Molecular Partners AG

Ensovibep/MP0420

Clinical Trial Protocol 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

Document type:	Amended Clinical Trial Protocol
EUDRACT number:	2021-000890-10
Version number:	01
Clinical Trial Phase:	Phase 2 and Phase 3
Release date:	19-Oct-2021

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List of abbreviations

ACE2	Angiotensin converting enzyme
ADA	Antidrug antibody
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	The area under the concentration-time curve
AUC_{inf}	The area under the concentration-time curve from time zero to infinity
AUC_{last}	The area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BMI	Body mass index
BUN	Blood Urea Nitrogen
CI	Confidence interval
CL	Apparent total body clearance of the drug from plasma
C_{max}	The observed maximum concentration
COVID-19	Coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DARPin®	Designed ankyrin repeat protein
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
eSource	Electronic Source
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
H	Hour

I	Human Serum Albumin
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio
IP	Investigation product
IQR	Interquartile range
IRB	Institutional Review Board
IRR	Infusion-related reactions
IRT	Interactive Response Technology
ITT	Intention-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IWRS	Interactive web response system
Lambda z (λ_z)	The terminal elimination rate constant
LDH	Lactate Dehydrogenase
LFT	Liver function test
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
mAb	Monoclonal antibody
MCS	Mental Component Summary
MedDRA	Medical dictionary for regulatory activities
MoA	Mechanism of action
NOAEL	No-observed-adverse-effect-level
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
PCS	Physical Component Summary
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PRO	Patient Reported Outcomes
PT	Prothrombin Time
PT	Preferred term
QMS	Quality Management System
RAN	Randomized set

RBD	Receptor Binding Domain
RT-PCR	Reverse transcriptase-polymerase-chain-reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	Screened set
SD	Standard deviation
SF-36	Short Form 36 Questionnaire
SMQ	Standardized MedDRA Query
SOC	System organ class
SRG	Safety Review Group
SS	Safety set
ß-HCG	Beta-chorionic gonadotropin
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	The terminal elimination half-life
TBL	Total bilirubin
TE-ADA	Treatment-emergent antidrug antibody
TEAE	Treatment-emergent adverse event
T_{max}	The time to reach the maximum concentration
ULN	Upper Limit of Normal
V_z	The apparent volume of distribution during terminal phase associated with λ_z
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), [redacted] tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as web-based applications, interactive voice response systems, and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly diagnosed disease
Patient	A trial participant
Patient number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.

Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the investigator that is coded and transferred to the sponsor for the purpose of the clinical trial. This data includes participant identifier information, study information, and biological samples.
Premature patient withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet, or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s), or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination; may consist of 1 or more cohorts
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent	Withdrawal of consent (WoC) from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 1 dated 19-Oct-2021 (global protocol amendment)

Amendment rationale

As of 19-October-2021, 381 patients have been treated in the study.

The purpose of this protocol amendment is to provide clarification around the data included in the primary analyses of Part A of the study. Clarification regarding the laboratory data available at the time of the database lock, unblinding after database lock and statistical analysis are the key changes reflected here.

For the primary analysis the laboratory analysis of some of the biomarker samples may not be fully completed in time for the reporting out of primary analysis for Part A and for planned regulatory submission(s). In order to allow study results to be shared with regulatory agencies as early as possible with the commitment to provide additional data in a timely fashion once it becomes available, some of these data may therefore need to be delivered in a staggered approach.

In this context, updates have been made to the unblinding process after the primary analysis for Part A and reference to the unblinding charter is included.

The primary estimand wording has been updated to follow recently published guidelines (FDA 2021). COVID-19 related hospitalizations have been added as intercurrent event for the primary endpoint of Part A, a composite strategy will be used to handle these intercurrent events.

The definition of AESIs has been updated and is no longer limited to AE onset within 24 hours after dosing, it includes infusion site reactions and any type of hypersensitivity reactions (CTCAE Grade 2 and above). The requirements for reporting renal events have been adjusted and also renal follow-up testing requirements (Appendix 4) have been updated for serum creatinine values, to account for the study patient population with acute COVID-19 infection (including use of concomitant medications like NSAIDs).

The EOS assessments have been clarified per a footnote in the assessment schedule to further guide the investigational team to make sure that, depending on when a patient`s last visit occurs, the correct assessments are being performed.

The study stopping rules have been clarified to follow CTCAE grading and explicitly include laboratory findings.

A clarification has been added to distinguish between hospitalizations due to worsening of COVID-19 (secondary endpoint) and between hospitalizations for the purpose of isolating patients following a positive SARS-CoV-2 test (not counted towards secondary endpoint).

The requirements for viral genotyping have been updated to make sure all PCR positive samples at baseline and from Day 8 onwards are being assessed for testing for viral variants.

In the statistical section, the changes related to the topics listed above have been implemented. In addition, clarification on the wording of the dose finding step in the MCP-Mod procedure has been added. [redacted] Other changes are minor clarifications, adjustments or corrections.

Also, the two local amendments for the USA and for India have been incorporated into this global amendment.

The exclusion of high risk patients is limited to the USA, since it is the only participating country where high risk patients have access to therapeutic mAbs. The change is currently applicable to Part A of the protocol, as if continuing with Part B will require a positive PoC per Part A, so placebo control may be warranted, pending health authority input if deemed necessary.

Finally, typos and inconsistencies have been corrected and minor editorial updates included.

Changes to the protocol

Protocol Summary:

In **Study design** and also in **Treatment of interest**, *Day 29 data analysis* has been changed to *primary analysis*.

In **Key exclusion criteria**, wording to exclusion criterion #2 was added to reflect changes in the local protocol amendment 1 for India.

Also, exclusion criterion # 11 was added to reflect the wording in the local protocol amendment 1 for the USA.

Section 2 Objectives and endpoints:

Table 2-1: The wordings related to IRRs (infusion related reactions) in the context to AESIs have been deleted as the definition of AESIs has been updated in Section 10.1.4 accordingly.

In Section 2.1.1 *COVID-19 related hospitalization* has been added to *death* to be handled as intercurrent event by composite strategy.

Section 3 Study design:

One sentence which had been added in the local amendment 01 for the USA has now been deleted to reflect the fact that in the USA also some high risk patients were enrolled by mistake (reported as PDs) and were stratified into the high risk stratum.

Section 4 Rationale:

Table 4-1: Per editorial update, *resistance mutation* was changed to *mutation analysis*.

Section 4.4 was updated to reflect the changes related to planned analyses in Part A and Part B of the study.

Section 5 Study population:

Wording to exclusion criterion #2 was added to reflect changes in the local protocol amendment 1 for India.

Exclusion criterion # 11 was added to reflect the wording in the local protocol amendment 1 for the USA.

Section 6 Treatment:

Section 6.4: The text related to the unblinding process prior and after the primary analysis has been updated.

Section 8 Visit schedule and assessments:

Tables 8-1 and 8-2 have been corrected for defining the EOS assessments, the investigational product, the laboratory and the PRO assessments.

Section 8.3.2: A clarification has been added for defining hospitalizations due to COVID-19.

Section 8.3.3.3: Missing information related to the required study days for SF-36 assessments has been added.

[redacted]

Section 9 Study discontinuation and completion:

Section 9.1.4: Study stopping rules have been corrected.

Section 10 Safety monitoring and reporting:

Section 10.1.4: The definition of AESIs has been updated.

Section 12 Data analysis and statistical methods:

Section 12.1: Wording updated for protocol deviations.

Section 12.2: High Level Term added for relevant medical histories and current medical conditions at baseline.

Section 12.4.2: The Dose-finding step wording and the Safety endpoints wording has been updated.

Section 12.4.3: The intercurrent events of the primary estimand for Part A have been updated.

Section 12.4.4: The wording for Handling of missing values not related to intercurrent events for Part A has been modified.

Section 12.5: The text for the Analysis of secondary endpoints has been corrected.

Section 12.5.2: The Adverse events section has been updated.

Section 12.6.1: The version of the SF-36 questionnaire used in the study has been corrected from version 2 to version 1 [redacted]

Section 12.7: The process for the primary analysis for Part A has been clarified.

Section 12.8.1: The text for the power calculations related to the primary endpoint for Part A has been updated.

Section 15 References:

Two references have been added.

Section 16 Appendices:

Appendix 1: A symptom response option has been corrected.

Appendix 3, Table 16-2: A footnote has been added to clarify handling of isolated AST elevations.

Appendix 4, Table 16-4: The follow-up testing requirements for renal AESIs have been updated.

Amendment 1 dated 17-Jun-2021 *(local amendment for the sites in India only)*

Amendment rationale

For patients in India, exclusion criterion 2 has been adjusted at the request of the Indian Subject Expert Committee (SEC) of the Central Drugs Standard Control Organization (CDSCO) and in alignment with the hospitalization criteria in AIIMS/ICMR Working Group Guidelines dated May 17, 2021 [A1]:

Patients with a respiratory rate of ≥ 24/min or with an oxygen saturation (SpO2) ≤ 93% on room air are not eligible for the study. The updated exclusion criterion will be limited to India.

Amendment reference:

[A1] All India Institute of Medical Sciences (AIIMS)/Indian Council of Medical Research (ICMR) COVID-19 Task Force, Joint Monitoring Group (Dte.GHS), Ministry of Health & Family Welfare, Government of India, Clinical Guidance for Management of Adult COVID-19 Patients, dated 17-May-2021

Changes to the protocol

Protocol Summary: This section has been revised to exclude patients with a respiratory rate of ≥ 24/min or with a SpO2 ≤ 93% (only applicable for patients to be enrolled in India).

Section 5.2: The protocol exclusion criterion has been revised to exclude patients in India with a respiratory rate ≥ 24/min or with a SpO2 ≤ 93%.

Amendment 1 dated 14-Apr-2021 *(local amendment for USA sites only)*

Amendment rationale

Several monoclonal antibody (mAb) therapies are now available in the USA under EUA (Emergency Use Authorization) for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Since conducting a placebo-controlled trial in this population may not be appropriate, the protocol has been amended to exclude COVID-19 patients in the USA who are at high risk for developing severe COVID-19 symptoms or the need for hospitalization. This has been done in alignment with the FDA.

The exclusion of high risk patients will be limited to the USA, since it is the only participating country where high risk patients have access to therapeutic mAbs. The change is applicable to Part A of the protocol.

Changes to the protocol

Protocol Summary: This section has been revised to exclude patients who are at high risk of progression to severe COVID-19 illness or hospitalization (only applicable for the patients to be enrolled at the USA sites in Part A).

Section 3: One sentence has been added to clarify that since in the USA only non-high risk patients for COVID-19 disease progression will be enrolled in Part A, these patients will be randomized into the "not at high risk patients" stratum.

Section 5.2: The protocol exclusion criteria have been revised to include that patients in the USA who are at high risk of progression to severe COVID-19 illness or hospitalization** must not be enrolled in Part A of the study as a placebo-controlled study may not be appropriate in this patient population due to the availability of anti-viral mAbs under EUA in the USA.

** "High risk of progression to severe COVID-19 illness or hospitalization" is defined to match the eligibility criteria for authorized therapy with therapeutic mAbs in the USA, i.e. as meeting at least one of the following criteria: Body mass index (BMI) ≥ 35; chronic kidney disease; diabetes mellitus; immunosuppressive disease; ongoing immunosuppressive treatment; age ≥ 65 years; or age ≥ 55 years in a patient with cardiovascular disease, or hypertension, or COPD / other chronic respiratory disease.

Protocol summary

Protocol number	MP0420-CP302 (CSKO136A12201J)
Full title	A randomized, double-blind, placebo-controlled, multicenter study of ensovibep (MP0420) in ambulatory adult patients with symptomatic COVID-19 – The "EMPATHY" Trial
Brief title	A study of ensovibep (MP0420) in ambulatory adult patients with symptoms of COVID-19
Sponsor	Molecular Partners AG
Responsible for conducting the study	Novartis Pharma AG
Responsible CRO	IQVIA (engaged by Novartis Pharma AG)
Clinical phase	Phase 2 and Phase 3
Investigation type	Biological
Study type	Interventional
Purpose and rationale	Establish the antiviral efficacy of ensovibep against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in humans, identify the optimal dose, and demonstrate its clinical value for treating COVID-19 in adult ambulatory patients
Primary objectives	**Part A** The primary objective of this Part is to demonstrate superiority of ensovibep, compared to placebo, in reducing SARS-CoV-2 viral load through Day 8. **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.
Secondary objectives	**Part A** The secondary objectives of this Part 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 through Day 29 • To evaluate safety and tolerability of ensovibep • To characterize the pharmacokinetics (PK) of ensovibep **Part B** The secondary objectives of this Part are: • To assess the effect of ensovibep, compared to placebo, in reducing SARS-CoV-2 viral load through Day 8 • To assess the effect of ensovibep, compared to placebo, in reducing COVID-19 symptoms up to Day 29 • To evaluate the immunogenicity of ensovibep and its clinical relevance (pharmacokinetic, efficacy, and safety). • To evaluate safety and tolerability of ensovibep

Study design	This is a randomized, double-blind, placebo-controlled, multicenter study of ensovibep (MP0420) in ambulatory adult 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) to progress into Phase 3, 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). Study duration for individual patients is 91 ± 7 days for both Parts. **Part A** This dose-ranging part of the study will include at least 400 randomized patients in four arms (3 active arms and one placebo arm), randomized 1:1:1:1 to receive ensovibep (75 mg, 225 mg, or 600 mg) or placebo, administered as a single intravenous (i.v.) infusion over 60 minutes, and stratified by risk for COVID-19 disease progression ("high-risk patients" versus "not at high-risk patients"). **Part B** Recruitment will begin in Part B once the most safe and efficacious dose has been selected from Part A based on the primary [day 8 viral load] analysis. Part B will recruit 1717 patients randomized 1:1 to either the selected dose of ensovibep or placebo, administered as a single i.v. infusion over 60 minutes. An interim analysis for early efficacy will be conducted when at least 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").
Study population	The study will recruit ambulatory symptomatic adult patients diagnosed with COVID-19 with onset of symptoms within 7 days prior to dosing and with a positive rapid antigen test on the day of dosing.
Key inclusion criteria	1. Men or women ≥ 18 years of age on the day of inclusion (no upper limit). 2. Presence of two or more COVID-19 symptoms and onset within 7 days prior to dosing: Feeling hot or feverish, cough, sore throat, low energy or tiredness, headache, muscle or body aches, chills or shivering, and shortness of breath. 3. Positive test for SARS-CoV-2 in upper respiratory swab on the day of dosing (rapid antigen test). 4. Understand and agree to comply with the planned study procedures. 5. The patient or legally authorized representative give signed informed consent.
Key exclusion criteria	1. Requiring hospitalization at time of screening, or at time of study drug administration. 2. Oxygen saturation (SpO2) ≤ 93% on room air at sea level or ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2) < 300, respiratory rate ≥ 30 per minute, and heart rate ≥ 125 per minute. **In India**, patients with a respiratory rate ≥ 24 per minute or with an oxygen saturation ≤ 93% on room air (SpO2) are not eligible. 3. Known allergies to any of the components used in the formulation of the ensovibep or placebo. 4. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides SARS-CoV-2) that in the opinion of the investigator could constitute a risk when taking intervention. 5. Any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, should preclude participation in this study. 6. Any co-morbidity requiring surgery within 7 days of dosing, or that is considered life-threatening within 29 days of dosing. 7. Prior or concurrent use of any medication for treatment of COVID-19, including antiviral agents, convalescent serum, or anti-viral antibodies. Purely symptomatic therapies (e.g., over-the-counter [OTC] cough medications, acetaminophen, and nonsteroidal anti-inflammatories [NSAIDs]) are permitted. Prior vaccination for COVID-19 is permitted.

	8. In the USA, patients who are at high risk of progression to severe COVID-19 illness or hospitalization (only applicable for the patients to be enrolled in Part A at the USA sites).
Study treatment	The investigational drug is ensovibep, provided in isotonic buffer matrix with 15 mg/mL. For Part A, 10 mL vials are used. Isotonic saline is used as placebo. For Part B, 5 mL vials are used, with a modified buffer (detail see Section 6.1.1). A dedicated placebo will be provided.
Treatment of interest	**Part A** Patients in Part A will be randomized in a ratio of 1:1:1:1 on Day 1 to receive a single i.v. dose of one of the following four treatment arms: • Ensovibep, 75 mg • Ensovibep, 225 mg • Ensovibep, 600 mg • Placebo **Part B** Once the optimal safe and efficacious dose has been selected from Part A, patients in Part B will be randomized in a ratio of 1:1 on Day 1 to receive a single i.v. dose of one of the following two treatment arms: • Ensovibep (dose selected from Part A based on primary [Day 8] analysis) • Placebo
Biomarkers	[redacted] • Anti-drug antibodies (ADAs) [redacted] • Inflammatory biomarkers
Pharmacokinetic assessments	Assessment of free ensovibep (ensovibep not bound to target) and total ensovibep (sum of ensovibep bound to target and ensovibep not bound to target) concentration in serum and calculated PK parameters.
Key safety assessments	• Adverse event (AE) monitoring • Physical examination • Vital signs • Laboratory evaluations
Data analysis	**Part A** Time-weighted change from baseline (Day 1) to Day 8 in $\log_{10}$ SARS-CoV-2 viral load in nasopharyngeal swabs will be calculated for each patient. The generalized MCP-mod methodology (Bretz 2005; Pinheiro 2014) will be implemented using time-weighted change from all time points until Day 8 to confirm an overall dose-response signal and to estimate the optimum dose that corresponds to the clinically relevant effect over placebo. The following candidate model set will be used: E_{max} (ED_{50}) = 8, 40, 180 and sigmoid E_{max} (ED_{50}, h) = (120, 4), (450, 3). Effect on time-weighted change will be evaluated using an analysis of covariance (ANCOVA) adjusting 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 other relevant parameters (specified in the SAP) as covariates using the Full Analysis Set (FAS) for statistically significant model(s) from candidate set. Testing will be done at the one-sided 10% alpha level. **Part B** 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.
Key words	COVID-19, COVID 19, SARS-CoV-2, Coronavirus, ensovibep, MP0420, DARPin

1 Introduction

1.1 Background

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While most cases are mild or asymptomatic, progressive disease can result in hospitalization, requirement for mechanical ventilation, and substantial morbidity and mortality (Johns Hopkins University). SARS-CoV-2 is estimated to be about 10 times more deadly than seasonal influenza virus (Faust 2020). Risk factors for an unfavorable course include advancing age (Zhou 2020), obesity (Hamer 2020), and comorbidities such as diabetes mellitus (Caballero 2020) and hypertension (Wu 2020, Choi 2020).

COVID-19 has a median incubation period of 4 days (interquartile range [IQR] 2 to 7 days) (Guan 2020) and the mean serial interval defined as the time duration between a primary case-patient (infector) having symptom onset and a secondary case-patient (infected) having symptom onset for COVID-19 was calculated as 3.96 (95% confidence interval [CI] 3.53 to 4.39) days (Du 2020). Viral kinetic studies have demonstrated extensive SARS-CoV-2 viral replication in the pharynx just before and early after symptom onset (He 2020).

The clinical course of SARS-CoV-2 infection is non-specific at the beginning; the most common symptoms at onset of illness are fever, cough, fatigue, and myalgia (Cevik 2020). A majority of patients recover within 2 to 3 weeks. Those who progress to more severe symptoms typically develop dyspnea between Day 4 and Day 10 of illness (Cohen 2020).

Weeks and months after the onset of acute COVID-19 some infected patients still continue to suffer from symptoms. This prolongation of illness after the acute COVID infection is known as Long-COVID-19 or Post-COVID-19 syndrome (Morley 2020). This seems to affect patients with mild COVID-19 as well as those with moderate-to-severe disease. The symptoms of Long-COVID-syndrome include shortness of breath, fatigue, coughing, and neurological symptoms such as altered taste, depression, and reduction in the abilities of daily living. The cause of these prolonged symptoms is unknown. The scale of the pandemic makes the prevention of Long-COVID-syndrome an imperative. It has been hypothesized that by managing the infection earlier post viral syndromes (including Long-COVID-syndrome) could be reduced in incidence and severity.

Several vaccines against SARS-CoV-2 have become available for use, and vaccinations have been initiated in many countries for the most vulnerable and the most exposed population. These vaccines appear to have high vaccine efficacy of > 90%; however, it's currently unknown if vaccine effectiveness will be maintained long-term (COVID-19 vaccines - EMA 2021). In addition, vaccine availability and logistics of vaccinations are current bottlenecks, anticipated to be overcome before the end of 2021 in high-income countries. Nevertheless, the proportion of individuals who are skeptical about vaccinations is globally between 40% and 80% (Yougov 2021). In many middle- or low-income countries, limited availability of vaccines is

anticipated to remain a bottleneck well beyond 2021, and herd immunity is unlikely before 2023 (The Conversation 2021).

In addition, since December 2020, the emergence of multiple mutated strains of SARS-CoV-2 with higher infectivity is causing increasing concerns. Measures effective to prevent transmission in the wild-type strain may be insufficient to prevent spreading of more infective mutant strains. Mutations are mostly found in the spike protein region, which is the target for current vaccines. Research to evaluate the effectiveness of currently available vaccines versus emerging mutant strains is ongoing.

Some treatment options for patients with severe disease requiring hospitalization have become available: Remdesivir, the only currently approved drug against COVID-19, reduced the time to discharge in early hospitalized patients, and has entered the standard of care in several countries, although it is not recommended by the World Health Organization (WHO) based on "no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient reported outcomes". Corticosteroids have emerged as the treatment of choice for critically ill patients.

Still, interventions that can be administered early during the course of infection to prevent disease progression and longer-term complications are urgently needed (Kim 2020). Multiple antiviral monoclonal antibodies (mAbs) are under development, specifically targeting SARS-CoV-2's spike protein and thereby its ability to enter the host cell for viral replication. Recent data indicate this therapeutic mode of action is beneficial in ambulatory patients treated within the first 7 days after symptom onset, reducing by the need for subsequent "medically attended visits" (hospitalizations, emergency room visits, urgent case or other physician contact for COVID-19) by half (Chen 2020, Weinreich 2020, Gottlieb 2021). However, mutant strains are capable to escape the therapeutic effects of mAbs (Starr 2021), as well as endogenous immunity of recovered patients (Greany 2021).

Ensovibep is a designed ankyrin repeat protein (DARPin®) molecule consisting of a chain of five covalently linked DARPin® domains with, sequentially, two N-terminal anti-human serum albumin (HSA) domains followed by three domains that specifically bind to the trimeric receptor binding domain (RBD) of the SARS-CoV-2 spike protein. The three RBD binding domains bind to the same epitope but their paratope sequences are different. The cooperative binding of these domains prevents the RBD from binding to angiotensin-converting enzyme 2 (ACE2) on the surface of target cells. The anti-HSA domains are intended to confer an extended half-life in vivo. The HSA-binding domains are cross-reactive to the respective mouse, hamster, and cynomolgus monkey homologs.

The rationale for the clinical development of ensovibep (MP0420) is to provide a safe and effective therapy for SARS-CoV-2 infections. Effective in that it prevents or reduces the need for hospitalization and safe in that it does not provoke excessive immunological and inflammatory responses in patients with pre-existing SARS-CoV-2 infection. Due to its multi-specificity (see below), it is expected to maintain efficacy as virus spike protein mutants

emerge. In addition, it is anticipated that lower doses of ensovibep will be required compared to monoclonal antibodies because of its smaller size and higher in vitro antiviral potency.

The SARS-CoV-2 spike glycoprotein is key for host-cell interaction of the virus (Zhou P 2020, Walls 2020, Hoffmann 2020). It comprises two functional units: S1, which includes RBD responsible for interaction with host receptors (Hoffmann 2020) such as ACE2, and S2, which is responsible for virus-host cell membrane fusion by way of conformational change following protease cleavage (Walls 2020, Wrapp 2020).

Ensovibep has been well-tolerated in healthy volunteers at doses of 3 mg/kg and 9 mg/kg when administered as a single infusion over 1 hour as a part of an ongoing Phase 1 First-in-Human (FIH) clinical trial (Study MP0420-CP101).

1.2 Purpose

The clinical assessment of safety, tolerability, and pharmacokinetics (PK) of ensovibep is ongoing in Study MP0420-CP101, a dose-escalation study in healthy volunteers, exploring doses of 3, 9, and 20 mg/kg, under surveillance by a Safety Review Group (SRG). Doses (3 mg/Kg and 9 mg/Kg) have been administered as single 60-minute infusions and have been well tolerated; 20 mg/Kg dose cohort is pending. The safety, tolerability and PK of administration times less than 10 minutes ("bolus injection") will also be assessed in additional cohorts of healthy volunteers within the same study.

Study MP0420-302, is an operationally seamless two part, randomized, double-blind, multicenter, Phase 2 and Phase 3 study designed to assess the efficacy, safety, tolerability, and PK of ensovibep in adult ambulatory patients with symptomatic COVID-19. Part A is the Phase 2 component of the study that will serve to show proof of efficacy in order to progress to Phase 3 and to support selection of the best efficacious and safe dose; Part B is the Phase 3 component of the study that will confirm efficacy and safety of ensovibep at the dose selected based on the data from Part A.

The study will use the acronym EMPATHY: **E**nsovibep **M**ulticenter **P**lacebo-controlled study in **A**mbulatory patients with symp**T**omatic COVID-19 (P**H**ase 2 and 3 for efficac**Y** and safety).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Part A	
Primary objective	**Endpoint for primary objective**
• 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
Secondary objectives	**Endpoints for secondary objectives**
• To assess the effect of ensovibep, compared to placebo, in reducing the occurrence of hospitalizations	• Proportion of patients experiencing hospitalizations (≥ 24 hours of acute care) and/or

(≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29	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:
	  • Serious adverse events (SAEs), including death from any cause
	  • 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	• Change from baseline in log_{10} SARS-CoV-2 viral load in nasopharyngeal swabs at Day 3, Day 5, and 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 and its clinical relevance (pharmacokinetic, efficacy and safety).	• 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:
	  • Serious adverse events (SAEs), including deaths from any cause
	  • AEs of Special Interest (AESIs)
	• Vital signs
	• Clinical laboratory measurements

Exploratory objectives	Endpoints for exploratory objectives
[redacted]	[redacted]
[redacted]	[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]	[redacted]
[redacted]	[redacted]

2.1 Primary estimands

2.1.1 Part A

The primary clinical question of interest is: what is the dose response of ensovibep compared to placebo on $\log_{10}$ SARS-CoV-2 viral load through Day 8 in ambulatory adult patients with newly symptomatic COVID-19?

The primary efficacy response time-weighted change from baseline in $\log_{10}$ SARS-CoV-2 viral load in nasopharyngeal swabs through Day 8 and rationale for selection as a primary objective can be found in Section 4.1.

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 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
3. **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
4. **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.
5. **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.

2.1.2 Part B

The primary clinical question is: what is the effect of ensovibep compared to placebo on reducing the percentage of patients requiring hospitalizations and/or emergency room visits related to COVID-19 or death from any cause up to Day 29 in ambulatory adult patients with newly symptomatic COVID-19? Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

The primary efficacy response is hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29 and rationale for selection as a primary objective can be found in Section 4.1.

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

2.2 Secondary estimands

Not applicable.

The secondary objectives for both Parts will be referred to as endpoints.

3 Study design

This is a randomized, double-blind, placebo-controlled, multicenter study of ensovibep (MP0420) in ambulatory adult 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

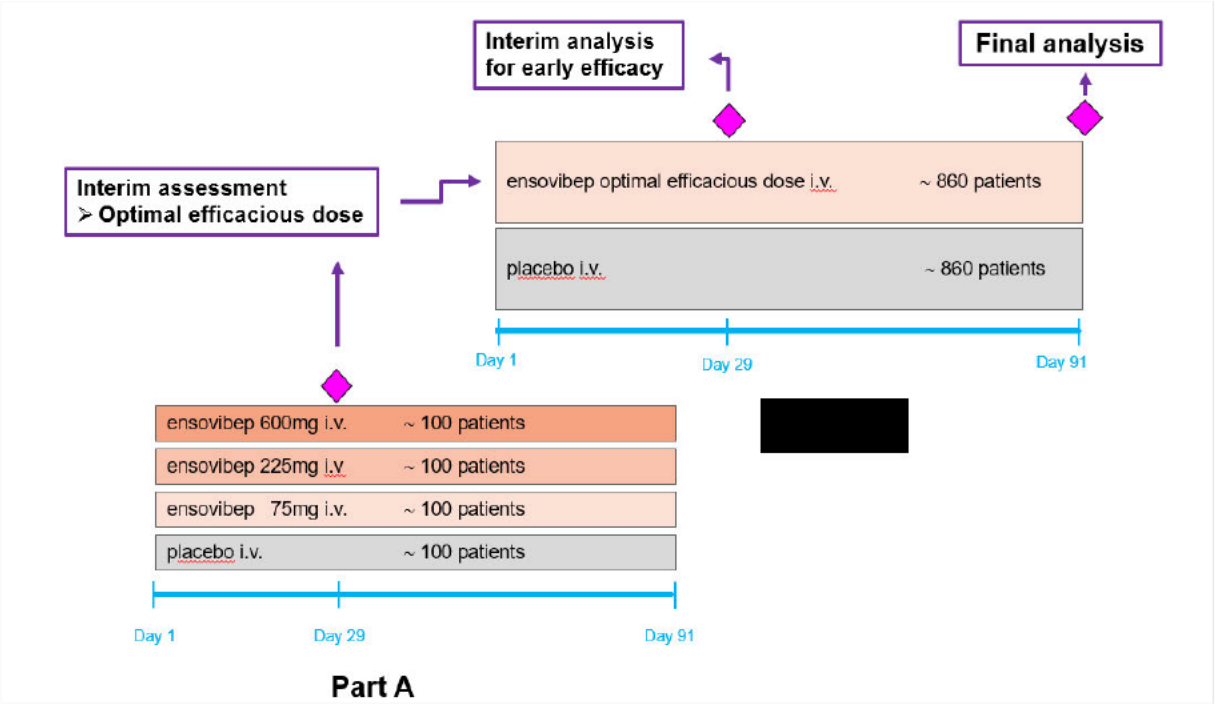
This dose-ranging part of the study will include at least 400 randomized patients in four arms (3 active arms and one placebo arm), randomized 1:1:1:1 (see also Figure 3-1) to receive ensovibep (75 mg, 225 mg, or 600 mg) or placebo, administered as a single intravenous (i.v.)

infusion over 60 minutes, and stratified by risk for COVID-19 disease progression ("high-risk patients" versus "not at high-risk patients", see Section 6.3.2).

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 1717 patients randomized 1:1 (see also Figure 3-1) to either the selected dose of ensovibep or placebo, administered as a single i.v. infusion over 60 minutes. An interim analysis for early efficacy will be conducted when at least 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", see Section 6.3.2).

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

The rationale for the various study design aspects of the study is presented in Table 4-1.

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Part A primary endpoint selection of time-weighted change from baseline (measured at Day 1 (pre-dose), Day 3, Day 5, and Day 8) in log_{10} SARS-	To assess antiviral activity of the compound, anticipated to be the most informative parameter for dose selection. It is expected

Study Design Aspect	Rationale
CoV-2 viral load in nasopharyngeal swabs through Day 8.	that in the first week after symptom onset the effect of ensovibep is most prominent.
Part B primary endpoint selection of proportion 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.	To assess a clinically meaningful endpoint as requested by regulatory authorities for up to 4 weeks after treatment.
Duration of long-term follow-up at Day 91.	To evaluate long-term safety and track for long-COVID symptoms.
Parallel design, 4 treatment arms in Part A.	To evaluate different dose levels of ensovibep versus placebo and determine the optimal efficacious and safe dose.
Parallel design, 2 treatment arms in Part B.	To confirm efficacy and safety of the optimal dose identified based on data from Part A versus placebo.
Randomization and placebo arm.	Randomization and the inclusion of a control arm are essential to control unintended introduction of bias into the study results necessary to establish the safety and efficacy of ensovibep in COVID-19. A placebo arm is planned for comparison as no antiviral therapy is approved for treatment of ambulatory COVID-19 patients.
Blinding.	The double-blinded design is important, to make objective assessments of the pharmacological effect of the study treatment and to minimize the effect of assessment bias.
Single-dose study.	Based on the predicted serum half-life of two to three weeks in humans, a single systemic dose regimen is proposed for treatment of COVID-19.
Phase 2 and Phase 3 study in the same protocol.	To improve the operational efficiency between identifying a safe and efficacious dose in the dose-ranging study Part A and the initiation of the Phase 3 confirmatory study in Part B.
Interim analysis in Part B.	To allow for early stopping for efficacy using appropriate alpha spending.
COVID-19 Tests: • Swab: Rapid SARS-CoV-2 antigen test. • Swab: SARS-CoV-2 PCR test. • Swab: SARS-CoV-2 mutation analysis. • Anti-SARS-CoV-2 antibody test.	The rapid antigen test will be performed to quickly identify patients with ongoing presence of viral load at randomization; the RT-PCR test will be used in retrospect for confirmation of the rapid antigen test. For patients with a positive rapid test not confirmed by a positive PCR test (Day 1 or Day 3), SARS-CoV-2 infection will be considered uncertain. A sensitivity analysis excluding these patients will be conducted.

4.1.1 Rationale for choice of background therapy

Background standard of care therapy should be maintained in all treatment arms according to local practice. To alleviate symptoms and prevent complications related to COVID-19, symptomatic treatments and anticoagulants/blood thinners should be continued. Based on the mechanism of action (MoA) of ensovibep, no drug-drug-interactions are expected. Please also see Section 6.2.

4.2 Rationale for dose/regimen and duration of treatment

Clinical dose and regimen projections for ensovibep are based on an integrated analysis of the following: pre-clinical pharmacology results, available clinical safety, tolerability and PK results from the ongoing Phase 1 dose-escalation FIH study (MP0420-CP101), and PK/pharmacodynamic (PD) modeling. Each of these elements are briefly summarized below. Based on these investigations a single, i.v. infusion of 75 mg is projected to have a near-maximal effect. To allow for uncertainty within the projections, it is recommended that the Phase 2 dose and regimen proceed with single, i.v. infusions at 75, 225, and 600 mg in SARS-CoV-2 patients. Parenteral administration is required because of the chemical structure (protein). A single administration is used because the half-life of approximately 2 weeks will ensure a sufficient duration of exposure for the disease. Three doses separated by approximately a factor of 3 are an appropriate approach for capturing an eventual dose-effect relationship.

Preclinical pharmacology for MP0420

In vitro pharmacology studies demonstrated that MP0420 displays sub-pM binding affinities to the SARS-CoV-2 RBD (SPR assessment) and has IC_{50} values in the range of 10-50 pM (1-5 ng/mL) in SARS-CoV-2 neutralizing assays against wild-type, pathogenic, and pseudo-type viruses. Furthermore, IC_{50} values in the same range were observed for pseudo-type viruses with different spike serotypes suggesting that MP0420 could be effective against mutational escape. Based on non-clinical pharmacology assessment in SARS-CoV-2 infected hamsters, therapeutic dosing regimen for MP0420 have been identified between 3 and 20 mg/kg. When dosed during infection (acute) rather than prior to infection (prophylactic) efficacious doses are observed at 9 mg/kg and higher with significant improvement in mortality that are generally associated with a reduction in SARS-CoV-2 viral load.

Initial human safety, tolerability, and PK results from MP0420-CP101

The safety-focused no-observed-adverse-effect-level (NOAEL) approach was used to determine FIH doses of 3, 9 and 20 mg/kg for MP0420-CP101 (summary of the relevant pre-clinical safety data can be found in the Investigator's Brochure [IB]). Dosing of healthy volunteers with single i.v. infusions of 3 and 9 mg/kg (8 mg/kg would equate to a single dose of 600 mg in a 75 kg person) was completed. MP0420-CP101 Phase 1 investigation of the safety, tolerability, and PK of MP0420 in healthy participants is ongoing, and to date MP0420 was assessed as safe and well-tolerated and no serious adverse effects have been reported. A 20 mg/kg cohort will be enrolled in Q1 2021. Based on this, the proposed doses of 75, 225, and 600 mg are expected to be safe in SARS-CoV-2 infected patients.

Preliminary PK data from cohort 1 (i.v., 3 mg/kg) and cohort 2 (i.v., 9 mg/kg) are available. The estimated half-life for MP0420 across cohorts is approximately 14.4 days (mean, range: 11.4-24.0 days). Slightly greater than dose-proportional increases in exposure were observed from cohort 1 to cohort 2 (3.8-fold increase in AUC with a 3-fold increase in dose). Cohort 1 exhibited serum concentrations on Day 14 of 31.9 ± 6.3 ug/mL (mean ± standard deviation [SD]), which corresponds to 378 ± 75 nM (mean ± SD), and is > 1000-fold above the IC_{50} determined for MP0420 in infected Vero E6 cells. Cohort 1 exposures approximate the 225 mg single dose, which is the mid-dose in this dose-range finding study.

PK/PD modeling

The PK/PD model was constructed from publicly available data describing viral kinetics from SARS-CoV-2 patient throat swabs from untreated COVID-19 patients and calibrated to describe reported viral load data from patients treated with a neutralizing antibody therapeutic (LY-CoV555). The PK/PD model accounts for MP0420 PK, binding affinities, and MoA to predict effects in the lung. Simulations from the PK/PD model indicate that near-maximal binding of SARS-CoV-2 RBD is observed for MP0420 with a single, i.v. dose of 75 mg (> 95% reduction in free viral spike protein AUC), which is expected to correlate with clinical efficacy. Due to uncertainties in both the modeling predictions and the severity of disease at onset of therapy it is recommended that 75 mg, 225 mg, and 600 mg doses should be tested as part of a dose-range finding study in SARS-CoV-2 infected patients.

4.3 Rationale for choice of control drug (placebo)

Given that no products have received full approval for the sponsor's intended label claim, the sponsor proposes that placebo is the most appropriate comparator for this study. This approach is best scientific practice and has been endorsed by regulatory authorities in United States of America and Europe at recent Health Authority interactions.

4.4 Purpose and timing of planned analyses/design adaptations

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general, or in case of any safety concerns.

Additional information is presented in the interim analysis section.

Part A

A primary analysis based on viral load up to Day 8 is planned. This analysis is planned after all patients have completed the Day 29 visit. Additional unplanned data analyses may be required to fulfill regulatory requests. A final analysis for Part A is planned once all participants in Phase 2 complete the study, i.e. Day 91 of follow up. Additional details will be included in the SAP and finalized prior to the database lock for the primary analysis.

Part B

A single interim analysis is planned after at least 50% of patients enrolled on Part B have completed Day 29 assessments. The interim analysis allows for stopping due to efficacy, to allow for possible accelerated development of ensovibep. A final analysis for Part B will be done once all patients in Phase 3 complete the study, i.e. Day 91 of follow up.

4.5 Risks and benefits

Unmet medical need - There is an ongoing need for effective antiviral treatment of COVID-19. Vaccines have started to become available, but their ability to prevent transmission or to create long term immunity remains to be determined, their acceptance by the population is currently mixed, their effectiveness against actual and future mutant virus strains is unclear, and – most importantly – their limited availability (in particular, outside the Western World) will result in an ongoing need for therapies for the next 2-3 years or longer. The first monoclonal antibodies targeting SARS-CoV-2 have obtained emergency use authorizations for ambulatory patients with COVID-19 who are at high risking of developing severe COVID-19 and/or hospitalization, but their high cost of production, limited supplies, and the challenges of administration have resulted in very limited use outside clinical trials.

Potential benefits - Based on non-clinical studies, ensovibep has the potential to produce antiviral effects which could be beneficial in patients with confirmed SARS-CoV-2 infection as well as prophylactically in subjects at risk of infection. The potential benefits are expected to be related to an early resolution of symptoms and a lower probability of progressing to severe disease requiring hospitalizations or leading to death.

Potential risks - Due to its specificity for the virus target and based on non-clinical studies, ensovibep is expected to have an acceptable safety profile. In healthy volunteers, excellent tolerability has been confirmed for 3 mg/kg and 9 mg/kg doses.

However, as ensovibep is a biological agent there is a potential risk of infusion reactions occurring. Consequently, guidance for infusion reaction management is provided in the clinical trial protocol.

There is a potential for patients to develop antidrug antibodies (ADAs), therefore emergence of ADAs will be closely monitored during the study.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria and close clinical monitoring, including by an independent data monitoring committee (IDMC).

Conclusion - Taking these potential benefits and risks into consideration, the sponsor is of the opinion that the potential benefits of ensovibep outweigh the potential risks.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol.

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Refer to the IB.

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 91 days, from each patient as part of the study. Additional samples with a volume smaller than a typical blood donation may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage, and shipment information are also available in the Laboratory Manual.

5 Study population

The study will recruit ambulatory symptomatic adult patients diagnosed with COVID-19, with onset of symptoms within 7 days prior to dosing and with a positive rapid antigen test on the day of dosing.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** the following criteria:

1. Men or women ≥ 18 years of age on the day of inclusion (no upper limit).
2. Presence of two or more of the following COVID-19 symptoms with an onset within 7 days of dosing: Feeling hot or feverish, cough, sore throat, low energy or tiredness, headache, muscle or body aches, chills or shivering, and shortness of breath.
3. Positive test for SARS-CoV-2 in upper respiratory swab on the day of dosing (rapid antigen test).
4. Understand and agree to comply with the planned study procedures.
5. The patient or legally authorized representative give signed informed consent.

5.2 Exclusion criteria

Patients meeting **any** of the following criteria are **not** eligible for inclusion in this study.

1. Requiring hospitalization at time of screening, or at time of study drug administration.
2. Oxygen saturation (SpO2) ≤ 93% on room air at sea level or ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2) < 300, respiratory rate ≥ 30 per minute, and heart rate ≥ 125 per minute.

   In India, patients with a respiratory rate ≥ 24 per minute or with an oxygen saturation ≤ 93% on room air (SpO2) are not eligible.

3. Known allergies to any of the components used in the formulation of the ensovibep or placebo.
4. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides SARS-CoV-2) that in the opinion of the investigator could constitute a risk when taking intervention.
5. Any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study.*
6. Any co-morbidity requiring surgery within 7 days of dosing, or that is considered life--threatening within 29 days of dosing.
7. Prior or concurrent use of any medication for treatment of COVID-19, including antiviral agents, convalescent serum, or anti-viral antibodies. Purely symptomatic therapies (e.g., over-the-counter [OTC] cough medications, acetaminophen, and nonsteroidal anti-inflammatory drugs [NSAIDs]) are permitted. Prior vaccination for COVID-19 is permitted.
8. Are concurrently enrolled or were enrolled within the last 30 days or within 5 half-lives (whichever is longer) in any other type of medical research judged not to be scientifically or medically compatible with this study.
9. Are pregnant or breast feeding.
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception at the time of dosing and for 11 weeks after dosing of study drug. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (i.e., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not acceptable methods of contraception.
    b. Female sterilization (have had bilateral surgical oophorectomy [with or without hysterectomy], total hysterectomy, or bilateral tubal ligation at least 6 weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    c. Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.
    d. Use of oral, injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

11. For Part A only: Patients in the USA who are at high risk of progression to severe COVID-19 illness or hospitalization** must not be enrolled in Part A of this study as a

placebo-controlled study may not be appropriate in this patient population due to the availability of anti-viral mAbs under EUA in the USA.

** "High risk of progression to severe COVID-19 illness or hospitalization" is defined to match the eligibility criteria for authorized therapy with therapeutic mAbs in the USA, i.e. as meeting at least one of the following criteria: Body mass index (BMI) ≥ 35; chronic kidney disease; diabetes mellitus; immunosuppressive disease; ongoing immunosuppressive treatment; age ≥ 65 years; or age ≥ 55 years in a patient with cardiovascular disease, or hypertension, or COPD / other chronic respiratory disease.

* Co-morbidities defining clinically vulnerable patients (with high risk for progression to serious COVID-19 disease), for example obesity or diabetes, are generally *not* exclusion criteria.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 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. For Part B [redacted]

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Part A

Patients in Part A will be assigned on Day 1 at Visit 1 to one of the following 4 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 optimal 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 (optimal safe and efficacious dose, selected in Part A)
- Placebo

6.2 Other treatments

6.2.1 Concomitant therapy

Ongoing long-term medications should be continued and adjusted as needed for the management of underlying conditions.

Symptomatic therapy to manage COVID-19 symptoms, such as antipyretics, analgesics, or oxygen, is permitted. If local standard of care includes further medications tailored to prevent COVID-19 complications (e.g., anticoagulation), these may be used, with the exception of drugs that are immunomodulators (e.g., interferon, tocilizumab, sarilumab, colchicine), immunosuppressives (e.g., steroids) or antivirals. Patients will be required to get upfront approval from the investigator to start any new prescription, OTC, and herbal medication treatments, with the exception of paracetamol up to 3 g/day, which does not require upfront investigator approval.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded on the appropriate Case Report Forms (CRFs). Prior concomitant therapy defined as all medications taken within 30 days prior to enrollment will also be recorded appropriately in the CRFs.

SARS-CoV-2 vaccinations must not be scheduled up to the Day 29 visit, and if possible, should be postponed to take place after completion of the study (Day 91 visit) as ensovibep may neutralize the effectiveness of the vaccine. If such vaccinations take place prior to the last visit, they need to be documented in the relevant electronic Case Report Form (eCRF).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the medical monitor before randomizing a patient or allowing a new medication to be started.

6.2.2 Prohibited medication

The following concomitant therapies are prohibited: SARS-CoV-2 antiviral medication (experimental or approved), including convalescent serum or anti-viral antibodies; immune-modulating (e.g., interferon, tocilizumab, sarilumab) or immunosuppressive (e.g., steroids) medications initiated for management of COVID-19. However, patients who use immunosuppressive drugs as long-term or chronic treatment for pre-existing conditions and are on a stable dose and regimen may continue to use them.

6.2.3 Rescue medication

Study participants who have progression of their COVID-19 such that they require treatment at the discretion of the investigator or treating physician should receive appropriate medical care, which may include: Anti-SARS-CoV-2 antiviral medication (experimental or approved), including convalescent serum or anti-viral antibodies; immune-modulating (e.g., interferon, tocilizumab, sarilumab, and colchicine) or immunosuppressive (e.g., steroids) medications for management of COVID-19.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is enrolled for screening and is retained for the patient throughout his/her participation in the trial. A new Patient No. will be assigned at every subsequent enrollment if the patient is re-screened. The Patient No. consists of the Center Number (Center No.) (as assigned to the investigative site) with a sequential patient number suffixed to it, so that each patient's participation is numbered uniquely across the entire database. Upon signing the ICF, the patient is assigned to the next sequential Patient No. available.

6.3.2 Treatment assignment, randomization

At Visit 1, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the preparation of investigational product (IP) infusion to be administered to the patient. There will be a blinded and unblinded access to the IP allocation from IRT depending on site staff role for Part A. Part B will be fully blinded.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates

the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced using a validated system that automates the random assignment of medication numbers to vials containing the study treatment.

Stratification criteria

Randomization will be stratified by risk of progression to severe COVID-19 and/or hospitalization: "high risk" or "not at high risk". The stratum will be determined by the investigator according to below and entered into the interactive web response system (IWRS) at the time of randomization.

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".

6.4 Treatment 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 Contract Research Organization [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 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 [redacted] The pharmacometrician and the pharmacokineticist will work independently and will only disclose results once the database is locked after all patients complete Day 29 in Part A.

Unblinding after the primary analysis database lock in Part A

After the database lock for the primary analysis in Part A, a small 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 team members will 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.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The start and end date/time of each infusion as well as any infusion interruptions (stop and restart times) will be documented in the eCRF. The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

Compliance will not be evaluated for this single-dose study.

6.6.2 Recommended treatment of adverse events

For treating patients who deteriorate in their symptoms or conditions related to COVID-19, please refer to Section 6.2. Any infusion-related reactions should follow standard of care (symptomatic treatment), please see Section 9.1.1.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Blinding codes may also be broken after a patient discontinues treatment due to disease progression if deemed essential to allow the investigator to select the patient's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the clinical monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- name (if available)
- patient number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

Drug preparation and dilution according to study arm, prior to administration, is described in the IMP handling and administration manual.

A unique medication number is printed on the study medication label.

6.7.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the IMP handling and administration protocol.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective sponsor`s Quality Assurance.

Study treatment will be prepared by independent pharmacist or qualified site personnel in order to ensure treatment masking. Following labeling and secondary packaging, the MP0420 IMP is supplied as a sterile solution for i.v. infusion. For clinical administration, the required volume of MP0420 IMP will be calculated as defined in the MP0420 clinical trial protocol. Sterile 0.9 % NaCl infusion bags will be used. First, a sodium chloride solution volume equivalent to the required MP0420 IMP volume will be removed from the bag. Second, the required volume of MP0420 IMP will be injected into the bag. The i.v. infusion will then be performed according to standard clinical procedures using a 0.2 µm in-line filter, and followed by an infusion set flush using 25 mL from a fresh 0.9 % NaCl infusion bag.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log will be returned to the CRO as part of the final drug accountability filing.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

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

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

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

The following informed consents are included in this study:

- Main study consent for Phase 2 study
- Main study consent for Phase 3 study

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements.

8 Visit schedule and assessments

The Assessment Schedule (Part A: Table 8-1, Part B: Table 8-2) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Part A: Table 8-1, Part B: Table 8-2) or as close to the designated day/time as possible. Study visits can be performed as home visits by a healthcare provider (e.g., a nurse). Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, AE and concomitant medications will be recorded on the CRF.

When the following assessments are scheduled to be performed at the same time point, the order of priority will be as follows: questionnaire, vital signs, swab/blood sample.

Every effort will be made to take the PK sample at the protocol specified time.

Table 8-1 Part A: Assessment schedule

Visit Name	S1 [6]	V1		V2	V3	V4	V5	V6	V7	V8	V9
Study Day	-3 to -1	1		3	5	8 ± 2	15 ± 3	22 ± 4	29 ± 5 (EOS) [7]	61 ± 5	EOS[8] / 91 ±7
		pre-dose	post-dose								
STUDY ENTRY AND GENERAL ASSESSMENTS											
Informed consent	(X)	X									
Inclusion/Exclusion criteria	(X)	X									
Demographics	(X)	X									
Complete medical history	(X)	X									
INVESTIGATIONAL PRODUCT											
Ensovibep (MP0420)/Placebo			X								
SAFETY ASSESSMENTS											
Prior/concomitant medication evaluation	Continuous starting after ICF signature, until 3 months after study medication										
Prior/concomitant hospitalization and procedures	Continuous starting after ICF signature, until 3 months after study medication										
AE evaluation	Continuous starting after ICF signature, until 3 months after study medication										
Local tolerability			X								
Physical examination and vital signs [1]	(X)	X									
General physical appearance and vital signs [1]				X	X	X	X		X		X
Body temperature, respiratory rate, oximetry	(X)	X		X	X	X	X		X		X

Visit Name	S1 [6]	V1		V2	V3	V4	V5	V6	V7	V8	V9
Study Day	**-3 to -1**	**1**		**3**	**5**	**8 ± 2**	**15 ± 3**	**22 ± 4**	**29 ± 5 (EOS) [7]**	**61 ± 5**	**EOS[8] / 91 ±7**
		pre-dose	**post-dose**								
Weight	(X)	X									X
Height	(X)	X									
Hematology, chemistry and coagulation safety tests		X		X			X		X	X	X
Pregnancy test in WOCBP [2]	(X)	X									X
Birth Control	Continuous until EOS [3]										
VIROLOGY & SEROLOGY ASSESSMENTS											
Rapid SARS-CoV-2 antigen test	(X)	X									
SARS-CoV-2 sample (quantitative RT-PCR, mutation analysis)		X		X	X	X	X		X		X
[redacted]											
PK blood sample		X	XX [4]	X		X	X		X	X	X
[redacted]											
Blood sample for serum biomarkers		X		X		X	X		X		X
CLINICAL ASSESSMENTS											
Symptom score [5]		X		Daily assessment				X	X		
[redacted]											

Visit Name	S1 [6]	V1		V2	V3	V4	V5	V6	V7	V8	V9
Study Day	-3 to -1	1		3	5	8 ± 2	15 ± 3	22 ± 4	29 ± 5 (EOS) [7]	61 ± 5	EOS[8] / 91 ±7
		pre-dose	post-dose								

[redacted]; AE=adverse event; EOS=end-of-study; FDA=Food and Drug Administration; ICF=informed consent form; PCR=polymerase chain reaction; PK=pharmacokinetics; PRO=patient-reported outcome; RT=reverse transcriptase; S=screening; [redacted]; V=visit; WOCBP=women of child-bearing potential.

1. Vital signs consist of systolic and diastolic blood pressure and heart rate.
2. Urine test with minimum sensitivity 25 mIU/mL for WOCBP in stable contraception for at least 3 months before screening and at EOS. Serum test in other cases, e.g., no previous contraception or unstable (e.g., due to missed days of oral contraceptive or change in contraceptive method).
3. Birth control method will be documented only in source data.
4. Two PK samples: 15 minutes and 90 minutes after end of administration (defined as end of the saline flush).
5. FDA's recommended 14-item symptom assessment (FDA 2020a) to be used (from which the 8-point score can also be extracted). Options: Daily documentation by patient until Day 15 via PRO-tool, then weekly; or dedicated phone assessment on pre-specified days.
6. Although it is anticipated that most patients will be screened and administered study medication on the same day (Day 1) at Visit 1, patients may have screening procedures performed up to 3 days before study medication administration (Days -3 to -1) and study medication administered on Day 1. The following screening procedures do NOT need to be repeated pre-dose in such case: Informed consent, demographics, complete medical history, height, and weight.
7. Patients who discontinue before Day 29 will complete all V7 (Day 29) assessments as their EOS visit except for the Long-COVID-19 or SF-36 questionnaires.
8. Patients discontinuing between Day 29 and Day 91 to complete V9 (Day 91) assessments as EOS visit.

Table 8-2 Part B: Assessment schedule

Visit Name	S1 [6]	V1		V2	V3	V4	V5	V6	V7	V8	V9
Study Day	**-3 to 1**	**1**		**3**	**5**	**8 ± 2**	**15 ± 3**	**22 ± 4**	**29 ± 5**	**61 ± 5**	**EOS / 91 ±7**
		pre-dose	**post-dose**								
STUDY ENTRY AND GENERAL ASSESSMENTS											
Informed consent	(X)	X									
Inclusion/Exclusion criteria	(X)	X									
Demographics	(X)	X									
Complete medical history	(X)	X									
INVESTIGATIONAL PRODUCT											
Ensovibep (MP0420)/Placebo			X								
SAFETY ASSESSMENTS											
Prior/concomitant medication evaluation	Continuous starting after ICF signature, until 3 months after study medication										
Prior/concomitant hospitalization and procedures	Continuous starting after ICF signature, until 3 months after study medication										
AE evaluation	Continuous starting after ICF signature, until 3 months after study medication										
Local tolerability			X								
Physical examination and vital signs	(X)	X									
General physical appearance and vital signs [1]				X	X	X	X		X		X
Body temperature, respiratory rate, oximetry	(X)	X		X	X	X	X		X		X
Weight	(X)	X									X
Height	(X)	X									
Hematology, chemistry and coagulation safety tests		X		X			X		X	X	X
Pregnancy test in WOCBP [2]	(X)	X									X
Birth Control	Continuous until EOS [3]										

Visit Name	S1 [6]	V1		V2	V3	V4	V5	V6	V7	V8	V9
Study Day	**-3 to 1**	**1**		**3**	**5**	**8 ± 2**	**15 ± 3**	**22 ± 4**	**29 ± 5**	**61 ± 5**	**EOS / 91 ±7**
		pre-dose	**post-dose**								
VIROLOGY & SEROLOGY ASSESSMENTS											
Rapid SARS-CoV-2 antigen test	(X)	X									
SARS-CoV-2 sample (quantitative RT-PCR, mutation analysis)		X		X	X	X	X		X		X
[redacted]											
ADA blood sample		X					X		X	X	X
Blood sample for serum biomarkers		X					X		X		X
CLINICAL ASSESSMENTS											
Symptom score [5]		X		Daily assessment				X	X		
SF-36 Questionnaire [redacted]									X	X	X

ADA=anti-drug antibodies; AE=adverse event; EOS=end-of-study; FDA=Food and Drug Administration; ICF=informed consent form; PCR=polymerase chain reaction; [redacted] PRO=patient-reported outcome; RT-reverse transcriptase; S=screening; SF-36=Short Form 36 Health Questionnaire; V=visit; WOCBP=women of child-bearing potential.

1. Vital signs consist of systolic and diastolic blood pressure and heart rate.
2. Urine test with minimum sensitivity 25 mIU/mL for WOCBP in stable contraception for at least 3 months before screening and at EOS. Serum test in other cases, e.g., no previous contraception or unstable (e.g., due to missed days of oral contraceptive or change in contraceptive method).
3. Birth control method will be documented only in source data.
4. [redacted]
5. FDA's recommended 14-item symptom assessment (FDA 2020a) to be used (from which the 8-point score can also be extracted). Options: Daily documentation by patient until Day 15 via PRO-tool, then weekly; or dedicated phone assessment on pre-specified days.
6. Although it is anticipated that most patients will be screened and administered study medication on the same day (Day 1) at Visit 1, patients may have screening procedures performed up to 3 days before study medication administration (Days -3 to -1) and study medication administered on Day 1. The following screening procedures do NOT need to be repeated pre-dose in such case: Informed consent, demographics, complete medical history, height, and weight.

8.1 Screening

Screening and re-screening

Re-screening can only occur once a patient has failed screening. It is permissible to re-screen a participant if he/she was potentially exposed to SARS-CoV-2 but has no positive rapid antigen test for SARS-CoV-2 by upper respiratory swab.

8.1.1 Information to be collected on screening failures

Patients who sign an ICF form and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event (SAE) during the screening phase (see SAE section for reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

Patients who are randomized and fail to start treatment, e.g., patients randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate CRF.

8.2 Patient demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Patient demographics: date or year of birth, sex, race, predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Patient race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

All prescription medications, OTC drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

8.3.1 SARS-CoV-2 viral load

The viral load will be measured by means of a nasopharyngeal swab, which will be followed by quantitative reverse transcriptase-polymerase-chain-reaction (RT-PCR) assay at a central laboratory. (Details of the nasopharyngeal swab and the RT-PCR testing will be in the Lab Manual.)

8.3.2 Medically attended visits related to COVID-19 or death from any cause

Hospitalizations (≥ 24 hours of acute care) and emergency room visits related to COVID-19 and deaths from any cause will be recorded on the appropriate CRF page. Admission to an isolation ward for social or logistic reasons is not considered a hospitalization due to worsening of COVID-19 condition.

8.3.3 Patient reported outcomes

Patients are being requested to complete 3 Patient Reported Outcomes (PROs) during the study. In case a patient is too ill to complete the PRO assessment, this should be documented in the eCRF.

8.3.3.1 FDA-recommended 14-symptom questionnaire

Acute COVID-19 symptoms will be collected up to Day 29 to evaluate the efficacy of ensovibep using a COVID-19 symptoms collection tool containing a 14-symptom questionnaire (Appendix 16.1): 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. This questionnaire will be an electronic clinical outcomes assessments (eCOA) tool completed by the patient.

The 14-symptoms will collectively be referred to as the Food and Drug Administration (FDA) COVID-19 questionnaire (FDA 2020a).

Also a subset of the most clinically relevant symptoms (feeling hot or feverish, chills or shivering, cough, sore throat, low energy or tiredness, headache, muscle or body aches, shortness of breath) are being analyzed to assess the patients` disease status.

[redacted]

8.3.3.3 SF-36

Patients will be asked to complete the SF-36 questionnaire on Days 29, 61 and 91.

The Short Form 36 Questionnaire (SF-36) is a widely used measure of health status that can be scored to provide two summary measures of health, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The SF-36 has been used in other COVID-19 studies (clinicaltrials.gov). In this study the acute version (1 week recall period) of the SF-36 is being used.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Assessment	Specification
Physical examination	A complete physical examination (Day 1) will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. An assessment of general physical appearance will include the examination of general appearance and vital signs (systolic and diastolic blood pressure [BP], heart rate [HR], temperature and pulse oximetry). An assessment of general physical appearance will be performed at all visits starting from Day 3. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs will include the collection of BP and HR. After the patient has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, e.g., OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If vital signs are out-of-range at screening and/or baseline (see Section 5.2 of the protocol for details), two additional readings can be obtained, so that a total of three consecutive assessments are made, with the patient seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the patient to qualify. In case of repeated vital assessments, the eCRF should contain all repeat measurements.
Temperature, respiratory rate and oximetry	Body temperature (in °C), respiratory rate and oxygen saturation (pulse oximeter) will be assessed simultaneous to vital signs.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as specified in Table 8-1 and Table 8-2. Body mass index (BMI) will be calculated using the following formula: BMI = Body weight (kg) / (Height [m])^2

8.4.1 Laboratory evaluations

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

In all cases, the investigator must document in the source documents the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

A central laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

All abnormal lab results must be evaluated for criteria defining an AE and reported as such if the criteria are met. For those lab AEs, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

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, alanine aminotransferase (ALT), aspartate aminotransferase (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), C-reactive protein (CRP), D-Dimer, Ferritin
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Electrocardiogram

Not evaluated.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male patients to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male patients should not donate sperm for the time period specified above.

All pre-menopausal women who are not surgically sterile will have pregnancy testing at screening and end of study (EOS). Additional pregnancy testing might be performed if requested by local requirements.

Screening: Women who have been on stable highly effective contraception in the last 3 months prior to enrollment will have a urine beta-human chorionic gonadotropin (ß-HCG) pregnancy test with minimum sensitivity 25 mIU/mL. In other cases, e.g., no previous contraception or unstable (e.g., due to missed days of oral contraceptive or change in contraceptive method), women will have a serum ß-HCG pregnancy test.

EOS: Urine ß-HCG pregnancy test. In the case of a positive test at the EOS, the pregnancy will be reported. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been terminated or until 6 months after the delivery. The outcome of the pregnancy will be reported to the sponsor without delay within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The result of each pregnancy test will be reported on an eCRF.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, follicle stimulating hormone (FSH) testing is required of any female patient regardless of reported reproductive/menopausal status at screening/baseline, otherwise the contraception measures described for women of child-bearing potential apply.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

8.5 Additional assessments

8.5.1 Pharmacokinetics

Venous blood samples will be collected for assessment of free ensovibep (ensovibep not bound to target) and total ensovibep (sum of ensovibep not bound to target and ensovibep bound to target) concentrations in serum at the visits defined in the assessment schedule.

Pharmacokinetic samples will be obtained and evaluated in all participants and at all dose levels except the placebo group. Free and total ensovibep will be determined by validated analytical methods. Concentrations will be expressed in mass per volume units.

[redacted]

[redacted]

Results will be presented in the Bioanalytical Data Report.

[redacted]

The PK parameters will be determined using the actual recorded (elapsed) sampling times relative to start of infusion and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher).

The following PK parameters will be determined: Cmax, Tmax, AUClast, AUCinf, T1/2, λz, Vz, CL. Additional pharmacokinetic parameters may be calculated as necessary. Further details are provided in the SAP.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal serum elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUC, CL, and Vz.

8.5.2 Biomarkers

8.5.2.1 Rapid antigen test

An immunoassay (COVID-19 Rapid Antigen Test) for the qualitative detection of SARS-CoV-2 antigens in nasopharyngeal swab samples will be used to confirm ongoing presence of viral load with SARS-CoV-2 prior to randomization.

8.5.2.2 SARS-CoV-2 viral load

SARS-CoV-2 viral load will be quantified during the course of the study according to the Assessment Schedule (Table 8-1 and Table 8-2). Viral load will be measured to determine its correlation with other clinical and pharmacodynamic parameters by the use of a validated RT-PCR test on a sample of specimen of the respiratory mucosa (nasopharyngeal swab), reported as copies of viral RNA per milliliter of transport media (copies/mL). The same sample will be used to analyse viral genome to determine and monitor the virus genetic variants. Instructions for sample collection, processing, and shipment will be provided in the Laboratory Manual.

[redacted]

8.5.2.5 Soluble biomarkers

Serum for analysis of cytokines and other markers of inflammation shown to be implicated in the severity of COVID-19 (e.g., interleukin [IL]-6, IL-8, etc.) will be collected at the indicated timepoints throughout the study as shown in Table 8-1 and Table 8-2. Changes in circulating concentrations of serum biomarkers associated with inflammation and disease progression will be assessed in the ensovibep treatment groups as compared to the placebo groups. The association between changes in disease related biomarkers with clinical endpoints will be evaluated. Samples may also be evaluated on a broad proteomics discovery platform (e.g., SomaScan). Sample collection and processing will be described at the Lab Manual.

8.5.3 Immunogenicity

Immunogenicity testing will be performed on each patient according to the Assessment Schedule (Table 8-1 and Table 8-2). All immunogenicity samples will be listed by treatment group, patient and visit/time and the instructions for sample collection, numbering, processing, and shipment will be provided in the Laboratory Manual.

The presence of antibodies against ensovibep will be determined using a stepwise approach. Samples will be assessed using a validated screening immunoassay. Positive results from the screening assay will be re-assessed in a validated confirmatory assay. Confirmed samples will then be analyzed using a titration assay.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Interruption of study drug infusion and study discontinuation

Study treatment consists of a single dose infusion. In case of interruption of infusion due to AEs, time and relative amount of study drug administered should be recorded in the CRF, as well as restart and end time (as applicable). Adverse event should be captured in appropriate CRF. Treatment of AEs should follow standard of care (symptomatic treatment).

Infusion of study drug must be interrupted or stopped under the following circumstances:

- Patient/guardian decision.
- Suspected hypersensitivity reaction occurs, including any of the following: fever, chills, dyspnea, headache, myalgia, hypotension. Immediate interruption of the infusion to administer study treatment is required in such cases. In case of fever, restart of infusion is permitted under close medical surveillance if the fever subsides with antipyretic treatment. In case of chills, dyspnea, headache or myalgia, restart of infusion is permitted under close medical surveillance if the event was already a noted symptom of COVID-19 at study enrollment and it subsides without treatment within 15 minutes.
- Emergence of any other infusion related reaction: anaphylaxis, angioedema, urticaria, rash, administration site reaction. Immediate interruption of the infusion to administer study treatment is required in such cases. Restart of infusion is not recommended.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2 'Withdrawal of Informed Consent' section). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore,
  and
- Does not want any further visits or assessments,
  and
- Does not want any further study related contacts.

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

Legal framework of certain countries does not require consent to the use of personal and coded data. However, patients in these countries do retain the right to object to the further use of their personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits may not be collected and will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the patient's study discontinuation should be made as detailed in the assessment table.

All research results (data) that have already been collected for the study evaluation will continued to be used.

9.1.3 Lost to follow-up

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

9.1.4 Study stopping rules

Overall study stopping rules

Enrollment in the study will be placed on hold if any of the following occurs cumulatively across all treatment arms:

During Part A:

- 3 or more study drug-related SAEs;
- 6 or more patients experience hypersensitivity reactions or injection reactions of moderate to severe intensity;
- 3 or more patients experience a similar AE, or a similar laboratory finding, which was assessed as CTCAE Grade 3 or 4 and considered as potentially study drug related;
- The sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold.

During Part B (cumulative):

The study may resume following a safety review by the IDMC, if the investigator and sponsor agree it is safe to proceed.

9.1.5 Early study termination by the sponsor

The study can be terminated by the sponsor at any time.

Reasons for early termination

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, the sponsor will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator shall be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator or, in the event of an early study termination decision, the date of that decision.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of the individual patient and identifying and documenting AEs.

Qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

Throughout the study, the investigator will determine whether any AEs have occurred by evaluating the participant. These events may be directly observed, reported spontaneously by the patient or by questioning the patient at each study visit or by laboratory test findings. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms.

Note that any symptoms collected by the PROs (see Section 8.3.3) will not be considered AEs and will not be reconciled with AEs.

Adverse events should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. Adverse events must be accompanied by the following information (as far as possible):

1. Intensity, graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
2. Its causal relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be ‘Not suspected.’ However, worsening of COVID-19 that exceeds anticipated fluctuations or course of the disease should be documented as AE, and may qualify as an adverse event of special interest (AESI) (see Section 10.1.4).
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE, and Section 10.1.3 for SAE reporting) and which seriousness criteria have been met
5. All AEs must be treated appropriately. Treatment may include interrupting or withdrawing of study drug
6. Its outcome

Relevant conditions apart from COVID-19 infection, which were already present at the time of informed consent should be recorded in medical history of the patient. However, worsening of these conditions after study start should be recorded as an AE.

Adverse event monitoring should be continued until EOS visit (see Table 8-1). After the EOS, only serious events assessed as related to study drug should continue to be reported, and only to the safety database.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of [or worsening of any pre-existing]) undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening (see definition below)

Life-threatening in the context of an SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until last study visit must be reported to the medical monitor safety desk within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are included in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, further information may urgently be required from the investigator for health authority reporting. An Investigator Notification (IN) may need to be issued to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 AEs of Special Interest

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 judgment, with onset within 1 week of study drug administration.
- Liver events requiring follow-up (see Appendix 16.3)
- Renal events requiring follow-up (see Appendix 16.4)

The reporting of AESIs, even if non-serious, follows the same procedures and timelines as the reporting of SAEs: They must be reported to the medical monitor safety desk within 24 hours of learning of their occurrence, using the same forms.

10.1.5 Pregnancy reporting

Reporting of pregnancy in female study participants follows the same procedures and timelines as the reporting of SAEs: They must be reported to the medical monitor safety desk within 24 hours of learning of their occurrence, using a pregnancy form.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to the medical monitor safety desk within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy follow-up should be reported on the same form and should include an assessment of the possible relationship to the study treatment for any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy of a male participant's female partner is not considered to be an AE. However, the outcome of all pregnancies occurring from dose administration until end of study (13 weeks after administration of IP) should, if possible, be followed up and documented.

Information on the pregnancy of a male participant's partner must be obtained directly from the patient's partner; the male participant should not be asked to provide this information. Prior to obtaining information related to the pregnancy and outcome of the pregnancy, the investigator must obtain the participant's partner consent. A consent form specific to this situation must be used.

10.1.6 Reporting of study treatment errors

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (European Medicines Agency [EMA] definition).

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional safety monitoring

10.2.1 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1, Table 16-2, and Table 16-3 in Appendix 16 for complete definitions of liver laboratory triggers.

Once a patient is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL], prothrombin time [PT]/international normalized ratio [INR], alkaline phosphatase [ALP] and gamma-glutamyl transferase [G-GT]) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the patient. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should be recorded as part of the liver AE.
    - If the initial elevation is confirmed, close observation of the patient will be initiated
    - Hospitalization of the patient if appropriate
    - Causality assessment of the liver event
    - Thorough follow-up of the liver event should include
- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

Once a patient is exposed to study treatment, the following abnormal renal laboratory alert value should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status

Abnormal renal event findings must be confirmed within 24 to 48 hours after the first assessment.

Once a patient is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Table 16-4.

Every renal laboratory trigger or renal event as defined in Table 16-4 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-4.

10.3 Independent data monitoring committee

This study will include an IDMC that will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The IDMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial. See also Section 12.7.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of IDMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the IDMC.

11 Data collection and database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1 and Table 8-2) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Certain data may be captured via other source documentation (such as safety laboratory data report, imaging) and then transcribed, uploaded or transferred into the eCRF RAVE system. This, and any additional data treated in this manner, will be source data reviewed by the study monitor per the monitoring plan and the location of source data (i.e., source, paper or a local electronic system) will be documented prior to study start. When using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application. Rather, the electronic source record directly populates the study database.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected as data is entered into IQVIA EDC system.

Remote monitoring of the original electronic source records will take place, due to COVID-19 pandemic conditions. to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

The investigator must certify that the data entered into eSource are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

A CRO will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures, as well as randomization codes and all dosage changes will be tracked using an IRT. The system will be supplied by [redacted], who will also manage the database. The blinded data will be sent electronically to the sponsor (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of the sponsor.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by the sponsor.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a sponsor representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study, there are several methods employed to ensure protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The blinded study monitor will perform remote visits to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the study monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized CRA. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original ICF form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12 Data analysis and statistical methods

Summary statistics will be provided for:

- **continuous variables:** N, mean, SD, minimum, lower quartile (25th percentile), median, upper quartile (75th percentile), and maximum
- **binary or discrete variables:** absolute number of patients in each category and relative frequencies

Presentation, unless otherwise specified, of:

- **P-values:** 2-sided with a 5% significance rate
- **Confidence intervals:** 95% intervals

The baseline value is defined as the last assessment prior to treatment administration. The value at screening will be used, if available, if the scheduled baseline assessment value is missing.

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).

Any data analysis carried out independently by the investigator should be submitted to the sponsor, as detailed in the CTAs, before publication or presentation.

Part A: Efficacy and safety data during the Part A treatment period will be presented by treatment group (ensovibep 75 mg, ensovibep 225 mg, ensovibep 600 mg, and placebo) administered as an i.v. infusion over 60 minutes.

Part B: Efficacy and safety data during the Part B treatment period will be presented by treatment group (ensovibep [dose determined in Part A] and placebo) administered as an i.v. infusion over 60 minutes.

12.1 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
- **Safety set (SS):** all patients who initiated i.v. infusion of study drug

- **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

For the FAS following the intention to-treat (ITT) principle, patients will be analyzed according to their randomized treatment assignment. Unless otherwise specified, all efficacy analysis will be performed on the FAS.

For the SS following the per-protocol (PP) principle, patients will be analyzed according to the treatment received. Unless otherwise specified, all safety analyses will be performed on the SS.

Important protocol deviations for exclusion from PK analysis set may be identified by the clinical team before the primary analysis and final database lock in Part A and interim and final database lock in Part B.

12.2 Patient demographics and other baseline 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) in each Part.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class (SOC), high level term (HLT), preferred term (PT), and treatment arm for the FAS in each Part.

12.3 Treatments

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group using the SS in each Part.

12.4 Analysis of the primary endpoints

12.4.1 Definition of primary endpoints

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 log10 SARS-CoV-2 viral load in nasopharyngeal swabs.

To calculate the time-weighted change from in log10 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.

The primary estimand definition for the Part A endpoint is in Section 2.1.1.

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 for the Part A endpoint is in Section 2.1.2.

12.4.2 Statistical model, hypothesis, and method of analysis

Part A

The primary objective of this Part is to demonstrate superiority of ensovibep, compared to placebo, on reducing SARS-CoV-2 viral load through Day 8 using the response of time-weighted change from baseline in log10 SARS-CoV-2 viral load through Day 8. The MCP-Mod methodology (Bretz 2005, Pinheiro 2014, EMA 2014, FDA 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 log10 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 log10 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 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 is analyzed using analysis of covariance (ANCOVA) to obtain covariate adjusted treatment effects and corresponding variance covariance matrix. The ANCOVA will adjust for baseline log10 SARS-CoV-2 viral load, treatment group, baseline risk of progression to severe

COVID-19 and/or hospitalization ("high risk" versus "not at high risk") and other relevant parameters (specified in the SAP) as covariates.

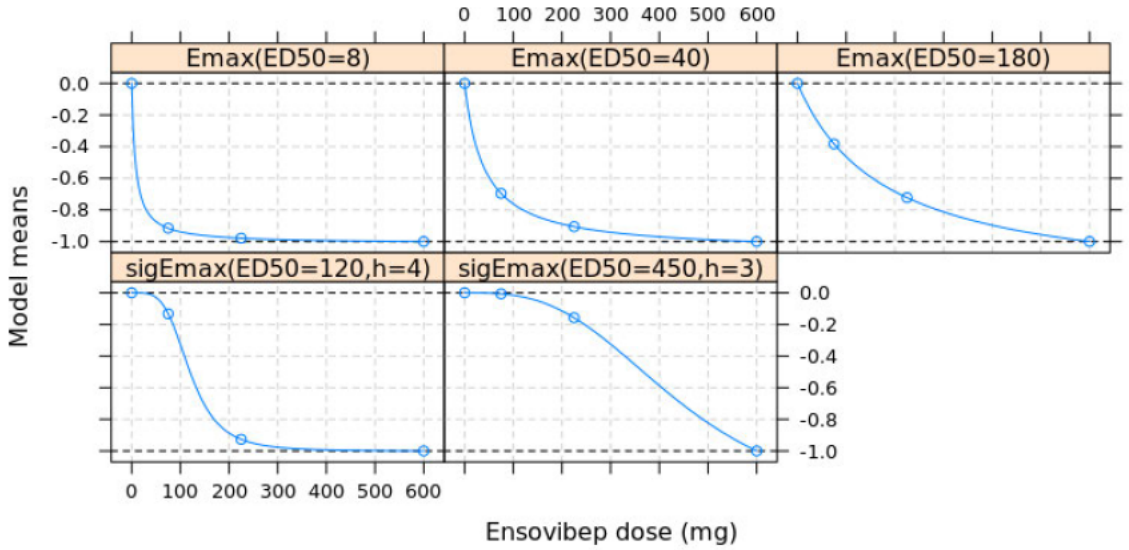
- Proof-of-concept step - multiple contrast tests

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 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 2014). For that purpose, the Emax dose-response shape ($E_0 + E_{max} * d/(d + ED_{50})$) with three shapes of $ED_{50} = 8, 40, 180$ and the sigmoid Emax 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 12-1).

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 12-1 Candidate models for ensovibep dose



- Dose-finding step – dose-response model fitting

A bootstrap sample (from a normal distribution with LS Means (Least Squares Means) 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 (Akaike Information Criterion) over all 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% CIs. 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 2014). The dose-response estimate will be the median across the bootstrap model predictions and 95% CIs based on bootstrap quantiles.

The dose 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 symptom score; AND,
- Safety endpoints including ADAs (as available), 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% CIs (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% CIs 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" versus "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.

12.4.3 Handling of remaining intercurrent events of primary estimand

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 log10 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.

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.

12.4.4 Handling of missing values not related to intercurrent event

Part A

Missing measurement in log10 SARS-CoV-2 viral load will be imputed using last observation carried forward (LOCF) approach.

Part B

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.

12.4.5 Supplementary analysis

Part A

A supplemental analysis:

- excluding patients who experienced a negative PCR COVID-19 test following a positive swab; and,
- using multiple imputation to handle the missing data will be performed.

Further details on supplementary analyses can be found in the SAP.

Part B

Simple event rate estimates (proportion of events) will be presented for the primary composite efficacy endpoint.

An alternative estimand may be considered with a composite strategy account for the intercurrent events of (1) post-treatment initiation of all antivirals (including convalescent serum, antiviral antibodies and antiviral small molecules), ambulatory oxygen, and immunomodulating or immunosuppressive medications; and, (2) post-treatment increase in dose of ambulatory oxygen, and immunomodulating or immunosuppressive medications, for the treatment or management of COVID-19. The primary endpoint will be considered a failure at the time of the intercurrent event.

The primary efficacy analysis may be repeated excluding patients who experienced a negative PCR COVID-19 test following a positive swab.

A tipping point analysis will be conducted to assess the impact of the missing data strategy in Section 12.4.4.

Additional analyses to address sensitivity of assumptions may be performed including inverse probability of censoring modeling.

Further details on supplementary analyses can be found in the SAP.

12.4.6 Supportive analysis

The subgroup evaluation of baseline risk of progression to severe COVID-19 and/or hospitalization ("high risk" versus "not at high risk") on ensovibep will be performed for both Parts. Further details on supportive analyses will be specified in the SAP.

12.5 Analysis of secondary endpoints

For all secondary objectives analysis details are described in the SAP.

12.5.1 Efficacy endpoints

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

This secondary objective applies only to Part A. In Part B, this endpoint is the primary objective. For handling of the secondary analysis on the 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, see details in the SAP.

12.5.1.2 SARS-CoV-2 Viral load

This secondary objective applies only to Part B. In Part A, this endpoint is the primary objective. For handling of the secondary analysis on log10 SARS-CoV-2 viral load in nasopharyngeal swabs through Day 8, see details in Section 12.4.

12.5.1.3 COVID-19 symptoms

Acute COVID-19 symptoms will be collected up to Day 29 to evaluate the efficacy of ensovibep using a COVID-19 symptoms collection tool containing a 14 symptoms questionnaire, collectively be referred to as the FDA COVID-19 questionnaire (FDA 2020a). This questionnaire will be an eCOA tool completed by the patient. Each of the symptoms is rated on a scale of 0 to 3: 0 – none, 1 – mild, 2 – moderate, 3 – severe.

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.

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

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% CIs and associated p-value for the test of no difference between groups will then be obtained.

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" versus "not at high risk").

12.5.2 Safety endpoints

Adverse events

Adverse events (AEs) are to be coded with the MedDRA dictionary that gives PT and primary SOC information. The number (and percentage) of patients with treatment emergent

- AEs
- SAEs
- AESIs (see Section 10.1.4)

will be summarized for each Part by:

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

Treatment-emergent deaths will be summarized for each Part by treatment, SOC, and PT.

A patient with multiple AEs within a primary SOC will be only counted once towards the total of the primary SOC.

AEs and SAEs will be summarized for each Part by treatment and treatment-emergent ADAs (TE-ADA) status as defined in Section 10.1.1.

AEs of Special Interest are defined in Section 10.1.4.

- The number (and percentage) of patients with each of the AESIs will be summarized for each Part by treatment and by treatment and maximum severity.

Vital signs

All vital signs data will be summarized by treatment in each Part at Day 1, Day 3, Day 5, Day 8, Day 29, and Day 91. Changes from baseline to values at each time point will be summarized for each Part by treatment. Patients with abnormalities will be listed.

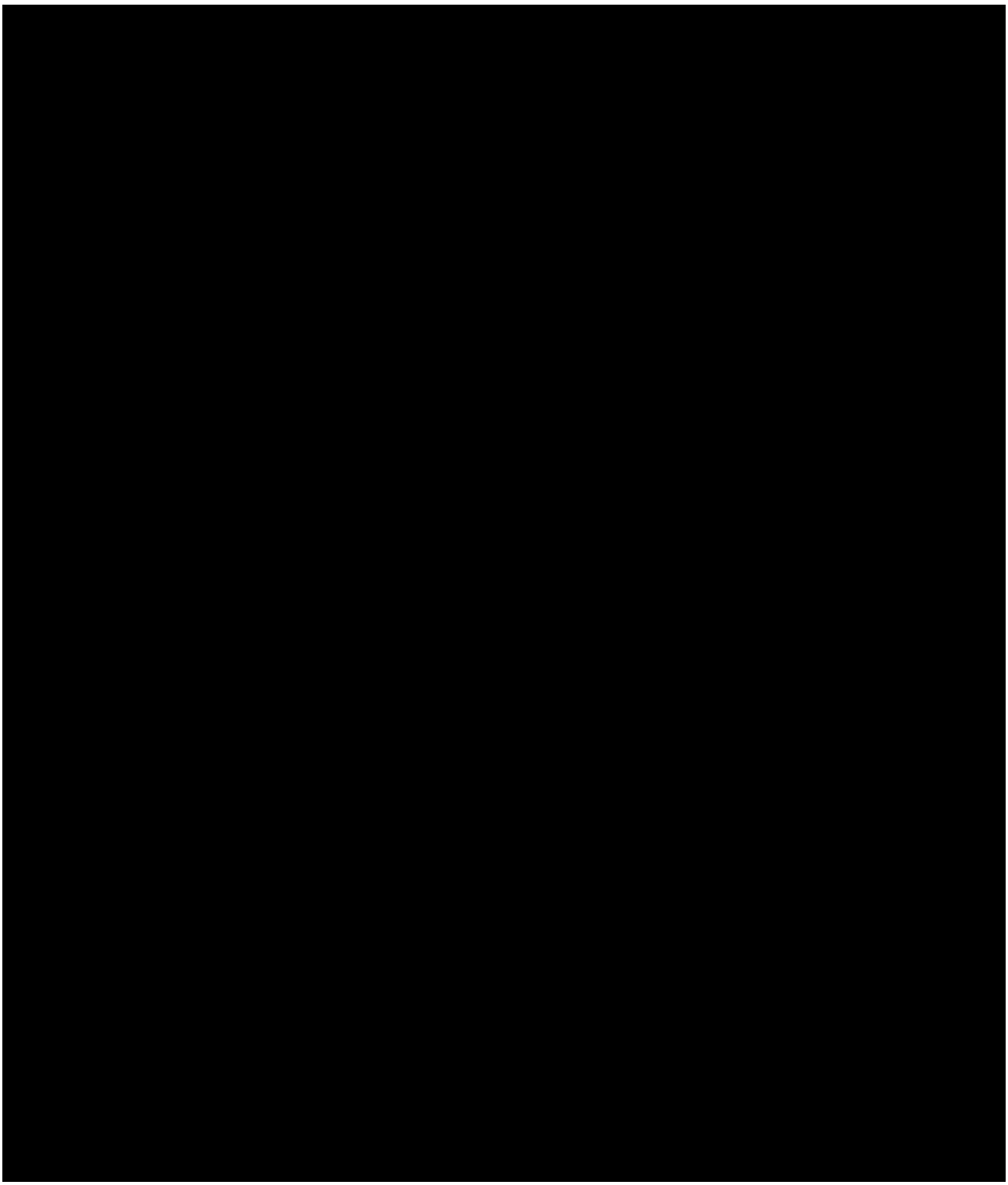
A complete list of the vital sign parameters will be provided in the SAP.

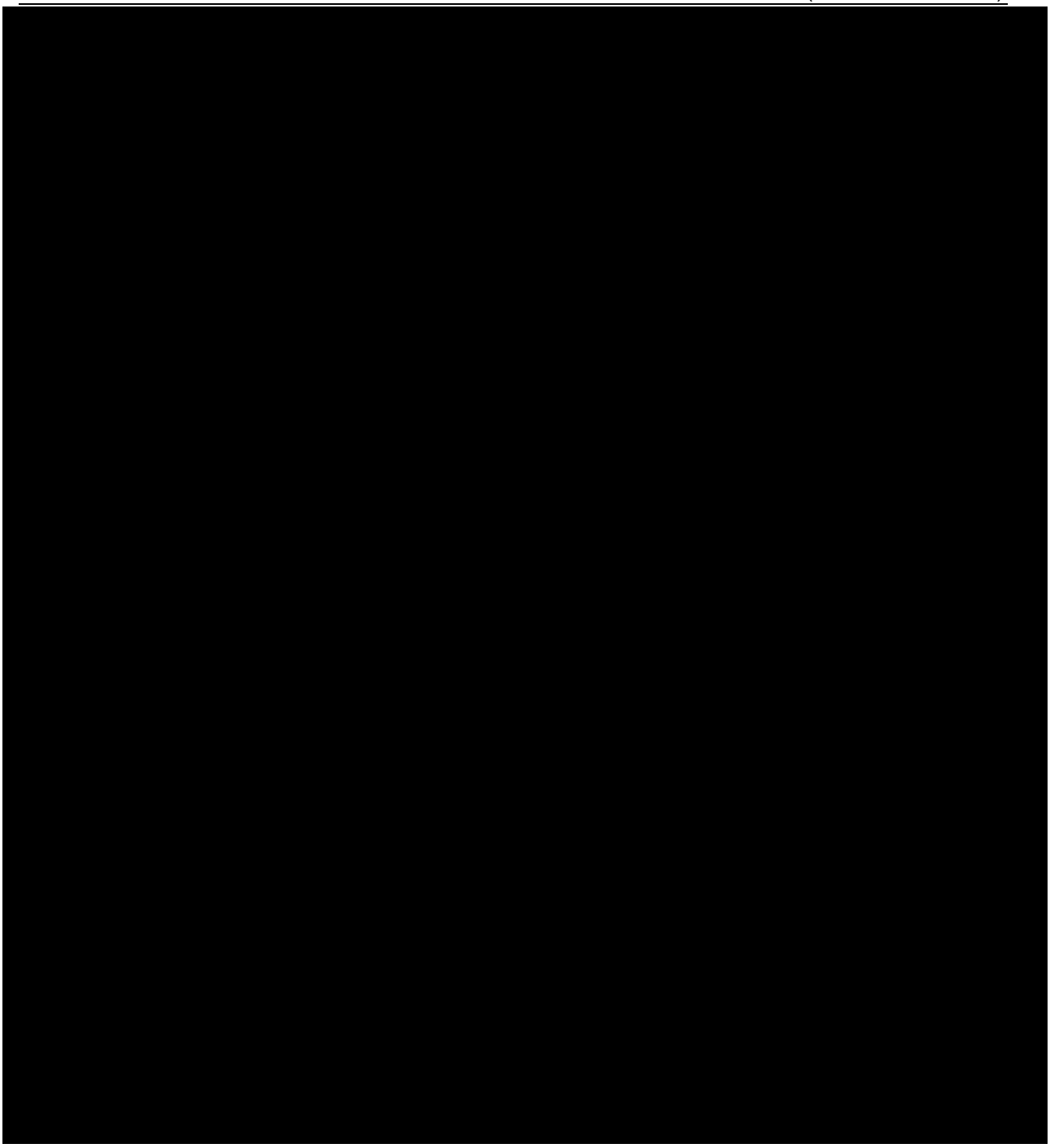
Clinical laboratory evaluations

All laboratory data, including hematology and biochemistry data, will be summarized by treatment in each Part at Day 1, Day 5, Day 8, Day 29, and Day 91. Changes from baseline to values at each time point will be summarized for each Part by treatment. Shift tables using the

low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value. Patients with abnormalities will be listed.

A complete list of the laboratory parameters, including hematology and biochemistry parameters, will be provided in the SAP.





12.7 Interim analysis

An external IDMC will be established and perform review as defined in Section 10.3. The details of the analysis required for IDMC will be specified in a separate IDMC charter and analysis plan.

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.

Part B

There is one interim analysis after at least 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).

Further details will be provided in a separate Interim Analysis SAP.

12.8 Sample size calculation

12.8.1 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 log10 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 107 copies at baseline and the estimated SD 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 calculations 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 (84)and are presented in Table 12-1.

Table 12-1 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

	1	99.98
-0.68	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 12-2.

Sample size calculations are performed in nQuery 8.4.1.0.

Table 12-2 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

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, the sponsor's Quality Assurance representatives, designated vendors, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the sponsor's clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the sponsor's publication policy including authorship criteria, please refer to the sponsor's publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality control and quality assurance

Molecular Partners AG, either itself or through Novartis Pharma AG (Novartis) that is responsible for conducting this study and has engaged the CRO IQVIA for that purpose, maintains a Quality Management System (QMS) that includes relevant activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures, and are performed according to written processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures, and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including

incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to the sponsor and not use it for any purpose other than the study, except for the appropriate monitoring on study patients.

Investigators ascertain, they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Symptom questionnaire

Questions to evaluate the presence and severity of COVID-19 symptoms, following FDA's recommended list of questions. The questionnaire is programmed onto an App that will play on the patient's own device (e.g., Smartphone). Patients who don't own a device will be given one for the duration of the study.

Opening instructions:

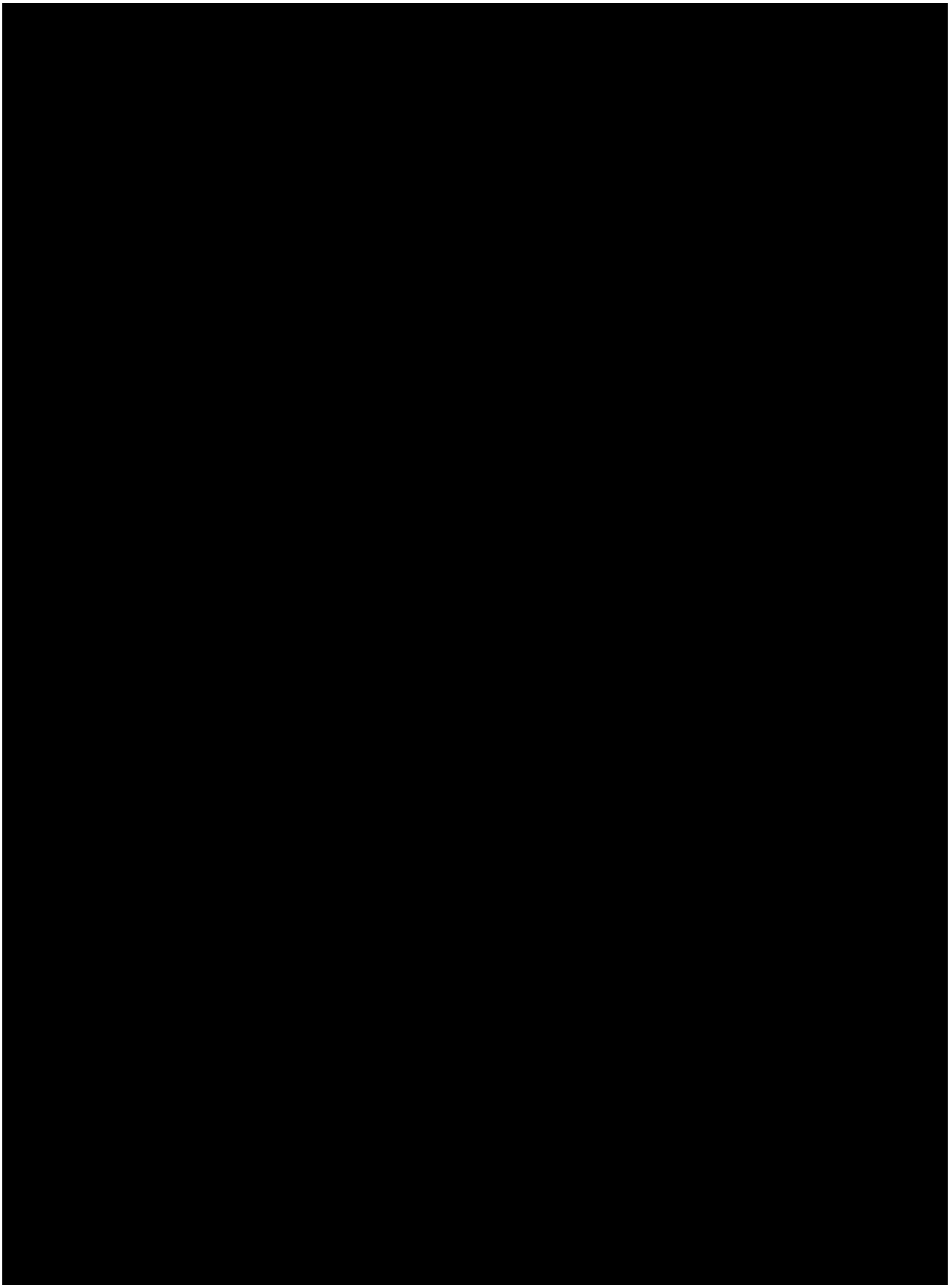
A variety of possibly symptoms are described and if present, should be rated by severity. If you don't have the symptom, click "None".

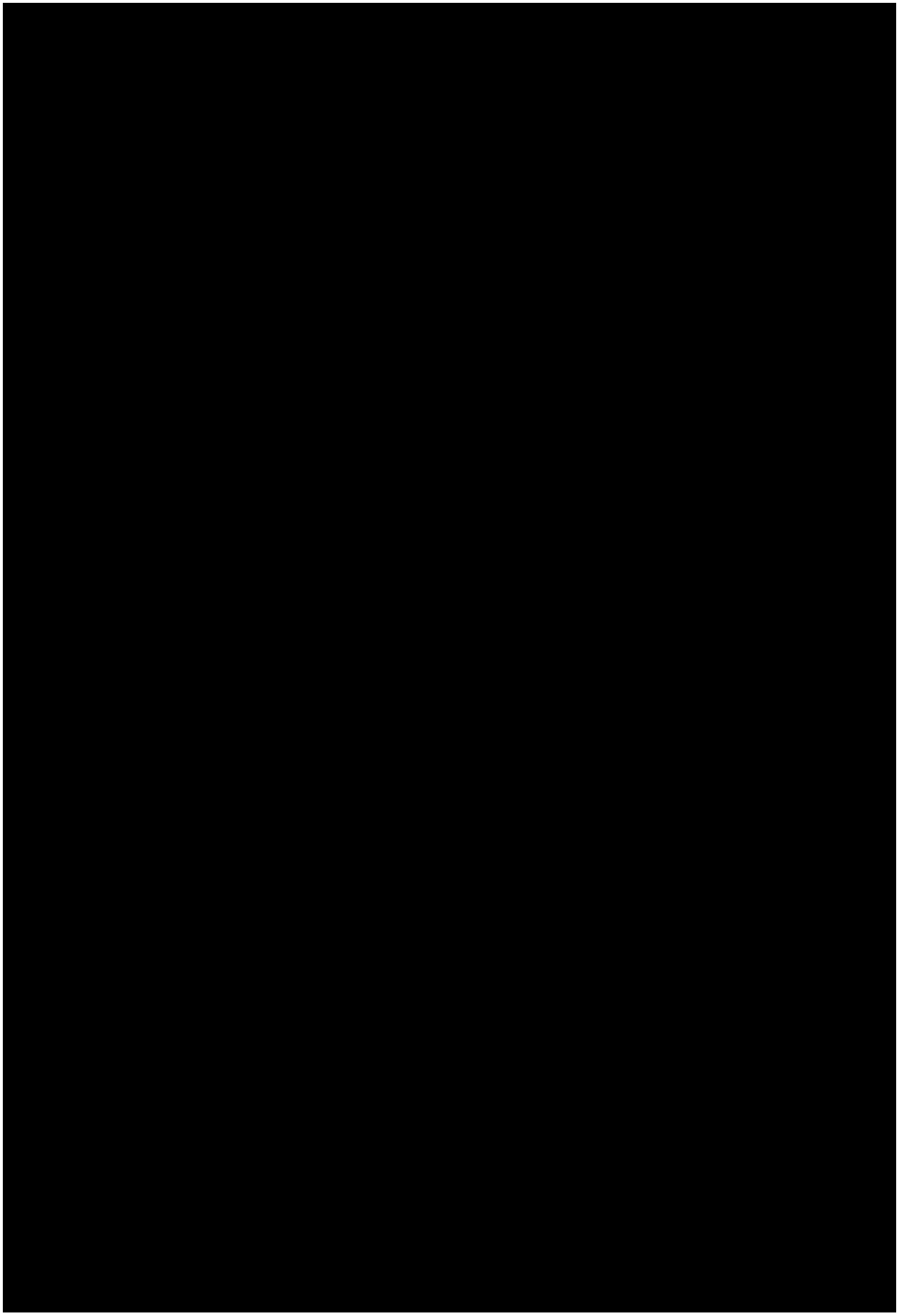
	Questions	**Response options**
Runny nose	What was the severity of your **stuffy or runny nose** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Sore throat	What was the severity of your **sore throat** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Breathlessness	What was the severity of your **shortness of breath (difficulty breathing)** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Cough	What was the severity of **cough** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Fatigue	What was the severity of **low energy or tiredness** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Body pain	What was the severity of your **muscle or body aches** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe

	Questions	**Response options**
Headache	What was the severity of your **headache** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Chills	What was the severity of your **chills or shivering** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Feeling hot	What was the severity of your **feeling hot or feverish** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Nausea	What was the severity of your **nausea (feeling like you wanted to throw up)** at its worst over the last 24 hours?	☐ none ☐ mild ☐ moderate ☐ severe
Vomiting	How many times did you **vomit (throw up)** in the last 24 hours?	☐ I did not vomit at all ☐ 1-2 times ☐ 3-4 times ☐ 5 or more times
Diarrhea	How many times did you have **diarrhea (loose or watery stools)** in the last 24 hours?	☐ I did not have diarrhea at all ☐ 1-2 times ☐ 3-4 times ☐ 5 or more times
Sensory: smell	Rate you sense of **smell** in the last 24 hours	☐ My sense of smell is THE SAME AS usual ☐ My sense of smell is LESS THAN usual ☐ I have NO sense of smell
Sensory: taste	Rate you sense of **taste** in the last 24 hours	☐ My sense of taste is THE SAME AS usual ☐ My sense of taste is LESS THAN usual ☐ I have NO sense of taste
Usual health	In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?	☐ Yes ☐ No

	Questions	**Response options**
Usual activities	In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?	☐ Yes ☐ No
Overall COVID symptoms	In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst?	☐ none ☐ mild ☐ moderate ☐ severe

[redacted]





16.3 Appendix 3: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	• ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies.
If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Isolated elevation of AST >3 x ULN needs to be interpreted in context of the clinical picture and other liver parameters, and further investigated for non-liver related etiology.

Table 16-3 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48-72 hours Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	Hospitalize the participant Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Hospitalization if clinically appropriate Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.4 Appendix 4: Specific renal alert criteria and actions and event follow-up

Table 16-4 Specific renal alert criteria and actions

Serum Event	
Serum creatinine increase 25% – 49% compared to baseline, exceeding the normal range and/or considered clinically significant	Confirm 25% increase after 24-48 hours Follow-up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow-up within 24-48 hours if possible Consider participant hospitalization /specialized treatment
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed	
Monitor participant regularly (frequency at investigator's discretion) until either:	
Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or	
Event stabilization: sCr level with ± 10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months.	

16.5 Appendix 5: Sponsor's signature page

Molecular Partners AG

Ensovibep/MP0420

Clinical Trial Protocol MP0420-CP302

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

Document type: Protocol Signature Page

Referring to: Amended Protocol V01 released on 19-Oct-2021

Molecular Partners AG approval signature for:

Amended Clinical Trial Protocol MP0420-CP302 V01

CMO		
Title	Signature	Date

16.6 Appendix 6: Investigator's signature page

Investigator approval signatures for:

Amended Clinical Trial Protocol MP0420-CP302 V01

Investigator signature

I have read the amended protocol and agree to conduct this trial in accordance with all stipulations of the protocol, with applicable laws and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

Investigator	Signature	Date

Center name and address

Center name: _____

Address: _____