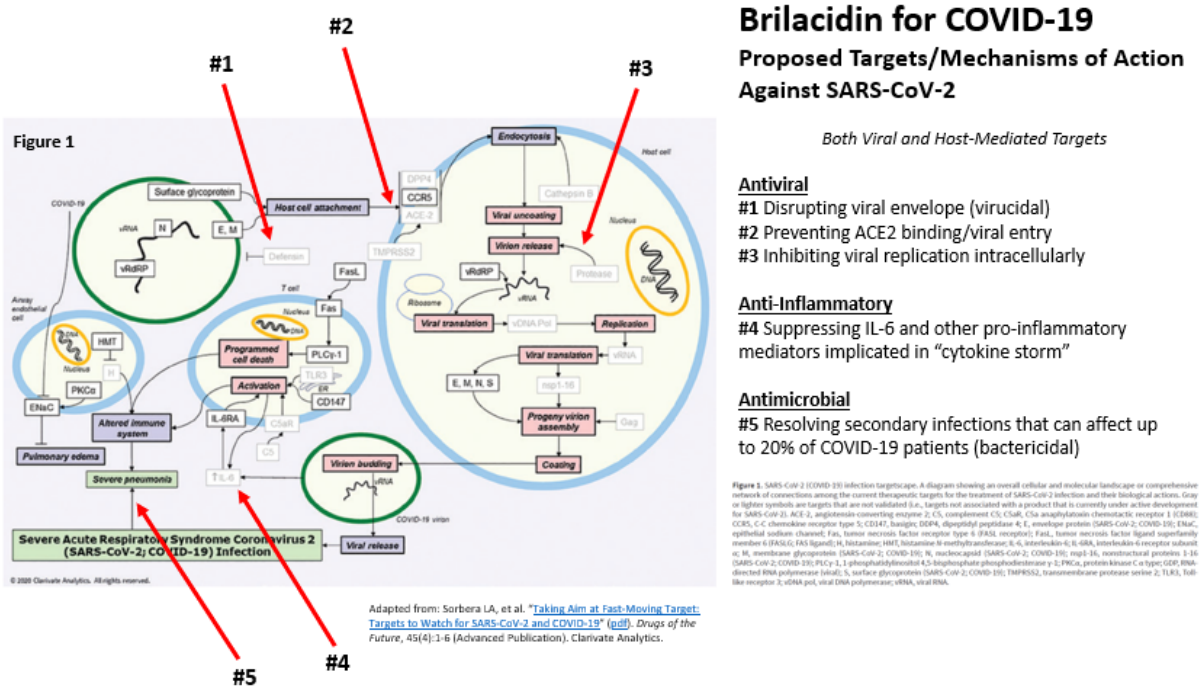
Additional nonclinical (see Section 1.3.1.3) and clinical data support Brilacidin's potential to function through the cAMP/cGMP pathway, by inhibition of phosphodiesterase. Phosphodiesterase type 4 (PDE4) is the predominant phosphodiesterase expressed in neutrophils, T cells and macrophages. PDE inhibitors show broad spectrum of anti-inflammatory effects in almost all inflammatory cells. PDE4 inhibitors block the degradative action of PDE4 on cAMP, thereby increasing intracellular levels of cAMP levels which mediate phosphorylation of protein kinases. PDE4 inhibitors reduce neutrophil chemotaxis, recruitment and activation; inhibit the activation of CD4+ and CD8+ T cells; and inhibit monocytes chemotaxis (Tamimi et al 2012). Therefore, inhibition of PDEs is expected to have a therapeutic effect on the inflammatory state.

Inhibition of PDE4 and PDE3 has been demonstrated for Brilacidin in vitro (see Section 1.3.1.3). PDE4 and PDE3 inhibition results in subsequent down-regulation of pro-inflammatory cytokines and chemokines (such as TNF-α, IL-6, IL-1β, MMP-9, MCP-1, IL-8, CINC-3), which have been identified as central drivers in the worsening prognoses of hospitalized COVID-19 patients. Experiments have been conducted to confirm such down-regulation by Brilacidin in ex vivo cell-based assays (see Section 1.3.1.3), and also from clinical biomarker data (Phase 2 retention enema study, Section 1.3.2.3).

Brilacidin's antimicrobial properties, as demonstrated in a Phase 2b clinical trial of intravenous Brilacidin in the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI), may also help to fight or prevent secondary bacterial infections, which can co-present in up to 20 percent of COVID-19 cases (Cox et al 2020; Kim et al 2020; Mirzaei et al 2020).

Collectively, these data support Brilacidin as a highly unique 3-in-1 combination—antiviral, anti-inflammatory, antimicrobial—novel COVID-19 therapeutic candidate (Figure 1).

Figure 1: Brilacidin, a 3-in-1 Combination of Therapeutic Properties



1.3. Nonclinical and Clinical Studies with Brilacidin

Please refer to the Investigator's Brochure for full background information.

1.3.1. Nonclinical Studies

1.3.1.1. Nonclinical Toxicology and Safety Pharmacology

Toxicology

Single and repeat dose toxicity studies have been conducted with intravenous (IV) and oral gavage administration of Brilacidin.

For Brilacidin administered IV for up to 28 days, dose-limiting pharmacological effects have been relatively consistent in both rats and dogs. Salivation, retching, weight loss, and diminished feces relate to the gastrointestinal system; tremors and diminished activity to the neurological system; and labored respirations and changes in pulmonary tidal volumes to the respiratory system. Effects on peripheral nerves were observed as well as increases in blood pressure and heart rate. Brilacidin-related microscopic findings in repeat dose IV toxicity studies in rat and dog included microvacuolation of the axon hillock of neurons from the dorsal root ganglia, and microscopic changes in the kidney (tubular basophilia). There were no associated degenerative changes in the neuronal bodies or nerves/nervous tracts. The toxicological investigations indicate that the dog is the more sensitive of the species tested by IV administration, with a NOAEL dose of 0.25 mg/kg/day and associated mean Day 28

AUC(0-t) of 10902 ng•h/mL (males) or 10187 ng•h/mL (females). The nonclinical findings of a mild peripheral sensory axonopathy in rats and dogs administered Brilacidin are consistent with the clinical findings of mild transient paresthesia observed clinically. The onset of functional neurological changes has been reported to precede microscopic changes allowing for clinical monitoring, through adverse event reporting, and adjustment of dose and duration of administration if needed (Petterson et al 2008).

Brilacidin demonstrated no genotoxic potential in vitro or in vivo.

In a fertility and early embryonic development study in male and female rats, no effects on fertility parameters were observed at doses up to 1.5 mg/kg IV; the NOAEL was considered 0.75 mg/kg based on clinical signs and decreased organ weights (prostate, seminal vesicle) considered adverse in males.

Safety pharmacology

In vivo, cardiovascular effects of increased blood pressure and heart rate at the highest dose tested (4 mg/kg IV) were observed without effect on cardiac rhythm or ECG. Decreased respiratory rate and minute volume and increased tidal volume at the highest dose (25 mg/kg IV) were observed in the respiratory system study. Nervous system effects observed were salivation and labored respiration in the highest dose group (25 mg/kg IV). In a nerve conduction study (non-GLP), the highest dose group (10 mg/kg IV) demonstrated slowing down of caudal nerve conduction velocity after 5 days administration and histopathological changes (intracytoplasmic granules) in dorsal root ganglion at the end of the recovery phase. Sensory and coordination studies (non-GLP) demonstrated marginal effects up to 10 mg/kg IV.

In vitro, Brilacidin at the highest feasible test concentration (0.3 μM) did not result in hERG inhibition. Results from studies (non-GLP) using patch clamp assays support disturbances in channel function as a potential cause for observed paresthesias associated with high dose Brilacidin treatment when administered IV in the clinic. However, Brilacidin shows little if any accumulation in the CNS so any ion channel interactions would be expected to be localized in the periphery. In evaluating the significance of these interactions on the safety of Brilacidin IV, it can be recognized that several widely used drugs and drug classes target ion channels for therapeutic effects, e.g., repaglinide, nateglinide, disopyramide, and phenytoin and other widely used drugs display off-target activities at ion channels, e.g., haloperidol, fluoxetine, and verapamil. These marketed drugs are used chronically and support the rationale that ion channel effects should be adequately tolerated.

1.3.1.2. Nonclinical Pharmacokinetics and metabolism

After IV single dose administration, the half-life (t½) was approximately 8 hours in rats. (Human pharmacokinetics have been conducted and t½ ~20 hours after IV administration of Brilacidin to healthy subjects [Study PMX63-102, Study PMX63-103]).

Plasma protein binding of Brilacidin in vitro for mouse, rat, rabbit, monkey, and human plasma proteins was comparable, ranging from 94.4% to 98.5%. The plasma/blood partitioning studies indicated no preferential accumulation of [14C]-Brilacidin to human blood cells.

Tissue distribution after IV administration of [14C]-Brilacidin (2 mg/kg) showed that in the lung, concentrations were high at the 1 hour and 3 hours post-dose timepoints, with lower concentrations from 24 hours post-dose onwards. The higher concentrations were mainly observed in the liver, lung, kidney, adrenal glands and cartilage at 1-hour post-dose; at 1 and 3 hours post-dose, the small intestine mucosa contained the highest concentration of radioactivity, in both male and female rats. Highest concentrations of radioactivity were subsequently observed in small intestine mucosa at all time points (24, 168 and 504 hours post-dose), which would indicate biliary excretion as a possible route of elimination for Brilacidin. Tissues with the lowest concentrations of radioactivity were bone, brain, eye, white fat, seminal vesicles (male rats only), spinal cord, and urinary bladder (male rats only) at all time points.

Rat, rabbit, dog, monkey, and human hepatocytes in vitro did not metabolize Brilacidin. In the rat following a single IV dose, in all three matrices (kidney, liver and feces) the major component detected was Brilacidin. Two additional components/potential metabolites were observed, although it is also possible that both are artifacts formed during the extraction process.

Using the January 2020 FDA Guidance for in vitro DDI studies, available data indicates there is a potential for Brilacidin to reversibly inhibit CYP2C8, CYP2C9, and CYP3A4 with a possible although probably not likely time-dependent inhibition of CYP2B6. To further investigate any potential for drug-drug interactions with substrates metabolized by CYP2C8, CYP2C9, and CYP3A4 enzymes, an in vitro study (to accurately determine Ki's) is planned to be performed in parallel with the conduct of this study. Please refer to Section 6.1.1 for details on cautionary monitoring for adverse effects of those drugs which are sensitive substrates of CYP2C8, CYP2C9, and CYP3A4 enzymes or are substrates with a narrow therapeutic range during study treatment. The likelihood for drug-drug interactions is low and will be further confirmed through additional study(ies). Of note, the safety profile of Brilacidin has already been established from intravenous dosing of over 400 subjects in the Brilacidin program, and no notable alerts regarding any drug-drug interactions have occurred to date.

In the rat, following a single IV dose in a mass balance study, any radioactivity excreted was largely via the fecal route and indicates that possible excretion in the bile (and/or via the gut mucosa) is an important route of elimination of Brilacidin.

These ADME data, demonstrating pulmonary exposure to Brilacidin from IV administration, are reassuring for the indication of COVID-19. As Brilacidin is excreted unchanged in the feces, there is also potential for treatment to address gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) that also appear to be common clinical manifestations of COVID-19.

1.3.1.3. Nonclinical Efficacy

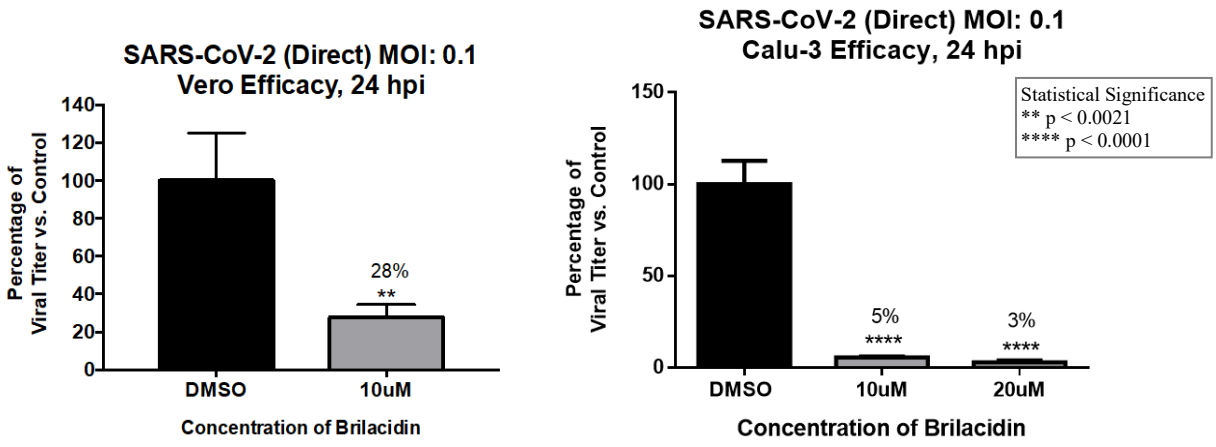
Pharmacodynamics: Anti-viral activity

Using a pre-treatment assay, performed in monkey kidney Vero cells and also in human lung epithelial Calu-3 cells, researchers observed robust inhibition of SARS-CoV-2 virus multiplication. At 24 hours post-infection in the Vero cell assays, Brilacidin tetrahydrochloride at a concentration of 10 µM showed ~72% inhibition ($p<0.01$) (Figure 2, left panel), and in the Calu-3 cell assays, a concentration of 10 µM gave 95% inhibition ($p<0.0001$) and at 20 µM 97% inhibition ($p<0.0001$) (Figure 2, right panel).

In the pre-treatment assay method, live virus was pre-treated with Brilacidin (before virus presentation to cells), with cells additionally pre-treated with drug and Brilacidin also present in the viral inoculum during the process of infection, and present post-infection. Virus was incubated with the respective concentrations of Brilacidin tetrahydrochloride tested for one hour, and virus treated with vehicle alone (DMSO) maintained alongside as control. The pretreatment virus-Brilacidin mix was then added to cells (which had been pre-treated with Brilacidin for two hours), with Brilacidin maintained in the medium concentration, and cells were infected with SARS-CoV-2 at a MOI: 0.1. The infection was allowed to proceed for 1 hour at 37°C, after which the viral mix overlay was removed and Brilacidin-containing medium was added back to the cells. Cells were maintained at 37°C for 24 hours, at which time the supernatants were collected to assay for infectious virus. Supernatants were queried for infectious virus load by plaque assay.

Without direct pre-treatment of virus, the inhibition achieved in the assay for a concentration of Brilacidin was reduced. For example, without pre-treatment of virus, the inhibition achieved in the Calu-3 cell assays was 39% inhibition with 10 µM and 61% inhibition with 20 µM Brilacidin tetrahydrochloride, compared to 95% and 97% inhibition, respectively, with pre-treatment of virus. The pre-treatment assays, both in Vero and Calu-3 cells, support Brilacidin's ability to prevent viral entry by, it is proposed, disrupting the viral envelope and/or preventing viral attachment to host cells. A majority of antiviral agents targeting SARS-CoV-2 attempt to inhibit viral replication, post-infection, rather than eliminating or blocking the virus prior to infection.

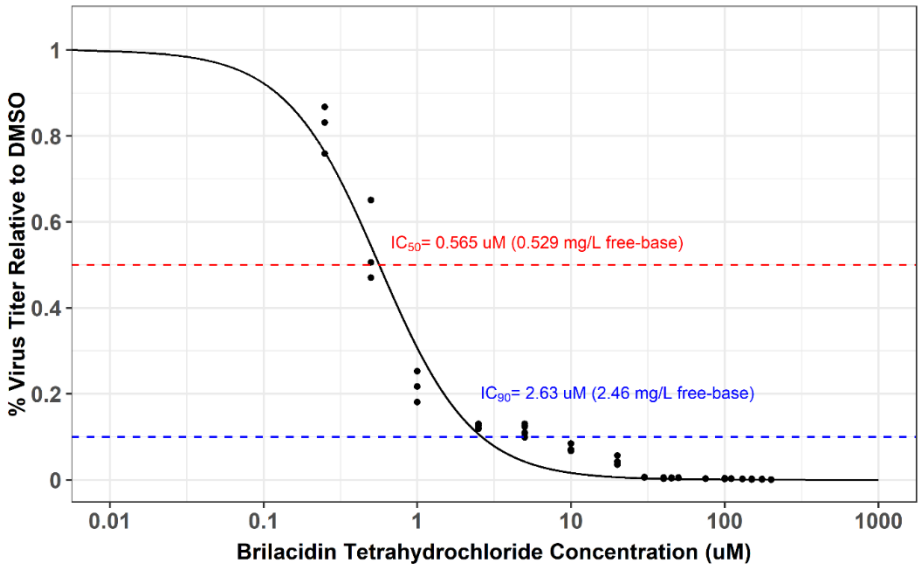
Figure 2: Pre-Treatment Efficacy of Brilacidin against SARS-CoV-2



Additional testing, using the same pre-treatment assay across a range of Brilacidin concentrations, showed Brilacidin tetrahydrochloride achieved ~90% inhibition against SARS-CoV-2 (IC90) at a concentration of 2.63 µM and an IC50 value of 0.565 µM (Figure 3), both of which are below clinically-achievable concentrations based on pharmacokinetics observed in a Phase 2b clinical trial of Brilacidin in treatment of ABSSSI: median Cmax in plasma was 7.67 µM Brilacidin (free-base) from a single IV dose of 0.6 mg/kg.

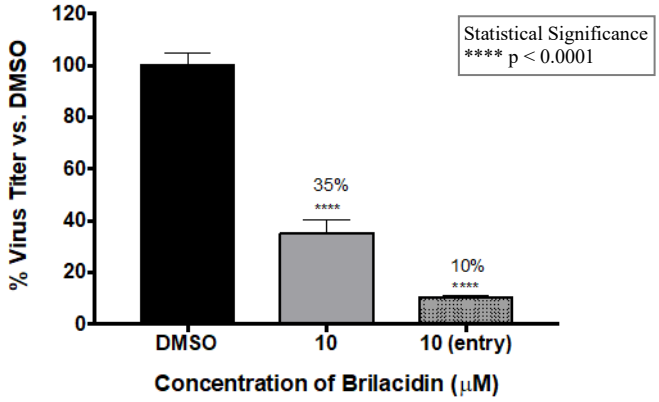
Figure 3: Inhibitory Dose-Response assessment of Brilacidin on SARS-CoV-2 virus multiplication in Calu-3 cells

Sigmoidal Hill-type function showing the relationship between the percent virus titer relative to DMSO and Brilacidin tetrahydrochloride concentration, with dashed lines showing the derived IC50 and IC90 values



In a slightly different assay, cells were not exposed pre- or post-infection to Brilacidin and only the viral inoculum was pre-treated (with 10 µM Brilacidin tetrahydrochloride), and the treated inoculum used to infect Vero cells. At 24 hours post-infection, the infectious virus titer in the supernatant was quantified by plaque assay, which revealed a dramatic 90% reduction of virus titer (Figure 4, indicated as [entry]). This inhibition was approximately 25% higher than that observed when, in comparison, cells were exposed pre- and post-infection to Brilacidin and with no pre-treatment of virus nor drug present during infection. These data support the concept that Brilacidin has a direct inhibitory effect on the virus in a manner similar to the neutralization of antibodies, potentially by disrupting viral integrity and thus impairing the virion's ability to complete the viral entry process.

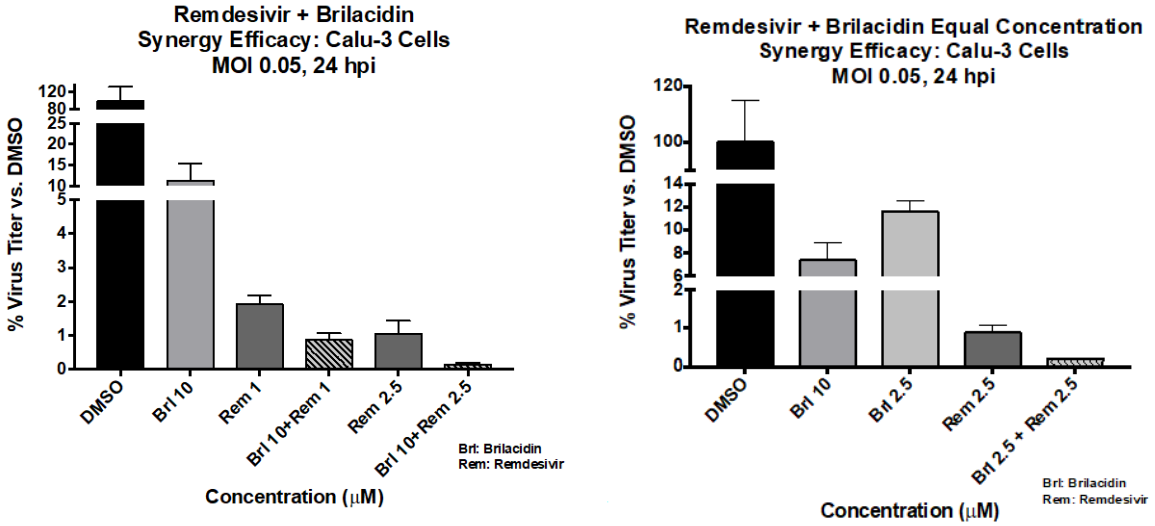
Figure 4: Assay Method Variation and Efficacy of Brilacidin Against SARS-CoV-2 in Vero cells



Brilacidin has also undergone *in vitro* testing (in Calu-3 cells) in combination with other antiviral agents. Preliminary data of Brilacidin in combination with remdesivir (one of only two current COVID-19 treatments that has received Emergency Use Authorization, as well as a frontline treatment worldwide), demonstrates a statistically significant synergistic effect (Figure 5), with a combined overall inhibition against SARS-CoV-2 of ≥99%, reducing overall viral load to near undetectable levels.

Brilacidin appears to have primarily an extracellular mechanism of action, by disrupting viral integrity and blocking viral entry. In contrast, remdesivir has an intracellular mechanism of action, affecting viral replication post-infection. Exhibiting different but synergistic antiviral properties, these two drugs may be an especially potent drug combination in treating COVID-19.

Figure 5: Efficacy of Brilacidin in combination with Remdesivir against SARS-CoV-2



Combination in vitro testing is ongoing, and future investigations of efficacy against other coronaviruses (e.g., SARS-CoV-1, MERS-CoV, H-COVs) are planned. An article detailing *in vitro* results against SARS-CoV-2 and proposed mechanisms of action is being submitted for peer review publication, with a pre-print (Bakovic et al 2020) made available. Future in vivo studies are planned.

Pharmacodynamics: Anti-inflammatory activity

As demonstrated in vitro and ex vivo cell-based assays, the anti-inflammatory effect of Brilacidin is proposed to be based largely on inhibition of PDE4 and PDE3 with subsequent down-regulation of pro-inflammatory cytokines/chemokines (such as TNF-α, IL-1β, IL-6, IL-8) and its regulators. Assays conducted include LPS-induced cytokine release ELISA (rat macrophages and human monocytic leukemia (THP-1) cells) and PDE-Glo™ PDE assay.

Animal anti-inflammatory pharmacology data are available from two animal models.

In both acute and fractionated radiation hamster models of oral mucositis, Brilacidin administered topically TID (to irradiated left buccal cheek pouch) over 28- or 35-day treatment periods, respectively, significantly reduced the number of days animals exhibited ulceration and the daily mean mucositis grades. Experiments in the fractionated radiation-induced OM model clearly identified that a continuous Brilacidin 3 mg/mL TID regimen was most effective and all but eliminated ulcerative OM in experiments conducted, with reductions in the number of animal days with ulcerative OM over 90% relative to the control group responses (46.7% to 56.0% for control groups, and <4% for Brilacidin 3 mg/mL group).

In a murine DSS-induced colitis model, despite the presence of severe colitis, after dosing with Brilacidin 400 mg/kg solution per rectum compared to DSS-treated controls rectal bleeding was significantly decreased and stools were significantly more firm. In addition, IL-6 and IL-1β levels in colon tissue decreased with Brilacidin treatment and were lower than that of DSS-treated controls. Efficacy results similar to those for the Brilacidin treatment group were obtained with the positive control 5-ASA treated group.

Pharmacodynamics: Anti-bacterial activity

Brilacidin has demonstrated potent activity against Gram-positive bacteria, including staphylococci, beta-hemolytic streptococci and *E. faecium*, and several Gram-negative bacteria. Minimal propensity for the development of resistance has been demonstrated and broad-spectrum activity against multi-drug resistant strains of *S. aureus*, *S. epidermidis* and *S. hemolyticus*, including organisms resistant to two or more of the antibiotics methicillin, daptomycin, linezolid and vancomycin. Brilacidin has shown rapid bactericidal activity versus *S. aureus* and *E. coli*, plus significant antimicrobial activity against MSSA and MRSA at sub-MIC levels for up to 7 hours post-exposure. Also, potent and rapid bactericidal activity with Brilacidin has been demonstrated against stationary cultures of MSSA and MRSA.

Importantly for the treatment of acute bacterial skin and skin structure infections (ABSSSI), Brilacidin was potent against multi-drug resistant staphylococci.

1.3.2. Clinical Studies

The clinical development program for Brilacidin includes healthy volunteers and patients with acute bacterial skin and skin structure infections (ABSSI), head and neck cancer (HNC), and ulcerative proctitis (UP)/ ulcerative proctosigmoiditis (UPS).

As of December 2020, eight clinical trials have been completed;

- 5 clinical trials with Brilacidin administered intravenously (3 in healthy volunteers and 2 in patients with ABSSSI; total n treated with Brilacidin = 412); and
- 2 clinical trials with Brilacidin administered topically (1 in HNC patients, by oral rinse, in attenuating oral mucositis [n treated with Brilacidin = 29]; and 1 in patients, by rectal retention enema, for mild to moderate UP or UPS [n treated with Brilacidin = 17]); and
- 1 with Brilacidin administered orally (1 in healthy volunteers, by delayed release oral tablet [n treated with Brilacidin = 6]).

Please refer to the Investigator's Brochure for details on the studies conducted with administration other than intravenous; a summary of intravenous experience is presented here.

1.3.2.1. Clinical Safety

The safety profile of Brilacidin has already been established from intravenous dosing of over 400 subjects in the Brilacidin program. Intravenous administration of Brilacidin has identified transient, dose-limiting (non-serious) side effects of paresthesias and hypoesthesias, and elevation of blood pressure and heart rate at higher doses that normalized with treatment or discontinuation of study treatment.

The most prominent neurological symptoms related to Brilacidin dosed intravenously included tingling and or numbness of the following body regions: lips/mouth/throat (lips), face/head/neck (face), fingers/hands (fingers), toes/feet (toes), and torso or perineal sites. These symptoms and signs were transient in nature and resolved after drug discontinuation. There did not appear to be any gender differences. In the opinion of an independent neurologist expert, the neurological adverse events related to Brilacidin likely represent a pharmacologic effect and are unlikely explained by neurotoxicity.

Transient increases in blood pressure and heart rate have been noted in all IV-dosed clinical trials. While tachycardia is of concern, such adverse events are uncommon (i.e., 0, 1 or 2 non-serious AEs per Brilacidin treatment group in Phase 2 studies; total patients treated = 319). Resolution of the observed blood pressure increases is accompanied by normalization of heart rate. Therefore, blood pressure increase has been the focus of safety management for IV dosing with Brilacidin. Data across clinical trials indicate that blood pressure increases are

unlikely to be >180/110 mmHg or be associated with progressive target organ involvement resulting in neurological, cardiac or renal complications. However, there were three patients treated with Brilacidin in Study PMX63-203 (5-day treatment regimen) who developed hypertension near 220/120 mmHg. When study drug was discontinued and patients were treated with anti-hypertensive medications, their blood pressure decreased; in all cases, blood pressure increases were observed as gradual over hours or days allowing for prompt medical intervention. For the Phase 2b study CTIX-BRI-204, which included the initial 3-day treatment regimen to be tested in this Phase 2 study for COVID-19, none of the reported blood pressure events were considered serious or severe in any treatment arm.

In the IV program, 13 treatment-emergent serious adverse events (SAEs) have been observed (Table 2). Of these SAEs, none led to death, and 3/13 are considered treatment-related (10/13 are considered not treatment-related).

The three SAEs considered treatment-related occurred in the Phase 2a study (PMX63-203), on the treatment arm indicated;

- Thrombocytosis (0.4 mg/kg Day 1, followed by 0.3 mg/kg on Days 2 to 5)
- Hypertensive crisis (0.75 mg/kg Day 1, followed by 0.35 mg/kg on Days 2 to 5)
- Hypertensive crisis (1.0 mg/kg Day 1, followed by 0.3 mg/kg on Days 2 to 5)

All SAEs were followed to resolution.

Table 2: Serious Adverse Events reported in Clinical Trials with Brilacidin by intravenous administration

Study Number	Type of subjects exposed	Details of Serious Adverse Event			
		SOC	SAE (preferred term)	No. of events[a]	Related to Brilacidin?
PMX63-103	Healthy volunteers	Cardiac disorders	Atrial fibrillation	1	No
PMX63-203	Patients with ABSSSI	Blood and lymphatic system disorders	Thrombocytosis	1	Yes
		Infections and infestations	Staphylococcal infection	1	No
		Vascular Disorders	Deep Vein Thrombosis	1	No
			Hypertensive crisis	2	Yes
CTIX-BRI-204	Patients with ABSSSI	General disorders and administration site conditions	Chest pain	1	No
		Infections and infestations	Cellulitis	3	No
			Skin infection	1	No
			Tooth abscess	1	No
		Injury, poisoning and procedural complications	Multiple injuries	1	No

SOC = System Organ Class; SAE = Serious Adverse Event

a Counts reflect number of subjects reporting one or more adverse events that map to the MedDRA dictionary term. At level of summarization (Preferred Term) subjects are counted once.

1.3.2.2. Clinical Pharmacokinetics

In Phase 1 studies, plasma concentrations of Brilacidin from intravenous administration showed linear pharmacokinetics that were dose-dependent for all dosing regimens and tested dose-levels. Gender was not a significant factor on drug disposition. Renal excretion does not appear to be a significant elimination pathway given the little (<1%) unchanged drug recovered in urine (Study PMX63-103).

Given the relatively sparse PK sampling scheme employed in the Phase 2 studies, a population PK model was used to describe the time-course of Brilacidin using data pooled from the three studies conducted in healthy subjects and two Phase 2 studies conducted in patients with ABSSSI. The resultant predicted concentration-time profiles were used to estimate exposure to Brilacidin in the Phase 2 patients. Summary statistics for the resultant PK parameters and PK exposure estimates are provided in Table 3 for Study PMX63-203 and Table 4 for Study CTIX-BRI-204.

The three-compartment population PK model results in different estimates of half-life from the Phase 1 studies as the estimates from those studies are derived using non-compartmental

methods. Despite the differences in methodology, the median values for half-life of the distribution phase t1/2,β (~10 h) and the terminal elimination phase t1/2,γ (~60-70 h) are in the expected range given the half-life estimates from the non-compartmental analyses of Phase 1 studies, with mean values ranged from 16.9 to 23.0 h (multiple dose study PMX63-102).

Table 3: Median (mix, max) Brilacidin Plasma Pharmacokinetic Parameters derived in Study PMX63-203 (IV dosing)

Cohort	N	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	AUC_{0-24h} (µg•h/mL)	AUC_{0-72h} (µg•h/mL)	AUC_{0-168h} (µg•h/mL)	$t_{1/2}(\beta)$ (h)	$t_{1/2}(\gamma)$ (h)	Cl (mL/h/kg)	V_{ss} (mL/kg)
Low-dose (D1 0.4 mg/kg; D2-5 0.3 mg/kg/day)											
Day 1	50	5190 (3150, 33300)	1.00 (0.500, 1.17)	1040 (603, 3850)	50.0 (31.9, 198)	163 (98.8, 635)	333 (182, 1480)	10.0 (5.77, 13.3)	71.4 (26.8, 897)	4.01 (0.766, 7.54)	249 (74.5, 1550)
Day 2	50	5010 (3000, 28700)	1.00 (0.500, 1.00)	1260 (619, 5660)	54.3 (32.7, 200)						
Day 3	49	5310 (3060, 30500)	1.00 (0.500, 1.08)	1360 (623, 7150)	59.4 (31.7, 237)						
Day 4	49	5520 (3040, 32000)	1.00 (0.500, 1.08)	1630 (677, 8350)	62.2 (32.9, 268)						
Day 5	47	5610 (3060, 33200)	1.00 (0.500, 1.08)	NA	64.4 (27.4, 239)						
Medium-dose (D1 0.75 mg/kg; D2-5 0.35 mg/kg/day)											
Day 1	54	10300 (3910, 53600)	1.00 (0.920, 1.25)	1920 (717, 3300)	91.8 (47.8, 204)	243 (109, 434)	444 (173, 808)	9.93 (3.91, 13.8)	63.0 (20.5, 2000)	4.11 (0.316, 11.0)	265 (120, 1760)
Day 2	53	6640 (2770, 27700)	1.00 (0.830, 1.12)	1750 (516, 3500)	75.9 (32.7, 121)						
Day 3	52	6630 (2490, 27000)	1.00 (0.830, 1.17)	1830 (518, 3820)	73.9 (28.5, 130)						
Day 4	52	6710 (2390, 27200)	1.00 (0.920, 1.00)	1920 (544, 4100)	76.0 (29.0, 137)						
Day 5	52	6810 (2420, 27500)	1.00 (0.920, 1.58)	NA	70.1 (23.7, 143)						
High-dose (D1 1.0 mg/kg; D2-5 0.3 mg/kg/day)											
Day 1	53	14300 (7860, 29300)	1.00 (0.650, 1.08)	2630 (1610, 5380)	126 (83.7, 228)	289 (165, 572)	501 (208, 1140)	9.34 (6.43, 14.6)	57.5 (31.1, 184)	3.98 (1.70, 6.88)	221 (122, 670)

Cohort	N	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	AUC_{0-24h} (µg•h/mL)	AUC_{0-72h} (µg•h/mL)	AUC_{0-168h} (µg•h/mL)	$t_{1/2}(\beta)$ (h)	$t_{1/2}(\gamma)$ (h)	Cl (mL/h/kg)	V_{ss} (mL/kg)
Day 2	49	7840 (4660, 15600)	1.00 (0.520, 1.00)	2040 (815, 5040)	86.2 (48.4, 168)						
Day 3	48	7420 (4130, 15200)	1.00 (0.500, 1.00)	2090 (839, 5310)	81.1 (43.8, 177)						
Day 4	46	7380 (4340, 15500)	1.00 (0.520, 1.02)	2120 (816, 5630)	81.3 (44.5, 190)						
Day 5	46	7300 (4410, 15900)	1.00 (0.830, 1.00)	NA	74.0 (35.0, 182)						

Table 4: Median (mix, max) Brilacidin Plasma Pharmacokinetic Parameters derived in Study CTIX-BRI-204 (IV dosing)

Cohort	N	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	AUC_{0-24h} (µg•h/mL)	AUC_{0-72h} (µg•h/mL)	AUC_{0-168h} (µg•h/mL)	$t_{1/2}(\beta)$ (h)	$t_{1/2}(\gamma)$ (h)	Cl (mL/h/kg)	V_{ss} (mL/kg)
Single Low-dose D1 0.6 mg/kg	54	7190 (3650, 13600)	1.02 (0.750, 1.47)	NA	68.2 (38.1, 120)	103 (53.9, 207)	126 (63.1, 285)	10.6 (4.00, 13.9)	66.0 (30.9, 371)	4.16 (1.89, 8.82)	275 (108, 1310)
Single High-dose D1 0.8 mg/kg	53	8690 (4330, 17600)	1.00 (0.933, 1.83)	NA	86.9 (51.0, 145)	136 (69.0, 286)	167 (78.8, 383)	10.8 (5.08, 13.9)	57.3 (26.4, 553)	4.27 (1.95, 8.75)	251 (116, 1310)
Multiple-dose D1 0.6 mg/kg; D2-3 0.3 mg/kg/day											
Day 1	52	6570 (3740, 15100)	1.00 (0.850, 1.70)	1680 (402, 4250)	73.9 (39.2, 161)	180 (103, 463)	244 (132, 720)	10.5 (6.43, 15.3)	70.3 (32.0, 323)	4.33 (1.46, 8.41)	271 (100, 700)
Day 2	52	4850 (2610, 10800)	1.02 (1.00, 1.08)	1460 (680, 4950)	57.4 (24.5, 161)						
Day 3	50	4630 (2570, 11500)	1.02 (1.00, 1.22)	NA	47.4 (26.3, 140)						

1.3.2.3. Clinical Efficacy

Brilacidin by intravenous administration

Brilacidin demonstrated marked clinical efficacy in treatment of ABSSSI in two Phase 2 clinical trials. In a Phase 2a clinical study involving 215 patients with ABSSSI, clinical success in treating the infections was found in approximately 90% of patients in each of three Brilacidin treatment groups, varying slightly by timepoint and analysis population, compared with daptomycin as active control (SLD = single loading dose; dose in mg/kg): (1) 1.0 SLD + 0.35 qd x 4 days, (2) 0.75 SLD + 0.35 qd x 4 days, (3) 0.40 SLD + 0.30 qd x 4 days, and (4) daptomycin 4 qd x 7 days. In all efficacy analyses, across all treatment arms, the 95%

confidence intervals around the point estimates for clinical success overlapped, indicating a consistent and high clinical success rate, similar to the active comparator (daptomycin).

The clinical response results observed in Phase 2a Study PMX63-203 were confirmed in a Phase 2b clinical study (CTIX-BRI-204) which treated 209 patients with ABSSSI. Clinical success in treating the infections found was achieved across the three Brilacidin treatment groups and daptomycin active control group between 83.3% to 100%, and all 95% confidence intervals overlapped. The 4 treatment groups were (SLD = single loading dose; dose in mg/kg): (1) 0.6 SLD, (2) 0.8 SLD, (3) 0.60 SLD + 0.30 qd x 2 days, and (4) daptomycin 4 qd x 7 days. Patients given Brilacidin on active treatment days were also given placebo on other days to maintain the double-blind design.

After an extensive PK/PD analysis and discussion with experts (including a meeting with FDA), it was deemed that cardiovascular and neurosensory effects were dose-related, and when given systemically in lower doses, as in the Phase 2b ABSSSI trial, these effects are likely to reduce in both frequency and severity.

The lowest dose tested (0.6 SLD) in the Phase 2b Study CTIX-BRI-204 was efficacious (comparable to the daptomycin arm) and generally well-tolerated, and is the IV dose proposed for progression to Phase 3 testing in the ABSSSI indication.

Brilacidin by other routes of administration

Brilacidin administered as an oral rinse has demonstrated anti-inflammatory efficacy in a Phase 2 clinical trial for attenuation of oral mucositis in adult patients with HNC receiving chemoradiation therapy. Brilacidin oral rinse markedly reduced the incidence of severe oral mucositis through completion of radiation, relative to placebo. Safety findings observed were typical for patients with head and neck cancer being treated with chemoradiation therapy, with a safety profile for Brilacidin comparable to placebo.

Brilacidin administered per rectum as a daily (at night) retention enema has demonstrated anti-inflammatory efficacy in a Phase 2 clinical trial for induction of remission of active mild to moderate ulcerative proctitis (UP) or ulcerative proctosigmoiditis (UPS). Brilacidin rectal enema resulted in clinical remission after 6 weeks of treatment in a majority of subjects for the doses tested. Endoscopic improvement was demonstrated. Certain markers indicative of inflammation – including fecal calprotectin, and IL-1β and IL-6 measured in colon tissue biopsies (from rectum and sigmoid) at Week 6 – reduced with study treatment, supporting the treatment group clinical responses.

1.4. Dose Rationale

In this study, all subjects are to receive local SoC plus allocated study treatment in addition. Two IV study treatment arms are planned:

- SoC + Brilacidin IV 0.6 mg/kg (D1), 0.3 mg/kg (D2 and D3) with potential to expand dosing[a] of 0.3 mg/kg on D4 and D5
- SoC + Saline IV infusion (D1, D2, and D3) with potential to expand dosing[a] on D4 and D5

[a] Note: Dependent on safety review and recommendation by the Data Monitoring Committee (DMC).

D1, D2, and D3 (above) refer to Day 1, Day 2 and Day 3 of study treatment. Similarly, D4 and D5 are Day 4 and Day 5.

The doses of Brilacidin are selected from the dose range previously tested in the IV program.

From the Phase 2 program conducted with Brilacidin administered IV for the indication of ABSSSI, a multiple dose regimen (0.6 mg/kg on Day 1, followed by 0.3 mg/kg on Days 2 and 3) from the Phase 2b study (CTIX-BRI-204) is initially selected for testing in this trial.

An independent Data Monitoring Committee (DMC) will be established to conduct periodic safety reviews (Section 8.1.6). An initial safety review is planned to occur after approximately 20 randomized subjects have completed up to Day 15. This initial interim analysis will focus on review of cardiovascular safety, vital signs and adverse events. At the time of the initial interim safety review (or any subsequent safety review), the DMC may recommend expanding dosing to Days 4 and 5 at the same doses as on Days 2 and 3. Brilacidin was also administered IV for 5 days of treatment in the ABSSSI program, in the Phase 2a study (PMX63-203), albeit with slightly different 5-day dosing regimens.

The rationale for looking to expand treatment duration to five days, from the initial dose regimen of three days, is to be able to provide a longer duration of systemic Brilacidin exposure at a level that can strongly suppress SARS-CoV-2 virus activity, and any associated symptoms, and thus provide a more optimal therapy to hospitalized patients with moderate or severe COVID-19. The longer treatment duration is expected to allow for greater impact of Brilacidin treatment and provide enhanced benefit to the patient, with the 5-day regimen incorporated only following recommendation by the DMC subsequent to DMC review of all available safety data following safety review interim analysis(es).

The safety profile of the proposed 3-day, and potential 5-day, regimens are covered by the dose range previously investigated, and the safety findings are regarded as manageable for hospitalized COVID-19 patients meeting the protocol entry requirements. The potential for the selected dose regimens to achieve efficacy in human has been modeled, using plasma concentration data from the prior ABSSSI development program and comparing to derived in vitro antiviral efficacy parameters (IC50 and IC90) from experiments with human lung epithelial cells.

1.4.1. Safety Profile for Selected Doses

Safety Profile: Up to three (3) days multiple dose regimen

The adverse events summary from Phase 2b Study CTIX-BRI-204 is presented in Table 5. Numbness/Tingling (N/T), defined as paraesthesia/paraesthesia oral or hypoaesthesia/ hypoaesthesia oral, was the most frequently reported AE, reported for 58.5% to 73.6% of subjects in the Brilacidin groups, and 8.0% for the daptomycin group, respectively. All numbness/tingling events tended to be transient, mild in intensity, and were reported by the investigator as related to study treatment.

Adverse events were reported for 46% of subjects in the daptomycin group and for 79.2-92.5% of subjects across the Brilacidin groups. Excluding N/T events, all-causality AE rates across all treatment groups were 52.8%, 56.6%, 69.8%, and 46.0%, and drug-related AE rates were 7.5%, 7.5%, 15.1%, and 26.0%, in the Brilacidin 0.6 mg/kg, 0.8 mg/kg, 0.6/0.3 mg/kg and daptomycin groups, respectively. Nausea was reported in 13.8% of the combined Brilacidin groups, and in 8.0% of the daptomycin group.

Infrequent, transient episodes of "hypertension" or "blood pressure increased" events (i.e., SBP >160 mmHg) were reported in 2 (3.8%), 9 (17.0%), 14 (26.4%), and 5 (10.0%) subjects, respectively, for the Brilacidin 0.6 mg/kg, 0.8 mg/kg, 0.6/0.3 mg/kg and daptomycin groups. Of note, the incidence of blood-pressure related AEs in the daptomycin group was higher than in the single dose 0.6 mg/kg arm, and daptomycin is not known to affect blood pressure. Hence, sensitivity of data collection and reporting would appear to indicate that, for the reporting in this study, the background rate for such blood pressure related AEs is up to ~10%, and that for the single dose 0.6 mg/kg arm, the incidence indicates no distinct drug-related adverse effects. None of the reported blood pressure events were considered serious or severe; in any treatment arm, and the majority were reported as related to study drug.

Table 5: Adverse Events summary for Study CTIX-BRI-204 (Safety Population)

Type of Adverse Event	Brilacidin D1 0.6 mg/kg	Brilacidin D1 0.8 mg/kg	Brilacidin D1 0.6 mg/kg; D2-3 0.3 mg/kg/day	Daptomycin D1-7 4 mg/kg/day
	N=53	N=53	N=53	N=50
None	20.8% (11)	18.9% (10)	7.5% (4)	54.0% (27)
At least 1 treatment-emergent	79.2% (42)	81.1% (43)	92.5% (49)	46.0% (23)
Leading to study drug withdrawal	5.7% (3)	1.9% (1)	3.8% (2)	2.0% (1)
At least 1 related	66.0% (35)	69.8% (37)	88.7% (47)	34.0% (17)
At least 1 SAE	5.7% (3)	1.9% (1)	3.8% (2)	0
At least 1 'tingling' and/or 'numbness'	58.5% (31)	62.3% (33)	73.6% (39)	8.0% (4)

Type of Adverse Event	Brilacidin D1 0.6 mg/kg	Brilacidin D1 0.8 mg/kg	Brilacidin D1 0.6 mg/kg; D2-3 0.3 mg/kg/day	Daptomycin D1-7 4 mg/kg/day
At least 1 'hypertension' and/or 'blood pressure increased'	3.8% (2)	17.0% (9)	26.4% (14)	10.0% (5)

There were no deaths in the study, and a total of 7 SAEs were reported for 6 subjects, all in the Brilacidin treatment groups: three in the 0.6 mg/kg group, one in the 0.8 mg/kg group, and two in the 0.6/0.3 mg/kg group. None were considered treatment-related by the investigator, and none were blood pressure-related or related to peripheral neurologic events.

Of the 7 withdrawals from the study due to adverse events, 6 were Brilacidin-treated subjects and 1 was a daptomycin-treated subject. Four (4) of these withdrawals were for serious adverse events. Of the other three withdrawals, two were classified as moderate severity hypoaesthesia related to study drug (one in the 0.8 mg/kg group and one in the 0.6/0.3 mg/kg group), occurring on Day 1 after completing the first Brilacidin dose. The remaining study withdrawal occurred after an allergic reaction to daptomycin.

Safety Profile: Five (5) days multiple dose regimen

The adverse events summary from Phase 2a Study PMX63-203 is presented in Table 6. Safety analysis showed 87% of patients in the highest dose group experienced at least one peripheral sensory effect, primarily tingling (paresthesia) and numbness (hypoesthesia). The lowest dose produced sensory effects in 65% of patients. Excluding numbness/tingling, the treatment-related adverse event rates were similar across treatment groups.

Table 6: Treatment-Related Adverse Events in Study PMX63-203 (Safety Population)

Treatment-Related Adverse Events (TRAEs)	Low-dose (D1 0.4 mg/kg; D2-5 0.3 mg/kg/day)	Medium-dose (D1 0.75 mg/kg; D2-5 0.35 mg/kg/day)	High-dose (D1 1.0 mg/kg; D2-5 0.3 mg/kg/day)	Daptomycin (D1-7 4 mg/kg/day)
	N=52	N=54	N=54	N=55
At least one TRAE	75% (39)	70.4% (38)	94.4% (51)	12.7% (7)
Excluding numbness & tingling	9.6% (5)	5.6% (3)	7.4% (4)	10.9% (6)
Numbness & tingling[a]	65.4% (34)	64.8% (35)	87.0% (47)	1.8% (1)
Discontinued due to TRAE[b]	1.9% (1)	3.7% (2)	9.2% (5)	0

a Including burning sensation
b TRAE discontinuations were due to hypertension, nausea/vomiting, vertigo, and injection site pain

Approximately 80% of the sensory effects caused by Brilacidin were mild and the remainder were moderate in intensity. Only one patient who was in the highest dose group experienced a severe sensory effect. The effects were noted earlier (Day 1) for the higher two Brilacidin

dose groups compared with the lowest dose group (Day 3). These events were transient and did not require medical intervention. All (100%) of patients having a sensory AE had resolution of these effects by the conclusion of the trial. There were no discontinuations due to sensory AEs (numbness/tingling).

There were no deaths in the study, and 5 patients experienced a serious adverse event (SAE) of which 3 SAEs were regarded as treatment-related. These treatment-related SAEs were hypertensive crisis (n=1 in medium-dose group; n=1 in high-dose group; both discontinued study), and thrombocytosis (n=1 in low-dose group).

Blood pressure was measured pre-dose, during infusion, and 3 hours post-infusion each day of the 7-day treatment period. Given that antibiotics are dosed acutely – and not over a period of months or years – the systolic blood pressure measurement was deemed more relevant than the diastolic blood pressure measurement by consulted cardiology experts. Although transient elevations in SBP were observed across the treatment groups, there was no evidence of end-organ involvement, nor of sustained hypertension by the end of the treatment period (Table 7).

Table 7: Mean Systolic Blood Pressure Effects in Study PMX63-203 (Safety Population)

Systolic Blood Pressure	Low-dose (D1 0.4 mg/kg; D2-5 0.3 mg/kg/day)	Medium-dose (D1 0.75 mg/kg; D2-5 0.35 mg/kg/day)	High-dose (D1 1.0 mg/kg; D2-5 0.3 mg/kg/day)	Daptomycin (D1-7 4 mg/kg/day)
	N=52	N=54	N=54	N=55
Screening Mean SBP (mmHg)	129.1	125.1	128.1	127.8
Day 5, 3 hr post-dose Mean SBP (mmHg)	129.9	127.3	128.8	125.3
Mean Change (mmHg)	+3.0	+3.8	+0.8	-2.3

Moreover, across the three Brilacidin treatment groups, the outlier analysis revealed a low rate (6/160; 3.8%) of hypertension events, defined as SBP ≥180 mmHg in at least one measurement during the treatment period. Consulted cardiology experts felt that this cut-off was the most clinically relevant for an acutely dosed drug. These six events appeared to be dose-related (low-dose, 1 event; medium-dose, 2 events; high-dose, 3 events); however, geographic clustering is a potential confounder, as these cases occurred at just 3 of the 21 enrolling sites. Only one of these patients (high-dose group) had elevated SBP ≥180 mmHg for two consecutive measurements (next day).

There were three patients (from the medium and high dose groups) who developed hypertension near 220/120 mmHg. When study drug was discontinued and patients were treated with anti-hypertensive medications, their blood pressure decreased. In all cases, blood

pressure increases were observed as gradual over hours or days allowing for prompt medical intervention.

Given the overall risk:benefit assessment for use of Brilacidin in treatment of COVID-19, the proposed protocol doses of Brilacidin are supported by the available safety data in the previous Phase 2, and additional Phase 1, clinical studies with Brilacidin administered intravenously. Blood pressure monitoring during study treatment to monitor for safety alerts is described in Section 1.4.2.

1.4.2. Vital Signs Measurements during Study Treatment

The blood pressure data from the prior Phase 2 ABSSSI program was examined for the following criteria:

- Systolic blood pressure increased: ≥180 and increase from baseline ≥20
- Diastolic blood pressure increased: ≥110 and increase from baseline ≥15

Table 8: Number of Patients meeting Blood Pressure Criteria in the ABSSSI Program, by Study (Safety Population)

Study PMX63-203

BP Criteria	Low-dose (D1 0.4 mg/kg; D2-5 0.3 mg/kg/day)		Medium-dose (D1 0.75 mg/kg; D2-5 0.35 mg/kg/day)		High-dose (D1 1.0 mg/kg; D2-5 0.3 mg/kg/day)		Daptomycin (D1-7 4 mg/kg/day)	
	N=52		N=54		N=54		N=55	
	Single	Confirmed	Single	Confirmed	Single	Confirmed	Single	Confirmed
SBP ≥180 and increase from baseline ≥20	1	1	2	2	3	1	0	0
DBP ≥110 and increase from baseline ≥15	1	0	4	4	5	2	0	0

Study CTIX-BRI-204

BP Criteria	Brilacidin D1 0.6 mg/kg		Brilacidin D1 0.8 mg/kg		Brilacidin D1 0.6 mg/kg; D2-3 0.3 mg/kg/day		Daptomycin D1-7 4 mg/kg/day	
	N=53		N=53		N=53		N=50	
	Single	Confirmed	Single	Confirmed	Single	Confirmed	Single	Confirmed
SBP ≥180 and increase from baseline ≥20	0	0	3	1	5	2	2	0
DBP ≥110 and increase from baseline ≥15	0	0	7	4	2	0	1	0

In Study PMX63-203, single BP values were measured; in Study CTIX-BRI-204, single BP values was reported as the average of triplicate measurements. A confirmed value is a value either repeated at timepoint, or by measurement meeting that criteria at a different timepoint.

In Study PMX63-203, patients that met the BP noted were typically treated for increased blood pressure, with IV and/or oral anti-hypertensive treatments; in Study CTIX-BRI-204, such concomitant treatment was not initiated.

Vital signs were measured more intensely in Study CTIX-BRI-204 than in Study PMX63-203.

In this study, blood pressure and pulse rate measurements will be measured more intensely during the treatment period with study drug, during hospitalization. On Days 1-3 (and potentially Day 4-5 also, after initial interim safety readout), measurements will be made pre-dose, within no more than 30 mins after the end of infusion, and 3 hours (±30 mins) post-start of infusion (i.e., ~2 hours post-end of infusion).

If systolic blood pressure ≥ 180 mmHg and increase from baseline ≥ 20 mmHg, the measurement is to be repeated within 15-30 minutes. If the repeat measurement is confirmed, the attending physician is to review the patient profile and determine if treatment for hypertension is needed. After a confirmed systolic blood pressure elevation, blood pressure measurements are to be performed approximately every 4 hours or as frequently as necessary in accordance with local standard of care.

Similarly, if diastolic blood pressure ≥ 110 mmHg and increase from baseline ≥ 15 mmHg, the measurement is to be repeated within 15-30 minutes. If the repeat measurement is confirmed, the attending physician is to review the patient profile and determine if treatment for hypertension is needed. After a confirmed diastolic blood pressure elevation, blood pressure measurements are to be performed approximately every 4 hours or as frequently as necessary in accordance with local standard of care.

See Section 8.1.5 (Adverse Events of Special Interest/ Blood Pressure category reporting) and Section 9.2 (Interim Analyses/ Data Monitoring Committee Reviews).

1.4.3. PK/PD Modeling of Antiviral Efficacy Parameters for Selected Doses

The potential for the selected dose regimens to achieve efficacy in human has been modeled, using plasma concentration data from the prior Phase 2b study (for the ABSSSI development program) and comparing to derived in vitro antiviral efficacy parameters (IC50 and IC90) from experiments with human lung epithelial cells. (The CC10 was also included in the preliminary modeling readouts, but is removed from final assessment readouts as that parameter – as an indicator of a safety margin – is not relevant since it is far above achievable Cmax concentrations following selected regimen dosing.)

Using a previously-developed population PK model describing the disposition of Brilacidin (developed for the ABSSSI program - Van Wart et al 2015; Van Wart et al [ICPD] 2016), calculated PK/PD targets generated from the in vitro antiviral analyses (i.e., the IC50 and IC90, see Section 1.3.1.3), and demographic characteristics from clinical studies conducted with Brilacidin in patients with ABSSSI, an R Shiny simulation application was created to evaluate various Brilacidin dosing regimens for the treatment of patients with COVID-19.

Protein binding is not adjusted for in the model, as the protein load in the in vitro assays has not been calculated - 10% fetal bovine serum is present in the Calu-3 cell culture. The total plasma Brilacidin concentrations is presented in the modeling, and the total concentration of Brilacidin present in vitro used.

Final modeling readouts for the selected dose regimens are shown in Figure 6 and Figure 7. The concentration-time profiles are presented on linear (A, left panel) and semi-log (B, right panel) Y axes.

Plots of the median and 90% prediction interval (PI) for total plasma Brilacidin concentrations are shown, simulated for the selected dosing regimens. The IC90 and IC50 parameters from in vitro, as Brilacidin free-base values, are shown as dotted red-lines and are labelled accordingly.

The figures demonstrate that the in vitro viral inhibition parameters of IC50 and IC90 are clinically-achievable concentrations for a sustained duration of time with the selected regimens:

- For the 3 days multiple dose regimen [of 0.6 mg/kg (D1), 0.3 mg/kg (D2 and D3)], over the 7 days (168 hours) after start of treatment the simulated population median is above the IC50 threshold for 103 hours, with the IC90 threshold exceeded for 40.7 hours.
- For the 5 days multiple dose regimen [of 0.6 mg/kg (D1), 0.3 mg/kg (D2 to D5)], over the 7 days (168 hours) after start of treatment the simulated population median is above the IC50 threshold for 152 hours, with the IC90 threshold exceeded for 63.7 hours.

Figure 6: PK/PD model simulation: Brilacidin 3 days multiple dose, 0.6 mg/kg (D1), 0.3 mg/kg (D2 and D3)

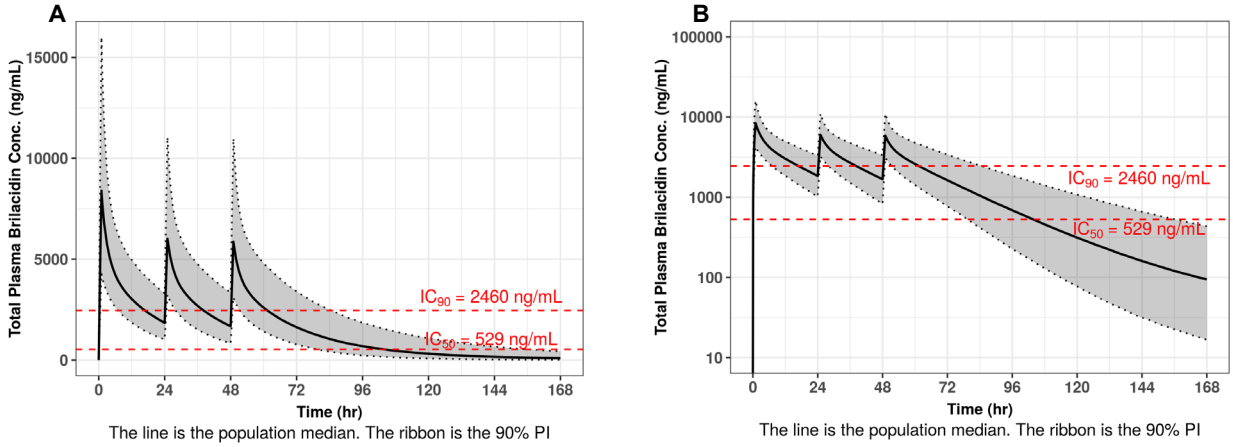
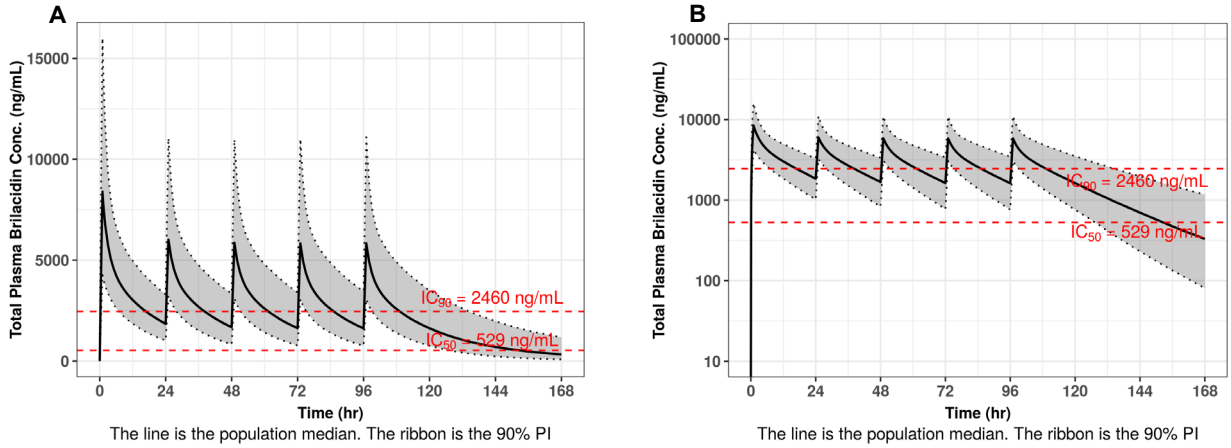


Figure 7: PK/PD model simulation: Brilacidin 5 days multiple dose, 0.6 mg/kg (D1), 0.3 mg/kg (D2 to D5)



The modeling is only taking one therapeutic property of Brilacidin into consideration - i.e., it's applying in vitro antiviral parameter targets to simulated in vivo human plasma concentrations, without taking into consideration the anti-inflammatory potential of Brilacidin in vivo, which should also be able to impact the course of COVID-19 disease.

Given the limitations of modeling, particularly application between in vitro and in vivo systems, the proposed doses selected appear appropriate for testing in this Phase 2 Proof-of Concept study. Selecting doses within the range previously tested in the Phase 2 program for the indication of ABSSSI also allows for an expected safety profile and known expectation of associated safety signals with those Brilacidin dose regimens.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 9: Objectives and Related Endpoints

Objective(s)	Endpoint(s)
PRIMARY	
• To evaluate the clinical efficacy of Brilacidin IV treatment in addition to SoC, compared with SoC alone, in subjects with COVID-19	Primary Endpoint based on the clinical status ordinal scale: • Time to sustained recovery through Day 29 Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale with response sustained through Day 29: - Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than for per protocol dosing or assessments, as appropriate); - Not hospitalized, limitation on activities and/or requiring home oxygen; - Not hospitalized, no limitations on activities.
SECONDARY	
• To assess multiple clinical measures of disease severity and disease burden - Composite endpoints, from the ordinal scale	• Achieving recovery status scores (see definition in primary endpoint above) at Day 29 • Composite endpoint by Day 29, defined as: - Death OR - Respiratory failure (requires invasive mechanical ventilation)
- Clinical status measures, from the ordinal scale	Endpoints based on the 8-point ordinal scale: • Achieving at least one-point/ two-point improvement in clinical status at Days 8, 15 and 29 • Time to at least one-point/ two-point improvement in clinical status • Clinical status over time
- Change in the National Early Warning Score (NEWS2)	• Time to a NEWS2 of ≤2 and maintained for 24 hours • Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS2
• To assess the safety and tolerability of Brilacidin IV treatment in subjects with COVID-19	• Incidence and severity of treatment-emergent Adverse Events (AEs), including Serious Adverse Events (SAEs)

	• Clinically significant changes in laboratory measures and vital signs
EXPLORATORY/ OTHER	
• In-hospital outcomes	• Duration of hospitalization • Time to discharge • Duration of invasive mechanical ventilation • Duration of supplemental oxygen support • Duration of ECMO • No oxygen therapy (and/or peripheral oxygen saturation SpO_2 > 93% on room air) at Days 8, 15 and 29
• All-cause mortality	• 28-day mortality (to Study Day 29)
• To measure biological and immunological markers of illness/inflammation	• Changes from baseline in biomarkers from blood samples may include, but are not limited to: CRP, ferritin, LDH, D-dimer, troponin T hs, absolute neutrophil count [at Days 2, 3, 5, 8, 11 (while hospitalized) and/or on day of discharge; and Days 15 and 29 (by returning to the clinic/ by remote visit or if still hospitalized)]; and IL-1β, IL-6, IL-10, total IL-18, TNF-α [at Days 3, 5, 8, 11 (while hospitalized) and/or on day of discharge; and Day 15 (by returning to the clinic/ by remote visit or if still hospitalized)];
• To explore the change in the SARS-CoV-2 viral load	• Change from baseline in SARS-CoV-2 viral load from NP or OP samples at Days 3, 5, 8, 11 (while hospitalized) and/or on day of discharge; and Days 15 and 29 (by returning to the clinic/ by remote visit or if still hospitalized)
• To estimate the plasma pharmacokinetics of Brilacidin	• Plasma concentrations of Brilacidin measured from blood samples collected on Days 1 to 4

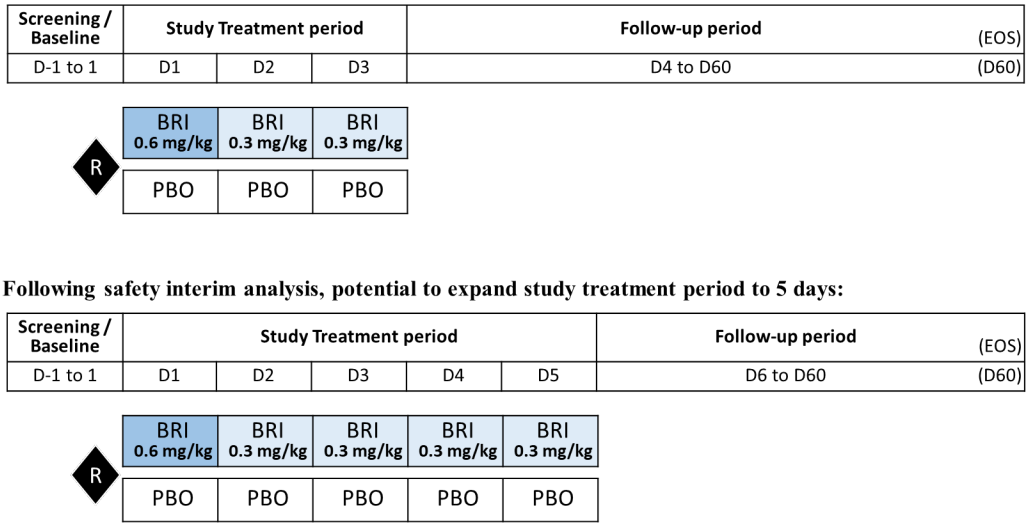
3. STUDY OVERVIEW

This Phase 2 study is a randomized, blinded, placebo-controlled, parallel group design.

The target population to be treated are patients with moderate to severe COVID-19, SARS-CoV-2 infection confirmed by positive standard polymerase chain reaction (PCR) test (or equivalent/ other approved diagnostic test) within 4 days prior to starting study treatment, and hospitalized with respiratory distress but not yet requiring high-level respiratory support (as defined in exclusion criterion #2).

The study is comprised of three parts (Figure 8):

Figure 8: Study Design Schematic



Note: Study treatment is in addition to standard of care (SoC)

BRI = Brilacidin; D = Day; EOS = End of Study; PBO = placebo; R = randomization

Screening/ Baseline visit (Day -1 to 1): Lasts up to 24-48 hours and comprises screening/ baseline assessments. This visit will confirm that study inclusion and exclusion criteria are met by participants prior to randomization.

Treatment period (Day 1-3 with potential to expand to Day 4-5): Randomized subjects will receive blinded study treatment once daily by IV infusion, in addition to SoC.

Follow-up period (Day 4-6 through Day 60): Subjects will be assessed daily while hospitalized. Discharged patients will be asked to attend study visits at Days 15 and 29. (Of note: the median hospital stay for COVID-19 has been reported to be 12 days with an interquartile range of 1 to 14 days [Cao et al 2020]). All subjects will undergo a series of efficacy and safety assessments, including laboratory assays. Blood samples and nasopharyngeal (NP) swabs will be obtained on Days 1, 3, 5, 8, 11 (while hospitalized) and/or

on day of discharge; and Days 15 and 29 (by returning to the clinic/ remote visit or if still hospitalized). **Note: NP swabs are to be collected.**

If subjects are discharged from hospital prior to Day 15, or Day 29, and a hospital visit is not possible, then visiting nursing services and mobile phlebotomy may support that visit remotely where these are available in accordance with local guidelines and should include all possible assessments (e.g., oxygen saturation with portable monitors). Every effort should be made to ensure discharged patient follow-up at Days 15 and 29, via a healthcare interaction (minimally by telephone call). A follow-up visit at Day 60(±10), by telephone call, is also included to confirm patient status.

All subjects receive local SoC, plus allocated study treatment in addition. Two IV study treatment arms are planned:

- SoC + Brilacidin IV 0.6 mg/kg (D1), 0.3 mg/kg (D2 and D3) with potential to expand dosing[a] of 0.3 mg/kg on D4 and D5
- SoC + Saline IV infusion (D1, D2, and D3) with potential to expand dosing[a] on D4 and D5

[a] Note: Dependent on safety review and recommendation by the DMC.

D1, D2, and D3 (above) refer to Day 1, Day 2 and Day 3 of study treatment. Similarly, D4 and D5 are Day 4 and Day 5.

Treatment randomization is 1:1 (n=60 per arm). Randomization will also be stratified by (1) Age (≤65 years, >65 years), (2) Severity of disease (moderate, severe), and (3) Country.

An independent Data Monitoring Committee (DMC) will be established to conduct periodic safety reviews (Section 8.1.6). An initial safety review is planned to occur after approximately 20 randomized subjects have completed up to Day 15. This initial interim analysis will focus on review of cardiovascular safety, vital signs and adverse events that have occurred in the approximately 20 subjects to receive Days 1-3 of study treatment. A further safety review by the DMC is planned to occur after approximately 50% of subjects have completed up to Day 29, to allow for unblinded monitoring of safety data around the study mid-point. The DMC may recommend expanding dosing to Days 4 and 5 (at the same doses as on Days 2 and 3), continuation of the Days 1-3 study dosing unchanged, or that the trial be interrupted or stopped for safety reasons. The DMC will be guided by the degree and incidence of hypertensive values/events observed in the ongoing study which should not exceed the number and/or severity of those observed in previous studies with Brilacidin IV treatment for expansion of dosing to occur as planned.

The rationale for looking to expand treatment duration to five days, from the initial dose regimen of three days, is to be able to provide a longer duration of systemic Brilacidin exposure at a level that can strongly suppress SARS-CoV-2 virus activity, and any associated symptoms, and thus provide a more optimal therapy to hospitalized patients with moderate or severe COVID-19. The longer treatment duration is expected to allow for greater impact of Brilacidin treatment and provide enhanced benefit to the patient, with the 5-day regimen

incorporated only following recommendation by the DMC subsequent to DMC review of all available safety data following safety review interim analysis(es).

Study stopping rules are presented in Section 7.7. Recommendation guidelines and details of the DMC will be prepared separately from this protocol in a DMC Charter. The charter may supersede the summary details presented here in the protocol.

4. STUDY POPULATION

4.1. Inclusion Criteria

Participants eligible for enrollment and inclusion in this study must meet all of the following criteria:

1. Signed and dated written Informed Consent Form (ICF) to participate in the clinical study by patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative.

2. Male or non-pregnant female adults between 18 and 80 years of age, inclusive, at time of informed consent.

3. SARS-CoV-2 infection confirmed by positive standard polymerase chain reaction (PCR) test (or equivalent/ other approved diagnostic test) ≤ 4 days before randomization.

4. Currently hospitalized and requiring medical care for COVID.

5. Moderate OR severe COVID-19, defined by respiratory function at screening, as below:

   Moderate, meet at least one of the following criteria:

   - Peripheral oxygen saturation SpO_2 > 93% on room air;
   - Respiratory rate ≥ 20 to < 30 breaths per minute.

   Severe, meet at least one of the following criteria:

   - Peripheral oxygen saturation SpO_2 ≤ 93% on room air OR arterial oxygen partial pressure (PaO_2) / fraction of inspired oxygen (FiO_2) < 300mmHg (1mmHg=0.133kPa) [corrective formulation should be used for higher altitude regions (over 1000m)];
   - Respiratory rate ≥ 30 breaths per minute.

6. Body mass index (BMI) of ≥18 to <40kg/m^2 at screening.

7. Agrees to the collection of nasopharyngeal (NP) swabs and venous blood per protocol.

8. In the opinion of the investigator, willing and able to comply with the study protocol assessments, and is committed to the study and the study follow-up visits.

4.2. Exclusion Criteria

Participants meeting ANY of the following criteria are not eligible for this study and are to be excluded:

1. Participation in any other clinical trial of an investigational treatment.

2. Requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) at the time of randomization.

3. Has explicitly expressed the wish not to receive intensive care support (Do not resuscitate or Do not intubate order) should this become necessary.

4. In the opinion of the investigator, progression to death is imminent and inevitable within the next 72 hours, irrespective of the provision of treatment, such as rapidly progressive multiorgan failure.

5. Requiring systemic anti-infective therapy for suspected or confirmed active bacterial/fungal/viral systemic infection other than COVID-19.

6. Hypertensive urgency (e.g., SBP >220 mmHg or DBP >120 mmHg) or hypertensive emergency within the last 72 hours, as assessed by the investigator following local guidelines.

7. If has a history of hypertension in the last 3 months, must have been receiving appropriate anti-hypertensive therapy in accordance with local guidelines.

8. Evidence of moderate or severe hepatic impairment (Child-Pugh Class B or C).

9. Estimated GFR (eGFR) <30 mL/min/1.73m^2 (based on CKD-EPI formula).

10. Prior to a participant's study entry, known allergies or intolerance to Brilacidin or formulation excipients.

11. Any serious medical or psychiatric condition or test abnormality(ies) that, in the investigator's judgment, puts the participant at significant risk, could confound the study results, or may interfere significantly with the subject's safe participation in and completion of the study.

12. Pregnancy or breast-feeding, or positive urine or serum pregnancy test in a pre-dose assessment.

13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception as defined below, throughout the study and for up to 30 days after stopping treatment.

    Effective contraception methods include:

    - Total abstinence (if this is the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before start of

study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male partner sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that female subject.
- Double barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
- Use of oral*, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
  (*In the case of oral contraception, subjects should have been using the same pill on a stable dose for a minimum of 3 months before start of study treatment).
- Intrauterine device (IUD) or intrauterine system (IUS)

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before start of study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

In addition, female subjects must also refrain from egg donation and in vitro fertilization during study treatment and for 7 days after stopping study treatment.

14. Sexually active males with female partners of childbearing potential unwilling to use a condom when engaging in intercourse of reproductive potential throughout the study and for up to 30 days after stopping treatment.

    In addition, male participants must not donate sperm during study treatment and for 7 days after stopping study treatment.

5. STUDY TREATMENT

A separate pharmacy manual will be provided.

5.1. Treatment Allocation

Subject registration and random assignment to treatment will be accomplished using an Interactive Response Technology (IRT) to one of the treatment groups.

Approximately 120 study participants will be randomized to receive either Brilacidin or placebo in addition to available SoC. Subjects that are eligible will be randomized to one of the following two IV study treatment arms in a ratio of 1:1 (n=60 per arm)

- SoC + Brilacidin IV 0.6 mg/kg (D1), 0.3 mg/kg (D2 and D3) with potential to expand dosing[a] of 0.3 mg/kg on D4 and D5
- SoC + Saline IV infusion (D1, D2, and D3) with potential to expand dosing[a] on D4 and D5

[a] Note: Dependent on safety review and recommendation by the DMC.

D1, D2, and D3 (above) refer to Day 1, Day 2 and Day 3 of study treatment. Similarly, D4 and D5 are Day 4 and Day 5.

Randomization of subjects to treatment will also be stratified by (1) Age (≤65 years, >65 years), (2) Severity of disease (moderate, severe), and (3) Country.

Brilacidin for Injection concentrated solution, for dilution with normal saline for subsequent IV infusion, will be provided by the Sponsor. SoC administered alongside the study treatment will be supplied by the investigational site.

5.2. Subject Numbering

Each subject screened is assigned a unique subject number, which is a combination of the site number (three-digit) that is provided by the Sponsor, and a three-digit sequential number assigned at the site. Once assigned to a subject, the subject number will not be reused.

At each study site, the first subject is assigned subject number -001, and subsequent subjects are assigned consecutive numbers (e.g., the second subject is assigned subject number -002, the third subject is assigned subject number -003). The Investigator or site staff will contact the IRT system and provide the requested identifying information for the subject to register them.

If the subjects fails to be randomized for any reason, the IRT system must be notified of the decision being taken that the subject was not treated. The reason for not being treated will be entered into the eCRF/IRT system.

5.3. Treatment Blinding

This is a double-blind study, and the identity of the investigational product and placebo control will be concealed by use of study treatments that are identical in presentation to the administering medical staff.

The subject's randomization number generated by the IRT system for a subject will be shared with the site's unblinded pharmacist, and they will consult the open randomization code previously provided to them for this study.

The unblinded pharmacist will keep the randomization code confidential throughout the conduct of the study, except in the event of subject medical emergencies for which individual subject unblinded may be initiated.

5.4. Emergency Unblinding of Treatment

In the event of a medical emergency, the subject-specific treatment may be identified; however, every effort should be made to maintain the blind. Unblinding at the study site for any other reason will be considered a protocol violation.

Where possible, the Investigator (or designated physician) shall contact the Medical Monitor before breaking the blind for any subject.

The subject-specific treatment code can be obtained from the site's unblinded pharmacist, or from contacting the appropriate emergency phone number for the IRT System. Instructions on how to perform an unblinding will be provided separately.

Any intentional or unintentional breaking of the blind is to be reported immediately to the Sponsor. When the blinding code for a subject has been broken, the reason must be fully documented.

5.5. Investigational Product Supplies

5.5.1. Description

The investigational drug product supplied is Brilacidin for Injection, 50 mg/mL (free base), provided in 2 mL glass vials with 1 mL extractable volume, to be stored frozen at -20±5°C.

The provided solution formulation contains 50 mg/mL of Brilacidin free base and 20% w/v hydroxypropyl-beta-cyclodextrin (Kleptose HPB) in water for injection. Brilacidin sterile concentrated solution is a clear, colorless to yellow to brown solution supplied in 2 mL clear glass vials with 13 mm Omniflex Plus serum stoppers and sealed with flip off seals. Each vial has a fill volume ~1.2 mL to ensure 1.0 mL extractable volume per vial. The sterile solution formulation provided requires further dilution with normal saline for subsequent intravenous infusion.

The 2 mL glass vials are labelled as containing “Brilacidin for Injection, 50 mg/mL (free base) for 1.0 mL extractable volume”.

Brilacidin IV infusion requires unblinded pharmacist preparation at the study site; allows for blinded treatment administration by use of local blinded labelling.

5.5.2. Storage Conditions

Brilacidin vials must be stored according to the labeled storage conditions, which is to be stored frozen at -20±5°C. The Investigator, or an approved representative (e.g., pharmacist, designated study site staff member), will ensure that all investigational product is stored in a secured and locked area with restricted access.

If any investigational product is deemed to have been exposed to temperatures outside the range noted above, the supplies should not be administered to any participant until the Sponsor provides further direction.

5.5.3. Packaging and Labeling

Vials will be packaged in cartons of at least 10 vials.

Vial and carton labels will be in the local language (or in English in case allowed according to local regulation) and comply with the legal requirements of each country, as applicable. Labeling will include storage conditions for the study treatment and clearly identify for investigational use only.

5.5.4. Dose Preparation

For intravenous infusion administration, Brilacidin for Injection is diluted in sterile 0.9% w/v sodium chloride (normal saline) to provide the desired final dose within 8 hours of administration. Placebo IV infusion will be sterile 0.9% w/v sodium chloride (normal saline).

Intravenous infusion requires unblinded pharmacist (or appropriate designee) preparation, with appropriate mg/kg per study participant prepared. The Brilacidin dose will be prepared according to the protocol-specified treatment regimen (see Section 5.1). Dose calculation for a subject’s study treatment infusions will be based on actual body weight measured at Screening.

Dose preparation is to be conducted by an identified unblinded study pharmacist (or appropriate designee), the “dose preparer”. Prior to dilution, the appropriate number of Brilacidin vial(s) will be removed from freezer storage and thawed at room temperature for approximately 1 hour. The thawed vial(s) should be mixed by gentle inversion. The dose preparer will document on the appropriate vial labels the subject randomization number and date the vial was opened/used.

Using aseptic technique, the appropriate volume of Brilacidin 50 mg/mL (free base) required for subject dosing is to be added to a plastic infusion bag containing sterile 0.9 % saline, to achieve a final volume of 100 mL.

An IV infusion set equipped with an in-line 0.2 μm membrane filter will be attached to the infusion bag. A label containing the subject's study number, randomization number, dose date, and protocol study number will be attached onto the infusion bag containing the prepared dose; the label will be blinded to the study treatment to be administered.

The desired final dose in the infusion bag can be prepared within eight (8) hours of administration. The prepared, diluted drug product in the infusion bag is to be stored at room temperature not above 25°C, 77°F, in-between preparation and administration.

Any unused Brilacidin 50 mg/mL (free base) solution remaining in an opened vial should be retained for performing drug accountability. Any next dose(s) for a subject is/(are) to be prepared from unopened frozen vials.

5.5.5. Administration of Prepared Dose

Diluted Brilacidin solution is stored at room temperature not above 25°C, 77°F, prior to use and is filtered through a 0.2 μm membrane when administered intravenously over 60 minutes. The placebo control arm will use 100 mL normal saline solution administered in the same way to maintain blinding.

The identity of the prepared dose will be concealed by use of study treatments that are identical in presentation to the administering medical staff.

The prepared study dose in the infusion bag provided to the medical staff will be administered intravenously by an infusion pump over a 60±5 minute interval into the peripheral vein; the IV infusion set must include an in-line 0.2 μm membrane filter.

The IV line for study treatment should be dedicated. IV lines should not be flushed with dextrose 5% in water (D5W). Approximately two (or more) mL of 0.9 % saline may be used to flush the line before and after administration. Heparin (in 0.9% saline) may also be used following study treatment administration to keep the catheter patent.

5.6. Investigational Product Handling and Accountability

Investigational product must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site staff have access. Upon receipt, all study treatment must be stored according to the instructions specified on the label.

It is the responsibility of the Investigator to ensure that the current disposition of the study treatments is maintained at his/her study site where investigational product is inventoried and dispensed.

Investigational product is to be dispensed only in accordance with the protocol.

A Drug Accountability Log must be maintained and contain an accurate record of the shipment and dispensing of investigational product. Monitoring of drug accountability will be performed by a study monitor during site visits or remotely, and at the completion of the trial. The original Drug Accountability Log should remain at the study site and a copy will be provided for the Trial Master File at the conclusion of the study.

5.7. Return of Clinical Supplies

All used and unused investigational product/packaging must be retained at the site until the conclusion of the study or until permission for disposition is granted. The study monitor will complete the final drug accountability and assist the site with return and/or destruction of investigational product/packaging at the end of the study. Used IV related supplies will be destroyed after use in compliance with local hospital or institutional policies.

6. THERAPIES AND MEDICATIONS

6.1. Concomitant Medications and Concurrent Procedures

All medications, procedures, non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study will be captured in the eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Study Medical Monitor before randomizing a participant or allowing a new medication to be started. If the subject is already enrolled, contact the Study Medical Monitor to determine if the participant should continue participation in the study.

For subjects discharged from hospital prior to Day 29, they must be told to notify the treating physician about any new medications he/ she takes through end of the study.

During the course of the study, subjects may receive antiviral treatment, intravenous, oral or inhaled corticosteroids, antibiotics and other agents where these forms part of SoC for the treatment of COVID-19 at their participating site.

6.1.1. Concomitant Medications to be used with caution

Using the January 2020 FDA Guidance for in vitro DDI studies, available data indicates there is a potential for Brilacidin to reversibly inhibit CYP2C8, CYP2C9, and CYP3A4 with a possible although probably not likely time-dependent inhibition of CYP2B6. (Please refer to the Investigator's Brochure for additional information).

Investigators may, at their discretion, co-administer known inhibitors of CYP2C8, CYP2C9, and CYP3A4 during study treatment, but their duration should be kept as short as possible, and patients are to be closely monitored. Particularly, caution is advised when study treatment is co-administered with drugs that are sensitive substrates of CYP2C8, CYP2C9, and CYP3A4 and/or have a narrow therapeutic index. Table 10 presents a list of some clinical substrates for CYP2C8, CYP2C9 and CYP3A P450-mediated metabolism

The patient and the treating physician should be aware of potential signs of adverse effects/ overdose of concomitant medication(s) and in the event of suspected study drug related toxicity; administration of study drug should be held according to the treating physician's judgement.

Table 10: List of Clinical Substrates for CYP2C8, CYP2C9 and CYP3A P450-mediated metabolism

	Sensitive substrates	Moderate sensitive substrates
CYP2C8	repaglinide[(b)]	montelukast, pioglitazone, rosiglitazone
CYP2C9	celecoxib[(c)]	glimepiride, phenytoin, tolbutamide, warfarin
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[(f)], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[(g)], midazolam, naloxegol, nisoldipine, saquinavir[(f)], simvastatin[(g)], sirolimus, tacrolimus, tipranavir[(f)], triazolam, vardenafil	alprazolam, aprepitant, atorvastatin[(c)], colchicine, eliglustat[(e)], pimozide, rilpivirine, rivaroxaban, tadalafil
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[(f)], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.

The list of clinical substrates was compiled from the FDA Guidance for in vitro DDI studies [link to "Table 3-1: Examples of clinical substrates for P450-mediated metabolism (for concomitant use clinical DDI studies and/or drug labeling) (12/03/2019)]"; from the Indiana University School of Medicine's "Clinically Relevant" Table; and from the University of Washington's Drug Interaction Database. Note that this may not be an exhaustive list. For a complete and most updated drug list, please check the website: https://.crediblemeds.org/healthcareproviders/drug-list.

(a) Listed based on an in vivo induction study and the observed effect might be partly attributable to induction of other pathway(s).
(b) OATP1B1 substrate.
(c) Listed based on pharmacogenetic studies.
(d) S-lansoprazole is a sensitive substrate in CYP2C19 EM subjects.
(e) Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.
(f) Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.
(g) Acid form is an OATP1B1 substrate

Abbreviations:

AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction; EM: extensive metabolizer; OATP1B1: organic anion transporting polypeptide 1B1.

7. STUDY PROCEDURES

Refer to Table 1 for the schedule of assessments, with specific timepoints for study procedures.

7.1. Subject Demographics/Other Baseline Characteristics

7.1.1. Informed Consent

Eligible participants may only be included in the study after providing IRB/EC-approved written informed consent prior to initiating screening for the study. Participants will be given the approved Informed Consent Form (ICF) describing the study and any risks associated with participation. The subject will be allowed as much time as needed to read and understand the information presented in the ICF. Appropriate study personnel will be available to answer any questions the subject might have regarding the study or study-related procedures. If the subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records.

If applicable, in cases where the participant's legal/authorized representative gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

7.1.2. Demographics

Subject demographic data collected includes year of birth or age, gender, ethnicity, race, and child-bearing potential (for females only).

7.1.3. Medical History

Any relevant medical history – including date of onset of COVID-19 disease symptoms, date of diagnosis of COVID-19, and COVID-19 disease protocol solicited medical history (including any paresthesia / dysesthesias at screening/baseline) – and current medical conditions will be captured.

Diagnoses and not symptoms will be recorded whenever possible.

7.2. Study Treatment

After confirmation of eligibility for study entry, blinded study drug treatment can commence. Details of IV infusion start and stop times will be recorded in the eCRF, and any interruption requirements captured.

7.3. Efficacy Assessments

7.3.1. Clinical Status

Assessment of clinical status will be made using an 8-point ordinal scale, adapted from scales published (WHO 2020a; WHO 2020c), and following the National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale framework (as used in ACTT trials).

Each day the worse score for the previous day will be recorded, i.e., on Day 3, Day 2 score is obtained and recorded as Day 2. For hospitalized patients, assessment is made for baseline (Day 1), Day 2, and every day until Day 29 (end of study). If a subject is discharged from the hospital, assessment is to be sought by telephone (between 7AM and 12 PM local time) up to Day 15 if a subject is successfully discharged before Day 15, and also on Day 29.

Table 11: Clinical Status 8-point Ordinal Scale

Score	Description
1	Death
2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3	Hospitalized, on non-invasive 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 requires ongoing medical care (other than for per protocol dosing or assessments, as appropriate)
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

7.3.2. National Early Warning Score 2 (NEWS2)

The National Early Warning Score 2 (NEWS2) has demonstrated an ability to discriminate subjects at risk of poor outcomes (Williams et al 2012). This score is based on seven (7) clinical parameters. NEWS2 values reported for the study will be calculated electronically based on vital sign parameters and NEWS2 related assessments recorded by the investigator in the appropriate eCRFs.

In addition to the vital signs – whereby, in addition to systolic blood pressure, the associated diastolic blood pressure must also be entered into the appropriate additional eCRF field – the patient's level of consciousness and the presence/absence of respiratory support must be recorded. The NEWS2 parameter for respiratory support is the selection of either air or "oxygen" can include other forms of ventilation to maintain oxygen saturation. These should be recorded at the same time points as the vital sign measurements (see Section 7.5.2).

Table 12: National Early Warning Score 2 (NEWS2)

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

SpO_2 = oxygen saturation

The oxygen saturation should be scored according to either the SpO_2 Scale 1 or 2 presented in Table 12. The SpO_2 Scale 2 is for patients with a target oxygen saturation requirement of 88%-92% (e.g., in patients with hypercapnic respiratory failure related to advanced lung diseases, such as chronic obstructive pulmonary disease [COPD]). This should only be used in patients confirmed to have hypercapnic respiratory failure by blood gas analysis on either a prior or their current hospital admission.

The decision to use the SpO_2 Scale 2 should be made by the treating physician and should be recorded in the eCRF. In all other circumstances, the SpO_2 Scale 1 should be used.

For physiological parameter "Air or Oxygen?": Any patients requiring the use of oxygen or other forms of ventilation to maintain oxygen saturations and support respiration should be assigned a score of 2.

The consciousness level should be recorded according to the best clinical condition of the patient during the assessment. Patients who are assessed as "Alert" (A) should be assigned a score of 0. Patients assessed as "New Confusion" (C), "Responsive to Voice" (V), "Responsive to Pain" (P), or "Unconscious" should be assigned a score of 3.

Scores should be assigned for respiratory rate, systolic blood pressure, pulse, and temperature according to Table 12.

For the duration of hospitalization while the subject is outside of the ICU, the measurements of the NEWS2 are to be performed twice daily. All parameters – including the vital sign parameters and oxygen saturation – should be recorded together in the morning, and then between noon and midnight, for the duration of hospitalization if outside of the ICU. Following hospital discharge these parameters should be recorded once at each return visit to the clinic (Days 15 and 29).

Repeat measurements may be taken, as clinically appropriate.

7.3.3. In-Hospital Outcomes

The following in-hospital outcomes will be captured on eCRFs or derived from other data collected on the eCRF:

- Duration of hospitalization*
- Time to discharge
- Duration of invasive mechanical ventilation
- Duration of supplemental oxygen support
- Duration of ECMO
- No oxygen therapy (and/or peripheral oxygen saturation SpO_2 > 93% on room air) at Days 8, 15 and 29

*If a subject is unable to be discharged due to administrative reasons, then the date that the subject, in the opinion of the investigator, is ready to be discharged to be reported in the hospitalization status as date of discharge.

7.4. Other Assessments

7.4.1. SARS-CoV-2 virus testing

SARS-CoV-2 virus is to be measured using PCR or equivalent/ other approved diagnostic testing at Screening, except for those subjects who have had another validated test done within 4 days of randomization. A positive PCR SARS-CoV-2 test result is needed prior to randomization.

Nasopharyngeal (NP) swab samples are to be collected from the pre-dose assessment through Day 11 (while hospitalized) and/or on day of discharge; and Days 15 and 29 (by returning to the clinic/ remote visit or if still hospitalized).

Swab collection is to be pre-dose on dosing days; efforts are to be made to allow for swabs to be collected at approximately the same time each collection day throughout the study.
Note: NP swabs are to be collected. In exceptional circumstances only, such as NP swabs cannot be used due to participant nasal physiology, the collection method for all samples from such a subject may be altered to Oropharyngeal (OP) swabs, if provided for by the central lab.

Collected swabs are to be stored in the refrigerator/ or a -20°C or -70°C freezer, with the temperature of storage likely dependent on the time between collection and shipment. Subsequently, samples are expected to be batch shipped on dry ice to a central laboratory for testing. Follow instructions provided in a separate laboratory manual.

Swab samples will be assayed using quantitative reverse transcriptase PCR to quantify SARS-CoV-2 viral load. Pretreatment and posttreatment samples with detectable SARS-CoV-2 may be sequenced for resistance monitoring of the viral polymerase gene.

Sample analysis may be performed ongoing or in batches. Analytical data will be shared with care while the study is ongoing, to ensure that for study personnel the subject treatment blinding is maintained.

7.4.2. Biomarkers

Blood samples will be collected for measurement of biological and immunological markers of illness/inflammation. These will include:

Local laboratory testing: CRP, ferritin, LDH, D-dimer, troponin T hs, absolute neutrophil count [at Screening, Days 1, 2, 3, 5, 8, 11 (while hospitalized) and/or on day of discharge; and Days 15 and 29 (by returning to the clinic or if still hospitalized)] – see Section 7.5.3.

Central laboratory testing: IL-1β, IL-6, IL-10, total IL-18, TNF-α [at Days 1, 3, 5, 8, 11 (while hospitalized) and/or on day of discharge; and Day 15 (by returning to the clinic or if still hospitalized)].

For central laboratory testing samples, follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, storage and shipment.

Sample analysis may be performed ongoing or in batches. Analytical data will be shared with care while the study is ongoing, to ensure that for study personnel the subject treatment blinding is maintained.

7.4.3. Drug Concentration Measurements (Pharmacokinetic Assessments)

Blood samples will be collected for measurement of Brilacidin concentration in plasma. Sparse sampling will be performed on Days 1 to 4.

All blood samples for PK assessments will be drawn from the opposite arm than that used to administer study treatment, or from an alternate site other than the arm used for the study treatment infusion.

Samples will be collected as follows:

- Day 1: pre-dose, within 30 mins after the end of infusion, and between 8-12 hours from start of the Day 1 infusion.
- Day 2: pre-dose (approximately 24 hours from start of the Day 1 infusion)
- Day 3: pre-dose (approximately 24 hours from the start of the Day 2 infusion)
- Day 4: at approximately 24 hours from the start of the Day 3 infusion.

The exact time of the sample collection and the exact time of study drug dosing preceding the sample are recorded in the eCRF.

Blood samples (approximately 3 mL) to provide approximately 1 mL of plasma for PK analysis will be collected in appropriately labeled tubes containing potassium EDTA at the times specified. Samples are to be centrifuged at approximately 2000 g for about 10 minutes at 4°C within a target of 30 minutes after collection; separated plasma is to be transferred into the appropriately labeled screw-capped polypropylene tubes and stored at -20°C ± 5°C until shipped.

Additional instructions are outlined in the laboratory manual regarding sample collection, numbering, processing, storage and shipment.

Samples will be analyzed using a validated liquid chromatographic method with tandem mass spectrometry detection (LC-MS/MS) assay method. Sample analysis may be performed ongoing or in batches. Analytical data will be shared (with Sponsor study team members/designees) with care while the study is ongoing, to ensure that for study personnel the subject treatment blinding is maintained.

7.4.4. Recording Concomitant Medications and Concurrent Procedures

Relevant prior, and any concomitant medications or concurrent procedures used from the time the subject signs the ICF through the end of study, must be recorded in the eCRF on an ongoing basis. Details recorded may include the medication name/ dose/ route of administration or procedure name, start and stop dates, and indication for use.

7.5. Safety Assessments

7.5.1. Physical Exam, Height and Weight

Physical examinations will be performed by an Investigator, Sub-Investigator or appropriately qualified designee (e.g., Physician's Assistant, Advanced Practice Registered Nurse Practitioner, or Registered Nurse as per local regulations). At the Screening visit a complete physical examination is to be conducted, including skin, neck (including thyroid), HEENT (head, eyes, ears, nose and throat), heart, lungs, abdomen, lymph nodes, extremities, vascular and neurologic systems. Clinically relevant findings that are present prior to signing informed consent are to be recorded on the appropriate eCRF that captures medical history. Height will be measured at Screening also. Subsequent visit assessments can be an abbreviated physical examination (including at a minimum: HEENT, heart, lungs, abdomen, extremities and examination of any body system where there are symptoms reported by the subject).

Height and body weight are to be measured with the subject in indoor clothing and shoes removed. Height is to be recorded to the nearest 1 cm, and body weight to the nearest 0.1 kg. If not possible to measure, height can be reported by the subject.

If an on-study assessment is determined by the Investigator to be a clinically significant change from baseline for that subject, the finding may be considered an AE. Refer to Section 8.1.

7.5.2. Vital Signs and Respiratory Status

Vital signs include heart rate, systolic and diastolic blood pressures and body temperature (recorded in °C) as per local practice.

Respiratory status should be measured at the same time as the vital sign measurements, if possible. Documentation of respiratory status includes respiratory rate, and details of oxygenation and any oxygen supplementation (as below):

- Oxygenation: SpO_2 or PaO_2
- Oxygen supplementation: room air, low flow O_2 (L/min and %), high flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO.

Measurements are to be performed twice daily. (The measurements will assist in completing the NEWS2 score twice daily, while the subject is outside of the ICU). The vital sign parameters and oxygen saturation should be recorded together in the morning, and then between noon and midnight, for the duration of hospitalization. Following hospital discharge these parameters should be recorded once at each return visit to the clinic (Days 15 and 29).

Repeat measurements may be taken, as clinically appropriate.

If an on-study assessment is determined by the Investigator to be a clinically significant change from baseline for that subject, the finding may be considered an AE. Refer to Section 8.1.

During Study Treatment

Blood pressure and pulse rate measurements will be measured more intensely during the treatment period with study drug, during hospitalization. On Days 1-3 (and potentially Day 4-5 also, after initial interim safety readout), measurements will be made pre-dose, within no more than 30 mins after the end of infusion, and 3 hours (±30 mins) post-start of infusion (i.e., ~2 hours post-end of infusion).

If systolic blood pressure ≥ 180 mmHg and increase from baseline ≥ 20 mmHg, the measurement is to be repeated within 15-30 minutes. If the repeat measurement is confirmed, the attending physician is to review the patient profile and determine if treatment for hypertension is needed. After a confirmed systolic blood pressure elevation, blood pressure measurements are to be performed approximately every 4 hours or as frequently as necessary in accordance with local standard of care.

Similarly, if diastolic blood pressure ≥ 110 mmHg and increase from baseline ≥ 15 mmHg, the measurement is to be repeated within 15-30 minutes. If the repeat measurement is confirmed, the attending physician is to review the patient profile and determine if treatment for hypertension is needed. After a confirmed diastolic blood pressure elevation, blood pressure measurements are to be performed approximately every 4 hours or as frequently as necessary in accordance with local standard of care.

See Section 8.1.5 (Adverse Events of Special Interest/ Blood Pressure category reporting) and Section 9.2 (Interim Analyses/ Data Monitoring Committee Reviews).

7.5.3. Laboratory Evaluations

A certified local laboratory will perform the clinical laboratory tests for this study, as outlined in Table 13. The laboratory will be local to the study site.

Reports of laboratory results must be reviewed by the Investigator or qualified designee.

For each laboratory test result outside the reference range, the Investigator must ascertain if the abnormal lab result is a clinically significant result for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed; the Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

The Investigator must review the results of all laboratory tests as they become available. For each test result outside the reference range, on the printed document (or alternate source record) the Investigator must note Not Clinically Significant (NCS) or Clinically Significant (CS) for each out of range laboratory value, and is to initial to confirm their review.

All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels or are deemed clinically stable. If a subject has any clinically significant, study-related abnormalities at the end of the study, the Medical Monitor should be notified and every effort made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

Blood and urine samples will be collected at the timepoints identified in the Schedule of Assessments. Unscheduled clinical laboratory testing may be obtained at any time during the study to assess any perceived safety concerns.

If an on-study laboratory value is determined by the Investigator to be a clinically significant change from baseline for that subject, this may be considered an AE. Refer to Section 8.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., hemoglobin decreased).

Table 13: Clinical Laboratory Testing (local)

Laboratory Testing	Variables
Hematology	hemoglobin; hematocrit; red blood cell (RBC) count; platelet counts; white blood cell (WBC) count with differential [neutrophils (%, abs), lymphocytes (%, abs), monocytes (%, abs), eosinophils (%, abs), basophils (%, abs)]
Serum Chemistry	urea (BUN), uric acid, creatinine, glucose (random),bicarbonate, calcium, sodium, potassium, total bilirubin, alanine aminotransferase (ALT), gamma-glutamyl-transferase (GGT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, albumin, lactate dehydrogenase (LDH), CRP, ferritin, D-dimer, troponin T hs
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
WOCBP only: Pregnancy Testing	Urine/serum (ß-hCG) pregnancy testing required only for women of childbearing potential.

7.5.4. Electrocardiogram (ECG)

A single standard supine 12-lead ECG will be obtained after a subject has rested quietly for at least 10 minutes. The ECG may be repeated if the result is abnormal, as clinically appropriate. ECG data will be reviewed by the Investigator or appropriate local designee. The Investigator must review and initial the tracing (or alternate source record) and the assessment of any reviewer (if not themselves).

7.5.5. Recording Adverse Events (AEs)

Adverse events should be sought by non-directive questioning of the subject and are to be recorded, graded, and assessed as defined in Section 8.1 of this protocol.

All AEs, whether observed by an Investigator or Study Coordinator or reported by the subject, whether related to study drug or not related to study drug, shall be documented in the eCRF and subject records, together with details of the onset, duration, the relationship to the study drug and/or related to background standard-of-care and degree of severity, the action taken regarding study treatment, if other medication or therapies have been taken (concomitant medication/non-drug therapy), and the outcome.

If an AE constitutes a serious adverse event (SAE), the procedure outlined in Section 8.1.4 is to be followed.

7.6. Individual Subject Discontinuation

7.6.1. Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

Study treatment must be discontinued under the following circumstances:

- Subject decision, for any reason
- Investigator believes that continuation would negatively impact the subject's overall status or the risk/benefit of study treatment
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, and hypotension. Immediate discontinuation of study treatment and initiation of appropriate medical treatment is required in such cases.
- Any protocol deviation or situation that results in a significant risk to the subject’s safety.

Transient hypertensive episodes may be addressed by initiation of treatment for hypertension.

If adverse events emerge, as assessed by the investigator following local guidelines, that meet criteria for hypertensive urgency (e.g., SBP >220 mmHg or DBP >120 mmHg) or hypertensive emergency, the investigator is to consider temporarily stopping study treatment and potentially discontinuation of study treatment.

If discontinuation of study treatment occurs for a subject, the investigator must determine the primary reason for the discontinuation of study treatment and record this information. Subjects who discontinue study treatment or who decide they do not wish to participate in the

study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.6.2). Where possible, subjects are to continue with (if hospitalized) or return for the assessments indicated in the Schedule of Activities (Table 1). If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, and letter) should be made to contact the subject/pre-designated person contact as specified in the lost to follow-up section (Section 7.6.3). This contact should preferably be done according to the study visit schedule and documented in the site study file.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

Subjects who discontinue from the study will not be replaced.

7.6.2. Withdrawal of informed consent

A subject may voluntarily withdraw consent to participate in the study for any reason at any time at their own request.

Withdrawal of consent occurs only when a subject requests the following:

- Does not want to participate in the study any more;

and

- Does not want any further visits or assessments;

and

- Does not want any further study-related contacts.

In this situation, the investigator should make reasonable efforts (e.g., telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the subject's study discontinuation should be made as detailed in the assessment table. The Sponsor will continue to retain and use all research results (data) for the subject that have already been collected as part of study evaluations.

7.6.3. Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the completion of the study.

7.7. Study Stopping Rules

An independent Data Monitoring Committee (DMC) will review safety at intervals during the study, including mortality and SAEs. Enrollment in the study will be placed on hold if any of the following occurs:

- There is a doubling of the mortality rate on Brilacidin treatment compared to placebo, with data stratified by age/ severity/ country (assessed after approximately 50% of subjects have enrolled/completed)
- The number and/or severity of AEs, including Adverse Events of Special Interest (AESIs) (Section 8.1.5), abnormal safety monitoring assessments, or abnormal laboratory findings justify putting the study on hold (assessed after approximately 20 subjects, and after 50% of subjects, have enrolled/completed).

The study may resume following the safety review, if the DMC and Sponsor agree it is safe to proceed. Alternatively, the study may be stopped.

Recommendation guidelines and further details of the DMC will be prepared separately from this protocol in a DMC Charter. The charter may supersede the summary details presented here in the protocol. See Section 8.1.6.

7.8. Early Study Termination by the Sponsor

This study can be terminated at any time for any reason by the Sponsor. Should this be necessary, the Sponsor and the investigators will ensure that proper study discontinuation procedures are completed, and that adequate consideration is given to the protection of the subject’s interests.

8. SAFETY MONITORING

8.1. Adverse Events

8.1.1. Definitions

An Adverse Event (AE) is defined as any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury, or accident) in a clinical-trial subject that emerges or worsens after providing written informed consent for participation in the study. The untoward medical occurrence may not necessarily have a causal relationship with the use of medicinal [investigational] product. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal [investigational] product, whether or not considered related to the medicinal [investigational] product.

Pre-existing medical conditions/diseases (i.e., medical history(ies)) are considered AEs if they worsen after administration of a medicinal [investigational] product. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, or are considered clinically significant, or require therapy.

Serious Adverse Event (SAE) is defined as an adverse event that meets one or more of the following criteria:

- Results in death
- Is immediately life-threatening (i.e., the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Requires in-patient hospitalization or prolongs an existing hospitalization
- Results in a persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is another significant medical event as defined below:

  Significant medical events are those that may not result in death, be life-threatening, or require hospitalization, but are, in the opinion of the investigator, and based upon appropriate medical judgment, an event that might jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above

Any of the above must be reported immediately to the Sponsor or designee as indicated in the Immediately Reportable Serious Adverse Event section of this protocol.

Pre-Planned Hospitalization: A hospitalization planned prior to signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under

consideration but not performed prior to enrollment in the study will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Hospitalizations for social reasons or due to long travel distances are also not SAEs.

Note: The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition**.**

8.1.2. Severity of Adverse Events

The Investigator is responsible for evaluating all AEs and determining the severity of the event. Severity is graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 when applicable. For an AE not found on the CTCAE listing, they will be allocated a grade according to the following guidelines.

Grade 1 Mild Adverse Event (any of the following):

- Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated, or non-prescription intervention indicated; asymptomatic laboratory finding only; marginal clinical relevance.

Grade 2 Moderate Adverse Event (any of the following):

- Moderate; minimal, local, or noninvasive intervention indicated; limiting (age-appropriate) instrumental Activities of Daily Living [ADL] (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, laundry).

Grade 3 Severe Adverse Event (any of the following):

- Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, getting in and out of bed).

Grade 4 Life-threatening Adverse Event (any of the following):

- Life-threatening consequences; urgent intervention indicated; individual at risk of death at the time of the event if immediate intervention is not undertaken.

Grade 5 Fatal Adverse Event:

- Death related to AE.

8.1.3. Causality of Adverse Events

The relationship is characterized as:

- Not Related/ Unlikely Related: There is not a temporal or causal relationship between the use of the study drug and the onset of the AE; no association of the event to use of study drug.
- Possible: There may or may not be a reasonable temporal relationship between the use of the study drug and the onset of the AE; the association of the event with the study drug is unknown, however, a relationship between drug and event cannot be ruled out.
- Probable: There is a reasonable temporal relationship between the use of the study drug and the onset of the AE; the association of the event with the study drug seems likely and the AE is unlikely to be caused by the concurrent/underlying illness, other drugs or procedures.
- Definite: There is a reasonable temporal relationship between the use of the study drug and the onset of the AE, and it cannot be reasonably explained by any known characteristics of the subject's clinical state, environment or other drugs or procedures. It disappears or decreases upon discontinuation of the study drug and reappears with re-administration of the study drug.

For the purpose of regulatory safety reporting, AEs that are assessed as not related/unlikely related to the study drug, as per the protocol definition, will not qualify as adverse reactions (see Section 8.1.4).

Information about common side effects already known about the study medication can be found in the Investigator's Brochure. A summary of this information will be included in the informed consent and should be discussed with the subject during the study as needed.

8.1.4. Immediate Reporting of Serious Adverse Events (SAEs)

Any SAE during the Screening, Treatment, and Follow-up (through Day 29) periods, whether deemed related to study treatment or not, must be reported by the Investigator to Sponsor or the authorized representative within 24 hours of their awareness of the event. Any new SAE(s) reported by the subject to the Investigator that occur after the end of the Follow-up period (through Day 29) that are suspected by the Investigator to have a causal relationship with the study treatment should be reported to Sponsor or the authorized representative within 24 hours of their awareness of the event. Information about all SAEs (either initial or follow-up information) is collected and recorded on the Serious Adverse Event Form.

Summary of actions to be taken by the Investigator:

- Investigator to complete and forward an SAE Form (within 24 hours) with all information known to date, including Investigator's assessment of causality.
- If the event is fatal or life-threatening, the Investigator is to telephone the Sponsor or the authorized representative immediately on awareness of event.

- Obtain and maintain all pertinent medical records (discharge summary, autopsy report, etc.) relating to the subject's treatment and follow-up.
- Provide follow-up and/or updated information to Sponsor or the authorized representative, as it becomes available.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the investigational study drug, the Sponsor or the authorized representative may urgently require further information from the Investigator for Health Authority reporting. Sponsor or the authorized representative may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements (in participating countries) and any local requirements.

The Investigator will collect information on SAEs until a subject's health has returned to the baseline state of health, or the Investigator does not expect any further improvement or worsening of the subject's condition. The Investigator must report follow-up information as and when it becomes known to the Investigator.

Any new SAEs reported by the subject to the Investigator that occur after the last scheduled study contact and are determined by the Investigator to be reasonably associated with the administration of study drug should be reported to Sponsor or the authorized representative, and the IRB/IEC, as required.

8.1.5. Adverse Events of Special Interest/ Blood Pressure category reporting

Adverse events of special interest (AESIs) are (i) hypertension Grade 3 or greater, and (ii) paresthesias / dysesthesias Grade 2 or greater.

The CTCAE (version 5.0) details, including definitions, for AESIs are provided in Table 14. Hypertension is under the Vascular disorders System Organ Class (SOC); paresthesia and dysesthesia are under the Nervous System disorders SOC; and oral dysesthesia is under the Gastrointestinal disorders SOC.

Table 14: CTCAE Details for Adverse Events of Special Interest

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertension	Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg	Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated	Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Definition: A disorder characterized by a pathological increase in blood pressure.					
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and/or warmth.					
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.					
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-
Definition: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth.					

ADL = Activities of Daily Living; TPN = Total Parenteral Nutrition; WNL = Within Normal Limits

Blood pressure measurements will also be summarized for the following criteria:

- Systolic blood pressure increased: ≥180 and increase from baseline ≥20
- Diastolic blood pressure increased: ≥110 and increase from baseline ≥15

During study treatment, if a blood pressure values meets one of the above safety alert categories, the measurement is to be repeated within 15-30 minutes; if the repeat measurement is confirmed, the attending physician is to review the patient profile and determine if treatment for hypertension is needed (see Section 7.5.2). The Investigator or attending physician shall contact the Medical Monitor to review the patient profile as appropriate.

Ongoing during the study, the Sponsor will closely monitor the incidence and duration of related Grade 3 hypertension or greater (in accordance with CTCAE criteria), and monitor for incidence of confirmed hypertensive values. The Medical Monitor will review such data on a frequent basis; such safety data will also be a key component of the periodic safety review by the DMC (see Section 9.2).

The incidence and duration of all paresthesias / dysesthesias Grade 2 or greater (in accordance with CTCAE criteria) will also be closely reviewed ongoing during the study, by the Sponsor and Medical Monitor, and by the DMC. As numbness/paresthesia has been reported as an uncommon manifestation of COVID-19, events regarded both as related and unrelated to study treatment will be closely monitored, and will be reviewed in relation to frequency of other peripheral nervous system AEs.

8.1.6. Data Monitoring Committee

This study will include an independent Data Monitoring Committee (DMC) which will be composed of at least three external medical experts familiar with the conduct of and/or data review of clinical studies. The DMC will conduct periodic safety reviews, and will recommend to the Sponsor whether to continue, modify, or terminate a clinical trial.

Specific details regarding committee composition, responsibilities, data monitoring, recommendation guidelines, and meeting frequency/administration will be described in a separate DMC Charter, to be established between the Sponsor and the DMC.

See Section 7.7 (Study Stopping Rules) and Section 9.2 (Interim Analyses/ Data Monitoring Committee Reviews).

8.2. Reporting Pregnancy/Study Drug Exposure During Pregnancy

Although pregnancy itself is not regarded as an AE, the outcome of any pregnancy that occurs during the study must be documented.

Prior to study enrollment, study participants must agree in the ICF to take appropriate measures to avoid pregnancy at all times during the study, commencing from the time of consent, throughout the study and for 30 days after stopping treatment (i.e., approximately 4 weeks after the last dose of study drug). If pregnancy occurs, they must agree to report the pregnancy and cooperate with the Investigator as set forth below.

Should a pregnancy occur, the study participant must immediately inform the Investigator. Any female study participant receiving study drug who becomes pregnant must immediately discontinue study drug. The Investigator should counsel the study participant, discussing any risks of continuing the pregnancy and any possible effects on the fetus. The study participant must agree to follow up by the Investigator regarding the outcome of any pregnancy that occurs during the study. Outcome is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed by the Investigator for a minimum of eight weeks. Any

congenital anomaly/birth defect noted in the infant must be reported as an SAE [within 24 hours of awareness]. The Investigator will notify Sponsor or its authorized representative of a pregnancy occurring in a study participant within 14 days of first becoming aware of such pregnancy. All follow-up information gathered by the Investigator shall be reported to the Sponsor within 14 days of Investigator's first knowledge of such information.

9. STATISTICAL METHODS

Full details of the statistical methodology for summary and analyses of the data collected in this study will be prepared separately from this protocol in a Statistical Analysis Plan (SAP).

This Phase 2 Proof of Concept (PoC) study is exploratory in nature and will be initiated with a dose regimen of Brilacidin in addition to SoC, compared to placebo with SoC. Proof of concept will be established by a significant treatment effect on the primary endpoint or a positive direction of effect amongst multiple efficacy endpoints. Comparisons will be performed against placebo plus SoC at a one-sided type I error rate of 0.05 which will not be adjusted for multiple testing.

The selected primary efficacy endpoint is time to sustained recovery, where recovery is defined as the participant being well enough for hospital discharge, meaning the participant either no longer requires supplemental oxygen or ongoing medical care in the hospital, or is no longer hospitalized (with or without some limitation on activities).

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic, and safety parameters. For categorical variables, summary tables with number and percentage of subjects within each category will be presented. For continuous variables, descriptive statistics including the number of subjects, mean, median, standard deviation, minimum, and maximum values will be presented. Kaplan-Meier methods will be used to summarize time to event endpoints, including the 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 90% confidence intervals, as well as percentage of events and censored observations.

9.1. Sample Size Considerations

This study is exploratory in nature and the sample size (up to 60 per treatment arm) was selected to provide sufficient power under a range of alternative hypotheses to support initial PoC of Brilacidin versus SoC. The type I error will not be adjusted to account for multiple comparisons.

For the primary efficacy endpoint of time to recovery, assuming a total of 100 subjects (50 per treatment arm included in analysis), if a total of 75 recovery events are observed, the comparison between treatment groups would provide at least 90% power with a one-sided type I error rate of 0.05 and a hazard ratio of 2.0 [equivalent to median time to recovery of 5 days on Brilacidin versus 10 days on SoC]. If instead the hazard ratio is 1.67 (time to recovery on Brilacidin of 6 days versus 10 days on SoC) and 75 recovery events occur, the difference could be detected with at least 70% power. The assumptions for sample estimation are adapted from the median time to recovery data reported for the remdesivir (11 days) treatment group in Beigel et al 2020; remdesivir has Emergency Use Authorization (EUA) in multiple countries and has become SoC where available.

A total of 100 subjects with 50 per treatment group will also support secondary endpoints. For example, for the secondary endpoint of clinical improvement (2-point increase in ordinal

scale) at Day 15, applying an unadjusted one-sided type I error rate of 0.05, 50 subjects per arm would provide 80% power to detect a treatment effect of 0.2079 increase in proportion of clinical improvement within the Brilacidin treatment group over a proportion of 0.6500 in the SoC group. There would be at least 70% power to detect a treatment effect of 0.1854 under the same sample size. (The assumptions for sample estimation are based on clinical improvement data reported for SoC and remdesivir treatment groups in Spinner et al 2020).

9.2. Interim Analyses/ Data Monitoring Committee Reviews

An independent Data Monitoring Committee (DMC) will be established to conduct periodic safety reviews (Section 8.1.6).

Safety data summaries and listings will be produced for DMC safety monitoring when needed.

An initial safety review is planned to occur after approximately 20 randomized subjects have completed up to Day 15. This initial interim analysis will focus on review of cardiovascular safety, vital signs and adverse events that have occurred in the approximately 20 subjects to receive Days 1-3 of study treatment. A further safety review by the DMC is planned to occur after approximately 50% of subjects have completed up to Day 29, to allow for unblinded monitoring of safety data around the study mid-point. The DMC may recommend expanding dosing to Days 4 and 5 (at the same doses as on Days 2 and 3), continuation of the Days 1-3 study dosing unchanged, or that the trial be interrupted or stopped for safety reasons. The DMC will be guided by the degree and incidence of hypertensive values/events observed in the ongoing study which should not exceed the number and/or severity of those observed in previous studies with Brilacidin IV treatment for expansion of dosing to occur as planned.

The rationale for looking to expand treatment duration to five days, from the initial dose regimen of three days, is to be able to provide a longer duration of systemic Brilacidin exposure at a level that can strongly suppress SARS-CoV-2 virus activity, and any associated symptoms, and thus provide a more optimal therapy to hospitalized patients with moderate or severe COVID-19. The longer treatment duration is expected to allow for greater impact of Brilacidin treatment and provide enhanced benefit to the patient, with the 5-day regimen incorporated only following recommendation by the DMC subsequent to DMC review of all available safety data following safety review interim analysis(es).

Study stopping rules are presented in Section 7.7. Recommendation guidelines and further details of the DMC will be prepared separately from this protocol in a DMC Charter. The charter may supersede the summary details presented here in the protocol.

Other interim analyses may be conducted to support decision making concerning the current clinical study or in case of any safety concerns.

The primary efficacy analysis will occur once all subjects complete the Day 29 visit (or discontinue from study, if before Day 29). Final database lock and updated safety reporting will follow the completion of Day 60 follow-up telephone visits.

9.3. Definitions of Study Populations for Analysis

Efficacy analyses performed on the Intent-to-Treat (ITT) population will be considered primary, with the ITT population including all subjects who are randomized and receive at least one dose of study drug. Subjects in this population will be analyzed according to the treatment group to which they were randomized.

The Safety population includes all subjects in the ITT population. Subjects in this population will be analyzed according to treatment received. All safety analyses will be based on this population.

The Per Protocol (PP) population is a subset of the ITT population and includes subjects who meet particular study completion criteria with no major protocol deviations; these criteria will be described in the SAP and will be approved prior to database lock and study unblinding. Efficacy analyses performed using the PP population will be considered supportive.

All subjects in the ITT population who provide at least one PK sample and have at least one valid concentration measurement will be included in the PK population.

9.4. Handling of Missing Data

When analyzing time to sustained recovery, if subjects are lost to follow-up prior to achieving recovery or die prior to Day 29, their time to recovery will be censored at Day 29. Subjects who are lost to follow-up after achieving recovery but prior to Day 29 will be censored at the day of achieving recovery. Missing data rules for all endpoints will be described in the study SAP.

9.5. Baseline Characteristics and Demographic Variables

Summary statistics will be provided by treatment group for baseline characteristics and demographic variables. Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group. Summaries will be provided on the ITT population.

9.6. Efficacy Analysis

Summaries of efficacy parameters will be performed on the ITT population. Additional sensitivity analyses may be performed on the Per Protocol population or on subgroups. Additional detail will be provided in the SAP.

9.6.1. Primary Endpoint Analyses

The primary endpoint is time to sustained recovery through Day 29, where day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale (Table 11) with response sustained through Day 29:

- Score of 6: Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than for per protocol dosing or assessments, as appropriate);
- Score of 7: Not hospitalized, limitation on activities and/or requiring home oxygen;
- Score of 8: Not hospitalized, no limitations on activities.

The primary endpoint of time to sustained recovery will be analyzed with the log-rank test for treatment difference, stratified by age group, disease severity and country, with dose regimen as covariate (if expanded after DMC recommendation), and summarized using the Kaplan-Meier methodology. Subjects who are lost to follow-up prior to achieving recovery or who have died prior to Day 29 will be censored at Day 29. Subjects who are lost to follow-up after achieving recovery but prior to Day 29 will be censored at the day of achieving recovery.

All safety data, demographic and baseline characteristics will be summarized descriptively through appropriate data tabulations, descriptive statistics, and categorical summaries on the Safety Population.

9.6.2. Secondary and Exploratory/ Other Endpoint Analyses

Categorical endpoints will be summarized with frequencies and percentages. Comparisons between treatment arms will be performed using logistic regressions adjusted for randomization strata at specified timepoints. Longitudinal analyses using generalized estimating equations may be performed. Continuous measures will be summarized with descriptive statistics. Comparisons between treatment groups will be performed using analysis of covariance models adjusted for randomization strata at specified timepoints. Mixed models with repeated measures will be applied for longitudinal modeling of continuous measures.

The clinical status 8-point ordinal scale will be analyzed using ordinal categorical data methods, including a proportional odds logistic regression. Longitudinal analysis of the 8-point scale over time will be performed to investigate temporal patterns of improvement.

9.6.3. Sensitivity Analyses

Sensitivity analyses of efficacy parameters controlling for baseline covariates (such as presence of certain comorbidities) or on subgroups (such as those subjects treated with an antiviral therapy as SoC) may be performed. Full details of sensitivity analyses will be presented in the SAP.

9.7. Safety Analysis

All safety data, demographic and baseline characteristics will be summarized descriptively through appropriate data tabulations, descriptive statistics, and categorical summaries on the Safety Population.

The duration of exposure (in days) to Brilacidin and standard of care therapies will be summarized by descriptive statistics by treatment group. Changes from baseline in clinical laboratory parameters, vital signs (blood pressure and heart rate), and ECG parameters will be summarized. Treatment-emergent changes from values within normal range to abnormal values in clinical laboratory parameters will be characterized by summary of actual values and changes from baseline and shift tables.

Adverse event (AE) data will be listed individually and treatment-emergent adverse events (TEAEs) will be summarized by MedDRA system organ class (SOC) and preferred term (PT). SAEs, AEs leading to discontinuation and/or deaths will likewise be listed and summarized separately. AEs will be further summarized by grade and relatedness as judged by the Investigator. Each subject will be counted only once within a SOC or a PT using the event with the highest severity and strongest relationship, respectively, within each category. Prior and concomitant medications and concurrent procedures will be classified on the basis of World Health Organization Drug Dictionary (WHO-DDE) terminology. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

10. SITE MONITORING AND QUALITY ASSURANCE

10.1. Site Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor/designee representative will review the protocol and study Case Report Forms (CRFs) with the investigator(s) and their staff. During the study, a study monitor will visit the site regularly (as possible, due to COVID-19 restrictions) to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the investigational drug is being stored, dispensed and accounted for according to specifications. The Investigator and key trial personnel must be available to assist the monitor during these visits.

The investigator has ultimate responsibility for maintaining source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center; on CRFs, subjects will only be identified by initials and unique subject numbers. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/ exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan.

If planned on-site monitoring visits are not possible due to COVID-19 restrictions, use of central and remote monitoring programs will be considered to maintain oversight of clinical sites. In addition, remote review of medical records may be explored with trial sites to support and allow for source document review.

10.2. Quality Assurance

During study conduct, the Sponsor or its designee will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. Study monitors will review source documents to confirm accuracy of data recorded on CRFs. The investigator and institution will allow monitors for the Sponsor or its designee, and appropriate regulatory authorities (as applicable), direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by the Sponsor or designee, and/or to inspection by appropriate regulatory authorities.

The investigator and their relevant personnel are to be available during the monitoring visits, and possible audits or inspections, and must allow for sufficient time in their schedule for such process.

11. RECORDS MANAGEMENT

11.1. Data Collection

A validated clinical data management system will be used for capturing and managing data from the study. Designated investigator site staff will enter the data required by the protocol into the electronic eCRFs following the CRF Completion Guidelines.

The Investigator should ensure the accuracy, completeness, and timeliness of the data recorded on the eCRFs. Data recorded on the eCRF will be consistent with source documents. Any discrepancies must be explained or resolved.

Completed eCRFs will be reviewed by the Sponsor's monitoring staff or the Sponsor's designee. An eCRF will be completed for each consented subject.

The monitor and Sponsor/designee staff review the data entered into the CRFs by site staff for completeness and accuracy, and request clarifications and data queries. Queries will be sent to the site using an electronic data query. Designated site staff are required to respond to each query and confirm or correct the data, or make any required additions to the CRF entries. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the Sponsor/designee staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

The investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the site.

11.2. Records Retention

The investigator agrees to keep study records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or by an agreement with the Sponsor (if needed), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period, the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor such as another investigator, another

institution, or to an independent third party. Notice of such transfer will be provided to the Sponsor in writing.

When retention requirements have been met, the investigator must obtain written permission from the Sponsor before disposing of any records.

12. ETHICS

12.1. Regulatory and Ethical conduct

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki, and will be conducted in compliance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable regulatory requirements.

12.2. Responsibilities of the Investigator and IRB/IEC

It is the responsibility of the investigator to have prospective approval of the study protocol, any protocol amendments, informed consent forms and subject information, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. A signed and dated statement that the protocol and informed consent/subject information have been approved by the IRB/IEC must be given to the Sponsor/designee before study initiation.

A copy of all reports relating to this study submitted to the IRB must be sent to the Sponsor/designee.

If an inspection of the clinical site is requested by a regulatory authority, the investigator must information the Sponsor/designee immediately that this request has been made

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate an apparent immediate hazard to trial subjects. In that event, the investigator must notify the IRB/IEC and Sponsor/designee in writing immediately after the implementation.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with this protocol and key responsibilities of study oversight, delegation, and information access. With any protocol amendment, the protocol signature page is to be resigned to confirm understanding and agreement with any protocol changes.

12.3. Informed Consent Procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant’s legal/authorized representative gives consent (if allowed according to local requirements), the participant must be informed about the study to

the extent possible. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures, and the process of obtaining informed consent should be documented in the subject source documents. The investigator will retain the original of each subject's signed consent form. A copy of the signed consent form will be given to the subject.

The Sponsor/designee will provide to investigators in a separate document a proposed Informed Consent Form (ICF) that complies with the ICH guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor/designee before submission to the IRB/IEC, and a copy of the approved version must be provided to the Sponsor/designee after IRB/IEC approval.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the ICF and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

12.4. Publication of Study Protocol and Results

The Sponsor will post the key design elements of this protocol in a publicly accessible database such as clinicaltrials.gov. The results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13. PROTOCOL ADHERENCE AND AMENDMENT

13.1. Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations, and no requests to approve deviations will be granted by the Sponsor/designee.

This protocol defines the study objectives, procedures and data to be collected on study participants. No additional procedures or data for any research related purpose may be performed or collected.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC it cannot be implemented.

All significant protocol deviations will be recorded and reported in the Clinical Study Report.

13.2. Protocol Amendment Policy

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, government regulatory authorities (where required), and the IRB/IEC. Only the Sponsor may formally amend the protocol text.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate an apparent immediate hazard(s) to trial subjects. In that event, the investigator must notify the IRB/IEC and Sponsor/designee in writing immediately after the implementation.

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