Molecular Partners AG

Ensovibep/MP0420

MP0420-CP302 (CSKO136A12201J) / NCT04828161

A randomized, double-blind, placebo-controlled, multicenter study of ensovibep (MP0420) in ambulatory adult patients with symptomatic COVID-19

The "EMPATHY" Trial

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
28-Apr-2021	Prior to Part A FPFV	Creation of first version	N/A - First version	NA
3-Nov-2021	Prior to Part A primary analysis database lock	Creation of Amendment 1	Changes according to protocol Amendment 1 implemented.	All Sections
			Alignment of description of Part A primary analysis and Part A final analysis with protocol.	Section 1
			Removed sentence that only listings explicitly specified in SAP will be done. Adjusted respective sections for mandatory listings. Other listings may only be specified in TFL-Shells. Added clarification how discontinuation visits and visit mapping for questionnaire data will be handled.	Section 2.1
			Added subgroups of interest: Age, gender, risk for disease progression according to updated FDA definition and severity of COVID-19, adjusted categories for mutations. Removed subset of ADAs as ADAs are not available for Placebo patients.	Section 2.2.1
			Criteria leading to discontinuation from analysis sets will only be listed.	Section 2.3.1
			Regions adjusted according to recruiting countries. Baseline BMI categories adjusted to reflect latest FDA guidance for COVID-19 risk for disease progression. Adjusted categories for mutations.	Section 2.3.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Removed body temperature as already covered by baseline vital signs.	
			Added analyses of prior COVID-19 vaccinations. Split analyses of concomitant COVID-19 related medications to those initiated prior to start of study drug infusion, and those initiated after start of study drug infusion.	Section 2.4.2
			Added handling of viral load measurements below the lower limit of quantification, including corresponding supplemental analysis. Added handling of viral load data above the upper limit of quantification.	Section 2.5
			Present event-rates instead of event-free rates. SF 36 version 1 used.	Section 2.7 and Section 4.2
			Secondary endpoint for part A: Hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29: Removed time to event analyses and present proportions and relative risk only as only very few events are expected for Part A.	Section 2.7
			Deaths will be summarized by SOC and PT. AEs possibly related and related to study drug will be summarized together as both will be considered to be study drug related. Added clarifications on AESIs and safety topics of interest. [redacted]	Section 2.8
			Added new definition of "High risk"	Section 5.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Definition of severity of COVID-19 changed to consider moderate and severe separately. Added oxygen saturation <=93% to notable criteria of vital signs.	Section 5.3
			Changes to protocol removed, as implemented in protocol amendment.	Section 4
			Added clarifications on Part A primary analyses and availability of data.	Section 2.14
			Minor changes, corrections and modifications.	All
7-Dec-2021	Prior to Part A primary analysis database lock	Creation of Amendment 2	Simplified derivation of target dose to make it easier to interpret and avoiding bias towards a lower dose. Target doses will be derived based on the estimated dose-response curve (median of bootstrap estimates) for the effects of delta=0.36 and delta=0.68 which were also considered in the sample size calculation.	Section 2.5.2
			[redacted]	[redacted]
			Questions of COVID-19 symptom questionnaire regarding return to usual health and activities will be presented for post-baseline visits only, no shift from baseline as these questions are only answered post-baseline. Added descriptive analysis of COVID-19 symptom score	Section 2.7.2.2
			Minor changes, corrections and modifications.	All

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List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
DBL	Database Lock
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Sheet
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Patient First Visit
IA	Interim Analyses
IDMC	Independent Data Monitoring Committee
IRR	Infusion-related Reactions
ITT	Intention-to-treat
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PCS	Physical Component Summary
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
PRO	Patient-Reported Outcomes
PT	Preferred Term
RAN	Randomized Set
RT-PCR	Real Time Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCR	Screened Set
SF-36	Short Form 36 Health Survey Questionnaire
SMQ	Standard MedDRA Query
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-emergent Adverse Event

1 Introduction

This document presents the detailed statistical analysis plan (SAP) for Study MP0420-CP302 (CSKO136A12201J), "A randomized, double-blind, placebo-controlled, multicenter study of ensovibep (MP0420) in ambulatory adult patients with symptomatic COVID-19."

Following the operationally seamless design, analysis of Part A and Part B will be handled separately (e.g., primary, secondary, and exploratory analyses in Part A will be performed only on Part A patients and primary, secondary, and exploratory analyses in Part B will be performed only on Part B patients).

This SAP will include the details for the clinical study report (CSR) analysis of Part A and Part B. In this version, the full details for the CSR analysis of Part A is provided. An outline of the protocol-specified CSR analysis of Part B is provided in the SAP. Further details will be provided in a SAP amendment prior to first patient first visit (FPFV) of Part B.

The analysis for Part A is performed in two parts:

- **Part A primary analysis:** performed when all patients enrolled completed Day 29 or discontinued prematurely and have viral load data up to Day 8; the analysis will include available data on the day of cutoff. Further details are provided in Section 2.14.
- **Part A final** analysis: performed when all patients completed the study at the final database lock (DBL); the analyses of the primary endpoint and secondary efficacy endpoints will not be repeated.

The analyses will result in one clinical study report (CSR) for each Part A and Part B.

Regular safety IDMC analyses will be performed, detailed information regarding IDMC analysis will be provided in the IDMC charter and a separate IDMC SAP.

The SAP is based on the following documents:

- Clinical Trial Protocol version 01 (Global Amendment 1)
- Electronic case report form (eCRF)
- Electronic case retrieval form (eCRS)

1.1 Study design

This is a randomized, double-blind, placebo-controlled, multicenter study of ensovibep (MP0420) in ambulatory patients with symptomatic COVID-19. The study has two parts: A Phase 2 dose-ranging study to select the best dose over the therapeutic range (Part A) and a confirmatory Phase 3 safety and efficacy study of the dose determined in Part A (Part B).

Screening will be used to determine eligibility. Randomization and treatment will be conducted on Day 1 (screening can optionally be done up to 3 days earlier, or also at Day 1) and with a study duration for individual patients of 91 ± 7 days for both Parts.

Part A

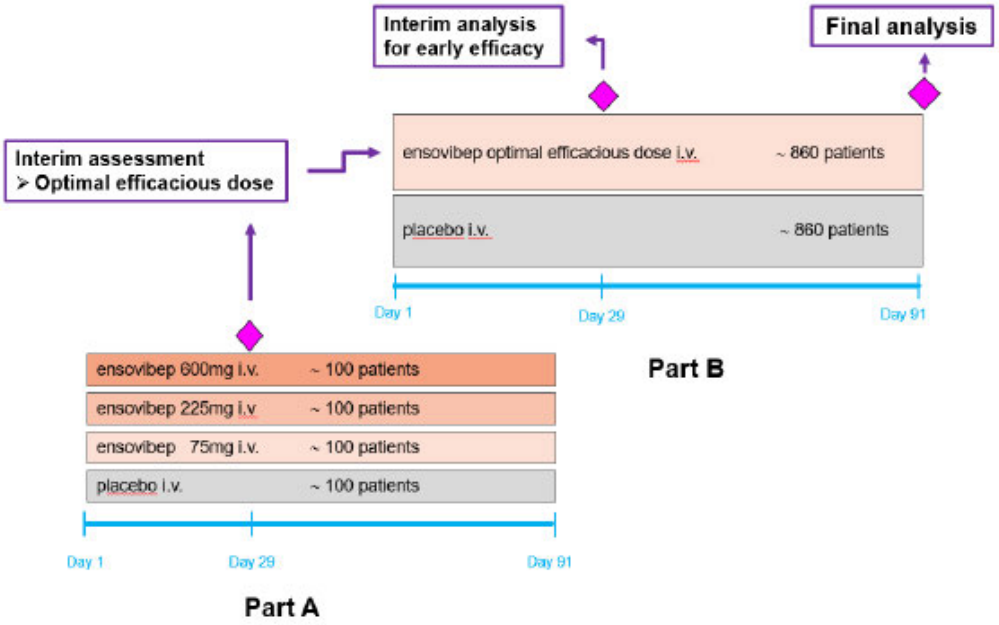
This dose-ranging part of the study will include approximately 400 randomized patients in four arms (3 active arms and one placebo arm), randomized 1:1:1:1 (see also Figure 1-1) to receive ensovibep (75 mg, 225 mg, or 600 mg) or placebo, administered as a single i.v. infusion over

60 minutes, and stratified by risk for COVID-19 disease progression ("high-risk", "not at high-risk")..

Part B

Recruitment will begin in Part B once the best safe and efficacious dose has been selected from Part A based on Day 29 data analysis. Part B will include at least 1717 patients randomized 1:1 (see also Figure 1-1) to either the selected dose of ensovibep or placebo, administered as i.v. infusion over 60 minutes. An interim analysis for early efficacy will be conducted when approximately 50% of patients have completed the Day 29 assessments. Patients will be stratified by risk for COVID-19 disease progression ("high-risk patients" versus "not at high-risk patients").

Figure 1-1 Study design



1.2 Study objectives and endpoints

The study objectives and endpoints for the primary CSR can be found in Table 1.2-1.

Table 1.2-1 Objectives and related endpoints

Part A	
Primary Objective	**Endpoint for primary objective**
• To demonstrate superiority of ensovibep, compared to placebo, in reducing time-weighted change from baseline in log_{10} SARS-CoV-2 viral load through Day 8	• Time-weighted change from baseline (measured at Day 3, Day 5, and Day 8) in log_{10} SARS-CoV-2 viral load in nasopharyngeal swabs through Day 8
Secondary Objectives	**Endpoints for secondary objectives**

• To assess the effect of ensovibep, compared to placebo, in reducing the occurrence of hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29	• Proportion of patients experiencing hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29
• To assess the effect of ensovibep, compared to placebo, in reducing COVID-19 symptoms up to Day 29	• Time to sustained clinical recovery, defined as (a) all symptoms from the modified FDA COVID-19 symptom list scored as moderate or severe at baseline are subsequently scored as mild or absent, AND (b) all symptoms from the modified FDA COVID-19 symptom list scored as mild or absent at baseline are subsequently scored as absent, with no subsequent worsening up to Day 29
• To evaluate safety and tolerability of ensovibep	• Proportion of patients up to end of study with: o Treatment Emergent Adverse events (TEAEs) o Serious adverse events (SAEs), including death from any cause o AEs of Special Interest (AESIs), • Vital signs • Clinical laboratory measurements
• To characterize the pharmacokinetics (PK) of ensovibep	• Free and total ensovibep concentration in serum and calculated PK parameters
Exploratory Objectives	**Endpoints for exploratory objectives**
[redacted]	

[redacted]

Part B

Primary Objective	Endpoint for primary objective
• To demonstrate superiority of ensovibep, compared to placebo, in reducing the occurrence of hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29	• Proportion of patients experiencing hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29

Secondary Objectives	Endpoints for secondary objectives
• To assess the effect of ensovibep, compared to placebo, in reducing SARS-CoV-2 viral load through Day 8	• Time-weighted change from baseline (measured at Day 3, Day 5, and Day 8) in $\log_{10}$ SARS-CoV-2 viral load in nasopharyngeal swabs through Day 8
• To assess the effect of ensovibep, compared to placebo, in reducing COVID-19 symptoms up to Day 29	• Time to sustained clinical recovery, defined as (a) all symptoms from the modified FDA COVID-19 symptom list scored as moderate or severe at baseline are subsequently scored as mild or absent, AND (b) all symptoms from the modified FDA COVID-19 symptom list scored as mild or absent at baseline are subsequently scored as absent, with no subsequent worsening up to Day 29
• To evaluate the immunogenicity of ensovibep during the study	• Proportion of patients exhibiting treatment-emergent ADAs (TE-ADA) over time
• To evaluate safety and tolerability of ensovibep	• Proportion of patients up to end of study with: o Treatment Emergent Adverse events (TEAEs) o Serious adverse events (SAEs), including deaths from any cause o AEs of Special Interest (AESIs) • Vital signs • Clinical laboratory measurements

Exploratory Objectives	Endpoints for exploratory objectives

[redacted]

- To evaluate the effect of ensovibep, compared to placebo, on general health status
- Absolute MCS and PCS scores from Short Form Health Survey (SF-36) questionnaire over time

[redacted]

2 Statistical methods

2.1 Data analysis general information

All CSR analyses of Part A and B will be performed by DATAMAP GmbH. The most recent version of SAS and R available in the statistical programming environment of DATAMAP will be used for the analysis.

The following general data conventions will apply:

- For the Part A primary analysis, performed when all patients completed Day 29 or visit or discontinued prematurely and have viral load data up to Day 8. For the analysis a cut-off date will be applied. All available data up to the cut-off date will be included in the analysis. The cut-off date is defined as the date when the last patient completed Day 29 visit or discontinued prematurely.
- The Part A final analysis will be performed when all patients completed the study at the final database lock (DBL). All data will be included in the analysis.
- Categorical data will be presented as frequencies and percentages for each category including a category labeled as "missing" when appropriate.
- Continuous variables will be presented with number of non-missing observations, mean, standard deviation, lower quartile (25^{th} percentile), median, upper quartile (75^{th} percentile), minimum, maximum.
- Unless otherwise specified, 95% confidence limits will be presented.

2.1.1 General definitions

2.1.1.1 Study treatment

Table 2.1-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Ensovibep 15 mg/mL for Part A	Solution for infusion	i.v.	Non-blinded vials	Sponsor (global)
Placebo for Part A	Solution for infusion	i.v.	Saline infusion bag	Sponsor (global)
Ensovibep 15 mg/mL for Part B	Solution for infusion	i.v.	Double-blind vials	Sponsor (global)
Placebo for Part B	Solution for infusion	i.v.	Double-blind vials	Sponsor (global)

The investigational drug is ensovibep.

The formulation for Part A is 15 mg/mL ensovibep provided in isotonic buffer matrix [redacted]

The formulation for Part B is 15 mg/mL ensovibep provided in isotonic buffer matrix [redacted]

Isotonic saline will be used as placebo for Part A of the study. [redacted]

The terms study treatment and study drug are used throughout the document and refer to the infusion of double-blind treatment, i.e. Ensovibep/Placebo.

2.1.1.2 Treatment arms

Part A

Patients in Part A will be assigned on Day 1 at Visit 1 to one of the following four treatment arms in a ratio of 1:1:1:1 and will be dosed accordingly:

- Ensovibep 75 mg
- Ensovibep 225 mg
- Ensovibep 600 mg
- Placebo

Part B

Once the best safe and efficacious dose has been selected from Part A, patients in Part B will be assigned on Day 1 at Visit 1 to one of the following 2 treatment arms in a ratio of 1:1

- Ensovibep (best safe and efficacious dose, selected in Part A)
- Placebo

2.1.1.3 Study days

Study Day 1 (or Day 1 or reference start date) is defined as the day of first dose of study treatment.

All other study days are labeled as the number of days relative to Day 1. Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the date of first administration of study treatment:
  Study day = Assessment date – date of study drug infusion + 1
- for dates prior to the date of first administration of study treatment:
  Study day = Assessment date – date of study drug infusion

Moreover, duration of an event is calculated as:

Duration of an event = Event end date – event start date + 1.

2.1.1.4 Baseline

The baseline value is generally defined as the last non-missing value prior to the start of study drug infusion. If the date of assessment is the same as date of infusion but time is not available for comparison, the assessment is assumed to be prior to the administration of study treatment.

2.1.1.5 Post-baseline measurement

Post-baseline measurements are defined as assessments performed after start of study drug infusion.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value.

2.1.1.6 Visits

Measurements will be collected with the windowing defined in the protocol and outlined in Table 2.1-2.

Table 2.1-2 Visit windows

Visit label	Visit collection window (study days)
Screening	-3 to -1
Day 1	1
Day 3	3
Day 5	5
Day 8	8 ± 2
Day 15	15 ± 3
Day 22	22 ± 4
Day 29	29 ± 5
Day 61	61 ± 5

EOS (Day 91)	91 ± 7

Visit labels as reported in the eCRF will be used for analysis. Discontinuation visits will be mapped to the next scheduled visit, if within modified protocol defined visit window, otherwise these will be handled as unscheduled visits. For the mapping the following modification will be applied to the protocol defined windows to avoid overlapping days: Day 22 (22 ± 3) and Day 29 (29 -3/+ 5) and Day 61 (± 7).

For ePRO data visits is not captured on the eCRF, visits will be assigned using ePRO assessment dates based on the modified protocol defined window.

Efficacy outputs will not include unscheduled visits. For laboratory and safety outputs, unscheduled visit information will be used in the summaries of the worst post-baseline measurement. Further details will be found in the respective Sections.

2.1.1.7 On-treatment/Treatment-emergent

If not stated otherwise, all post-baseline measurements will be considered as on-treatment/treatment emergent and included in the analyses.

A treatment-emergent adverse event (TEAE) is defined as any AE that started after the start of study drug infusion. If the AE start date is the same as date of infusion but time is not available for comparison, the AE will be considered to be treatment emergent.

2.1.1.8 Last contact date

Last contact date is defined as the date the patients completes the study or discontinues prematurely. If a patient discontinues the study due to "lost to follow up" the latest date out of assessment dates and event/medication start and end dates will be used as last contact date.

For patients ongoing at time of primary analyses, the cut-off date will be used as last contact date.

2.1.1.9 Stratification factor

Randomization is stratified by risk for COVID-19 disease progression (“high-risk patients” versus “not at high-risk patients”).

According to the inclusion criteria for the USA only patients "not at high-risk" will be included in the trial, however in case of protocol deviators US patients could technically be randomized to the high-risk stratum

The stratification of “high-risk” and “not at high-risk” for COVID-19 disease progression will be programmed based on eCRF data for the analysis.

A comparison between COVID-19 disease progression strata recorded in the IRT data, and programmed risk for COVID-19 disease progression (from data reported on the eCRF) will be performed.

Details on stratification definition are included in Section 5.2.

2.1.1.10 Blinding

Site firewalls to prevent unblinding and fully dedicated unblinded clinical teams managing the study will be assigned to ensure that the unblinded treatment assignment, the unblinded IRT outputs, the unblinded treatment administration and handling are overseen in such a way as to ensure patient safety and protocol adherence without risking unblinding the site study staff and the clinical teams. Refer to Pharmacy Manual for IP handling.

This is a patient, investigator, and sponsor-blinded study. Patients, investigators, and the sponsor will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single patient at site for safety reasons (necessary for patient management) will occur via an emergency system in place at the site.

Drug product will be supplied in bulk only for the 3 treatment arms in Part A, therefore an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. Patient treatment allocation can be obtained by the unblinded pharmacist through the IWR system. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

There will be fully blinded drug vials for both the active treatment arm and the placebo arm, in Part B of the trial, so unblinded site and clinical staff would not be needed for Part B.

Sponsor staff or staff engaged to manage the study

The following unblinded sponsor staff or staff (such as CRO) engaged to manage and run the study is required for this study during Part A:

- Unblinded drug accountability monitors
- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analyst(s) (PK, ADA)

In Part A, unblinded drug accountability monitors are required to review drug accountability, preparation, and allocation remotely. The unblinded monitors will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual patients. These unblinded monitors will also have access to the treatment allocation of the patients through the IWR system.

The following unblinded staff will be applicable to both Part A and Part B:

The external independent data review committee (IDMC) assessing unblinded results and the independent analysis team (independent statistician, independent programmer) will be allowed

to access treatment information for the purpose of creating, reviewing, and assessing unblinded interim results. More details will be provided in an IDMC charter.

An independent pharmacometrician and an independent pharmacokineticist may be unblinded prior to the database lock after all patients complete Day 29 in Part A in order to explore PK. The pharmacometrician and the pharmacokinetisist will work independently and will only disclose results once the database is locked after all patients complete Day 29 in Part A at the time of the Part A primary analysis.

Unblinding after the primary analysis database lock in Part A

After the database lock for the primary analysis in Part A, an unblinded study team will perform the analysis and undertake submission related activities. Treatment assignment will continue to remain blinded to all investigators, site personnel, patients and other study team members until all patients have completed the entire study participation and the final database lock for Part A has occurred.

All unblinded staff will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until final clinical database lock. Primary analysis results and reports generated prior to the final database lock that would reveal subject-level data will be kept in a secure and restricted area until the end of the study. The detailed procedures for maintaining data integrity after primary analysis database lock will be described in a charter.

Following final database lock all staff may be considered unblinded.

Health authorities will be granted access to unblinded data if needed.

2.2 Analysis sets

The analysis sets are defined as follows:

- **Screened set (SCR):** all unique patients who signed the informed consent (e.g. only the chronologically last screening data is counted in the case of re-screened patients)
- **Randomized set (RAN):** all patients who received a randomization number, regardless of receiving study treatment
- **Full analysis set (FAS):** all patients in the RAN that initiated i.v. infusion of study treatment during the treatment period excluding mis-randomized patients, where mis-randomized patients are defined as cases where IRT contacts were made by the Investigator/qualified site staff either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and treatment was not administered to the patient. Following the intention to-treat (ITT) principle, patients will be analyzed according to the randomized treatment arm.
- **Safety set (SS):** all patients who initiated i.v. infusion of study treatment whether being randomized or not. Patients will be analyzed according to the actual dose received. If the actual dose received is not a study dose level, the analyzed dose level will be the next lowest active dose arm.

- **PK analysis set:** all patients with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study treatment and with no protocol deviations that impact PK data

Unless otherwise specified, all efficacy analysis will be performed on the FAS and safety analyses will be performed on the SS.

2.2.1 Subgroup of interest

The following subgroups will be used for the primary variable:

- Subgroups:
  - Risk for COVID-19 disease progression ("high-risk", "not at high-risk") – as per protocol
  - Risk for COVID-19 disease progression ("high-risk", "not at high-risk") - as per FDA updated definition on May 19, 2021
  - Geographical region (North America, Europe, Africa, Asia)
  - Gender (Male, Female)
  - Age (<55 years, 55-<65 and ≥65 years)
  - Mutation type (Wild type; Alpha B.1.1.7; Beta B.1.351; Gamma P.1; Delta B.1.617.2; Lambda C.37; Other)*, if available
  - Baseline $\log_{10}$ SARS-CoV-2 viral load ($\log_{10}$ SARS-CoV-2 viral load < 6, $\log_{10}$ SARS-CoV-2 viral load ≥ 6)
  - SARS-CoV-2 antibodies at baseline (No, Yes)
  - Baseline severity of COVID-19 (mild, moderate)

* List of mutation types may be updated if new variants of concern are detected during the study.

Mutation type data will only be partially available at the time of part A primary analysis, therefore this subgroup will be analyzed at the time of final lock i.e., day 91 analyses only.

Subgroups may need to be combined if there is not a sufficient number of patients (e.g. at least 10%) in a respective subgroup. Regions will only be combined if models fail to converge, whether or not having less than 10%.

For tables presenting results from statistical models, the treatment effects in the subgroup will be derived using an additional covariate as a fixed effect and the appropriate interaction terms in the model, if necessary.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of patients in each analysis set will be presented overall for the SCR and by treatment group for the RAN.

The number of patients in the FAS will be summarized by region, country, center and treatment group.

The number and percentage of patients in the SCR who were randomized or discontinued study prior to randomization, including the reason for discontinuation will be presented overall.

The number and percentage of patients in the RAN who completed or discontinued study, including the reason for discontinuation will be presented overall and by treatment group.

The frequency (%) of patients with CSR reportable protocol deviations will be presented for the RAN. Other criteria leading to exclusion from analysis sets will be listed.

These summaries will be produced independently for Part A and Part B.

2.3.2 Background and demographic characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm for the FAS and SS (if different from the FAS).

Demographics listed below will be summarized:

- Age (years)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple, Unknown, Not reported)
- Ethnicity (Hispanic, Non-hispanic)
- Age group (<25 years, 25-<45 years, 45-<65 and ≥65 years)
- Geographical region (North America, Europe, Africa, Asia)

The following baseline characteristics will be summarized:

- Body weight (kg)
- BMI (kg/m^2), calculated as weight in kg divided by (height in m)²
- BMI group (<18.5 kg/m^2, 18.5-<25 kg/m^2, 25-<35 kg/m^2, >= 35 kg/m^2)
- Risk for COVID-19 disease progression (“high-risk”, “not at high-risk”) – as per protocol
- Risk for COVID-19 disease progression (“high-risk”, “not at high-risk”) – as per FDA updated definition on May 19, 2021
- Chronic kidney disease (No, Yes)
- Diabetes mellitus (No, Yes)
- Immunosuppressive disease (No, Yes)
- Currently receiving immunosuppressive treatment (No, Yes)
- >= 65 years of age (No, Yes)
- >= 55 years of age and cardiovascular disease, or hypertension, or chronic obstructive pulmonary disease / other chronic respiratory disease (No, Yes)
- Baseline ADA status (ADA+, ADA-)*
- Baseline log_{10} SARS-CoV-2 viral load (copies per mL)
- Baseline log_{10} SARS-CoV-2 viral load (log_{10} SARS-CoV-2 viral load < 6, log_{10} SARS-CoV-2 viral load ≥ 6)

- Mutation type (Wild type; Alpha B.1.1.7; Beta B.1.351; Gamma P.1; Delta B.1.617.2; Lambda C.37; Other)*, if available
- SARS-CoV-2 antibodies as baseline (No, Yes)
- Baseline severity of COVID-19 (mild, moderate, severe (if appears)). Details on definition are included in Section 5.2.

* ADA samples will not be analyzed for Placebo patients, therefore ADA status will be missing for Placebo patients.

2.3.3 Medical history/current medical condition

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. History/conditions, including pre-specified events, will be summarized for the FAS by primary system organ class, high level term (HLT), and preferred term.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The analysis of study treatment will be based on the SS. All study treatment summaries will be presented by treatment arm.

The number and percentage of patients with discontinuation of study medication, if applicable, will be summarized by reason for discontinuation.

2.4.2 Prior, concomitant and rescue therapies

Prior, concomitant, and rescue therapies will be summarized based on the FAS.

Prior medications are defined as medications started prior to start of study drug and discontinued prior to start of study drug.

Concomitant medications are defined as medications starting prior to start of study drug and are ongoing at Day 1, or started after/at Day 1.

All medications will be summarized separately for prior and concomitant medications by anatomical main group (the 1st level of the ATC codes), ATC code (4th level or if not available next higher level), preferred term and treatment group.

A patient with multiple medications of the same anatomical main group, ATC class or preferred term will only be counted once towards the specific anatomical main group, ATC class or preferred term.

Number and percentage of patients who received COVID-19 vaccinations will be presented along with the number of doses received and time since most recent dose (<15 days, 15-<180 days, >=180 days).

In addition, the number and percentage of patients who received concomitant medications related to COVID-19 will be summarized by category (anti-virals, immune-

modulating/immunosuppressant, other) and by preferred term, separately for concomitant medications initiated before study medication and concomitant medications initiated after study medication.

Rules for imputing incomplete dates are described in Section 5.1.3.

2.5 Analysis of the primary objective

Part A

The primary analysis in Part A is conducted on the data cut performed after the last enrolled Part A patient completes Day 29 visit or discontinues prematurely.

Part B

The primary analysis in Part B is conducted on the data cut performed after the last enrolled Part B patient completes Day 91 visit.

An outline of the protocol-specified analysis of Part B is provided in the SAP. Further details will be provided in a SAP amendment before FPFV of Part B.

2.5.1 Primary endpoint

Part A

In Part A, the primary variable for the study is a virologic endpoint defined as time-weighted change from baseline to Day 3, 5, and 8 (2, 4, and 7 days after dosing, respectively) in $\log_{10}$ SARS-CoV-2 viral load in nasopharyngeal swabs.

To calculate the time-weighted change from in $\log_{10}$ SARS-CoV-2 viral load through Day 8 for each patient, the equation below is used:

$$\frac{\sum_{i=a}^{b-1}\{0.5(Y_i + Y_{i+1})(t_{i+1} - t_i)\}}{t_b - t_a}$$

where Y_i is the change from baseline in $\log_{10}$ SARS-CoV-2 viral load at Visit i, t_i is the time at the Visit i (the actual study day), a is the baseline assessment at Day 1, and b is the last assessment at or prior to Day 8. Viral load values below the lower limit of quantification (LLOQ) will be imputed as 0.5*value of the LLOQ. Viral load values above the upper limit of quantification (ULOQ) will be imputed as value of the ULOQ.

The primary estimand definition is as follows:

- **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted population, ambulatory adult patients with newly symptomatic COVID19 with onset of symptoms within 7 days prior to dosing and with a positive rapid antigen test on the day of dosing
- **Treatment of interest**: the randomized treatment (ensovibep 75 mg, 225 mg, 600 mg, or placebo) added to concomitant symptomatic/preventive treatments, including symptomatic therapies (e.g., antipyretics/analgesics such as ibuprofen, paracetamol/acetaminophen, aspirin) and anticoagulants (e.g., heparin), used for mild-to-moderate COVID-19

- **Endpoint**: time-weighted change from baseline (measured at Day 3, Day 5, and Day 8) in $\log_{10}$ SARS-CoV-2 viral load in nasopharyngeal swabs through Day 8
- **Handling of intercurrent event(s)**: A combination of treatment policy and composite strategy will be used to handle the intercurrent events. A treatment policy strategy will be used to handle (1) post-treatment initiation of all antivirals (including convalescent serum, antiviral antibodies, and antiviral small molecules), immunomodulating medications; and, (2) post-treatment increase in dose of immunosuppressive medications, for the treatment or management of COVID-19. A composite strategy will be used to handle (3) death from any cause and (4) COVID-19 related hospitalization.
- **Summary measure**: adjusted mean time-weighted change from baseline (measured at Day 3, Day 5, and Day 8) in $\log_{10}$ SARS-CoV-2 viral load in nasopharyngeal swabs between the ensovibep 75 mg, 225 mg, and 600 mg compared to placebo arms.

Part B

In Part B, the primary variable is a clinical efficacy endpoint defined as any of the following up to Day 29:

- Hospitalizations (≥ 24 hours of acute care) related to COVID-19; OR,
- Emergency room visits related to COVID-19; OR,
- Death from any cause.

If a patient experiences more than one of the events, the first event to occur will be counted towards the clinical efficacy endpoint and the date at which the first event occurred will be used as time date at which the clinical efficacy endpoint was achieved.

The primary estimand definition is as follows:

1. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted population, ambulatory adult patients with newly symptomatic COVID-19 with onset of symptoms within 7 days prior to dosing and with a positive rapid antigen test on the day of dosing
2. **Treatment of interest**: the randomized treatment (ensovibep [dose selected from Part A] or placebo) added to concomitant symptomatic/preventive treatments, including symptomatic therapies (e.g., antipyretics/analgesics such as ibuprofen, paracetamol/acetaminophen, aspirin) and anticoagulants (e.g., heparin), used for mild-to-moderate COVID-19
3. **Endpoint**: the binary response of patients experiencing hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29 (Yes/No)
4. **Handling of intercurrent event(s)**: A treatment policy strategy will be used to handle (1) post-treatment initiation of all antivirals (including convalescent serum, antiviral antibodies, and antiviral small molecules), immunomodulating medications; and, (2) post-treatment increase in dose of immunosuppressive medications, for the treatment or management of COVID-19.

5. **Summary measure**: difference in proportions of patients experiencing hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29 of ensovibep (dose selected from Part A) compared to placebo

2.5.2 Statistical hypothesis, model, and method of analysis

Part A

The primary objective of this Part is to demonstrate a dose-response effect of ensovibep compared to placebo defined as time-weighted change from baseline in $\log_{10}$ SARS-CoV-2 viral load through Day 8. The MCP-Mod methodology (Bretz et al 2005, Pinheiro et al 2014, Qualification Opinion on MCP-Mod EMA 2014, FDA endorsement 2016) to address this objective and confirm an overall dose-response signal, characterize the dose response efficacy relationship across the dose range of ensovibep, and estimate the smallest dose(s) that corresponds to the clinically relevant effect over placebo with regards to time-weighted change from baseline in $\log_{10}$ SARS-CoV-2 viral load through Day 8.

The null hypothesis of a constant dose-response curve for the time-weighted change from baseline in $\log_{10}$ SARS-CoV-2 viral load through Day 8 will be tested at a one-sided 10% alpha level against the alternative hypothesis of a non-constant dose-response curve using the MCP-Mod methodology.

Generalized MCP-Mod (Pinheiro et al 2014) will be employed in a three-step approach in the steps is given below:

- Conventional step – covariate-adjusted mean response for each dose

  The data are analyzed using analysis of covariance (ANCOVA) to obtain covariate adjusted treatment effects and corresponding variance covariance matrix. The ANCOVA will adjust for baseline $\log_{10}$ SARS-CoV-2 viral load, treatment group, baseline risk of progression to severe COVID-19 and/or hospitalization ("high risk" vs. "not at high risk") and presence of SARS-CoV-2 antibodies (Yes vs. No) and Geographical region (North America, Europe, Africa, Asia) as covariates.

  The estimated treatment difference and the associated 95% confidence intervals will be presented for the treatment contrast of each dose versus placebo.

- Proof-of-concept step – multiple contrast tests

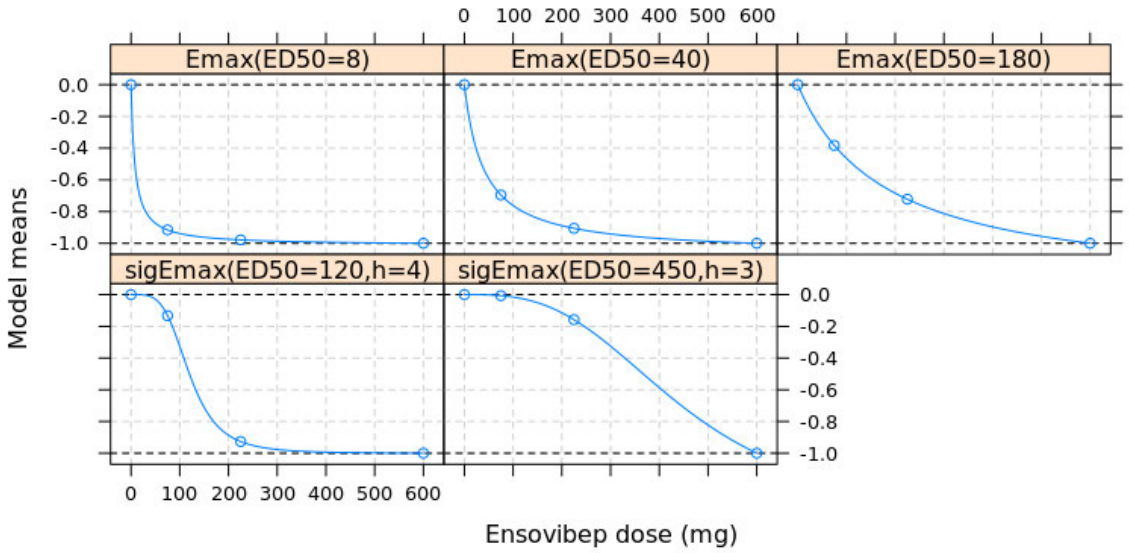
  The null hypothesis of flat dose-response relationship as compared to placebo for the primary efficacy endpoint will be tested at a significance level of one-sided 10% against the alternative hypothesis of a non-constant dose-response curve using a multiple contrast test as described in the Generalized MCP-Mod methodology (Pinheiro et al 2014). The contrast test statistic is a linear combination of the optimal contrast coefficients corresponding to the candidate dose-response curve with the adjusted mean responses at each individual dose obtained from Step 1.

  The contrast coefficients will be chosen to maximize the power to detect pre-specified candidate models (Pinheiro et al 2014). For that purpose, the E_{max} dose-response shape $(E_0 + E_{max} * d/(d + ED_{50}))$ with three shapes of $ED_{50} = 8, 40, 180$ and the sigmoid

E_{max} dose-response shape ($E_0 + E_{max} * d^h/(d^h + ED_{50}^h)$) with two shapes of $(ED_{50}, h) = (120, 4)$ and $(450, 3)$ will be used where E_0 is the expected placebo effect, E_{max} is the maximum change in effect over placebo, ED_{50} is the dose at which 50% of E_{max} is achieved, and h is Hill parameter (Figure 2-1).

The global test decision is based on the maximum of the contrast test statistics. A critical value q controlling the type I error rate can be derived from the fact that the contrast test statistics approximately follow a multivariate normal distribution and that their maximum follows the distribution of the maximum of a multivariate normal distribution. If the maximum contrast test statistic exceeds the critical value q, the overall null hypothesis of a constant dose-response curve is rejected and one proceeds to characterize the dose response efficacy relationship and estimate the optimum dose(s) that corresponds to the clinically relevant effect over placebo.

Figure 2-1 Candidate models for ensovibep dose



For each candidate dose-response curve, the test statistics and corresponding adjusted p-values will be presented.

- Dose-finding step – dose-response model fitting

  A bootstrap sample (from a normal distribution with LSMeans and corresponding covariance matrix from an ANCOVA) is used to fit the non-linear dose-response functions and obtain parameter estimates for each model. Bootstrap model averaging based on AIC over all significant model families considered in the analysis will be used to estimate the final dose-response shape, to calculate the optimum dose(s) by substituting the values for the placebo-adjusted dose response in the model and solving for dose, and to derive the 95% confidence intervals. Bootstrap simulation will be performed using the multivariate normal distribution of the adjusted estimates of the population means for each dose and generalized least-squares fitting of the resulting

simulated values (Pinheiro et al 2014). The dose-response estimate will be the median across the bootstrap model predictions and 95% confidence intervals based on bootstrap quantiles.

The dose-response curve estimate with the model-based two-sided 95% confidence interval will be presented graphically. In addition, the plot will include the mean responses from the ANCOVA and the associated 95% confidence intervals for each of the studied dose groups.

Further details on the MCP-mod are described in Section 5.7.1.

The target dose(s) will be estimated from MCP-mod for a delta of 0.36 and 0.68 based on the estimated dose-response curve (median of bootstrap estimates). The target dose is the smallest dose among the investigated doses which reaches the effect of delta..

The target dose(s) suggested by MCP-Mod based on viral endpoint serves as an important consideration in dose selection. However, the final dose selection for Part B will be determined based on the following

- Efficacy of doses based on rate of occurrence of hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID 19 or death from any cause up to day 29, FDA/modified FDA symptom score; AND,
- Safety endpoints including [redacted] AESIs, AEs, and SAEs.

Part B

The primary objective of this Part is to demonstrate superiority of ensovibep, compared to placebo, in reducing the occurrence of hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID 19 or death from any cause up to Day 29.

The cumulative proportion of experiencing hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID 19 or death from any cause up to Day 29 will be estimated for each randomized group using Kaplan-Meier methods to take account of losses to follow-up.

The difference between randomized groups in the estimated log cumulative proportion will be calculated and the variance for this difference will be obtained using Greenwood's formula. Two-sided 95% confidence intervals (adjusted for an interim analysis) and associated p-value for the test of no difference between groups will then be obtained.

The hazard ratios for these comparisons for the occurrence of hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID 19 or death from any cause and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model, stratified by baseline risk of progression to severe COVID-19 and/or hospitalization ("high risk" vs. "not at high risk").

Time to hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID 19 or death from any cause will be presented graphically with a Kaplan-Meier plot.

2.5.3 Handling of missing values/censoring/discontinuations

Part A

A combination of treatment policy and composite strategy will be used to handle the intercurrent events.

A treatment policy will be used to handle (1) post-treatment initiation of all antivirals (including convalescent serum, antiviral antibodies, and antiviral small molecules) and immunosuppressive medications; and, (2) post-treatment increase in dose of immunosuppressive medications, for the treatment or management of COVID-19, and a patient will be evaluated regardless of experiencing either of these intercurrent events.

A composite strategy will be used to handle (3) death from any cause and (4) COVID-19 related hospitalization. In the event a patient experiences death or COVID-19 related hospitalization, all values after the time of death/start of the COVID-19 related hospitalization for change from baseline in $\log_{10}$ SARS-CoV-2 viral load will be set as the worst observed value based on observed values at each time point within each treatment arm independently.

All measurements in $\log_{10}$ SARS-CoV-2 viral load missing for other reason than death or COVID-19 related hospitalization will be imputed using last observation carried forward (LOCF) approach.

Part B

A treatment policy will be used to handle (1) post-treatment initiation of all antivirals (including convalescent serum, antiviral antibodies, and antiviral small molecules) and immunosuppressive medications; and, (2) post-treatment increase in dose of immunosuppressive medications, for the treatment or management of COVID-19, and a patient will be evaluated regardless of experiencing either of these intercurrent events.

Patients who prematurely discontinue the study and whose outcomes after discontinuation are not ascertainable will have follow up censored at the date of last known status.

2.5.4 Supplementary analyses

Part A

The following supplemental analysis will be performed:

- excluding patients who experienced a negative PCR COVID-19 test following a positive swab; and,
- imputing values below the LLOQ with the LLOQ value; and
- using the approach for the handling of the intercurrent events specified and jump-to-reference (J2R), a control-based pattern imputation method, for the handling of the remaining missing data.

Further details on supplementary analyses can be found in Section 5.7.1.

Part B

Analysis will be specified a future SAP amendment as outlined in Section 1.

2.5.5 Supportive analyses

For all analyses specified in this section, the estimand in Section 2.5.1 and the missing data plan in Section 2.5.3 2.5.3for the primary analysis will be applied.

Part A

Subgroup analyses as described in Section 2.2.1 will be performed as supportive analysis on primary variable. Subgroup analysis will be performed using ANCOVA but not the full MCP-mod procedure.

Change from baseline in $\log_{10}$ SARS-CoV-2 viral load at visits (Day 3, Day 5 and Day 8) will be analyzed using a repeated measures ANCOVA (MMRM) including terms of treatment, baseline $\log_{10}$ SARS-CoV-2 viral load, baseline risk of COVID-19 progression, presence of SARS-CoV-2 antibodies (Yes vs. No) and Geographical region (North America, Europe, Africa, Asia), visit, treatment*visit and baseline*visit interaction. Estimated treatment differences at visit and corresponding 95% CI will be tabulated and presented graphically.

MCP-mod procedure will be conducted for change from baseline at Day 8 in $\log_{10}$ SARS-CoV-2 viral load as outlined in Section 2.5.2. LSMeans and covariance estimates from the MMRM on change from baseline at Day 8 in $\log_{10}$ SARS-CoV-2 viral load will be used to conduct the MCP-mod procedure. Similar outputs will be provided as in the primary analysis.

A descriptive summary will be provided for time-weighted change from baseline in $\log_{10}$ SARS-CoV-2 viral load through Day 8. Additionally, for absolute values and change from baseline in $\log_{10}$ SARS-CoV-2 viral load will be presented by visit.

Further details on supplementary analyses can be found in Section 5.7.1.

Part B

Analysis will be specified a future SAP amendement as outlined in Section 1.

2.6 Analysis of the key secondary objective

Not applicable. See Section 2.7 for secondary objectives.

2.7 Analysis of secondary efficacy objectives

Part A

Secondary efficacy objectives for Part A are:

- To assess the effect of ensovibep, compared to placebo, in reducing the occurrence of hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29
- To assess the effect of ensovibep, compared to placebo, in reducing COVID-19 symptoms up to Day 29

All secondary efficacy endpoints will be analyzed using the FAS.

Part B

Analysis will be specified a future SAP amendment as outlined in Section 1.

2.7.1 Secondary endpoints

2.7.1.1 Hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29

This secondary variable is defined as the event of experiencing

- Hospitalizations (≥ 24 hours of acute care) related to COVID-19; OR,
- Emergency room visits related to COVID-19; OR,
- Death from any cause.

If a patient experiences more than one of the events, the first event to occur will be counted towards the clinical efficacy endpoint and the date at which the first event occurred will be used as time date at which the clinical efficacy endpoint was achieved.

2.7.1.2 COVID-19 symptoms

Acute COVID-19 symptoms will be collected using a COVID-19 symptoms collection tool containing a 14-symptom questionnaire: feeling hot or feverish, chills or shivering, cough, sore throat, low energy or tiredness, headache, muscle or body aches, shortness of breath, nausea, vomiting, diarrhea, stuffy or runny nose, impaired sense of smell, and impaired sense of taste. The 14-symptoms will collectively be referred to as the FDA COVID-19 questionnaire (FDA 2020a).

At baseline, patients will have two or more COVID-19 symptoms as per inclusion critera.

The endpoint to assess the reduction of COVID-19 symptoms up to Day 29 is time to sustained clinical recovery.

Sustained clinical recovery is defined as (a) all symptoms from the modified FDA COVID-19 symptom list scored as moderate or severe at baseline are subsequently scored as mild or absent, AND (b) all symptoms from the modified FDA COVID-19 symptom list scored as mild or absent at baseline are subsequently scored as absent, with no subsequent worsening, up to Day 29.

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 Hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29

Proportion of patients experiencing hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID 19 or death from any cause up to Day 29 will be presented along with relative risk to Placebo.

In addition, the number and percentage of patients with hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to day 29 will be summarized overall and separately for hospitalizations (≥ 24 hours of acute care), emergency room visits related to COVID-19 and death from any cause.

2.7.2.2 COVID-19 symptoms

The cumulative proportion of achieving sustained clinical recovery up to Day 29 will be estimated for each treatment group using Kaplan-Meier methods to take account of losses to follow-up.

The treatment differences in the estimated log cumulative proportion will be calculated and the variance for this difference will be obtained using Greenwood's formula. Two-sided 95% confidence intervals and associated p-value for the test of no difference between groups will then be obtained.

Number and percentage of patients with and without event will be tabulated along with the time at risk, event rates and corresponding 95%CI. Additionally, a Kaplan-Meier plot will be presented.

Time to sustained clinical recovery will be presented graphically with a Kaplan-Meier plot. A Cox proportional hazards model will be used, stratified by baseline risk of progression to severe COVID-19 and/or hospitalization ("high risk" vs. "not at high risk"). The model will include treatment, presence of SARS-CoV-2 antibodies (Yes vs. No), Geographical region (North America, Europe, Africa, Asia). Time of onset of COVID-19 symptoms (days relative to Day 1) will also be evaluated as a predictor in the model.

As a descriptive summary, shift tables presenting shifts from baseline to post-baseline will be provided for each question by selected visits (Day 3, Day 8, Day 15, and Day 29) and treatment group. Question on return to usual health and return to usual activities will be summarized for post-baseline visits only. Further a descriptive summary of the COVID-19 symptom score will be provided by scheduled timepoint. The symptom score ranges from 0 to 24 and includes eight domains (cough, breathlessness, feeling hot, fatigue, body pain, sore throat, chills and headache), each is graded on a scale of 0 (no symptoms) to 3 (severe symptoms).

Prior to database lock for primary analyses it was detected that due to non-compliance at sites some patients did not complete the COVID-19 symptom questionnaire prior to start of infusion. These patients do not have valid baseline data for COVID-19 symptom questionnaire. Therefore the following supportive analysis will be performed:

1) Time to sustained recovery analyses will be repeated using extended definition of sustained recovery: Sustained recovery is defined as (a) all symptoms from the modified FDA COVID-19 symptom list scored as moderate or severe at baseline are subsequently scored as mild or absent, AND (b) all symptoms from the modified FDA COVID-19 symptom list scored as mild or absent at baseline are subsequently scored as absent, with no subsequent worsening up to Day 29. For patients with missing baseline COVID-19 symptom questionnaire sustained recovery is defined as all symptoms from the modified FDA COVID-19 symptom list are scored as absent, with no subsequent worsening up to Day 29.

2) Time to event analyses will be repeated modifying baseline definition for COVID-19 symptom questionnaire. All values up to the end of infusion at Day 1 will be considered as baseline. Since the COVID-19 symptom questionnaire has a recall period of last 24 hours, study medication is unlikely to have an impact on patients' assessment of their symptoms over the last 24 hours, before infusion is completed.

2.7.3 Handling of missing values/censoring/discontinuations

2.7.3.1 Hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29

Missing data will not be imputed.

2.7.3.2 COVID-19 symptoms

Missing data due to premature discontinuations prior to Day 29 are covered with the censoring approach.

Patients being too ill to complete the questionnaire will be considered as not achieving sustained recovery and will be censored at the earlier date or (last contact date, visit date of Day 29).

Patients who complete the questionnaire due to other reasons than 'being too ill to complete the questionnaire', do not achieve sustained recovery up to Day 29 and discontinue prior to Day 29 visit will be censored at the last date questionnaire was completed.

For any missing questionnaires between non-missing assessments, if reason for this is that patient is too ill to complete the questionnaire, the respective day will be considered as not achieving recovery.

2.8 Safety analyses

For all analyses in this section, the safety set will be used, if not specified otherwise.

2.8.1 Adverse events (AEs)

Adverse events (AEs) will be coded based on the latest available MedDRA version practically possible (version 23.0 or above) that gives preferred term (PT) and primary system organ class (SOC) information. The MedDRA version will be displayed in the respective output footnotes. AEs will be graded using the common toxicity criteria for adverse events (CTCAE) version 5.0.

The number (and percentage) of patients with treatment-emergent

- Treatment emergent AEs (TEAEs)
- Serious adverse events (SAEs)
- AEs of Special Interest (AESIs; see Section 2.8.1.1)

will be summarized by:

- treatment, SOC and PT;
- treatment, SOC, PT, and CTCAE grade; and,
- treatment, Standardized MedDRA Query (SMQ) and PT.

In addition, the following events will be summarized by treatment, SOC and PT as well as by SOC, PT and maximum CTCAE grade:

- TEAEs leading to discontinuation of study drug;
- and,
- TEAEs suspected to be study drug related.

Deaths will be summarized by SOC and PT.

Dot plots of the most frequent TEAEs of CTCAE grade 3 or higher, and serious TEAEs will be provided.
AEs , SAEs, and AESIs will be listed, treatment emergent events will be flagged.

In AE summaries, the primary SOC will be presented alphabetically and the PTs will be sorted within the primary SOC in descending frequency of the highest ensovibep dose. If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the SOC level, where applicable. An AE with missing CTCAE grade will be included in 'All grades' of the summary tables only.

AEs and SAEs will be summarized by SOC, PT and ensovibep treatment arms for each treatment-emergent Anti-Drug Antibodies (TE-ADA) status (TE-ADA-, TE-ADA+induced, TE-ADA+boosted, and a combined TE-ADA+). ADA status is assessed at Day 1, 15, 29, 61 and 91. AE will be summarized according to the TE-ADA status at start of the event. For the event start date, the TE-ADA status used will be the TE-ADA status assessed on the date of the event, if available, or on the first assessment after the event start date. If TE-ADA status following the event is not available, the last available TE-ADA status will be used. Percentages will be based on the number of patients with the respective ADA status at any time post-baseline. For more detail regarding TE-ADAs refer to Section 2.13.1.

ADA data will only be partially available at the time of part A primary analysis, therefore adverse event analyses by TE-ADA status will be analyzed only at the time of final lock i.e., day 91 analyses.

2.8.1.1 Adverse events of special interest / grouping of AEs

The following events are AEs of Special Interest (AESI) for this study:

- A CTCAE grade 2 or higher (i.e. requiring intervention) of:Infusion site reactions:
- Hypersensitivity reactions (including anaphylaxis, immune complex mediated hypersensitivity, cytokine release syndrome and other hypersensitivity reactions)
- Worsening of COVID-19 disease that is reported as a moderate or severe AE per investigator judgement, with onset within 1 week of study drug administration.
- Liver events requiring follow-up
- Renal events requiring follow-up

The number (and percentage) of patients with each of the AESIs will be summarized for each Part

- by treatment;
- by treatment and maximum CTCAE grade; and,
- and by treatment, primary system organ class, and preferred term.

A listing of AESIs will be provided. AESIs will be analyzed as flagged by the investigator on the eCRF.

Safety topics of interest are defined in the electronic case retrieval sheet (eCRS). These will by summarized for each part

- by safety topic of interest
- by safety topic of interest and preferred term
- by safety topic of interest and preferred term for those AEs marked as AESI by the investigator

AESIs and safety topics of interest will be in addition will be summarized for each treatment-emergent Anti-Drug Antibodies (TE-ADA) status. ADA data will only be partially available at the time of part A primary analysis, therefore this analysis will only be done at the time of final lock i.e., day 91 analyses.

2.8.2 Deaths

See Section 2.8.1. A listing will be provided for all deaths by treatment for each Part.

2.8.3 Laboratory data

Laboratory data include measurements of all parameters below:

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting), CRP, D-Dimer, Ferritin
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Pregnancy Test	Serum / Urine pregnancy test

Clinically notable abnormalities and abnormalities in liver function tests (LFT) are described in Section 5.5.

Absolute values and change from baseline will be summarized for continuous laboratory parameters by treatment and scheduled visit, including the worst post-baseline value. The direction of interest for worst post-baseline value for selected hematology and biochemistry parameters is shown in Section 5.4.

For selected laboratory tests, the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria at any time post-

baseline, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits, will be summarized by treatment and laboratory parameter.

Furthermore, the number and percentage of patients with newly occurring or worsening abnormalities in liver function tests (LFT) will be summarized by treatment and at any time post-baseline considering all post-baseline data from scheduled, unscheduled and premature discontinuation visit.

The number (%) of patients with newly occurring or worsening of notable laboratory values will be provided.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst post-baseline value.

Listing of all laboratory data of patients with notable abnormal laboratory values will be provided with the classifications relative to the laboratory normal ranges.

Urine pregnancy test data will be summarized using frequency and percentage by treatment. A listing of all pregnancy test data will be provided.

2.8.4 Other safety data

2.8.4.1 Vital signs

Vital signs variables include measurements of systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate, oximetry and weight. Clinically notable abnormalities are described in Section 5.6.

Absolute values and change from baseline will be summarized for all vital signs parameter by treatment and scheduled visit.

For selected vital sign parameter, the number and percentage of patients with newly occurring or worsening abnormalities meeting the clinically notable criteria at any time post-baseline, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits, will be summarized by treatment and parameter.

A listing of all vital signs of patients with notable abnormal vital signs values (with clinically notable abnormalities being flagged) will be generated.

2.9 Pharmacokinetic endpoints

For all analyses in this section, the PK analysis set will be used.
The PK analysis is specified as a secondary objective in Part A [redacted]

Free (ensovibep not bound to target) and total (sum of ensovibep not bound and ensovibep bound to target) concentration in serum will be summarized by treatment in each Part at Day 1 pre-dose, Day 1 post-dose (at minute 15 and minute 90), Day 3, Day 8, Day 15, Day 29, Day 61 and Day 91, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Median concentrations and median log(concentration) over scheduled time-points will be presented graphically by treatment group.

The following PK parameters will be determined: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, λ_z, V_z, CL. PK parameters will be summarized by treatment in each Part and will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. The maximum concentration or peak after a dose administration (Cmax) and the area under the concentration versus time curve (AUC) will be provided.

In addition, population PK modeling will be performed and data from other clinical studies may be pooled. If performed, results of the population PK modeling may be reported separately and will not be part of the CSR.

[redacted]

2.11 Patient-reported outcomes (PRO)

Answers to Short Form 36 Health Survey (SF-36), FDA-recommended 14-symptom [redacted] will be reported in each Part. The FDA-recommended 14-symptom questionnaire is described as secondary efficacy objective in Section 2.7.

2.11.1 SF-36

The analysis of SF-36 is specified [redacted] a secondary objective in Part B.

In each Part, SF-36 version 1 domain scores, Physical Component Summary (PCS) and Mental Component Summary (MCS), will be summarized by treatment on Days 29, 60 and 91.

Between treatment differences in SF-36v1® summary scores will analyzed using repeated measures analysis of covariance (ANCOVA) including terms of treatment, baseline risk of progression to severe COVID-19 and/or hospitalization ("high risk" vs. "not at high risk") visit, and treatment*visit interaction and will include covariates for presence of SARS-CoV-2 antibodies (Yes vs. No) and Geographical region (North America, Europe, Africa, Asia).

Estimated treatment differences at visit and corresponding 95% CI will be tabulated and presented graphically.

In addition a descriptive summary by visit and treatment group will be provided.

SF-36 will be assessed at visit Day 29, Day 61 and Day 91 therefore the repeated measure ANCOVA will be performed only at the time of final lock i.e., day 91 analyses.

[redacted]

[redacted]

2.12 Biomarkers

[redacted]

2.12.2 SARS-CoV-2 antibodies

To assess the effect of ensovibep, compared to placebo, on the occurrence of anti-SARS-CoV-2 antibodies (IgG and IgM), the number (and percentage) of patients withanti-SARS-CoV-2 antibodies at Day 91 will be summarized by treatment.

Neutralizing SARS-CoV-2 antibodies may be summarized descriptively at time of final lock i.e., day 91 analyses. Neutralizing SARS-CoV-2 antibodies data will not be available at the time of part A primary analysis.

2.12.3 Soluble Biomarker

All biomarker data, including cytokines and other markers of inflammation implicated in the severity of COVID-19, will be summarized and visualized (including spaghetti plots, boxplots and mean plots with SD) by treatment for Day 1, Day 3, Day 8, Day 15 Day 29 and Day 91. Changes from baseline to values at each time point will be summarized for each Part by treatment.

[redacted]

[redacted]

2.14 Interim analysis

Part A

No interim analysis will be performed for the efficacy evaluation. Analysis of primary endpoint will be carried out when all patients have completed the Day 29 visit (or withdrawn prematurely) and have viral load data up to Day 8. Final analyses of part A will occur when all patients have completed Day 91 visit (or withdrawn prematurely). However, analyses of primary endpoint will not be repeated.

For the Part A primary analysis a cut-off date will be applied. All available data up to the cut-off date will be included in the analysis. The cut-off date is defined as the date when the last patient completed Day 29 visit or discontinued prematurely.

At time of primary analyses not all data up to the cut-off date will be available. Incomplete data are expected for

- Viral load data beyond Day 8.
- SARS-CoV-2 IgM / IgG antibodies data for Day 91
- Anti-SARS-CoV-2 neutralizing antibody test data – no data will be available
- [redacted]
- PK data beyond Day 8
- [redacted]
- Serum biomarker data – any visit

If not stated otherwise in the respective section, all analyses will be included in the Part A primary analyses. Analyses will include all available data.

Part B

There will be one interim analysis after 50% of patients complete Day 29 and one final analysis after at least 1717 patients have completed Day 91. The interim analysis permits early stopping due to efficacy controlling overall type I error rate. The interim analysis upper stopping bound in Z scale is 2.963 (corresponding to alpha is 0.03).

3 Sample size calculation

3.1 Primary endpoint(s)

Part A

In Documentation for the EUA for emergency use of casirivimab and imdevimab, issued 21 Nov 2020, it is shown that the treatment effect in time-weighted change from baseline (Day 1) to Day 8 of $\log_{10}$ SARS-Cov-2 viral load in nasopharyngeal swabs was -0.36 for the overall population and -0.68 for the subgroup of patients with at least 10^7 copies at baseline and the estimated standard deviation was between 1.0 and 1.2.

Assuming the published evidence to be predictive over 8 days, a sample size of at least 100 patients per treatment group, for a total of 400 patients, would have at least 80% power (minimum power over the considered candidate shapes) with a one-sided Type I error rate of 0.10 to detect a dose-response trend versus placebo using MCP-Mod to select the smallest dose for consideration in the decision to move into Part B.

The power calculation given the range of operating characteristics (treatment effect: -0.36, -0.68, and standard deviation: 1, 1.1, 1.2) were performed based on MCP-Mod in R (Pinheiro 2006) and are presented in Table 3.1-1.

Table 3.1-1 Power for Part A given a range of operating characteristics given 400 patients, 100 patients in each arm and a one sided significance level of 10%

Treatment Effect	Standard Deviation	Power (%)
-0.36	1	90.03
	1.1	85.25
	1.2	80.25
-0.68	1	99.98
	1.1	99.92
	1.2	99.73

Part B

Assuming the proportion of patients achieving the composite endpoint (of hospitalizations (≥ 24 hours of acute care) and/or emergency room visits, related to COVID-19, or death from any cause) up to Day 29 is 6.5% based on Gottlieb et al (2021) in the placebo group and 50% reduction with to 3.25%, a sample size of 1717 patients 1:1 randomized to two treatment groups provides at least 90% power that the primary analysis will be statistically significant using a two-sided log rank test with 5% significance level assuming that the survival rates are exponential. These results assume that the group sequential design has one interim analysis for

stopping the trial early for efficacy after 50% of patients complete Day 29 visit (two total analysis including final analysis) and the O'Brien-Fleming spending function is used to determine the efficacy test boundary.

Given possible enrichment for more severe COVID-19 cases, a range of operating characteristics were evaluated and presented in Table 3.1-2.

Sample size calculations are performed in nQuery 8.4.1.0.

Table 3.1-2 Power for Part B given a range of operating characteristics

Total Sample Size	Placebo Event Rate (%)	Drug Event Rate (%)	Power (%)
1717	**6.5**	**3.25**	**90.02**
1588	7	3.5	90.01
1476	7.5	3.75	90.01
1380	8	4	90.04
1295	8.5	4.25	90.06
1217	9	4.5	90.03
1148	9.5	4.75	90.02
1086	10	5	90.02

3.2 Key secondary endpoint(s)

Not Applicable.

3.3 Other secondary endpoint(s)

Not Applicable.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

Any date incompletely reported is split into its day, month, and year components. In SAS, a numerical date value can only be defined if all these date components are known; incomplete dates are to be handled as text strings (character-type variables); as such, they could not be easily processed. An imputation rule for incomplete dates will be performed.

5.1.1 Study drug

Missing/partial start date/time or end date/time of study treatment will not be imputed.

5.1.2 AE date and hospitalization date imputation

This algorithm is expressed in the Variable Source Derivation column as **#IMPUTAEV(*event*)** where *event* is the partial start date of the AE. Table 5.1-1 explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed. Note, if the imputed AE (or HO) start is after AE (or HO) end date, then set AE (or HO) start equal to AE (or HO) end date. Missing AE (or HO) end dates will not be imputed.

Table 5.1-1 Imputation logic for partial AE dates

	Day	Month	Year
Partial AE (or Concomitant Medication) Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	NC	NC	NC	NC
YYYY < TRTY	(D)	(C)	(C)	(C)
YYYY = TRTY	(B)	(C)	(A)	(A)
YYYY > TRTY	(E)	(A)	(A)	(A)

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates AE (or CM) start date prior to Treatment Start Date
After Treatment Start	Partial date indicates AE (or CM) start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of AE (or CM) start date to Treatment Start Date
Imputation Calculation	
NC / Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSDT+1)
(B) Uncertain	TRTSDT+1
(C) Before Treatment Start	15MONYYYY
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

5.1.3 Concomitant medication and therapies date imputation

The notation used is in the logic matrix of Table 5.1-2. Rules for imputing the medication start date:

1) Medication start date year value is missing:
    a) If the medication start date year value is missing and the question "Started prior to start of study medication" is answered with "Yes", the imputed medication start date is set to one day prior to treatment start date, if not after the medication end date. Thus the imputed medication start date will be the minimum of one day prior to treatment start date and the medication end date.
    b) If the medication start date year value is missing and the question "Started prior to start of study medication" is answered with "No", the imputed medication start date

is set to treatment start date + 1 day, if not after the medication end date. Thus the imputed medication start date will be the minimum of one day after treatment start date and the medication end date.

2) If the medication start date year value is less treatment start date year value, the medication started before treatment start. Therefore:
   a) If the medication start year is less than treatment start year and the medication month is missing, the imputed medication start date is set to 01JulYYYY.
   b) Else if the medication start year is less than the treatment start year and the medication month is not missing, the imputed medication start date is set to 15MONYYYY.
3) if the medication start date year value is greater than treatment start date year value, the medication started after treatment start. Therefore:
   a) If the medication start year is greater than the treatment start year and the medication month is missing, the imputed medication start date is set to 01JanYYYY.
   b) Else if the medication start year is greater than the treatment start year and the medication month is not missing, the imputed medication start date is set to 01MONYYYY.
4) If the medication start date year value is equal to treatment start date year:
   a) If the medication start month is missing or the medication start month is equal to treatment start month, then the imputed medication start date is set to the minimum of one day prior to treatment start date and the medication end date if the question "Started prior to start of study medication" is answered with "Yes".
   b) If the medication start month is missing or the medication start month is equal to treatment start month, then the imputed medication start date is set to the minimum of one day after treatment start date and the medication end date if the question "Started prior to start of study medication" is answered with "No".
   c) Else if the medication start month is less than the treatment start month, the imputed medication start date is set to 15MONYYYY.
   d) Else if the medication start month is greater than the treatment start month, the imputed medication start date is set to 01MONYYYY.

Table 5.1-2 Imputation logic for partial concomitant medication enddates

	Day	Month	Year
Partial Conmed. end Date	Not used	MON	YYYY
Last Contact Date (LASTDT)	Not used	LSTM	LSTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < LSTM	MON = LSTM	MON > LSTM
YYYY MISSING	NC	NC	NC	NC
YYYY < LSTY	(C)	(A)	(A)	(A)

YYYY = LSTY	(B)	(A)	(B)	(A)
YYYY > LSTY	(C)	(A)	(A)	(A)

The following table is the legend to the logic matrix.

Relationship	
Before Last contact date	Partial date indicates CM end date prior to Last Contact Date
After Last contact date	Partial date indicates CM end date after Last Contact Date
Uncertain	Partial date insufficient to determine relationship of CM end date to Last Contact Date
Imputation Calculation	
NC / Blank Uncertain	No convention
(A) Before/After Last contact date	Last day MONYYYY
(B) Uncertain	LASTDT
(C) Before/After Last contact date	31DECYYYY

If the above logic is applied and the imputed end date is after the cut-off date, then the imputed end date will be replaced with the cut-off date.

5.2 Derivation of risk of progression to severe COVID-19 and/or hospitalization

High risk of disease progression as per protocol:

Patients will be considered "high risk" if they meet at least one of the following criteria:

- Have a body mass index (BMI) ≥ 35
- Have chronic kidney disease
- Have diabetes mellitus
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥ 65 years of age
- Are ≥ 55 years of age AND have
  - Cardiovascular disease, OR
  - Hypertension, OR
  - Chronic obstructive pulmonary disease/other chronic respiratory disease.

All patients not meeting the above high-risk criteria will be considered "not at high risk".

Additional criteria for 'High risk' of disease progression as per FDA updated definition on May 19, 2021

- Adults with BMI between 25 kg/m2 and 35 kg/m2
- Pregnancy
- Age < 55 and cardiovascular disease (including congenital heart disease) or hypertension, chronic lung diseases / other chronic respiratory disease
- Sickle cell disease

- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

5.3 Derivation of baseline COVID-19 severity

Baseline COVID-19 severity will be calculated based on the FDA guidance (CDER 2020b). Derivation for severe or critical COVID-19 are not included as these patients will not be enrolled in the trial.

Mild COVID-19:

- No presence of dyspnea (as found in the eCRF); AND,
- Respiratory rate < 20 breaths/minute; AND,
- Heart rate < 90 beats/minute.
- AND no criterion for moderate or severe COVID-19

Moderate COVID-19:

- Presence of dyspnea with exertion (as found in the eCRF); OR,
- Respiratory rate 20 - < 30 breaths/minutes; OR,
- Heart rate 90 - < 125 beats/minute
- AND no criterion for severe COVID-19.

Severe COVID-19:

- Presence of dyspnea at rest (as found in the eCRF); OR,
- Respiratory rate ≥ 30 breaths/minutes; OR,
- Heart rate ≥ 125 beats/minute; OR
- Oxygen saturation SpO2 <=93%

5.4 AEs coding/grading

Adverse events (AEs) are to be coded with the MedDRA dictionary based on the latest version available at the time of the analyses (version 24 or above) gives preferred term (PT) and primary system organ class (SOC) information. AEs will be graded using the common toxicity criteria for adverse events (CTCAE) version 5.0.

5.5 Laboratory parameters derivations

Table 5.5-1 shows the criteria for clinically notable laboratory values and includes the direction of interest when analyzing worst case values in form of maximum and/or minimum post-baseline values.

Not all parameters have notable criteria defined.

If the direction of interest is given as "High" the maximum value will be calculated and used as worst value, if the direction is given as "Low" the minimum value will be taken, and if it is given as "Low and high", both the minimum value and the maximum value will be calculated and presented in summary tables.

Table 5.5-1 Clinical notable criteria for selected laboratory tests

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range	Direction of interest for worst case value
A. Hematology			
Hematocrit (v/v)			
Male	0.37		Low
Female	0.32		Low
Hemoglobin (g/L)			
Male	115		Low
Female	95		Low
Erythrocytes			Low
WBC (x10E9/L)	2.8	16.0	Low and High
Basophils	-		High
Eosinophils	-		High
Lymphocytes (x10E9/L)	0.5	4	Low and High
Monocytes	-		High
Neutrophils (x10E9/L)	1.5	10	Low and High
Platelets (x10E9/L)	75	700	Low and High
B. Chemistry			
Albumin (g/L)	25	-	Low
Alkaline Phosphatase (U/L)	-	3xULN	High
ALT/SGPT (U/L)	-	3xULN	High
AST/SGOT (U/L)	-	3xULN	High
Bilirubin Total (mmol/L)	-	34.2	High
Direct bilirubin	-		High
BUN (mmol/L)	-	10.7	High
Creatinine (umol/L)	-	177	High
Creatinine kinase	-	3 x ULN	High
Gamma GT (U/L)	-	3 x ULN	High
Bicarbonate			Low and High
Chloride	90	115	Low and High
Potassium (mmol/L)	3	5.5	Low and High
Magnesium (mmol/L)	0.51	1.07	Low and High
Calcium	1.75	3.0	Low and High
LDH	-		High
Phosphorus	0.6	1.6	Low and High
Sodium (mmol/L)	130	150	Low and High
C-Reactive Protein (CRP) (mg/L)	-	100	High

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range	Direction of interest for worst case value
Fibrinogen	-		High
Total protein (g/L)	45	-	Low
Uric Acid			
Male	-	595	High
Female	-	476	High
Amylase	-	1.5 x ULN	High
Lipase	-	1.5 x ULN	High
Glucose (mmol/L)	3.0	11	Low and High
D-dimer	-	3 x ULN	High
Ferritin (ng/mL)		3 x ULN	High
C. Coagulation			
PT		-	Low
INR		1.5 x ULN	High
APTT		1.5 x ULN	High

v = volume, ULN = upper limit of normal

Table 5.5-2 shows the criteria for clinically notable liver test values.

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur within a 3-day window. A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline and will be considered as worsening if the criteria are met at baseline and at least one component is worsening from baseline irrespective of whether the other(s) are better.

Table 5.5-2 Notable liver function test values

Criterion
ALT > 3 x the upper limit of normal range (ULN)
ALT > 5 x ULN
ALT > 8 x ULN
ALT > 10 x ULN
ALT > 20 x ULN
ALT or AST > 3 x ULN
ALT or AST > 5 x ULN
ALT or AST > 8 x ULN
ALT or AST > 10 x ULN
ALT or AST > 20 x ULN
Total bilirubin > 1 x ULN
Total bilirubin > 1.5 x ULN
Total bilirubin > 2 x ULN
Total bilirubin > 3 x ULN
ALP > 1.5 x ULN
ALP > 2 x ULN
ALP > 3 x ULN
ALP > 5 x ULN
ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN
ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
ALT or AST > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 8 x ULN and total bilirubin > 2 x ULN
ALT or AST > 10 x ULN and total bilirubin > 2 x ULN
ALT or AST > 20 x ULN and total bilirubin > 2 x ULN
ALP > 3 x ULN and total bilirubin > 2 x ULN
ALP > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP < 2 x ULN (Hy's law)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase

5.6 Vital signs – definition of clinically notable values

Table 5.6-1 shows the clinical notable criteria for vital signs.

Table 5.6-1 Clinical notable criteria for vital signs

Vital sign	Direction	Patient age at screening	
		< 18 years	≥ 18 years
Systolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group1	≥ 180 with increase from baseline of ≥20 mmHg
	Low	≤ 5th percentile of the age and height group1	≤ 90 with decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group1	≥ 105 with increase from baseline of ≥15 mmHg
	Low	≤ 5th percentile of the age and height group1	≤ 50 with decrease from baseline of ≥15 mmHg
	High	≥ 38.4°C	≥ 39.1°C

Vital sign	Direction	Patient age at screening		
		< 18 years		≥ 18 years
Oral body temperature [°C]	Low	≤ 35.0°C		
Pulse rate [bpm] 2	High	1-6 months	> 160	≥120 with increase from baseline of ≥15 bpm
		6-12 months	>150	
		12-18 months	> 140	
		18-24 months	> 135	
		2-3 years	> 128	
		3-4 years	> 123	
		4-6 years	> 117	
		6-8 years	> 111	
		8-12 years	> 103	
		12-15 years	> 96	
		≥ 15 years	> 92	
	Low	1-6 months	<120	≤50 with decrease from baseline of ≥15 bpm
		6-12 months	<110	
		12-18 months	< 103	
		18-24 months	< 98	
		2-3 years	< 92	
		3-4 years	< 86	
		4-6 years	< 81	
		6-8 years	< 74	
		8-12 years	< 67	
		12-15 years	< 62	
		≥ 15 years	< 58	
Weight	High	increase from baseline3 of ≥ 2 BMI- for-age percentile categories4		Weight increase from baseline of ≥ 10%
	Low	decrease from baseline3 of ≥ 2 BMI- for-age percentile categories4		Weight decrease from baseline of ≥ 10%
Respiratory rate [breath per minute]2,6,7	High	1-6 months	>55	≥30bpm
		6-12 months	>50	
		12-18 months	> 46	
		18-24 months	> 40	
		2-3 years	> 34	
		3-4 years	> 29	
		4-6 years	> 27	
		6-8 years	> 24	
		8-12 years	> 22	
		12-15 years	> 21	
		≥ 15 years	> 20	
	Low	1-6 months	<33	≤ 10bpm
		6-12 months	< 30	

Vital sign	Direction	Patient age at screening		
		< 18 years		≥ 18 years
		12-18 months	<28	
		18-24 months	< 25	
		2-3 years	< 22	
		3-4 years	< 21	
		4-6 years	< 20	
		6-8 years	< 18	
		8-12 years	< 16	
		12-15 years	< 15	
		≥ 15 years	< 13	
Oxygen saturation Low <=93%				

bpm=beats per minute; NHLBI= National Heart, Lung, and Blood Institute;

1 Blood pressure percentiles are calculated for each blood BP record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

2 Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X.

3 Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to or greater than the 95th percentile);

4 BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P97) are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/);

Note: For patients less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the recumbent length;

6 Eldridge L. What is a Normal Respiratory Rate?, Updated May 16, 2014;

7.Kou .R., Shuei L., Bradypnea, Department of Physiology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, http://rd.springer.com/referenceworkentry/10.1007%2F978-3-540-29676-8_246

5.7 Statistical models

5.7.1 Primary analysis

The following ANCOVA will be used for time-weighted change from baseline in $\log_{10}$ SARS-Cov-2 viral load through Day 8:

Dependent variable = intercept + treatment + baseline in $\log_{10}$ SARS-CoV-2 viral load + baseline risk for COVID-19 disease progression + presence of SARS-Cov-2 antibodies at baseline + geographic region + error.

The SAS procedure PROC MIXED will be used for analysis. Results will be presented with LSM and standard error (SE) for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for treatment contrasts of each ensovibep dose versus Placebo.

- **MCP-Mod**

The Multiple Comparison Procedure – Modelling (MCP-Mod) methodology (see Bretz et al 2005 and Pinheiro et al 2014) will be employed to assess the primary objective. The following steps for the MCP-Mod methodology will be performed. The analysis will be implemented in SAS (used for ANCOVA) and R (MCP-Mod) using DoseFinding R package:

Step 1 (Testing an overall dose-response signal - MCP part):

a. Fit ANCOVA model. Extract estimates and variance-covariance matrix from fitted model.
b. Perform multiple contrast test with pre-defined model types and optimal contrasts, using variance-covariance matrix from the ANCOVA.

   Consider the following candidate models:

   - Emax (ED50=8)
   - Emax (ED50=40)
   - Emax (ED50=180)
   - sigEmax (ED50=120, h=4)
   - sigEmax (ED50=450, h=3)

   Present t-statistics and corresponding adjusted p-values for each candidate model.

   If there is at least one significant DR relationship, the DR signal is declared and Step 2 will be performed.

Step 2 (Estimation of the dose-response curve and target dose – Mod part):

a. Draw bootstrap samples (at least 1000) from a multivariate normal distributions N(μ,sigma) with parameter μ and sigma populated with the corresponding LSMeans and variance-covariance from the ANCOVA of step 1a. Fit each of the pre-defined models to the data of each sample. Select the model with the best fit based on generalized AIC and predict the dose-response curve with this model in each sample.
b. Derive median and other quantiles for predicted response over the dose range from the bootstrap samples. This will result in an averaged model.
c. Estimate the target dose(s) for a delta of 0.3, 0.8, and 1.5 using inverse regression techniques using the best model for each of the bootstrap samples. If at least 50% of the target doses are within the investigated dose range the target dose will be derived as the median of the bootstrap samples, the 95% interval will be derived from the respective quantiles. For this derivation only target doses within the boundaries for the parameter are included (i.e. range of 0 – 1.5*maxdose for Emax and sigEmax, 0 – 2*maxdose for exponential).

- **Multiple imputation for supplementary analysis**

A treatment policy will be used to handle (1) post-treatment initiation of all antivirals (including convalescent serum, antiviral antibodies, and antiviral small molecules) and immunosuppressive medications; and, (2) post-treatment increase in dose of immunosuppressive medications, for the treatment or management of COVID-19, and a patient will be evaluated regardless of experiencing either of these intercurrent events.

A composite strategy will be used to handle (3) death from any cause and (4) COVID-19 related hospitalization. In the event a patient experiences death or COVID-19 related hospitalization, all values after the time of death/start of COVID-19 related hospitalization for change from

baseline in log_{10} SARS-CoV-2 viral load will be set as the worst observed value based on observed values at each time point within each treatment arm independently.

All measurements in log_{10} SARS-CoV-2 viral load missing for other reason than death or COVID-19 related hospitalization will be multiply imputed assuming patients in the ensovibep treatment arms behave as patients in the placebo arm, i.e. using jump-to-reference (J2R). Missing data of patients in the placebo treatment arm will be imputed using missing at random (MAR) assumption.

For supplemental analysis using multiple imputation the following imputation steps need to be performed for missing data.

Missing data will be imputed for the visits before deriving the time-weighted change from baseline Imputations will be done for change from baseline log_{10} SARS-CoV-2 viral load, not for the absolute value:

1. Impute missing data using MAR for patient in the placebo arm:
   Select all patients from the placebo arm, impute missing values at Day 3, 5 and 8 using the MI approach based on the fully conditional specification (FCS) method for 100 time and obtain 100 imputed datasets. Missing Day 3 values will be imputed using a model with the imputed values of baseline risk of COVID-19 progression, baseline in log_{10} SARS-CoV-2 viral load, presence of SARS-Cov-2 antibodies at baseline and geographic region as predictors. Missing Day 5 values will be imputed using a model with the values of Day 3, baseline risk of progression, baseline in log_{10} SARS-CoV-2 viral load presence of SARS-Cov-2 antibodies at baseline and geographic region as predictors. Repeat the same for subsequent visits.
   This results in at least 100 imputed datasets.
2. Impute missing for patients in the ensovibep treatment groups using J2R:
   Select all patients, impute missing values at Day 3, 5 and 8 using the MI approach, under assumption of missing not at random (MNAR) that patients in ensovibep treatment groups will behave as patients treated with Placebo, based on the fully conditional specification (FCS) method for 100 time and obtain 100 imputed datasets. Missing Day 3 values will be imputed using a model with the imputed values of baseline risk of COVID-19 progression, baseline in log_{10} SARS-CoV-2 viral load, presence of SARS-Cov-2 antibodies at baseline and geographic region as predictors. Missing Day 5 values will be imputed using a model with the values of Day 3, baseline risk of progression, baseline in log_{10} SARS-CoV-2 viral load presence of SARS-Cov-2 antibodies at baseline and geographic region as predictors. Repeat the same for subsequent visits.
   This results in 100 imputed datasets.
3. Set datasets from step 1 and step 2.
4. Derive time weighted change from baseline for each patient and each imputed dataset.
5. Data of the final multiply-imputed dataset where all missing values are filled will be analyzed (by imputed dataset) using the ANCOVA as specified for the primary analysis.
6. The results for the treatment effect from at least 100 datasets will then be combined using Rubin's rule.

Step 1 to 6 will be implemented before MCP-Mod is used.

Step 5 and 6 will be used within MCP-Mod for step 1a Step 1b and 2a of the MCP-Mod will use the combined estimate and variance-covariance matrix of step 6.

- **Repeated measures ANCOVA (MMRM) for supportive analyses**

The following repeated measure ANCOVA (MMRM) will be used for change from baseline in log_{10} SARS-CoV-2 viral load:

Dependent variable = intercept + treatment + baseline log_{10} SARS-CoV-2 viral load + baseline risk for COVID-19 disease progression + presence of SARS-Cov-2 antibodies at baseline + geographic region + visit + treatment*visit + baseline log_{10} SARS-CoV-2 viral load *visit + error.

The within-patient correlation will be modeled using an unstructured covariance matrix in the mixed model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger 1997).

If the model fails to converge with unstructured covariance matrix, either a compound symmetry (first choice) or first order autoregressive (AR1) (second choice) covariance structure will be used.

The SAS procedure PROC MIXED will be used for analysis. Results will be presented with LSM and standard error (SE) for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for treatment contrasts of each ensovibep dose versus placebo.

Handling of intercurrent events follows the primary analysis. Any missing data for other reason than death/COVID-29 related hospitalization are considered MAR and handled as such in the MMRM.

5.7.2 Key secondary analysis

Not applicable.

5.8 Rule of exclusion criteria of analysis sets

Table 5.8-1 Subject Classification

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
SCR	NA	Not having ICF; Not having screening epoch disposition page
RAN	NA	Patients not being randomized.
FAS	NA	Not in RAN; Mistakenly randomized and no study drug taken
SS	NA	No study drug taken
PK analysis set	To be defined	Patients not having at least one available valid (i.e. not flagged for exclusion) PK concentration measurement No study drug taken.

6 Reference

Bretz, F., Pinheiro, J. C., and Branson, M. (2005). Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics 61, p 738–748.

CDER (2020a) US Department of Health and Human Services, Food and Drug Administration, Guidance for Industry: Assessing COVID-19-related symptoms in outpatient adult and adolescent subjects in clinical trials of drugs and biological products for COVID-19 prevention or treatment. Rockville, MD.

CDER (2020b) US Department of Health and Human Services, Food and Drug Administration, Guidance for Industry: COVID-19: Developing drugs and biological products for treatment or prevention. Rockville, MD.

EMA (2014) Qualification Opinion on MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty [http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/02/WC500161027.pdf].

FDA (2016) Fit-for-purpose determination letter, [https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM508700.pdf].

Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19. JAMA. 10.1001/jama.2021.0202 Published online January 21, 2021.

Pinheiro J, Bornkamp B, Glimm E, et al (2014) Model-based dose finding under model uncertainty using general parametric models. Statist Med; 33:1646–61.

Kenward, M. G., & Roger, J. H. (1997). Small sample inference for fixed effects from restricted maximum likelihood. Biometrics, 983-997.