NCT04784897

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STATISTICAL ANALYSIS PLAN

Study Code: IPI-BRIc-201

Protocol Version: Version 1.2

Protocol Date: 24-Dec-2020

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

Investigational Product	Brilacidin intravenous (IV)
Indication Studied	COVID-19 infection
EudraCT No	N/A
Phase of Study	Phase 2
Sponsor (company and address)	Innovation Pharmaceuticals Inc.
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]

[redacted]

Pages Nº	70
SAP Version	2.1 Final
SAP Date	28-Oct-2021

Statement:

By signing this document, I acknowledge that I have read the Statistical Analysis Plan and approve of the planned statistical analysis described herein.

I agree that the planned statistical analyses are appropriate for the objective of the study and are consistent with the methodology described in the protocol, clinical development plan, and all regulatory guidelines.

I also understand that any subsequent changes to the statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

CHANGES COMPARED TO PREVIOUS STATISTICAL ANALYSIS PLAN (SAP) VERSIONS

Previous SAP section	Change
SAP v1	Not approved version, v1 was considered a working draft version
SAP v2.0 – Several sections	Addition of a sentence with the consideration that a stratification factor will not be included in a model if it does not have enough sample size to be considered.

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1. LIST OF ABBREVIATIONS

1.1 Abbreviations

ACE	Angiotensin-converting enzyme
ACTT	Adaptive COVID-19 Treatment Trial
AE(s)	Adverse event(s)
AESI	Adverse Events of Special Interest
ANCOVA	Analyses of Covariance
ARDS	Acute respiratory distress syndrome
ATC	Anatomic and therapeutic category
BMI	Body mass index
BRI	Brilacidin
CHMP	Committee on Human Medicinal Products
CI	Confidence Interval
CIF	Cumulative incidence function
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRP	C-reactive protein
CS	Clinical Status
CSR	Clinical Study Report
D	Day
DBP	Diastolic Blood Pressure
DMC	Data monitoring committee
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EMA	European Medicine Agency
EOS	End of Study
EWP	Efficacy Working Party
FiO2	Fraction of inspired oxygen
HDP	Host defense proteins
HLGT	High level group term
HLT	High level term
HR	Hazard ratios
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL	Interleukin
IP	Investigational Product
IPI	Innovation Pharmaceuticals Inc.
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
LLT	Lower level term
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Affairs
NEWS2	National Early Warning Score 2
NP	Nasopharyngeal
OP	Oropharyngeal
OS	Overall Survival
PaO2	Arterial oxygen partial pressure
PBO	Placebo
PCR	Polymerase Chain Reaction
PDE	Phosphodiesterases

PEP	Primary Endpoint
PK	Pharmacokinetics
PoC	Proof of Concept
PP	Per Protocol
PT	Preferred term
Q1	First quartile
Q3	Third quartile
R	Randomization
SAE(s)	Serious adverse event(s)
SAP	Statistical Analyses Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
SE	Standard Error
SoC	Standard of Care
SOC	System organ class
SpO2	Peripheral oxygen saturation
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TNF-α	Tumor necrosis factor alpha
ULN	Upper Limit of Normal Range
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This study is being conducted under the sponsorship of Innovation Pharmaceuticals Inc., in both the US and Russia. [redacted]

Statistical analyses are being performed [redacted].

The statistical analysis plan (SAP) was written based on protocol version 1.2 (24 December 2020). This SAP provides a detailed description of the strategy and statistical techniques to be used to perform the analyses of data collected.

This document does not address the specific analysis of pharmacokinetic (PK) data collected in this study. These analyses will be discussed in a separate analysis plan to support the population PK report.

This SAP supersedes any statistical considerations that were identified in the study protocols approved prior to the date of this SAP. Substantial changes from the protocol version 1.2 are summarized in this plan.

This SAP may be revised prior to database lock and unblinding of the treatment codes to reflect any changes or additional details based on external information, regulatory feedback, or issues identified during the blinded data review. Any additional analyses or major changes performed after the last version of the SAP is finalized will be identified in the appropriate section of the clinical study report (CSR).

SAS code presented in this document is example code and may differ slightly from final analysis code.

2.1 Background & Rationale

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 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 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.

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 downregulation 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.

Brilacidin has three complementary anti-COVID-19 therapeutic properties combined in a single drug: antiviral; immunomodulatory/anti-inflammatory; and antimicrobial. Brilacidin has demonstrated antiviral activity against SARS-CoV-2 in cell-based assays (see Section 1.3.1.3 of the protocol), 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 SARSCoV-2 main protease (Mpro)

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). A peer-reviewed article detailing in vitro results and proposed mechanisms of action is published (Bakovic et al 2021), with a pre-print (Bakovic et al 2020) made available.

Additional nonclinical and clinical data support Brilacidin’s potential to function through the cAMP/cGMP pathway, by inhibition of phosphodiesterase. 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. PDE4 and PDE3 inhibition results in subsequent down-regulation of proinflammatory 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 downregulation by Brilacidin in ex vivo cell-based assays (see protocol Section 1.3.1.3), and also from clinical biomarker data (Phase 2 retention enema study (see protocol 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, 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.

2.2 Study Objectives

Primary, secondary and exploratory objectives are specified in sections below 2.2.1, 2.2.2 and 2.2.3, respectively.

2.2.1 Primary Objective

To evaluate the clinical efficacy of Brilacidin IV treatment in addition to SoC, compared with SoC alone, in subjects with COVID-19.

2.2.2 Secondary Objectives

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.

2.2.3 Exploratory Objectives

To evaluate the following In-hospital outcomes:

- Duration of hospitalization
- Time to discharge
- Duration of invasive mechanical ventilation
- Duration of supplemental oxygen support
- Duration of ECMO (Extracorporeal Membrane Oxygenation)
- No oxygen therapy (and/or peripheral oxygen saturation SpO2 > 93% on room air) at Days 8, 15 and 29

To evaluate All-cause 28-day mortality.

To measure biological and immunological markers of illness/inflammation.

To explore the change in the SARS-CoV-2 viral load.

To estimate the plasma pharmacokinetics of Brilacidin.

2.3 Study Design

This study is a Phase 2, randomized, double-blind, placebo-controlled, multicenter clinical trial with parallel group design to evaluate the efficacy and safety of Brilacidin in hospitalized participants with COVID-19.

Approximately 120 adult hospitalized subjects with COVID-19 will be randomized.

The key eligibility criteria includes adult subjects, aged between 18 and 80 years, 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).

Subjects that are eligible will be randomized to receive either Brilacidin or placebo in addition to available SoC, by randomization 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 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.

Randomization of subjects to treatment will also be stratified by (1) Age (≤65years, >65years), (2) Severity of disease (moderate, severe), and (3) Country. The generated randomization list will be uploaded into the IBM Clinical Development system (IRT system) which will manage the assignment.

The study is comprised of three parts, which are also shown in Figure 1:

- Screening/ Baseline visit (Day -1 to 1)
- Study treatment period (Day 1-3 with potential to expand to Day 4-5)
- Follow-up period (Day 4-6 through Day 60)

The schedule of visits and assessments can be found in the protocol Table 1 Schedule of Activities.

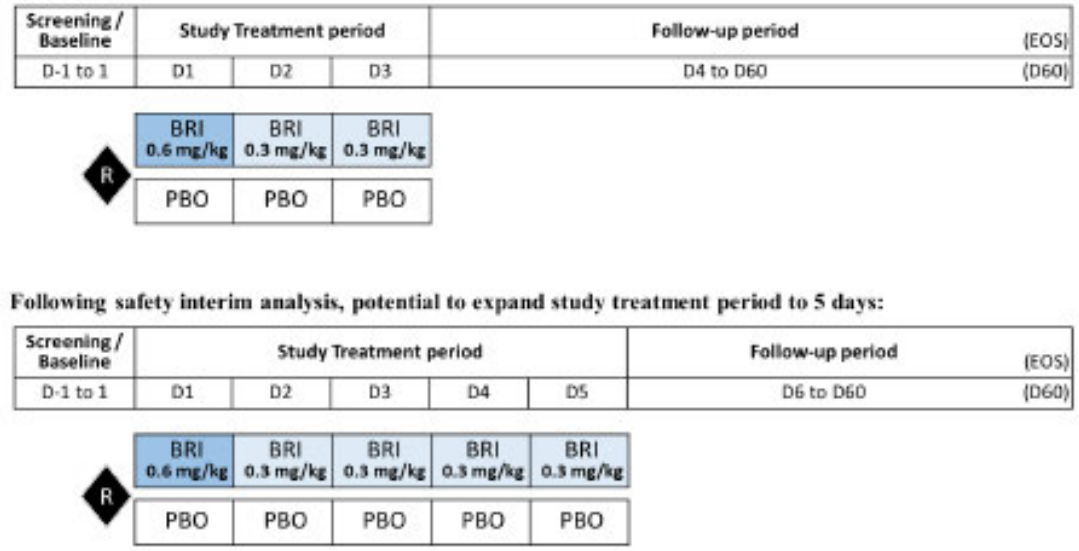

Figure 1: Study Flow Chart

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

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

Subjects will be screened (Day -1 to 1) and baseline assessments will be performed within a maximum of 48 hours. This visit will confirm that study inclusion and exclusion criteria are met by participants prior to randomization. Results confirming positive SARS-CoV-2 virus by PCR or equivalent/ other approved diagnostic testing should take place within 4 days prior to randomization and may be used for eligibility.

During the treatment period, on Study Days 1 to 3 (with potential to expand to Day 4-5, after initial interim safety readout), randomized subjects will receive blinded study treatment once daily for 3 days by IV infusion, in addition to SoC.

Subjects who successfully complete the treatment period, will enter a follow-up period, Day 4 or 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). 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.

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.

2.3.1 Eligibility and Randomization

After confirming eligibility, subjects will be randomized in blocks using a centralized randomization method with an allocation ratio of 1:1 for Brilacidin and Placebo, respectively. Once assigned to a patient, the randomization number will neither be replaced nor used a second time. A patient is considered enrolled when he or she is randomized into the trial, even if he or she does not receive study medication. The stratification factors are: country, categorized age group (≤ 65 years / > 65 years) and COVID-19 severity (moderate/ severe). The use of three stratification factors create 8 strata, and the block size used was 2. A separate Randomization documents the tools and methods used to generate the randomization list.

The randomization list has been generated using SAS 9.4 with a seed to ensure its reproducibility. The generated list is uploaded into the IBM Clinical Development system (IRT system) which will manage the random assignment to treatment. The unblinded randomization list will be provided from the Unblinded Statistician to the Unblinded Programmer who will upload it into the IBM Clinical Development system.

2.3.2 Eligibility Criteria

2.3.2.1 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.

2.3.2.2 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.

2.3.3 Withdrawals

Refer to sections 2.3.4.1 below and 7.6 of the protocol.

2.3.4 Study treatment

The investigational drug product (IP) supplied is Brilacidin for Injection, 50 mg/mlL(free base).

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. 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:

- SoC + Brilacidin IV 0.6 mg/kg (D1), 0.3 mg/kg (D2 and D3) with potential to expand dosing (dependent on safety review and recommendation by the DMC) of 0.3 mg/kg on D4 and D5
- SoC + Saline IV infusion (D1, D2, and D3) with potential to expand dosing (dependent on safety review and recommendation by the DMC) on D4 and D5

At the initial safety review by the DMC, the recommendation was to expand study drug dosing to Days 4 and 5 (at the same doses as on Days 2 and 3). This change was made by the Sponsor and sites were informed to move from the 3-dose regimen to the 5-dose regimen.

2.3.4.1 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.

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 Protocol Section 7.6.2). Where possible, subjects are to continue with (if hospitalized) or return for the assessments indicated in the Schedule of Activities (Protocol 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 (Protocol Section 7.6.3). This contact should preferably be done according to the study visit schedule and documented in the site study file.

Subjects who discontinue from study treatment or from the study will not be replaced.

All available data measured prior to withdrawal or discontinuation from the study will be used in analysis. The reason for early treatment discontinuation and/or study withdrawal should be recorded in the case report form and will be reported in the overall disposition summaries.

2.3.5 Replacement of Patients

No replacement of patients will be considered in this trial since will be carried out according to intent to treat principles.

2.3.6 Study termination

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.

3. ANALYSIS POPULATIONS

3.1 Intention-to-Treat Population

The Intent-to-Treat (ITT) population will include those randomized subjects who received at least one dose of study drug. Subjects in this population will be analyzed according to the treatment arm to which they were randomized.

The ITT will be the main population for demographic, baseline characteristics, efficacy, and exploratory analyses. Efficacy analyses performed on the ITT population will be considered primary.

3.2 Safety Population

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

3.3 Per Protocol Population

The Per Protocol population (PP) will consist of ITT subjects who meet all of the following criteria:

1. Complete study treatment (allocated regimen, either 3-dose or 5-dose)
2. No major protocol deviations that will potentially impact the primary study objective.

The following criteria have been identified a priori as major deviations that will potentially impact the primary study objective. Additional major deviations may be identified during the study. These will be reviewed and approved by the sponsor prior to database lock and unblinding of treatment assignment.

1. Deviation from key inclusion/exclusion criteria.
2. Receipt of treatment different from the randomized treatment assignment.
3. Receipt of prohibited medication per protocol in the treatment period.

The reason for excluding subjects from the per-protocol population will be summarized by randomized treatment arm and presented in a data listing.

The Per Protocol population will be used for sensitivity analysis of the efficacy endpoints. Efficacy analyses performed using the PP population will be considered supportive.

3.4 PK Population

The PK population will be defined in a separate PK analysis plan.

3.5 Screening Failures

Screen failure patients will be defined and a listing, including the number of patients, demography and why considered a screening failure, will be created.

4. STUDY ENDPOINTS AND DERIVED VARIABLES

This section is intended to outline the way to build the variables needed to assess all study endpoints and state definitions properly. For the statistical methods that will be used, refer to section 0.

The following table summarizes the endpoints corresponding to the objectives of the study:

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: - 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; and does not descend in the scale (being re-hospitalized with or without requiring supplemental oxygen or dies) in the remaining period of follow-up through Day 29
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 SpO2 > 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 hs (troponin T, troponin I), 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

4.1 Baseline and Demographics Characteristics

The baseline value is defined as the last available measurement prior to the first dose of study drug accounting for date, and time (where available), unless otherwise specified.

Specific disease history (COVID-19 related) variables include:

- **Time from onset of first COVID-19 symptoms until randomization** is defined as the time elapsed (in days) from the date of onset of first COVID-19 symptoms until the randomization date
- **Time from onset of first COVID-19 symptoms until hospitalization** is defined as the time elapsed (in days) from the date of onset of first COVID-19 symptoms until the hospitalization date
- **Time from diagnosis of COVID-19 until randomization** is defined as the time elapsed (in days) from the date of diagnosis of COVID-19 until the randomization date
- **Time from diagnosis of COVID-19 until hospitalization** is defined as the time elapsed (in days) from the date of diagnosis of COVID-19 until the hospitalization date
- **Time from hospitalization until randomisation** is defined as the time elapsed (in days) from the hospitalization date until the randomization date

4.2 Efficacy Endpoints

4.2.1 Rules Applicable to Ordinal Scale (Primary and Secondary Endpoints)

The primary and multiple secondary efficacy endpoints use data collected by an ordinal scale, developed specifically for efficacy assessment of COVID-19.

A special WHO committee arrived at an ordinal scale (WHO 2020a; WHO 2020c) that graduates the severity of the Clinical Status (CS) of a subject on an 8-point score. Following this scale along with the National Institute of Allergy and Infectious Diseases ordinal scale framework (as used in Adaptive COVID-19 Treatment Trial (ACTT) trials), an adapted scale has been used as follows:

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)

Score	Description
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

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. Each day (each nominal visit) the worse score for the previous day will be recorded in the CRF, i.e., on nominal visit Day 3, Day 2 score is obtained and recorded under date of assessment of Day 2.

The data source for Clinical status includes both the Clinical Status eCRF and the Discharge/ Rehospitalization Summary eCRF

- The Clinical Status eCRF within each nominal visit eCRF captures **Date of Assessment** for the clinical status of the previous study day; date of visit is "Date Recorded".
- At discharge from hospital, the Discharge/ Rehospitalization Summary eCRF requests **Clinical status at the time of Hospital Discharge**.

The baseline clinical status value will be taken from the Day 2 Clinical Status eCRF, where "Date Recorded" is that for Day 2, and the "Date of Assessment" is that of Day 1. As there is no separate pre-dose Clinical Status assessment captured, the Sponsor will confirm the baseline clinical status value for each subject, from review of oxygenation supplementation status parameters recorded on Day 1 pre- and post-infusion timings. Queries will be issued for resolution, as appropriate, to document appropriate clinical status used for baseline.

Post-baseline recordings other than D15, D29 and 60 will be taken as:

DX from DX+1, where X = Day 2 to Day 14; Day 16 to Day 28 (for example, D2 will take value recorded in D3 nominal visit)

Post-baseline recordings and imputations for Clinical Status (CS) at the Days 15, 29 and 60 visits are summarized below.

Hospitalization or Discharge condition	Recording/ imputation of post-baseline Clinical Status		
	CS for D15	CS for D29	CS for D60
If remains hospitalized (discharge not met)	CS from D16 Clinical Status eCRF	CS from Unscheduled Visit Clinical Status eCRF for D30, if recorded, ELSE	-

Hospitalization or Discharge condition	Recording/ imputation of post-baseline Clinical Status		
	CS for D15	CS for D29	CS for D60
		impute CS from D29 Clinical Status eCRF	
If discharge = visit	CS from Subject Status (Discharge/ Rehospitalization Summary) eCRF	CS from Subject Status (Discharge/ Rehospitalization Summary) eCRF	-
If discharged prior to	Impute CS from D15 Clinical Status eCRF; if missing refer to analysis visit windows*	Impute CS from D29 Clinical Status eCRF; if missing refer to analysis visit windows*	
NA	-	-	Impute CS from D60 Clinical Status eCRF

* Analysis Visit Windows:

For days 15, 29 and 60, analysis visit windows will be as below (to be confirmed prior to database lock):

Visit ID	Nominal Day	Lower Limit	Upper Limit
Day 15	15	13	18
Day 29	29	25	35
Day 60	60	48	73

i.e., for Day 15: data can be found in the CRF -2 to +3 days (Study Day 13 to 18); for Day 29, data can be found -4 to +6 days (Study Day 25 to 35); and for Day 60, data can be found -12 to +13 days (Study Day 48 to 73). In case several values are found in the visit window, the record collected on the day closest to the nominal day will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

The following additional rules also apply to Clinical Status (CS):

Situation	Additional Rules
If a subject dies	If a subject dies, CS for Death (score = 1) is to be populated to the corresponding Clinical Status nominal visit. "Date of death" is recorded in the AE eCRF (and should match "Date of study completion or discontinuation" recorded in the Subject Status (Subject Disposition) eCRF).
If a subject achieves CS score of 6	(Only applies to endpoints **Duration of Hospitalization** and **Time to Discharge**, in sections 5.3.4.1 and 5.3.4.2,) CS score of 6 = Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than for per protocol dosing or assessments, as appropriate). For those subjects that achieve a score of 6, and that score of 6 is maintained or increases to a 7 or 8 subsequently, the first instance score = 6 is recorded (date/time) is to be imputed as the date/time of hospital discharge.

4.2.2 Primary Efficacy Endpoint

The primary endpoint based on the ordinal scale is "**Time to sustained recovery through Day 29**", which is defined as time (in days) from randomization until the first day on which the subject satisfies one of the categories 6, 7 or 8 (meaning the subject 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]) on the 8-point ordinal scale and does not descend in the scale (being re-hospitalized with or without requiring supplemental oxygen or dies) in the remaining period of follow-up through Day 29. i.e., relapse by Day 29 after initial recovery negates that recovery.

If response after initial recovery is not sustained, and the subject experiences relapse, the initial recovery is not counted as such. Any subsequent recovery, sustained through Day 29, will be recognized and counted.

4.2.3 Secondary Efficacy Endpoints

The secondary endpoints for this trial are divided in two main groups:

1) Multiple clinical measures of disease severity and disease burden, as follows:

- *Composite endpoints, from the ordinal scale defined in section 4.2.1:*

  - Achievement of recovery status scores (score 6, 7 or 8 in the ordinal scale) at Day 29:

    The proportion of subjects achieving recovery status scores (6, 7, 8) in the 8-point ordinal scale at Day 29 will be derived as a binomial outcome from the ordinal status scale of 8 points as the proportion of subjects with a score of 6, 7, or 8 at Day 29. Any other case will be considered as not recovery status. Please refer to section 5.3.2 for details on the handling of intercurrent events and missing data.

  - Composite endpoint by Day 29, defined as: Death OR Respiratory failure (requires invasive mechanical ventilation):

    The proportion of subjects that meet the composite event of death or respiratory failure (considered when a subject requires invasive mechanical ventilation) by Day 29 will be derived as the proportion of subjects achieving one of the two events that compose the endpoint: death by Day 29 (score 1 in the clinical status scale) or respiratory failure (requiring invasive mechanical ventilation, score 2 the clinical status scale) by Day 29. Any other case will be considered as not achieving the composite event. Please refer to section 5.3.2 for details on the handling of intercurrent events and missing data.

- *Clinical status measures, from the ordinal scale defined in section 4.2.1:*

  - Achievement of at least one-point/ two-point improvement in clinical status at Days 8, 15 and 29:

    The proportion of subjects achieving at least one category improvement in clinical status at Day 8, 15 and 29 will be derived as the proportion of subjects with at least one point of improvement from baseline clinical status score at Days 8, 15 and 29 respectively. The change in the ordinal scale will be estimated as the difference “assessment score (Day 8, 15 or 29) – baseline score” and the improvement of at least one point will be when the result of the difference is >=1. Only subjects with available information at baseline and time-point of assessment will be considered in the analyses.

    The proportion of subjects achieving at least two category improvement in clinical status at Day 8, 15 and 29 will be derived as the proportion of subjects with at least two points of improvement from baseline clinical status score at Days 8, 15 and 29 respectively. The change in the ordinal scale will be estimated as the difference “assessment score (Day 8, 15 or 29) – baseline score” and the improvement of at least two points will be when the result of the difference is >=2.

Only subjects with available information at baseline and time-point of assessment will be considered in the analyses.

- Time to at least one-point/ two-point improvement in clinical status scale

Time to at least one category improvement in clinical status is defined as time (in days) from randomization until get an elevation of at least one point in the 8-point ordinal scale. The subjects will be considered as having achieved the event the first day in which they have an elevation of at least one point in the scale from baseline.

Time to at least two category improvement in clinical status is defined as time (in days) from randomization until get an elevation of at least two points in the 8-point ordinal scale. The subjects will be considered as having achieved the event the first day in which they have an elevation of at least two points in the scale from baseline.

- Clinical status over time

Clinical status over time is considered as the score of the 8-point ordinal scale at all time-points of assessment.

- *National Early Warning Score (NEWS2)*

  - Time to a NEWS2 of ≤2 and maintained for 24 hours

    Time to a NEWS2 of ≤2 and maintained for 24 hours is defined as time (in days) from randomization until get a NEWS2 score lower or equal to 2 being maintained for at least 24 hours (for example, if a subject achieves a NEWS2 ≤2 at Day 2, the NEWS2 should also be ≤2 at Day 3 to reach the event). Please refer to section 5.3.2 for details on the handling of intercurrent events and missing data.

  - Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS2:

    Change from baseline in NEWS2 at Days 3, 5, 8, 11, 15, and 29 will be derived taking the baseline score as reference, meaning that it will be the difference between the assessment score and the baseline score at each time-point of assessment. If NEWS2 score is not available at any of Days 3, 5, 8, 11 or 15, no change from baseline will be calculated for that assessment.

2) Endpoints to assess the safety and tolerability of Brilacidin IV treatment in subjects with COVID-19 infection:

   See section 4.3 for definition of safety and tolerability endpoints.

4.2.4 Exploratory and Other Endpoints

The following outcomes will be derived from data collected on the eCRF:

- Duration of hospitalization:

  Duration of hospitalization from randomization to discharge is defined as the time elapsed (in days) from randomization until hospital discharge.

  Please refer to section 5.3.4 for details on the handling of intercurrent events and missing data.

- Time to discharge:

  Time to discharge from randomization is defined as the time elapsed (in days) from randomization until hospital discharge.

  Please refer to section 5.3.4 for details on the handling of intercurrent events and missing data.

- Duration of invasive mechanical ventilation

  Duration of invasive mechanical ventilation is defined as the cumulative time (for all episodes of use of mechanical ventilation during the observation period [day 1 to 29]), in days, from the mechanical ventilation necessity until it is retired due to an improvement.

- Duration of supplemental oxygen support

  Duration of supplemental oxygen support is defined as the cumulative time (for all episodes of use of supplemental oxygen support (low flow O2, high flow O2, CPAP/BIPAP, mechanical ventilation, ECMO) during the observation period [day 1 to 29]), in days, from the supplemental oxygen necessity until it is retired due to an improvement.

- Duration of ECMO:

  Duration of ECMO is defined as the cumulative time (for all episodes of use of ECMO during the observation period [day 1 to 29]), in days, from the ECMO necessity until it is retired due to an improvement.

- No oxygen therapy (and/or peripheral oxygen saturation SpO2 > 93% on room air) at Days 8, 15 and 29

  The proportion of subjects with no oxygen therapy (and/or peripheral oxygen saturation SpO2 > 93% on room air) will be derived as the proportion of subjects without any oxygen therapy and/or peripheral oxygen saturation SpO2 > 93% on room air at the corresponding time-point of assessment.

- All cause-mortality

  Overall survival (OS) is defined as the time (in days) from randomization to death.

  28-day mortality is the proportion of subjects that are dead by Day 29. The proportion will be estimated from the OS survival analysis.

- Biological and immunological markers of illness/inflammation

  Biomarker values and changes from baseline include, but are not limited to: CRP, ferritin, LDH, D-dimer, troponin hs (troponin T, troponin I), 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 Days 15 (by returning to the clinic/ by remote visit or if still hospitalized)].

- SARS-CoV-2 viral load

  Viral load and 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).

  Number and percent of **subjects with a positive or negative SARS-CoV-2 PCR test** on 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).

  Time to viral clearance

  Time to viral clearance is defined as the time elapsed (in days) from randomization until negative viral load.

4.3 Safety Endpoints

Adverse Events (AEs) and Serious Adverse Events (SAEs)

Treatment Emergent Adverse Events (TEAEs):

TEAEs are AEs with an onset after the initiation of study drug or randomization date (whichever is earlier) until end of the follow-up period (Day 60±10). This will also include any AE with onset prior to initiation of study drug that increased in severity during the treatment period.

All AEs (including serious adverse events [SAEs]) will be coded to a lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and associated primary system organ class (SOC) will be coded according to the Medical Dictionary for Regulatory Affairs (MedDRA) version 23.1 or later.

SAEs:

An SAE is defined as any AE that fulfills any of the following criteria:

- Results in death.
- Is life-threatening.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which 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 inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is another significant medical event (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).

AEs by Relationship to Study Drug

The causality/relationship assessment of an AE to the IP will be rated as follows by the investigator:

- 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.

All AEs should be assigned with a relationship as above and missing relationship will be queries for resolution.

For analysis purposes, all AEs will be reclassified into 2 categories of related (include definitely, possibly related) and non-related (include not related and unlikely related) to IP.

AEs by Severity:

The investigator will also assess the severity (intensity) of each AE, grading 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.

All AEs should be assigned with severity as above and missing severity will be queried for resolution. Missing severity will not be imputed.

For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

Other safety endpoints include: Treatment exposure, physical examination, ECG, vital signs and oxygenation/respiratory parameters and laboratory safety evaluation. More details in section 5.

4.4 Pharmacokinetic Endpoints

Plasma concentrations of Brilacidin measured from blood samples collected on Days 1 to 4. More details will be given in a separate PK analysis plan.

4.5 Other Derived Variables

In the case that more derived variables than the ones described in this document are required for the analysis, they will be defined and described in the statistical report. Once the variables are created, it will be checked that their values are correct and that they represent exactly what it is expected.

5. GENERAL STATISTICAL METHODS

At the initial interim safety review by the DMC, the recommendation was to expand study drug dosing to Days 4 and 5 (at the same doses as on Days 2 and 3). This change was made by the Sponsor and sites were informed to move from the 3-dose regimen to the 5-dose regimen.

Therefore, all applicable baseline and safety data will be summarized by study drug treatment arm (placebo or Brilacidin) and dose regimen (3-dose or 5-dose), to be termed “study arms” (and overall, when appropriate). For efficacy data summarization, there will be three study drug treatment groups, comprised from the two treatment arms and two dose regimens, where placebo 3-dose regimen and placebo 5-dose regimen are pooled, i.e., pooled placebo group (which assumes there is no difference between regimens from a clinical point of view), with two active treatment groups of Brilacidin 3-dose regimen and Brilacidin 5-dose regimen.

Statistical comparisons will be performed between Brilacidin 5-dose regimen and pooled placebo as the main comparison of interest, and between Brilacidin 3-dose regimen and pooled placebo as secondary.

The assumption for considering both placebo dose regimens not clinically different and pooling in a combined group will be checked (for selected endpoints) as an appropriate action with specified sensitivity analyses (detailed in section 5.3.6). In addition, pooled Brilacidin is to be compared to pooled placebo (see section 5.3.6).

5.1 Sample Size

Sample size is based on the primary efficacy endpoint of time to recovery by Day 29, being the day of recovery defined under an ordinal scale related to hospitalization, limitation of activities and oxygen requirement by the subject.

Assuming that a median time to recovery of 5 days on Brilacidin versus 10 days on SoC (i.e., a hazard ratio of 2.0), and assuming that a total of 75 recovery events are observed if 100 subjects (50 per treatment arm) are included in analysis, the comparison between treatment arms would provide at least 90% power with a one-sided type I error rate of 0.05. If the assumption is that time to recovery for Brilacidin is of 6 days versus 10 days on SoC, which is equivalent to a hazard ratio of 1.67, the comparison between treatment arms would provide at least 70% power with a one-sided type I error rate of 0.05.

Assumptions for time to recovery for both arms of the study have been 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 in multiple countries and has become SoC where available.

A total of 100 subjects with 50 per treatment arm 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 arm 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).

Due to the exploratory nature of this study, a sample size up to 60 subjects per treatment arm randomised with a 1:1 ratio is considered to provide sufficient power under the alternative hypotheses exposed above in order to support initial PoC of Brilacidin versus SoC.

Interim analyses are planned for this study. Details can be found in section 5.3.5.

5.2 Subject´s Disposition

5.2.1 Subject´s Disposition and Withdrawals

This section describes subject disposition for both study status and the analysis populations.

Screened subjects will include all subjects who signed the informed consent form and are entered into the clinical database.

Randomized subjects will include all subjects who were provided a treatment assignment that was recorded in the interactive response technology database, regardless of whether the treatment kit was used.

The safety experience of subjects who were treated, but not randomized will be reported separately, and these subjects will not be included in the safety population. Subjects treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For subject study status, the total number and percentage of subjects in each of the following categories will be presented in the CSR using a flowchart diagram or summary table:

- Screened subjects.
- Screen failure subjects.
- Enrolled subjects.
- Nonrandomized but treated subjects (if applicable).
- Randomized subjects.
- Randomized but not treated subjects (if applicable).
- Subjects in the ITT Population.
- Subjects in the Safety Population.
- Subjects in the PP Population.
- Subjects discharged from the hospital.
- Subjects who discontinued study treatment early, including primary reason for discontinuation.

- Subjects who discontinued study early, including primary reason for discontinuation.

For all categories of subjects (except for the screened, enrolled and nonrandomized categories) the summaries will be provided by randomized treatment arms and dose regimen, and percentages will be calculated using the number of randomized subjects as the denominator.

The number (%) of subjects in each population will also be summarized by the stratification factors (country, categorized age group (≤ 65 / > 65 years) and COVID-19 severity), and by treatment arms and dose regimen. The number of mis-stratified subjects, will also be presented for randomized subjects. They will also be listed.

A listing of subjects with population assignment including individual reasons of exclusion from the respective analysis populations will be provided. Data listing for early termination reasons will be also provided.

5.2.2 Protocol Deviations

Protocol deviations, including violations of inclusion/exclusion criteria, will be collected and assessed as "minor" or "major" by the clinical team and the final version will be provided to the biostatistics contract research organization [redacted] prior to the database lock. Important deviations will be identified by the sponsor and project team prior to database lock. Important quantitative deviations will be verified programmatically from the database.

All protocol deviations will be collected separately from the database and listed. The final listing of protocol deviations will be reviewed before database lock to assist in the Per Protocol population selection and definition of the final study populations as well as a preliminary assessment of the quality of the trial data. All important deviations will be summarized by deviation type and listed in the CSR.

5.3 Summary of Statistical Methods

This study is designed as a phase 2 study, exploratory in nature, to evaluate the efficacy of Brilacidin. Comparisons will be performed between Brilacidin in addition to SoC against placebo plus SoC at a one-sided type I error rate of 0.05 which will not be adjusted for multiple testing. The study will be considered to have achieved proof-of-concept when the 1-sided p-value is <0.05. Accordingly, the primary and key secondary efficacy endpoints will present 2-sided 90% Confidence Intervals (90%CIs) when applicable.

Unless otherwise specified, efficacy analyses will be performed in the ITT population, where subjects will be in the treatment arm to which they were randomized. Moreover, supportive efficacy analyses will be performed in the PP population. Safety related analyses will use the safety population. Pharmacokinetic analyses will be carried out in the PK population (refer to separate analysis plan).

All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings. The listings will be generally sorted by treatment arm and regimen and then Subject ID, unless specified otherwise.

All applicable baseline and safety data will be summarized by treatment arm and dose regimen, termed “study arms” (and overall, when appropriate), unless specified otherwise. In addition, data will be summarized by time-point and/or follow-up date when appropriate. For efficacy data summarization, there will be three study drug treatment groups, comprised from the two treatment arms and two dose regimens, where placebo 3-dose regimen and placebo 5-dose regimen are pooled, i.e., pooled placebo group, with two active treatment groups of Brilacidin 3-dose regimen and Brilacidin 5-dose regimen.

Continuous variables will be summarized using the number of observations (n), mean (95%CI, if appropriate), standard deviation (SD), Standard error (SE, if appropriate), median, first quartile (Q1), third quartile (Q3), minimum, and maximum along with the total number of subjects contributing values.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The denominator for all percentages will be the number of subjects in the treatment arm and dose regimen (or treatment group, for efficacy endpoints) within the population of interest, unless stated otherwise in the table footnote.

Statistical comparisons will be performed between Brilacidin 5-dose regimen and pooled placebo as the main comparison of interest, and between Brilacidin 3-dose regimen and pooled placebo as secondary.

Kaplan-Meier model will be used to analyse time-to-event endpoints (such as time to recovery, time to at least one-point/ two-point improvement in clinical status, time to a NEWS2 of ≤2). For these analyses, in addition to the Kaplan-Meier curve, median,(corresponding 90%CI) and 25^{th} percentile (Q1) and 75^{th} percentile (Q3), and the number of events and censored cases distribution will be shown. Group comparisons will be done using the (stratified) log-rank test and the adjusted hazard ratios (HR) with 90%CI obtained from a Cox proportional hazards model.

Endpoints considering the proportion of subjects achieving an event (such as number of subjects achieving recovery status scores or the composite event death or respiratory failure requiring invasive mechanical ventilation at Day 29, or achieving at least one-point/two-point improvement in clinical status at Days 8, 15 and 29), or achieving no oxygen therapy (and/or peripheral oxygen saturation SpO2 > 93% on room air) at Days 8, 15 and 29) will be analyzed using logistic regression models with treatment group and stratification factors as covariates (in the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, that stratification factor will be not considered as a covariate in the model). Odds ratios and the corresponding 2-sided 90%CIs will be calculated for comparisons between each respective Brilacidin dose regimen versus the pooled placebo arm.

The shift analysis of proposed ordinal scale endpoint will be analysed using the proportional odds model and the stratification variables. The common odds ratio can also be interpreted as the average shift over the total ordinal outcome scale caused by the treatment under study. The stratified non-parametric van Elteren test, using modified ridit scores which is a direct extension of the Wilcoxon's rank-sum test for 2-samples, will be calculated as a sensitivity analysis to compare the scale as an ordinal rather than a binary outcome, without assuming proportional odds (see section 5.3.6).

The median of absolute values with 90%CI will be calculated using the Hodges-Lehmann methods (i.e. median of all cross differences between treatments based on the Mann-Whitney distribution).

Change from baseline for biomarkers, SARS-CoV-2 viral load and NEWS2 score will be analysed using Analyses of Covariance (ANCOVA) Models including baseline score as covariate and the stratification variables (country, categorized age group ($\leq$ 65 / > 65 years) and COVID-19 severity as factors (in the event that any of the stratification variables does not achieve enough size for obtaining reliable estimations, that stratification variable will be not considered as a factor in the model). In addition, selected biomarkers will be analysed using a repeated measures mixed model.

Handling of quantitation limits for laboratory, biomarkers and viral load data are discussed below.

Data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

Analyses of PK data will be discussed in a separate analysis plan to support the population PK report.

In general, values reported in Unscheduled or Successful Discharge visits are to be considered under the relevant Day for statistical analyses and summaries.

In addition to the study Protocol Deviation Logs, an Unresolved Data Issues Report has been created in order to reflect issues arisen during data collection which cannot be fitted appropriately in the eCRF. The unresolved data issues captured in the report will need to be taken into account by programming, for affected subject data entries, and will require confirmation with Data management on appropriate correction/ resolution prior to database lock.

5.3.1 Demographics, Other Baseline Characteristics and Medication

Summary statistics will be provided by treatment arm and dose regimen and overall for baseline characteristics and demographic variables; summaries will be provided on the ITT population. Prior and concomitant medications will be reported for the Safety population.

The baseline value is defined as the last available measurement prior to the first dose of study drug accounting for date, and time (where available) which can be found in screening, baseline/Day 1 or unscheduled visits of the CRF, unless specified otherwise.

5.3.1.1 Demographic Characteristics

Descriptive statistics by treatment arm and dose regimen and overall will be performed for the demographic characteristics and disease history. Listings will also be presented for the demographic characteristics and disease history, respectively.

5.3.1.2 Focused COVID-19 Medical History

The following variables for disease history will be summarized by treatment arm and dose regimen and overall:

- COVID Symptoms at study entry, including (categorized) body location of any tingling/numbness sensations
- Time from onset of first COVID-19 symptoms until randomization
- Time from onset of first COVID-19 symptoms until hospitalization
- Time from diagnosis of COVID-19 until randomization
- Time from diagnosis of COVID-19 until hospitalization
- Time from hospitalization until randomization
- Type of swab analyzed, type of test, and results of SARS-CoV-2 test (local)

Listings will also be presented.

5.3.1.3 Medical History

Medical history abnormalities will be coded to Medical Dictionary for Regulatory Activities (MedDRA) terms. The version used will be specified in the data display footnote. Conditions will be summarized by system organ class and preferred term by treatment arm and dose regimen and overall. Listings will also be presented.

5.3.1.4 Physical examination

Results of physical examination assessments (including skin, neck (including thyroid), HEENT (head, eyes, ears, nose and throat), heart, lungs, abdomen, lymph nodes, extremities, vascular and neurologic systems) will be summarized by treatment arm and dose regimen, according to:

- Normal
- Abnormal Not Clinically Significant
- Abnormal Clinically Significant

The result of the baseline physical exam and the significant findings will be presented by listing.

5.3.1.5 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).

Summary statistics (including number, mean, SD, median, Q1, Q3, minimum, and maximum) for all ECG variables at baseline will be calculated by treatment arm and dose regimen. Only evaluable data will be used, and missing data at baseline will not be imputed.

Summaries of evaluation (normal; abnormal not clinically significant; abnormal clinically significant) will be provided by treatment arm and dose regimen.

All ECG results will be listed on a by-subject basis.

5.3.1.6 Vital signs and Oxygenation/Respiratory parameters

The vital signs at baseline will be described by treatment arm and dose regimen. The variables to be included are:

- Blood Pressure:

  - Systolic (SBP)
  - Diastolic (DBP)
- Heart rate
- Body temperature (also for overall)
  - Temperature location
  - Temperature by location
- Height, weight and BMI (also for overall)

Respiratory parameters will be described by treatment arm and dose regimen and overall. The variables to be included are:

- Respiratory rate on (i) room air or (ii) oxygen supplementation
- SpO2 on room air or PaO2/FiO2 ratio if on oxygen supplementation
- Oxygen supplementation requirement (room air (none), low flow O2, high flow O2, CPAP/BIPAP, mechanical ventilation, or ECMO).

Summary statistics (including number, mean, SD, SE (for SBP and DBP), median, Q1, Q3, minimum, and maximum) for all vital signs and appropriate respiratory parameters at baseline will be calculated by treatment arm and dose regimen and overall (if appropriate). The proportion of subjects in each oxygen supplementation requirement category will be summarized. Only evaluable data will be used, and missing data at baseline will not be imputed

All vital signs and oxygenation/respiratory measurements will be listed.

5.3.1.7 National Early Warning Score (NEWS2)

The National Early Warning Score (NEWS2) will be summarized by the mean, SD, SE, median, Q1, Q3 quartiles and the minimum and maximum values by treatment arm and dose regimen. Listings will also be presented for the NEWS2 score and its sub-score components, respectively. In addition, if the subject has hypercapnic respiratory failure (yes/no) will be reported by treatment arm. Only evaluable data will be used, and missing data at baseline will not be imputed. Data will be listed by subject.

5.3.1.8 Clinical Status

For the clinical status 8-point ordinal scale, the number and percentage of subjects for all categories in the 8-point ordinal scale will be reported by treatment arm and dose regimen and overall. In addition, clinical status will be summarized by means of the median, Q1, Q3 quartiles and the minimum and maximum values by treatment arm and dose regimen. Listings will also be presented.

5.3.1.9 Laboratory Evaluations

Laboratory assessments at baseline include haematology (including absolute neutrophil count), blood chemistry (including CRP, ferritin, LDH, D-dimer, troponin hs [troponin T, troponin I]), coagulation and

additional biomarker parameters (which include, but are not limited to: IL-1β, IL-6, IL-10, total IL-18, TNF-α).

The summary statistics (including number, mean, SD, median, Q1, Q3, minimum, and maximum) of all quantitative laboratory variables at baseline will be calculated by treatment arm and dose regimen. Only evaluable data will be used, and missing data at baseline will not be imputed. Data will be listed by subject.

5.3.1.10 Prior and Concomitant Medications

Prior medications are those that the subject used prior to the randomization date. Concomitant medications are defined as medications that continued or started on or after the randomization date, collected up to 60±10 days after randomization.

Prior and concomitant medications will be summarized by treatment arm and dose regimen according to the World Health Organization Drug Dictionary (WHO-DD), using the version in effect at the time of database lock and considering the first digit of the anatomic and therapeutic category (ATC) class and the first 3 digits of the ATC class (therapeutic category). Subjects will be counted once in each ATC category (anatomic or therapeutic).

Prior and concomitant medications will be summarized separately; in these summarizes, medications indicated for COVID-19 will be excluded and reported separately. For those medications indicated for COVID-19, prior together with concomitant will be summarized.

Prior and concomitant medications and medications for COVID-19 will use the Safety population. Medications (indicating prior, concomitant or both) will be listed on a by-subject basis reporting to ATC level 5; this listing will exclude those indicated for COVID-19, and a separate listing will be provided for such medications.

Administration of new or altered anti-hypertensive treatment post-randomization will be summarized by onset timing (overall, during study; onset during study treatment period, onset during follow-up period), and supported by a separate listing.

A summary of non-drug therapies or procedures will also be presented (summarized by MedDRA coding), if appropriate, and a separate by-subject listing will be provided.

5.3.2 Efficacy Analyses

Analyses of efficacy endpoints will be performed in the ITT population. In addition, sensitivity analyses will be performed in PP population and will be considered supportive.

5.3.2.1 Primary endpoint

The primary endpoint “Time to sustained recovery through Day 29” will be considered as described in section 4.2.1

Subjects who remained hospitalized (having a score less than 6 in the ordinal scale for all available measurements), and remain alive, will be censored at their last evaluation time-point.

When analyzing time to sustained recovery, if subjects are lost to follow-up (for this endpoint) prior to achieving recovery (a score of 6, 7 or 8) 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.

Time to sustained recovery will be analyzed using Kaplan-Meier methods. The treatment difference for time to sustained recovery will be analyzed with the stratified log-rank test where each regimen, Brilacidin 3-doses and Brilacidin 5-doses, will be compared separately to the pooled placebo group.

The treatment effect will be evaluated by a Kaplan-Meier model. The Kaplan-Meier curve for time to recovery, the median (corresponding 90%CI) and Q1 and Q3 , as well as number/percentage of events and censored cases distribution will be presented.

The model to be used will be processed by:

```
proc lifetest data=<sas-data-set> method=km plots=(rmst rmtl) rmst
rmtl(tau=90) maxtime=29;
time <<time to recovery> * <event=recovery> (censor value=0)>;
strata <<treatment group>>/test=(logrank);
run;
```

Additionally, treatment regimen comparisons to the pooled placebo group will be performed using the adjusted hazard ratios (HR) with 90%CI for the stratification factors (country, categorized age group (≤ 65 / > 65 years) and COVID-19 severity (moderate/ severe) from the Cox model. In the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, the model will not be adjusted by that stratification factor.

The model to be used will be processed by:

```
proc phreg data=<sas-data-set>;
Class <<treatment group> <age group> <disease severity> <country>>/param=ref
ref=first;
model <<time to recovery> * <event=recovery> (censor value=0)> = <treatment
group> <country> <age group> <disease severity>> / eventcode=1 risklimits;
hazardratio <treatment group> / alpha=0.05; run;
```

Clinical status data will be listed by subject. In addition, listings will include primary endpoint derivation of time to sustained recovery.

5.3.2.2 Secondary endpoints

The secondary efficacy endpoints related with the clinical severity and disease burden will be assessed as:

- Composite endpoints, from the ordinal scale
- Clinical status measures, from the ordinal scale
- NEWS2 Score

Clinical status evaluations are performed as described in section 4.2.1. All parameters related to NEWS2 should be recorded together in the morning and then between noon and midnight, for the duration of hospitalization (if outside ICU). Following hospital discharge, these parameters should be recorded once at each return visit to the clinic (Days 15 and 29), with Clinical status captured at the Day 60 follow-up telephone contact.

Analyses to be performed are described in the following subsections.

5.3.2.2.1 Proportion of subjects achieving recovery status scores (categories 6, 7 or 8) in the 8-point ordinal scale at Day 29 of follow-up

The proportion of subjects achieving recovery status scores (6, 7, 8) in the 8-point ordinal scale at Day 29 will be derived as a binomial outcome from the ordinal status scale of 8 points as the proportion of subjects with a score of 6, 7, or 8 at Day 29. Any other score of the ordinal scale will be considered as not recovery status. Analyses will be based on the Last Observation Carried Forward (LOCF) approach meaning that the score for subjects lost-to-follow or with score not assessed at Day 29 will be the score in their last observation available. Listings will include this endpoint and LOCF values will be identified on them.

The number and proportion of subjects achieving recovery status scores (categories 6, 7 or 8) in the 8-point ordinal scale at Day 29 of study will be reported by treatment group. Additionally, the comparison of the proportion between treatment groups will be performed using a logistic regression model with treatment group and stratification factors (country, categorized age group (≤ 65 / > 65 years) and COVID-19 severity) as covariates (in the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, that stratification factor will be not considered as a covariate in the model). Odds ratios and the corresponding 2-sided 90%CIs will be calculated.

5.3.2.2.2 Proportion of subjects that die or develop respiratory failure by Day 29

The proportion of subjects that meet the composite event of death or respiratory failure (considered when a subject requires invasive mechanical ventilation) by Day 29 will be derived as the proportion of subjects achieving one of the events that compose the endpoint: death by Day 29 (score 1 in the clinical status scale) or respiratory failure (requiring invasive mechanical ventilation, score 2 the clinical status scale) by Day 29. Analyses will be based on the LOCF approach meaning that subjects lost-to-follow up or with score not assessed before Day 29 not having achieved any of the 2 endpoints before being lost (or score not assessed) will be considered as not having achieved the composite event by Day 29. If death (score 1) or invasive mechanical ventilation (score 2) by Day 29 are not achieved, the composite event will be considered as not being achieved. Listings will include this endpoint (differentiating death or respiratory failure development) and LOCF values will be identified on them.

The number and proportion of subjects achieving composite event of death or respiratory failure (requiring mechanical ventilation) by Day 29 will be reported by treatment group. Additionally, the comparison of the proportion between treatment groups will be performed using a logistic regression model with treatment group and stratification factors (country, categorized age group (≤ 65 / > 65 years) and COVID-19 severity) as covariates (in the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, that stratification factor will be not considered as a covariate in the model). Odds ratios and the corresponding 2-sided 90%CIs will be calculated.

5.3.2.2.3 Proportion of subjects achieving at least one or two points of improvement in clinical status scale at Days 8, 15 and 29

The proportion of subjects achieving at least one or two category improvement in the ordinal scale at Day 8, 15 and 29 will be derived as the proportion of subjects with at least one or two points of improvement from baseline clinical status score at Days 8, 15 and 29 respectively. The change in the ordinal scale will be estimated as the difference “assessment score (Day 8, 15 or 29) – baseline score”. The improvement

of at least one or two points will be considered when the result of the difference is >=1 or >=2 respectively. Analyses will be based on the LOCF approach meaning that the score for subjects lost-to-follow or with score not assessed at Days 8, 15 and 29 will be the score in their last observation available. Only subjects with available information at baseline and an additional time-point of assessment will be considered in the analyses. Listings will include this endpoint and LOCF values will be identified on them.

The number and proportion of subjects achieving at least one or two points of improvement in clinical status scale at days 8, 15 and 29 of study will be reported by treatment group. Additionally, the comparison of the proportion between treatment groups will be performed using a logistic regression model with treatment group and stratification factors (country, categorized age group (≤ 65 / > 65 years) and COVID-19 severity) as covariates (in the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, that stratification factor will be not considered as a covariate in the model). Odds ratios and the corresponding 2-sided 90%CIs will be calculated.

5.3.2.2.4 Time to at least one or two points of improvement in the ordinal scale of clinical status.

Time to at least one or two category improvement in clinical status is defined as time (in days) from randomization until get an elevation of at least one or two points in the 8-point ordinal scale. The subjects will be considered as having achieved the event the first day in which they have an elevation of at least one/two point/s in the scale from baseline. Those subjects without improvement by the Day 29 study follow-up visit will be censored at last available assessment. Only subjects with available information at baseline will be considered in the analyses. These endpoints will be included in listings.

A Kaplan-Meier analysis will be performed to assess the time to improvement. The median time to event as well as the estimated percent of subjects without event during the study period will be estimated based on Kaplan-Meier method for each treatment group.

Stratified log-rank test for comparisons between groups will be calculated. Additionally, treatment comparisons will be performed using a Cox Proportional Hazards Model where the adjusted hazard ratios (HR) with 90%CI between treatment regimens versus pooled placebo is adjusted for the stratification factors (country, categorized age group (≤ 65 / > 65 years) and COVID-19 severity). In the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, the model will not be adjusted by that stratification factor. Only subjects with available information of the clinical status scale at baseline will be included in the analyses.

NOTE: Subjects who need a re-hospitalization or with more than one improvement during the study period will only be counted once corresponding to the first improvement.

5.3.2.2.5 Subject clinical status and the mean change using ordinal scale at baseline, days 3, 5, 8, 11, 15 and 29/60.

The number and percentage of subjects in each clinical status category for each day from baseline (Days 3, 5, 8, 11, 15, 29 and 60), will be summarized by treatment group. In addition, stacked bar charts (%) by day will be produced. Shift tables will also be produced. These endpoints will be included in listings.

As a supportive analysis, the evolution of the clinical status will also be summarized in a descriptive way by mean, SD, SE, median, Q1, Q3, minimum, and maximum.

The shift analysis of proposed ordinal scale endpoint will be analysed using the proportional odds model. The odds of observing a better category (higher number) of clinical status will be analyzed at Days 3, 5, 8, 11, 15 and 29 with a proportional odds model (POM). The odds ratio for treatment group estimated from the POM can be interpreted as a summary of the odds ratios obtained from separate binary logistic regressions using all possible cutoff points of the ordinal outcome (e.g. the cutoff of level 3 'Hospitalized, on non-invasive ventilation or high flow oxygen devices' will combine levels 1 and 2 versus combined levels 3, 4, 5, 6, 7 and 8). The assumption of POM is that the effect of treatment is identical across all possible cutoff points of the ordinal outcome. The proportional odds assumption will be checked by a score test will include treatment group and the stratification variables (country, categorized age group (≤ 65 / > 65 years) and COVID-19 severity) as covariates. In the event that any of the stratification variables does not achieve enough size for obtaining reliable estimations, that stratification variable will be not considered as a covariate in the model. The estimated odds ratios, p-values and 90% confidence intervals will be presented.

The common odds ratio can also be interpreted as the average shift over the total ordinal outcome scale caused by the treatment under study.

The example of model is shown below:

```
proc glimmix data=<sas-data-set> empirical=mbn method=quad;
class <<subject_id> <treatment group> <age group> <disease severity>
<country>>;
model <<scale_score>> = <<treatment group> | <country> <age group> <disease
severity> > time/dist=mult link=clogit solution;
random int / subject = <subject_id>;
estimate 'treatment group vs placebo arm' trt 1 -1 / or;
run;
```

The stratified non-parametric van Elteren test, using modified ridit scores which is as a direct extension of the Wilcoxon's rank-sum test for 2-samples, will be calculated as a sensitivity analysis to compare the scale as an ordinal rather than a binary outcome, without assuming proportional odds.

The SAS proc freq with modified ridit scores will be used to obtain the Van Elteren test as follow:

```
proc freq data=<sas-data-set>;
ods select cmh;
table <time>*<treatment group>*<change_againts_baseline>/cmh2
scores=modridit;
run;
```

The median of the absolute values with 90% confidence interval (90%CI) will be calculated using the Hodges-Lehmann methods (i.e. median of all cross differences between treatments based on the Mann-Whitney distribution).

5.3.2.2.6 Time to a NEWS2 score of ≤ 2 and maintained for 24 hours.

All NEWS2 measurements will be considered for this analysis, regardless of being measured just once or twice daily. Maintenance for 24 hours will be checked across all available measurements for each subject.

Time to a NEWS2 of ≤2 and maintained for 24 hours is defined as time (in days) from randomization until get a NEWS2 score lower or equal to 2 being maintained for at least 24 hours (for example, if a subject achieves a NEWS2 ≤2 at Day 2, the NEWS2 should also be ≤2 at Day 3 to reach the event). This endpoint can only be calculated during hospitalization, since if a subject has been discharged measurements are recorded in intervals higher than 24 hours after discharge. Subjects who did not reach NEWS2 of ≤ 2 by Day 29 study follow-up visit will be censored at last available assessment. Those subjects followed up will be censored at the last assessment available date. Subjects who have died will be censored on date of death.

This endpoint and the sub-scores that compose the NEWS2 will be included in listings.

A Kaplan-Meier analysis will be performed to assess the time to achieve a NEWS2 score of ≤ 2. The median time to event as well as the estimated percent of subjects without event during the study period will be estimated based on Kaplan-Meier method for each treatment group. Treatment comparisons will be performed using the adjusted hazard ratios (HR) with 90%CI from a Cox Proportional Hazard Model, adjusted for the stratification factors (country, categorized age group (≤ 65 / > 65 years) and COVID-19 severity). In the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, the model will not be adjusted by that stratification factor.

Only subjects with available information for NEWS2 score at baseline will be included in the analyses.

NOTE: Subjects who need a re-hospitalization or with more than one improvement during the study period will only be counted once corresponding to the first improvement.

5.3.2.2.7 Change from baseline to Days 3, 5, 8, 11, 15 and 29 in NEWS2 score.

The baseline value will be taken from the time-point (before noon or between noon and midnight) whose date and time in the CRF is the last available prior to the first dose of study drug (that can be available in Screening, Day 1 or Unscheduled visits). For days after baseline where the NEWS2 score has been measured twice, the highest NEWS2 score will be used for change from baseline.

NEWS2 score used in this analysis will come from the derived value associated with the respiratory status eCRF.

Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS2 score will be derived taking the baseline score as reference, meaning that it will be the difference between the assessment score and the baseline score at each time-point of assessment. Change from baseline will be reported by treatment group. If NEWS2 score is not available at any of Days 3, 5, 8, 11 or 15, no change from baseline will be calculated for that assessment. Only subjects with available information for NEWS2 score at baseline will be included in the analyses. These endpoints will be included in listings.

Additionally, change from baseline of the NEWS2 score in the Brilacidin treatment groups will be compared to pooled placebo using an ANCOVA model, including the baseline score as covariate and the stratification variables (country, categorized age group ($\leq$ 65 / > 65 years) and COVID-19 infection severity) as factors. In the event that any of the stratification variables does not achieve enough size for obtaining reliable estimations, that stratification variable will be not considered as a factor in the model). Least square mean difference between the treatment groups will be provided with 2-sided 90%CIs.

In addition, a line plot of mean change from baseline (SE), will be displayed for NEWS2, by treatment group and visit.

5.3.3 Safety Analyses

The population used for safety analyses will be the Safety Population. Safety of treatment will be assessed on the basis to AEs during IV infusion, SAEs and AEs of special interest (AESIs).

In general, change from baseline is calculated only for subjects with non-missing values for both the baseline and the time-point of interest and will be missing otherwise. Unless otherwise specified, denominators for all percentages will be the total number of subjects in the safety population with non-missing values for the assessment of interest.

Safety analyses will be carried out for subjects by actual treatment received, irrespective of the treatment to which the subject was randomized.

5.3.3.1 Treatment Exposure

Subjects are initially planned to receive IV administration of Brilacidin on Day 1 (0.6 mg/kg), Day 2 (0.3 mg/kg) and Day 3 (0.3 mg/kg) or placebo Day 1, Day 2 and Day 3. Additionally, depending on safety review and recommendation by the DMC, they will receive doses on days D4 and D5 (Brilacidin 0.3 mg/kg or placebo). Exposure to the investigational product (Brilacidin IV or placebo) will be summarized by descriptive statistics by treatment arm and dose-regimen as follows:

- Number of subjects under each regimen (3-day or 5-day)
- Total number of doses administered and number of doses by dose level (0.6 mg/kg or 0.3 mg/kg)
- Duration of exposure (in days)

Treatment assignment as well as type of regimen (3-day or 5-day) will be listed by subject. A listing of investigational product infusion data by day of administration will be provided.

Randomization number assignment, and strata assignment, will be listed; those subjects that were mis-stratified (due to incorrect eCRF data entry at time of randomization relating to severity) will be identified.

5.3.3.2 Adverse Events

Summary of AEs:

The primary focus of AE reporting will be on TEAEs. All reported AEs (regardless of TEAE or not) will be included in a by-subject AE listing, identifying which is treatment-emergent and which it not. Subsets of AEs of special interest will also be listed.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as treatment-emergent or not. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of AEs with missing or partial-onset dates are provided in Section 5.3.7.

AE summaries will include number (n) and percentage (%) of subjects experiencing an AE within each treatment arm and dose regimen, and overall if appropriate. The denominator for computation of percentages is the number of subjects in the safety population within each treatment arm and dose regimen. The number of events will be included in some summaries as well whenever appropriate.

Unless otherwise specified, sorting order will be by decreasing number of events in PTs within SOCs based on total subjects. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

Multiple occurrences of the same event in the same subject will be counted only once in the tables within a treatment arm and dose regimen.

Summary of All TEAEs:

The following TEAE summaries will be generated for the safety population:

- An overview of TEAEs. Number (%) of subjects will be provided by treatment arm and dose regimen, to include following:
    - TEAEs.
    - Grade 3 (Severe), Grade 4 (Life-threatening), and Grade 5 (Fatal) TEAEs.
    - Serious TEAEs.
    - Treatment-related AEs (defined as those events other than ‘not related’ and ‘unlikely related’ as assessed by the investigator).
    - TEAEs serious leading to death.
    - TEAEs leading to study drug permanently discontinuation.
    - TEAEs leading to dose adjusted/ dose temporarily discontinued.
    - TEAEs leading to discontinuation/withdrawal from the study.
    - TEAEs of special interest: (i) hypertension Grade 3 or greater, and (ii) paresthesias / dysesthesias Grade 2 or greater.
- All TEAEs by primary SOC and PT.
- All TEAEs presented by PT.
- All treatment-related AEs presented by primary SOC and PT.
- All treatment-related AEs Grade 3 or higher, presented by primary SOC and PT.
- All TEAEs by maximal severity (ie, Grade 1, Grade 2, Grades 3 to 5), presented by primary SOC and PT.

Summary of Potentially Clinically Important TEAEs

- Most common TEAEs by primary SOC and PT. The most common TEAEs are defined as those PTs with incidence of ≥5% in any of the treatment arms and dose regimen. This cutoff maybe adjusted based on clinical judgement.
- TEAEs with potential difference between treatment arms and dose regimen, by primary SOC and PT. The events with potential difference are defined as those PTs with a difference in incidence rate of >10% between either Brilacidin treatment regimen and its matching placebo regimen. This cutoff maybe adjusted based on clinical judgement.
- TEAEs of special interest (all grades and per protocol) by onset timing (overall, during study; onset during study treatment period, onset during follow-up period), presented by primary SOC and PT.
- TEAEs of special interest (all grades and per protocol) by maximal severity, presented by primary SOC and PT.

5.3.3.3 Serious Adverse Events

Summary of SAEs and TEAEs leading to treatment change:

- All treatment-emergent SAEs by primary SOC and PT.
- TEAEs leading to study drug permanently discontinued or dose adjusted/ dose temporarily discontinued, by primary SOC and PT, defined as those AEs with action taken of treatment 'study drug permanently discontinued' or 'dose adjusted/ temporarily discontinued'.
- TEAEs resulting in study discontinuation/ withdrawal from the study

Summary of Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of subjects who died by study period (on study, during treatment period, during follow-up period) and reason(s) for death.
- TEAEs leading to death (death as an outcome in the AE eCRF as reported by the investigator) by primary SOC and PT.
- Listing of deaths with details on demographics, treatment, and cause of death.

Data Listings will be provided for:

- All AEs
- SAEs
- TEAEs of special interest (all grades and per protocol)
- TEAEs leading to premature study drug discontinuation/interruption or study discontinuation
- Study-Drug-Related TEAEs

5.3.3.4 Physical Examination

Physical examination after baseline maybe abbreviated (including at a minimum: HEENT, heart, lungs, abdomen, extremities and examination of any body system where there are symptoms reported by the subject).

Post-baseline physical exams will be presented by listing.

5.3.3.5 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).

Summary statistics (including number, mean, SD, median, Q1, Q3, minimum, and maximum) for all ECG variables (actual values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time-point) by treatment arm and dose regimen. Only evaluable data will be used, and missing data will not be imputed.

The baseline value is defined as the last available measurement prior to the first dose of study drug accounting for date, and time (where available) which can be found in screening or unscheduled visits of the CRF.

Summaries of evaluation (normal; abnormal not clinically significant; abnormal clinically significant) will be provided by visit and treatment arm and dose regimen.

Categorical analysis of QT and QTcB/ QTcF interval data based on the number and percentage of subjects meeting or exceeding predefined limits in terms of absolute interval values or changes from baseline will be presented by treatment arm and dose regimen for baseline (as appropriate) and post-baseline values.

Parameter (Unit)	Criteria
QT (msec)	>=500
QTcB (msec)	450 <480
	480 <500
	≥500
	Change from baseline >60
	Change from baseline >30 and <60
QTcF (msec)	450 <480
	480 <500
	≥500
	Change from baseline >60
	Change from baseline >30 and <60

All ECG results will be listed on a by-subject basis. In addition, a listing of subjects meeting criteria above will be produced.

There will be an analysis visit window for the Day 15 ECG, of -2 to +3 days (Study Day 13 to 18; to be confirmed prior to database lock). In case several values are found in the visit window, the record collected on the day closest to the nominal day will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

5.3.3.6 Vital Signs and Oxygenation/ Respiratory parameters

A summary of vital signs (including heart rate, systolic and diastolic blood pressure and body temperature (recorded in °C) including change from baseline (where appropriate), presented by descriptive statistics (including SE for SBP and DBP), will be displayed for each day from baseline through Day 15, and at Day 29. Temperature summarization also includes measurement location. Only evaluable data will be used, and missing data will not be imputed.

The baseline value for temperature and Oxygenation/Respiratory parameters is defined as the last available measurement prior to the first dose of study drug accounting for date, and time (where available) which can be found in screening, baseline/Day 1 or unscheduled visits of the CRF. For systolic and diastolic blood pressure and heart rate baseline is considered to be Day 1 pre-dose around infusion (Study drug administration form in eCRF).

For dosing days, the scheduled time-points around dosing will be summarized. For dosing and non-dosing days with available twice daily assessments, the daily values for a subject used in group summaries are those reported from the assessment, either “before noon” or “between noon and midnight”, at which the SBP recorded is highest, i.e., worst value (see below).

Additionally, change from pre-dose within each dosing day for post-dose values will be summarized by treatment arm and dose regimen. Pre-dose and post-dose vital signs (systolic and diastolic blood pressure and heart rate) on study drug treatment days are in the Study drug administration eCRF; the values will

be presented in a combined listing with all other Vital Signs eCRF data (including additional measurements).

In addition, a line plot of mean (SE) and/or median, and change from baseline (SE), will be displayed for systolic and diastolic blood pressure (mmHg), by treatment arm and dose regimen and visit. Individual line plots by subject (including all measurements for all days) will also be plotted to assist with interpretation of any study drug elevations; will only be created for individual subjects with any instance of SBP $\geq$ 160 mmgHg, and/or when DBP $\geq$ 100 mmHg .

The percentage of subjects meeting the following blood pressure measurement criteria (and the individual components of) will be summarized by treatment arm and dose regimen, overall for study and by visit (in addition, by time-point on infusion days). For this analysis, as for change from baseline, for days with available twice daily assessments, the daily values for a subject used in group summaries are those reported from the assessment, either “before noon” or “between noon and midnight”, at which the SBP recorded is highest.

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

If any subject meets the DBP substantial increase which is not captured by the SBP highest time-point, he/she will be reported on a footnote.

All vital signs measures and details of these substantial changes, and the individual components of, will be listed.

For Respiratory parameters of SpO2 and PaO2, PaO2/FiO2, these will not be summarized due to collection under different oxygen support statuses.

Respiratory rate will be summarized on each day from baseline (Day 1) through Day 15, and at Day 29, with summarization split by (i) on room air or (ii) on oxygen supplementation (excluding if on mechanical ventilation). For days with available twice daily assessments, the daily value for a subject used in group summaries is to be that reported from the assessment, either “before noon” or “between noon and midnight”, at which the respiratory rate recorded is (i) on oxygen supplementation (excluding if on mechanical ventilation) > on room air, or (ii) if both time-points have the same oxygen support, the highest respiratory rate value.

The number and proportion of subjects in each oxygen supplementation category (room air (none), low flow O2, high flow O2, CPAP/BIPAP, mechanical ventilation, ECMO) for each day from baseline (Day 1) through Day 15, and at Day 29, will be summarized by treatment arm and dose regimen. In addition, stacked bar charts for oxygen supplementation (%) by day (baseline through Day 15, and at Day 29) will be produced.

For days with available twice daily assessments for oxygen supplementation, the daily value for a subject used in group summaries is to be that reported from the assessment, either “before noon” or “between noon and midnight”, for the most intensive support, where ECMO > mechanical ventilation > CPAP/BIPAP, high flow O2 > low flow O2 > room air (no oxygen support).

Once discharged and no longer in hospital, oxygen therapy status is determined based on the clinical status ordinal scale captured by daily phone call. Note: the clinical status recordings and imputation rules apply to these data interpreted from the ordinal scale score as specified in Section 4.2.1.

See 5.3.4.4 for duration of supplemental oxygen support.

Oxygenation/Respiratory parameters will be listed.

Analysis Visit Windows for Vital Signs and Oxygenation/ Respiratory parameters:
For days 15 and 29, analysis visit windows will be as below (to be confirmed prior to database lock):

Visit ID	Nominal Day	Lower Limit	Upper Limit
Day 15	15	13	18
Day 29	29	25	35

In case several values are found in the visit window, the record collected on the day closest to the nominal day will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

5.3.3.7 Laboratory Evaluation

Local laboratory assessments include haematology, blood chemistry and coagulation parameters.

The summary statistics (including number, mean, SD, median, Q1, Q3, minimum, and maximum) of all quantitative laboratory variables (laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline and each post-baseline time-point), by treatment arm and dose regimen.

The baseline value is defined as the last available measurement prior to the first dose of study drug accounting for date, and time (where available) which can be found in screening, baseline/Day 1 or unscheduled visits of the CRF.

The number (%) of subjects with abnormal results (out of normal range) for each of the laboratory variables will be summarized by treatment arm and dose regimen and visit.

Shift tables for baseline versus Days 3, 8, 15, and 29 will be presented for the chemistry and hematology laboratory parameters tabulated below (where ULN = upper limit of normal range), based on four categories as specified.

Panel	Lab Test Label	Criteria			
		Level 1	Level 2	Level 3	Level 4
Chemistry	Alanine aminotransferase (ALT) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
	Aspartate aminotransferase (AST) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
	Gamma-glutamyltransferase (GGT) increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
	Total bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Hematology	Anemia/ Hemoglobin decreased	<LLN - 100 g/L	<100 - 80 g/L	<80 g/L	-
	Platelet count decreased	<LLN - 75.0 x 10^9 /L	<75.0 - 50.0 x 10^9 /L	<50.0 - 25.0 x 10^9 /L	<25.0 x 10^9 /L
	White blood cells decreased	<LLN - 3.0 x 10^9 /L	<3.0 - 2.0 x 10^9 /L	<2.0 - 1.0 x 10^9 /L	<1.0 x 10^9 /L

Data will be listed by subject. A listing of subjects meeting Level 3 or Level 4 abnormality criteria above will also be produced.

In addition, a box-plot will be presented for every quantitative laboratory parameter by treatment arm and dose regimen and visit.

Evaluable data for each nominal visit will take into account analysis visit windows (shown below) and other than this, missing data will not be imputed.

Note that as a general consideration, analysis visit windows will be included for laboratory safety parameters as presented below (to be confirmed prior to database lock):

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline/ Day 1	1	-	1 (pre-dose)
Day 2	2	2	2
Day 3	3	3	3
Day 5	5	4	6
Day 8	8	7	9
Day 11	11	10	12
Day 15	15	13	18
Day 29	29	25	35

If multiple valid, non-missing measurements exist for post-baseline analysis windows spanning multiple days, the record collected on the day closest to the nominal day will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

5.3.4 Exploratory and Other Analyses

The exploratory analyses comprise:

- 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 SpO2 > 93% on room air) at Days 8, 15 and 29
- 28-day all cause-mortality

Other analyses comprise:

- SARS-CoV-2 viral load
- Biological and immunological markers of illness/inflammation
- Plasma pharmacokinetics of Brilacidin

These exploratory and other analyses will be performed in the ITT population.

5.3.4.1 Duration of hospitalization

Duration of hospitalization from randomization is defined as the time elapsed (in days) from randomization until hospital discharge, where hospital discharge will be considered as the first date of either hospital discharge or achieving a maintained (not descending) or improved (ascending) clinical status of 6 [which implies the subject is ready to be discharged; see section 4.2.1]. Duration of hospitalization will be calculated only for those subjects discharged from hospital alive on or prior to Day 29. If a subject is re-hospitalized for COVID-19 after initial discharge, i.e., has more than one period of time in hospital for COVID-19, the initial and subsequent durations in hospital will be summated as long as the subject is discharged from the re-hospitalization alive on or prior to Day 29. For those subjects not being discharged during the study period through to Day 29, the duration of hospitalization will be set to 28 days (maximum observation time, between Day 1 and Day 29).

The duration of hospitalization will be summarized by means of descriptive statistics by treatment group.

Additionally, comparisons for each Brilacidin group vs pooled placebo will be performed by means of the Wilcoxon rank sum test.

A subject listing for duration of hospitalization and time to discharge will be included, along with details for dates of admission/ discharge/ and re-admission/ re-discharge, etc., as appropriate. If date/time of hospital discharge are imputed (see section 4.2.1), the listing will display original entry in the eCRF and the imputed data, identifying which is imputed for endpoint calculation.

5.3.4.2 Time to discharge

Time to discharge from randomization is defined as the time elapsed (in days) until hospital discharge, where hospital discharge will be considered as the first date of either hospital discharge or achieving a maintained (not descending) or improved (ascending) clinical status of 6 [which implies the subject is ready to be discharged; see section 4.2.1]. Time to discharge will be calculated only for those subjects discharged from hospital alive on or prior to Day 29. If a subject has more than one period of time in hospital during the study, i.e., is re-hospitalized for COVID-19 after initial discharge, the time to the latest discharge time-point will be that used in summarization, as long as the subject is discharged from the re-hospitalization alive on or prior to Day 29. Subjects not being discharged will be censored at Day 29 (maximum observation time of 28 days).

A Kaplan-Meier analysis will be performed to assess the time to discharge by treatment group. The median time to event as well as the estimated percent of subjects without event during the study period will be estimated based on Kaplan-Meier method for each treatment group. Group comparisons will be done using the (stratified) log-rank test. Curves will also be presented.

A subject listing for duration of hospitalization and time to discharge will be included, along with details for dates of admission and discharge. If date/time of hospital discharge are imputed (see section 4.2.1), the listing will display original entry in the eCRF and the imputed data, identifying which is imputed for endpoint calculation.

5.3.4.3 Duration of supplemental oxygen support

Duration of supplemental oxygen support will be considered as described in section 4.2.3

The duration of supplemental oxygen support will be summarized by means of descriptive statistics and by treatment group.

A subject listing stating duration of any oxygen supplementation by type will be included.

5.3.4.4 Duration of invasive mechanical ventilation

Duration of invasive mechanical ventilation will be considered as described in section 4.2.3

The duration of mechanical ventilation will be summarized by means of descriptive statistics and by treatment group.

A subject listing stating duration of invasive mechanical ventilation will be included.

5.3.4.5 Duration of ECMO

Duration of ECMO will be considered as described in section 4.2.3

The duration of ECMO will be summarized by means of descriptive statistics and by treatment group.

A subject listing stating duration of ECMO will be included.

5.3.4.6 Proportion of subjects achieving No oxygen therapy (and/or peripheral oxygen saturation SpO2 > 93% on room air) at Days 8, 15 and 29

The proportion of subjects without oxygen therapy (and/or peripheral oxygen saturation SpO2 > 93% on room air [when hospitalized]) will be considered as described in section 4.2.3.

During hospitalization, oxygen therapy status is determined from oxygen supplementation data entry; “no oxygen therapy” in these instances is considered met when the subject is on room air and SpO2 > 93% (from Respiratory Status eCRF); if oxygen supplementation “room air” entry is missing, SpO2 value can be taken (and will be sufficient to achieve the endpoint), and if SpO2 value entry is missing, oxygen supplementation “room air” entry alone can be taken (and will be sufficient to achieve the endpoint). Once discharged and no longer in hospital, oxygen therapy status is determined based on the clinical status ordinal scale captured by daily phone call; “no oxygen therapy” is considered met for grade 8.

If there are multiple values on the same day, if either value meets the SpO2 criteria (measured on room air), the subject will be counted as having achieved the endpoint.

Analyses will be based on the LOCF approach meaning that the value for subjects lost-to-follow up or with score not assessed at Days 8, 15 and 29 will be the value in their last observation available.

This number and proportion of subjects will be reported by treatment group, for the study overall (through Day 29) and by time-point of assessment.

A subject listing by specified time-point, containing Oxygen therapy (Yes/No) and SpO2 if measured on room air, will be included.

5.3.4.7 28-day Mortality

28-day Mortality rate will be estimated by treatment group.

A Kaplan-Meier analysis will be performed to evaluate overall survival as defined in section 4.2.3. Subjects alive at the Day 29 study follow-up visit will be censored at that assessment; time to death will be censored at the last known date of being alive (through Day 29).

The median time to event as well as the estimated percent of subjects without event during study period will be estimated based on Kaplan-Meier method for each treatment group. Group comparisons will be done using the (stratified) log-rank test. Curves will also be presented. This endpoint will be listed.

5.3.4.8 Change from baseline in biomarkers.

Change from baseline of the biomarkers will be considered as described in section 4.2.3

The baseline value is defined as the last available measurement prior to the first dose of study drug accounting for date, and time (where available) which can be found in baseline/Day 1 or unscheduled visits of the CRF.

A summary of biomarker data including change from baseline will be presented by descriptive statistics, displayed by visit and treatment group.

Only subjects with available information for biomarkers at baseline will be included in the analyses.

Change from baseline to Days 2, 3, 5, 8, 11, 15 and 29 of the biomarkers in the Brilacidin treatment groups will be compared to pooled placebo using ANCOVA, including the log2-transformed baseline value as covariate and the stratification variables (country, categorized age group ($\leq$ 65 / > 65 years) and COVID-19 infection severity) as factors. In the event that any of the stratification variables does not achieve enough size for obtaining reliable estimations, that stratification variable will be not considered as a factor in the model. Least square mean difference between each the treatment arm versus placebo will be provided with 2-sided 90%CIs.

In addition, a box-plot showing the underlying distribution of change from baseline will be presented for each parameter by treatment group and visit.

Data will be listed by subject.

Evaluable data for each nominal visit will take into account analysis visit windows (shown below) and other than this, missing data will not be imputed.

Note that as a general consideration, analysis windows will be included for pro-inflammatory biomarkers (IL-1β, IL-6, IL-10, total IL-18, TNF-α) and SARS-CoV-2 viral load parameters as presented below (to be confirmed prior to database lock):

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline/ Day 1	1	-	1 (pre-dose)
Day 3	3	2	3
Day 5	5	4	6
Day 8	8	7	9
Day 11	11	10	12
Day 15	15	13	18
Day 29[a]	29	25	35

a Applicable to SARS-CoV-2 viral load parameters only

If multiple valid, non-missing measurements exist for post-baseline analysis windows spanning multiple days, the record collected on the day closest to the nominal day will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

Serum CRP levels will also be analyzed on a log-scale fitting a repeated measures mixed model including treatment group, day (through Day 15), the three stratification factors and log2 transformed baseline CRP as a covariate. In the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, that stratification factor will be not considered in the model. Interactions between day and each of the terms in the model will also be included. The back-transformed ratios of Brilacidin in addition to SoC vs SoC alone will be reported with 90% CIs. In addition, IL-6 will be analyzed in the same manner.

5.3.4.9 Change from baseline in SARS-CoV-2 viral load.

Quantitative data per sample are: threshold value (Ct), copy/mL and log10 copy/mL; qualitative data per sample are: positive/ negative (for SARS-CoV-2)

Change from baseline of the SARS-CoV-2 viral load (copy/mL) will be considered as described in section 4.2.3

The baseline value is defined as the last available measurement prior to the first dose of study drug accounting for date, and time (where available) which can be found in baseline/Day 1 or unscheduled visits of the CRF.

Summary statistics of quantitative data (values and changes from baseline) will be calculated for each visit, by treatment group.

Change from baseline to Days 3, 5, 8, 11, 15 and 29 of the SARS-CoV-2 viral load in the Brilacidin treatment groups will be compared to pooled placebo using ANCOVA, including the baseline value (log10-transformed) as covariate and the stratification variables (country, categorized age group (≤ 65 / > 65 years) and COVID-19 infection severity) as factors. In the event that any of the stratification factors does not achieve enough size for obtaining reliable estimations, that stratification factor will be not considered in the model. Least square mean difference between each treatment group versus pooled placebo will be provided with 2-sided 90%CIs.

Only subjects with available information for SARS-CoV-2 viral load at baseline will be included in the analyses.

Data will be summarized by swab type: nasopharyngeal (requested by protocol) or oropharyngeal.

Qualitative viral load data will also be summarized. Number and percent of subjects with a positive or negative SARS-CoV-2 PCR test on Days 3, 5, 8, 11, 15 and 29 will be tabulated. Time to viral clearance, i.e., time to negative SARS-CoV-2 PCR test, will be determined with Kaplan-Meier analysis where subjects will be considered to have achieved the event the first day for which the SARS-CoV-2 PCR test result is negative. If subjects are lost to follow-up (for this endpoint) prior to achieving negative SARS-CoV-2 or die prior to Day 29, their time to viral clearance will be censored at their last test measurement day.

In addition, a box-plot showing the underlying distribution of change from baseline will be presented by treatment group and visit.

Data will be listed by subject.

Evaluable data for each nominal visit will take into account analysis visit windows (as shown in Section 5.3.4.8) and other than this, missing data will not be imputed.

5.3.4.10 Plasma pharmacokinetics of Brilacidin

This document does not address the specific analysis of PK data collected in this study. These analyses will be discussed in a separate analysis plan to support the population PK report.

5.3.5 Interim Analyses

An initial safety review occurred after approximately 20 randomized subjects had completed up to Day 15. This initial interim analysis focused on review of cardiovascular safety, vital signs and adverse events that occurred in the approximately 20 subjects to receive Days 1-3 of study treatment. A further safety review by the DMC also occurred, as planned, after approximately 50% of subjects had completed up to Day 29. The DMC recommended expanding dosing to Days 4 and 5 (at the same doses as on Days 2 and 3), after the initial safety review. The DMC was 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.

Study stopping rules for placing the enrollment on hold were defined in the protocol. In addition, recommendation guidelines and further details of the DMC were prepared separately from this plan in a DMC Charter.

Other interim analyses were allowed for as potential to 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.

5.3.6 Sensitivity Analyses

Pre-specified sensitivity analyses are limited in this analysis plan. Current proposals for inclusion as sensitivity analyses are included below. These details will be reviewed and determined prior to database lock.

An initial sensitivity analysis will be conducted with the specified study analyses, to evaluate the assumption that there is no difference between the placebo 5-dose regimen and the placebo 3-dose regimen. The primary efficacy endpoint and selected other endpoints (i.e., composite endpoint by Day 29, defined as Death OR Respiratory failure; achieving at least one-point/ two-point improvement in clinical status at Days 8, 15 and 29; duration of hospitalization; time to discharge; 28-day mortality; change from baseline in CRP; change from baseline in SARS-CoV-2 viral load) will be summarized for the two placebo regimens.

Also, if Brilacidin 5-dose or 3-dose regimen suggests efficacy > pooled placebo, pooled Brilacidin will be compared to pooled placebo for the primary efficacy endpoint. Summaries will also be presented.

For the secondary endpoint measuring the evolution of the clinical status using ordinal scale on days 3, 5, 8, 11, 15 and 29, the stratified non-parametric van Elteren test, using modified ridit scores which is as a direct extension of the Wilcoxon's rank-sum test for 2-samples, will be calculated as a sensitivity analysis to compare the scale as an ordinal rather than a binary outcome, without assuming proportional odds.

The SAS proc freq with modified ridit scores will be used to obtain the Van Elteren test as follow:

```
proc freq data=<sas-data-set>;
ods select cmh;
table <time>*<treatment group>*<change_againts_baseline>/cmh2
scores=modridit;
run;
```

The analyses of efficacy endpoint(s) will also be performed using the PP population. These analyses will be considered as supportive as a kind of sensitivity analyses. Pre-specified analyses using the PP population includes the primary endpoint only.

5.3.7 Study Estimand and Handling of Missing Data

As per the ICH E9(R1) (Addendum on estimands and sensitivity analysis in clinical trials EMA/CHMP/ICH/436221/2017), the plan for the assessment of the Primary endpoint (PEP) is described here after using the 4 attributes of the estimand:

1. **Population**: In essence, hospitalized adult (≥18 years old) patients with moderate or severe COVID-19, SARSCoV-2 infection confirmed by positive standard PCR test (or equivalent) within 4 days prior to starting study treatment, and hospitalized with respiratory distress but not yet requiring high-level respiratory support. A detailed description is given in section 2.3.2 of this SAP.

   Primary endpoint: The PEP is defined as time to sustained recovery (from COVID-19 infection) through Day 29, which is the time (in days) from randomization to the day of recovery without subsequent relapse. Day of recovery is defined as the first day on which the subject satisfies one of the categories 6, 7 or 8 on the following 8-point ordinal scale for clinical status with response sustained through Day 29:

(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

If response after initial recovery is not sustained, and the subject experiences relapse, the initial recovery is not counted as such, Any subsequent recovery, sustained through Day 29, will be recognized and counted. See sections 4.2.1 and 0 for details.

2. **Intercurrent events**: In principle, the rates of intercurrent events and missing data are estimated to be very low due to the type of endpoint, easily available with a fast-clinical assessment, and the early time-point of assessment. Thus, no impact is expected in the primary analysis. However, we describe hereafter the relevant intercurrent events expected to occur in this study and the methods for handling them:

    a. No treatment initiation with the IP: Not applicable since efficacy population requires treatment for analysing data.

    b. Treatment discontinuation: "Treatment Policy" strategy, i.e., the efficacy observed assessment will be used regardless of this intercurrent event.

    c. Death before the time of assessment: it will be handled as the "Composite" strategy, i.e., the PEP will be considered as censored at Day 29.

    d. Other reasons for not assessing the PEP:

        - Reasons likely related to the treatment (i.e. due to efficacy or safety issues) or to a bad clinical evolution: they will be handled as in 2.c. using the "Composite" strategy.

- Non treatment-related reasons. In principle no cases are expected, and the "Hypothetical" strategy will be used.

e. Any additional medication or any other potential reason for study discontinuation: "Treatment Policy" strategy, i.e., the efficacy observed assessment will be used regardless of this intercurrent event.

3. **Population-level summary**: Estimation of the p-value from the stratified log-rank test comparing groups (Brilacidin 5-dose regimen vs pooled placebo as main comparison and Brilacidin 3-dose regimen vs pooled placebo as secondary) and the hazard ratio (HR) for the PEP will be used as the population-level summary. The Cox model adjusted by the randomisation strata variables will be used for the inferential analysis (p-value, HR and 90% Confidence Intervals).

The following sensitivity analyses are proposed:

- For the PEP: Perform analyses using the PP population.
- For the PEP:

  Summarize pooled placebo and pooled Brilacidin and compare pooled placebo vs pooled Brilacidin; if Brilacidin 5-dose or Brilacidin 3-dose suggests efficacy against pooled placebo.

- For the PEP and selected endpoints:

  Summarize descriptively placebo 5-dose regimen and the placebo 3-dose regimen; to evaluate assumption of no differences between them;
  Composite endpoint by Day 29, defined as Death OR Respiratory failure; achieving at least one-point/ two-point improvement in clinical status at Days 8, 15 and 29; duration of hospitalization; time to discharge; 28-day mortality; change from baseline in CRP; change from baseline in SARS-CoV-2 viral load

- For the evolution of the clinical status using ordinal scale, comparison as ordinal rather than binary by means of a stratified non-parametric test

The handling of missing data will follow the principles specified in the ICH-E9 guideline.

Missing data for efficacy and exploratory endpoints are described in section 5.3 for statistical analyses. In general, missing baseline data will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data at baseline will be summarized for each treatment group using counts (n) and percentages (%). The denominator will be the analysis population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data: The analyses and summaries for variables with continuous scales will be based on observed data only.

Missing data commonly encountered during the study may comprise:

- Missing/Partial Dates: For incomplete days or months, an imputation will be done by assigning the first day of month or the first month of year, respectively. For incomplete years in dates after randomization, the year of randomization will be assigned.
- Categorical endpoints measured “at” or “by” pre-defined days: In general, analyses will be based on the LOCF approach. Details for each specific endpoint are described in their corresponding subsections of 5.3 section for statistical analyses.
- Continuous variables: mixed models are robust to the presence of missing at random and conducts the analysis with all participants despite the presence of missingness. Of note, this method calculates the estimations based on the variance-covariance structure but without any formal imputations.

Missing data commonly encountered for safety and baseline variables may comprise:

- Missing/Partial Dates for AEs or Concomitant Medications:

  Missing or partial AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

  No imputation for medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

- Handling of Missing Assessment of Relationship of AEs to IP

  If the assessment of the relationship to IP is missing, then the relationship to IP in the frequency tables is considered as possibly related, but no imputation should be done at the data level.

- Handling of Missing Severity of AEs

If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

5.3.8 Subgroup Analyses

Subgroup analyses will be performed to assess the impact on efficacy of certain factors.

The primary efficacy endpoint will be evaluated with respect to the following subgroups:

- COVID-19 infection severity at baseline, Moderate vs Severe
- Age, ≤65years vs >65years

5.3.9 Reporting Conventions

The descriptive statistics will be reported to 2 decimal places, except for 1) those parameters with low measurements such as biomarkers or others, that will be reported to 3 or 4 decimal places, as appropriate; 2) those parameters not requiring decimal places, that will be reported without any decimal place. Estimated parameters, such as regression coefficients will be reported to 3 decimal places. Percentages should be rounded to a single decimal place. P-values ≥0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as “<0.0001”. Vital Signs, oxygenation, laboratory and biomarker parameters will be reported in International Units.

5.3.10 Study Timelines

Date first subject enrolled: 22-Feb-2021
Date last subject enrolled: 02-Jun-2021
The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study and database close.

5.3.11 Technical Details

The most updated study protocol has been used as a reference for this document. SAS programs, SAS Logs and SAS outputs generated during the creation of the Statistical Report will be archived in the [redacted] File System.

5.3.12 Software

The statistical analysis will be performed using the scientific software SAS® V9.4 or later releases and SAS® Enterprise Guide V7.15 or later releases.

6. REFERENCES

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