STATISTICAL ANALYSIS PLAN

Study Title: **A Phase 2, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate CSL312 in Coronavirus Disease 2019 (COVID-19)**

Study Number:	CSL312_COVID-19
Study Product:	CSL312 (Garadacimab, Factor XIIa Antagonist Monoclonal Antibody)
Development Phase:	Phase 2
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia, PA 19406 United States of America
Version:	1.0
Version Date:	28 Aug 2020
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

COMMERCIAL IN CONFIDENCE

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1 Modification History

Version	Effective Date	Author of Modification	Reason for Change
1.0	28/AUG/2020		N/A – First Version

2 List of Abbreviations

Abbreviation	Definition
CCI [redacted]	CCI [redacted]
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
CCI [redacted]	CCI [redacted]
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration
CCI [redacted]	[redacted]
BiPAP	Bi-level positive airway pressure
BLQ	Below limit of quantification
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
C_{max}	Maximum plasma concentration
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation percentage
ECMO	Extracorporeal membrane oxygenation
EOS	End of Study
FiO_2	Fraction of inspired oxygen
HFNC	High-flow nasal cannula
ICF	Informed consent form
CCI [redacted]	[redacted]
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IL	Interleukin
INR	International normalized ratio

Abbreviation	Definition
IP	Investigational product
IRT	Interactive response technology
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LOS	Length of stay
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
n	Number of observations
NIAID	National Institute of Allergy and Infectious Diseases
PaO_2	Partial pressure oxygen
CCI	[redacted]
PK	Pharmacokinetic
PT	Prothrombin time
SaO_2	Peripheral arterial oxygen saturation
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SAS	Statistical Analysis System
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SMQ	Standardized MedDRA Query
SOC	Standard-of-care
SOFA	Sequential Organ Failure Assessment
SpO_2	Peripheral oxygen saturation
$T_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
TFL	Table, figure, and listing
TNF	Tumor necrosis factor

Abbreviation	Definition
T_{max}	Time to maximum plasma concentration
USA	United States of America

3 Purpose

This statistical analysis plan (SAP) provides a detailed and complete description of the planned final analysis for the study CSL312_COVID-19. Mock table, figure, and listing (TFL) shells will be provided in a separate supporting document along with details for the practical implementation of the analyses.

This SAP complies with the International Council for Harmonisation E9 'Statistical Principles for Clinical Trials' and E9 (R1) 'Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials'. It is based upon the following study documents:

- Study Protocol Amendment 2 (dated 25 Aug 2020)
- Case Report Form (CRF), Version 1.0 (dated 03 Jun 2020)
- Independent Data Monitoring Committee (IDMC) SAP 1.0 (dated 28 Aug 2020)
- CSL Behring's response to comments from the Federal Drug Agency (1.11.3 Clinical Information Amendment)

All decisions regarding the analysis of the study results, as defined in this version of the SAP, have been made before first unblinding for the IDMC analyses.

4 Study Design

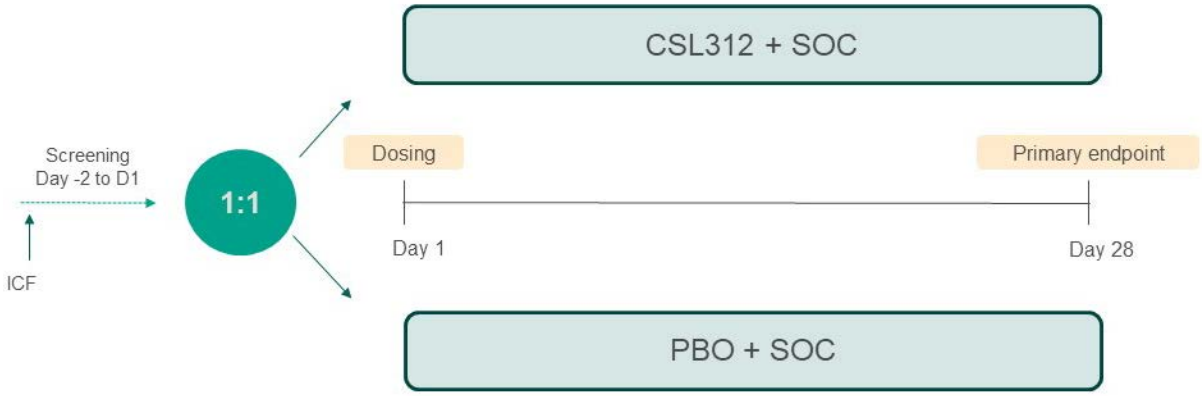
This is a prospective, phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety, pharmacokinetic (PK), and efficacy of intravenous (IV) administration of CSL312, administered in combination with standard-of-care (SOC) treatment, in subjects with COVID-19 (Figure 1).

This study will enroll a total of approximately 124 subjects and will be conducted at approximately 25 investigational sites; at least 15 sites in the United States of America (USA) and up to 10 sites in Brazil. Eligible subjects will be randomized to receive CSL312+SOC or placebo+SOC in a 1:1 ratio before dosing on Day 1.

After the first 62 subjects have completed the primary endpoint assessment or discontinued from the study prematurely, an interim analysis will be performed for futility monitoring and sample size re-estimation, which may result in an increase in the target sample size of up to 248 subjects.

The study consists of a Screening Period (up to 2 days) and a 28-days Treatment Period. If Screening occurs on Day 1, the assessments scheduled to occur at both on Screening and before dosing on Day 1 may be performed only once (i.e., do not need to be repeated). During the Treatment Period, CSL312+SOC or placebo+SOC will be administered once on Day 1.

Figure 1 Study Design



ICF = informed consent form; PBO = placebo; SOC = standard-of-care.

The schedule of assessments can be found in the protocol.

4.1 Objectives and Endpoints

4.1.1 Primary Objective

The primary objective of the study is to assess the treatment benefit of CSL312 after IV infusion in patients with COVID-19.

4.1.2 Primary Study Hypotheses

The study is designed to test the null (H_0) and the alternative (H_A) hypotheses for the risk difference as defined below:

H_0: $\pi_{CSL312} - \pi_{placebo} \geq 0$
H_A: $\pi_{CSL312} - \pi_{placebo} < 0$

Where π_{CSL312} is the risk to progress to tracheal intubation or die before tracheal intubation in the CSL312 group and $\pi_{placebo}$ is the risk to progress to tracheal intubation or die before tracheal intubation in the placebo group. Under the null hypothesis, the assumption is that no beneficial effect is afforded by CSL312, while the alternative hypothesis states that

CSL312 + SOC is effective in reducing the risk to progress to tracheal intubation or die before tracheal intubation compared to the placebo + SOC group.

4.1.3 Secondary Objectives

The secondary objectives of the study are:

1. To further assess the efficacy of CSL312
2. To assess the safety of CSL312
3. To assess the PK of CSL312

4.1.4 CCI

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Table 1 Study Objectives and Endpoints

Objectives		Endpoints	Summary Measure(s)
Primary		Incidence of tracheal intubation or death prior to tracheal intubation	Proportion of subjects progressing to tracheal intubation or dying prior to tracheal intubation from randomization to Day 28
Secondary			
1	All-cause mortality		Proportion of deaths from all causes occurring from randomization to Day 28
1	Incidence of tracheal intubation		Proportion of subjects intubated from randomization to Day 28
1	Clinical status as assessed on an 8-point National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale		• Number and proportion of subjects with ≥ 2-point improvement in the ordinal scale • Number and proportion of subjects within each of the categories of the ordinal scale
1	Use of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP)		Proportion of subjects using CPAP or BiPAP

Objectives	Endpoints	Summary Measure(s)
1	Use of high-flow nasal cannula (HFNC)	Proportion of subjects using HFNC
1	Use of extracorporeal membrane oxygenation (ECMO)	Proportion of subjects requiring ECMO
1	Change in Sequential Organ Failure Assessment (SOFA) score	• Median of maximum change from baseline in SOFA score • Change from baseline in SOFA score and in the individual components of SOFA score
1	Hospital length of stay (LOS)	• Median LOS in hospital stay
2	Subjects experiencing the following safety events: • Adverse events (AEs) • Serious adverse events (SAEs) • Adverse events of special interest (AESIs) • CSL312-induced anti-CSL312 antibodies • Clinically significant abnormalities in laboratory assessment that are reported as AEs	Number and proportion of subjects experiencing the specified safety events after treatment with CSL312 or placebo
3	CSL312 PK in plasma: • Maximum plasma concentration (C_{max}) • Time to maximum plasma concentration (T_{max}) • Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration ($AUC_{0\text{-last}}$) • Terminal half-life ($T_{1/2}$)	• Mean (± standard deviation [SD]) and geometric mean (geometric coefficient of variation percentage [CV%]) for all PK parameters except T_{max}. • Median (minimum, maximum) for T_{max}

CCI [redacted]

4.2 Study Treatments

Subjects will be randomized to receive a single dose of CSL312 or placebo along with SOC.

4.3 Randomization Procedures and Blinding

Randomization and blinding procedures are described in the protocol. Randomization will be conducted using an interactive response technology (IRT). Subjects will be randomly assigned to treatment with either CSL312 + SOC or placebo + SOC using a 1:1 randomization ratio and stratified by country (USA or Brazil). A centralized randomization schedule will be used. The randomization list will be generated according to the approved randomization specifications. The IRT service provider will keep the randomization code on file.

Study unblinding will take place after database lock, except in the situations as outlined in protocol sections 5.1.3.2, 5.1.3.3, and 5.1.3.4 related to emergency unblinding and unblinding for safety reasons.

Adequate procedures are in place to ensure the integrity of the blinded data within CSL. Study data will be provided to the IDMC as unblinded data.

The analyses planned for the IDMCs are described in a separate IDMC SAP.

4.4 Determination of the Initial Sample Size

There are limited data on the rates of subjects with COVID-19 who progress to tracheal intubation or death prior to tracheal intubation within 28 days. For sample size calculation, a rate of 30% in the control group and a rate of 10% in the CSL312 group have been assumed. With a 1-sided $\alpha = 0.025$ (which is equivalent to a 2-sided $\alpha = 0.05$) and 1:1 randomization ratio for CSL312 + SOC versus placebo + SOC, a total of 124 subjects need to be randomized (62 subjects to CSL312 + SOC and 62 subjects to placebo + SOC) to achieve 80% power to show superiority using a 2 group chi-square test. For the sample size calculation, it is further confirmed using simulations performed in East 6.5 that 80% power is maintained, accounting for the interim analysis for futility and sample size re-estimation.

Depending on the results after the interim analysis, the sample size may by increased up to 248 subjects (124 subjects in CSL312 + SOC and 124 subjects in placebo + SOC).

4.5 Planned Interim Analyses and Reviews.

4.5.1 IDMC Review Meetings for Safety Monitoring

Four IDMC review meetings are planned to monitor the critical safety data. Ad-hoc meetings are possible. Details are specified in the IDMC SAP.

4.5.2 IDMC Review Meeting for Futility and Sample Size Re-estimation

The IDMC will convene for an interim analysis meeting when the unblinded analysis of the key efficacy data (primary endpoint assessment plus premature study discontinuations) from the first 62 subjects (50% of the target sample size) is available to assess futility and the need for a sample size re-estimation. Details are specified in the IDMC SAP.

The analyses to be provided for the IDMC meetings are specified in the IDMC SAP.

5 Changes from the Protocol Planned Analyses

There are no changes to the analyses planned as specified in the study protocol.

6 Study Analysis Sets

6.1 Screened Analysis Set

The Screened Analysis Set comprises all subjects who provide written informed consent and who complete all of the Screening procedures.

Technical Note: Subjects with informed consent date and an eligibility assessment available will be included.

6.2 Intent-to-treat Analysis Set

The Intent-to-treat (ITT) Analysis Set comprises all subjects in the Screened Analysis Set who were randomly assigned to treatment. The ITT Analysis Set will be analyzed using the treatment to which the subject was randomized, regardless of the treatment actually received. Any subject who receives a treatment randomization number will be considered to have been randomly assigned to treatment.

Technical Note: Subjects in the Screened Analysis Set who have a randomization number will be included.

6.3 Modified Intent-to-Treat Analysis Set

The Modified Intent-to-treat (mITT) Analysis Set comprises all subjects in the ITT Analysis Set who were randomized and received any amount of study treatment (CSL312 + SOC or placebo + SOC). In the mITT Analysis Set, analyses will be based on the treatment to which subjects were randomly assigned, regardless of which treatment they actually received.

Technical Note: Subjects in the ITT Analysis Set who receive any amount of investigational product (IP) entered in the CRF will be included.

6.4 Safety Analysis Set

The Safety Analysis Set comprises all subjects in the ITT Analysis Set who receive any amount of IP (CSL312 + SOC or placebo + SOC) and analyses will be based on the actual treatment received.

Technical Note: Subjects in the ITT Analysis Set who receive any amount of IP entered in the CRF will be included.

6.5 Pharmacokinetic Analysis Set

The PK Analysis Set comprises all subjects in the Safety Analysis Set who received any amount of CSL312 + SOC and have ≥ 1 blood sample available after administration of CSL312 for CSL312 concentration measurement. PK analyses will not be performed for subjects who are treated with placebo + SOC.

Technical Note: Subjects included in the Safety Analysis Set who received CSL312 and who have at least 1 blood sample for CSL312 concentration measurement after administration of CSL312 available will be included.

6.6 CCI

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7 General Considerations

Datasets submitted to regulatory agencies will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards. Submission data will be provided in Study Data Tabulation Model (SDTM) format. Analysis data will be provided in Analysis Data Model (ADaM) format.

Statistical Analysis System (SAS) version 9.4 or higher will be used to perform all data analyses.

Continuous variables will be summarized in terms of the number of observations (n), mean, SD, median, first quartile, third quartile, minimum and maximum. Other descriptive statistics (e.g., standard error [SE], CV%) may be reported when appropriate. For repeated assessments of continuous variables, the change from baseline will also be summarized. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics identified with the analysis in the applicable SAP section.

Statistical tests will be 1-sided and will be performed at an alpha level of 0.025 unless otherwise stated.

8 Data Handling Conventions

8.1 Missing Data

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated using a "blank" in subject listing displays. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

The details of handling missing data are presented in the corresponding SAP sections (e.g., primary and secondary efficacy analyses, safety analyses).

8.2 General Derived Variables

The following sections provide a general description of the derived variables for data analyses.

8.2.1 Reference Dates and Study Day

Reference dates are used to assign study periods relative to IP.

- The reference date for safety, CCI and PK is the start date (and time) of treatment (i.e., the date [and time] of the administration of IP) and will be used to calculate the study day and to assess the baseline value to calculate changes from baseline or shifts to baseline.

- The reference date for efficacy is the date (and time) of randomization and will be used to calculate the time interval for the efficacy time-to-event endpoints and to assess the baseline value to calculate changes from baseline or shifts to baseline.

If the date of interest occurs on or after the reference date, then the study day will be calculated as (date of interest - reference date) + 1. If the date of interest occurs before the reference date, then the study day will be calculated as (date of interest - reference date). There is no study day 0.

8.2.2 Durations and Time to Event Data

Durations (e.g., the duration of an AE) calculated in full days (if time is not available) or in partial days (if time is available) are defined as

- event end date - event start date + 1, if time is not available;
- event end date and time - event start date and time, if both end time and start time are available. In this case, the duration needs to be transformed to days.

Thus, there will be no duration of 0 if the time is not available. If an event has missing or partially missing start or end date no duration will be calculated. For durations which usually last less than a day (e.g., the duration of an infusion), the duration will only be calculated if start and end time are available.

For elapsed time (e.g., the time to event), use

- event date - reference date, if time is not available;
- event date and time - reference date and time, if both event and reference time are available. This will require transformation to the desired unit (e.g., days).

Thus, an event which happens on the same date as the reference date will have an elapsed time of 0, if event time or reference time are not available. For the analysis of time-to-event observations that are equal to 0, these values will be set to a very small value (0.0000001) to avoid that the observation is excluded from the analysis in some SAS procedures.

To transform durations or elapsed time which are calculated in days into weeks, divide the number of days by 7; to report in months divide the number of days by 30.4375; to report in

years divide the number of days by 365.25. These algorithms return decimal numbers and ignore the actual numbers of days in the months or years between start date and stop date (i.e., the calendar days are ignored). The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

8.2.3 Baseline Definition

For efficacy endpoints, baseline is defined as the most recent, non-missing value before randomization (including unscheduled visits) unless otherwise stated. If no value before randomization exists, the most recent, non-missing value before IP administration will be used as baseline value.

For safety, baseline is defined as the most recent, non-missing value before IP administration (including unscheduled visits) unless otherwise stated.

8.2.4 Change from Baseline

Change from baseline is calculated as:

- visit value - baseline value.

Percentage change from baseline is calculated as:

- (change from baseline / baseline value) * 100.

If either the baseline or visit value is missing, the change from baseline and percentage change from baseline will also be missing.

8.2.5 Multiple Assessments

All data will be reported according to the nominal visit date for which it was assessed (i.e., no visit windows will be applied during dataset creation and the visit will not be re-allocated if the actual visit date deviates from the planned date according to the visit schedule in the protocol). Unscheduled data will not be included in by-visit summaries, but may contribute to the Baseline value, the End of Study (EOS) value, or best/worst case value (e.g., shift tables) and will be displayed in the listings.

If multiple assessments on the same day or on different days are reported for the same scheduled visit, then the assessment for that scheduled visit will be analyzed according to the following rules:

- if an assessment was repeated as safety follow-up (e.g., laboratory value out of normal range) use the initial, abnormal assessment for that scheduled visit;

- in all other cases, use the last valid assessment for that scheduled visit; rationale: the assessment was repeated either because the initial assessment was missing or invalid (e.g., due to technical issues, loss of sample, clotting of sample or other reasons of this type) or the assessment was repeated but the reasons were not collected or unknown.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in the listings.

8.2.6 Actual Treatment

The subject's actual treatment will be derived from the exposure data (kit number from drug administration). If a subject receives a study treatment different from the randomized treatment, the actual treatment is the treatment received.

8.2.7 Derived Variables

The derived variables used for the analysis will be defined and specified in detail in the respective section of the SAP.

8.2.7.1 Subgroup: Sex

- Male;
- Female.

8.2.7.2 Subgroup: Age Group

- < 65 years;
- ≥ 65 years of age.

For the demography table, additional categories for subjects < 65 years of age will be displayed:

- < 18 to 29 years;
- 30 to 39 years;
- 40 to 49 years;
- 50 to 64 years.

These categories will not be used in the subgroup analyses for efficacy.

8.2.7.3 Subgroup: Comorbidity

- Any comorbidity factor present: yes (including hypertension; diabetes; obesity, defined as body mass index [BMI] ≥ 30);

- Any comorbidity factor present: no.

For assignment of comorbidity see Section 9.3.

8.2.7.4 Subgroup: Use of Approved / Emergency-authorization Usage of Anti-COVID-19 Drugs

- Any concomitant usage of anti-COVID-19 drugs during the trial: yes;
- Any concomitant usage of anti-COVID-19 drugs during the trial: no.

8.2.7.5 Subgroup: Country

- USA;
- Brazil.

8.3 Study Periods Relative to Treatment

Screening Period starts with the date (and time) of the signed informed consent and ends before the date (and time) of randomization.

Treatment Period starts with the date (and time) of randomization and ends on the Day 28 visit.

EOS is at Day 28, the last day of the Treatment Period.

9 Study Population

Unless otherwise stated, tables in this section will be based on the ITT Analysis Set. Listings will be based on the ITT Analysis unless otherwise stated.

9.1 Subject Disposition

Number and percentage of subjects will be presented in a summary table for the Screened Analysis Set (where meaningful by treatment and total) including the following information:

- Subjects who underwent Screening – only total;
- Screening failures with reason for failure – only total;
- Subjects randomized – by treatment and total;
- Subjects randomized but not treated – by treatment and total;
- Subjects treated – by treatment and total;
- Subjects treated who completed the study – by treatment and total;
- Subjects treated who discontinued from the study with reason – by treatment and total.

Reasons for study discontinuation will be presented in the order they are displayed in the CRF.

Number and percentage of randomized subjects per site and country will be presented.

The following by-subject listings will be provided including all available data:

- Randomization scheme based on the ITT Analysis Set;
- Subject disposition with date of Screening (in case of re-screening, all screening records will be listed), date (and time) of the randomization, date (and time) of IP administration, Day 28 date/date of withdrawal;
- Screening failures with reason;
- Subjects who discontinued from the study with reason for discontinuation.

9.2 Protocol Deviations / Reasons for Exclusion From Analysis Sets

A protocol deviation occurs when an investigator, site, or study subject, does not adhere to protocol-stipulated requirements. Deviations will be assessed by CSL as they are reported and then evaluated periodically during study conduct.

In this study, protocol deviations will not lead to exclusion of a subject from an analysis set.

Other reasons than protocol deviations may exist to exclude a subject from an analysis set. The final decision about the assignment of subjects to analysis sets will be made during the Blind Data Review Meeting prior to database lock.

The list of reasons presented in Table 2 may lead to exclusion of a subject from an analysis set and will be discussed during the Blind Data Review Meeting. The list may be modified, and other reasons may be added. The final decision about the exclusion of subjects from analysis sets will be made during the meeting and will be documented in the meeting minutes.

Table 2 Potential Reasons for Exclusion From an Analysis Set

Reason for Exclusion	(Potentially) Leading to Exclusion From
Informed consent date missing	Screened, ITT, mITT, Safety, PK, CCI
No eligibility assessment	Screened, ITT, mITT, Safety, PK, CCI

Reason for Exclusion	**(Potentially) Leading to Exclusion From**
Not randomized	ITT, mITT, Safety, PK, CC
Not treated with IP	mITT, Safety, PK, CC
No blood sample available for CSL312 concentration measurement after CSL312 administration	PK
No blood sample available for the analysis of CCI	CCI

The following summaries for number and percentage of subjects will be provided by treatment and total using the Screened Analysis Set:

- Number and percentage of subjects in each of the analysis sets described in Section 6;
- Inclusion and exclusion criteria violations;
- Reasons for exclusion from an analysis set.

The following by-subject listings will be provided based on the Screened Analysis Set:

- Inclusion and exclusion criteria violations;
- All other protocol deviations;
- Subject assignment to analysis sets and reasons for exclusion.

9.3 Demographic and Baseline Characteristics

Descriptive statistics as specified in Section 7 will be provided for continuous variables, number and percentage of subjects for categorical variables.

BMI (kg/m^2) will be calculated as body weight (kg) / height $(m)^2$.

Number of pack-years = (packs smoked per day) * (years as a smoker)
= number of cigarettes per day/20 * duration of smoking (years).

Duration of smoking will be derived from start year of smoking and year of randomization for current smokers and using the stop year of smoking for former smokers.

Comorbidity will be defined as indication for the presence of:

- hypertension;
- diabetes or;
- obesity, defined as BMI ≥ 30.

For each subject, the presence and type of the above comorbidities will be identified. BMI will be used to assess obesity. The preferred terms entered for diabetes and hypertension in the medical history CRF page will be used to assess the comorbidity factors. CSL will provide a list of preferred terms indicative for diabetes or hypertension.

The following summaries will be provided by treatment and total for the ITT and the mITT Analysis Set.

- Demographic characteristics (age, race, ethnicity, sex, height, body weight, and BMI at Screening). In addition to summarization as a continuous variable, age will also be categorized and summarized by the categories given in Section 8.2.7.2;
- Disease history (Positive SARS-CoV-2 test, time since onset of symptoms relative to randomization, time since admission to hospital relative to randomization, time since admission to ICU relative to randomization, chest-CT or chest-X-ray [yes, no], signs of interstitial pneumonia [yes, no]);
- Smoking status and pack years of cigarettes for current and former smokers;
- Comorbidity factors (yes, no) and type of comorbidity (hypertension, diabetes, obesity);
- Medical history (coded using the Medical Dictionary for Regulatory Activities [MedDRA] – MedDRA version will be provided in the output) will be presented by System Organ Class and Preferred Term –medical history terms with end date / evidence for end date before informed consent date will be included;
- Concomitant diseases –medical history terms with end date / evidence for end date on or after informed consent date will be included.

The following by-subject listings will be provided based on the ITT Analysis Set:

- Demographics and baseline characteristics;
- Disease history (SARS-CoV-2 CRF page, chest-CT and chest-X-ray CRF page);
- Smoking status, pack-years of cigarettes, and comorbidity factors;
- Medical history and concomitant diseases;
- Reproductive system findings, pregnancy tests, and contraception in man.

9.4 Prior/Concomitant Medications and Procedures

Prior/concomitant medications will be coded using the World Health Organization Drug Dictionary. The version will be provided in the output tables and listings.

The reported medication will be classified as 'Prior', 'Prior and Concomitant' or 'Concomitant Only':

- 'Prior': if the subject has not taken any IP; or if the medication end date is before IP start date. If the medication end date is partially missing, the medication will only be assigned to 'Prior' if the partial date gives clear evidence that the medication stopped before IP start;
- 'Prior and Concomitant': if the medication is not classified as 'Prior' or as 'Concomitant Only';
- 'Concomitant Only': if the medication started on or after IP start date. If the medication start or end date are partially missing, the medication will only be assigned to 'Concomitant Only' if the partial dates give clear evidence that the medication started on or after IP start.

Concomitant medications, i.e., medications classified as 'Concomitant Only' or 'Prior and Concomitant', will be summarized for the ITT Analysis Set by treatment and total showing the number and percentage of subjects taking concomitant medications by Anatomical Therapeutic Chemical (ATC) classification level 4 and preferred term. If the ATC level 4 coding is not available for a preferred term, the next available lower level ATC code will be used.

Concomitant medications flagged as anti-COVID-19-drugs will be summarized by treatment and total with their ATC classification showing the number and percentages of subjects stratified by prior use, prior and concomitant use, and concomitant only use. The duration of anti-COVID-19 drug use will be summarized descriptively for the categories prior, prior and concomitant, and concomitant only.

The following by-subject listings will be provided based on the ITT Analysis Set:

- Prior/concomitant medication;
- Use of anti-COVID-19 drugs.

10 Efficacy

The randomized treatment will be used for the efficacy analyses described in this section.

10.1 Progression to Tracheal Intubation or Death Prior to Tracheal Intubation

Progression to tracheal intubation will be defined as presence of a record for this procedure ("Endotracheal Intubation" ticked on the Respiratory Support CRF) with a start date from randomization to Day 28. All deaths will be reported as SAEs. An SAE with outcome "Death Related to Adverse Event" and SAE end date from randomization to Day 28 will be considered as death for the primary endpoint.

10.1.1 Primary Estimand

Clinical question of interest: Is there a treatment benefit of CSL312 after IV infusion in patients with COVID-19, i.e. does treatment with CSL312 + SOC reduce the risk to progress to tracheal intubation or to die prior to tracheal intubation in subjects with severe COVID-19 disease while subjects are treated with SOC?

The primary estimand in line with the primary interest of the study follows the treatment policy strategy and is described as follows:

A. Subject population: the target subject population defined by eligibility criteria.
B. Treatment condition of interest: One dose (700 mg) of IP (CSL312 + SOC or Placebo + SOC) via IV infusion on peripheral vein.
C. Variable: subject's progression to tracheal intubation or death prior to tracheal intubation at any time from randomization to Day 28.
D. Intercurrent events:
    1. Concomitant use of anti-COVID-19 drugs.
    2. Early discontinuation of the study for any reason.
    3. Randomized without treatment.
E. Population level summary: risk difference of progression to tracheal intubation or death prior to tracheal intubation (CSL312 + SOC minus placebo + SOC).

In this study, the treatment policy strategy will be used for all intercurrent events. It is reasonable to assume for subjects who are losses to follow-up after hospital discharge likely not to have experienced the event under randomized treatment. If subjects are still in hospital after withdrawal from the study (but not withdrawal of consent), missing data is unlikely to occur.

10.1.2 Primary Efficacy Analysis

The primary endpoint for this study is the risk of tracheal intubation or death prior to tracheal intubation from randomization to Day 28. The ITT Analysis Set will be used for the primary efficacy analysis.

Subjects with less than 28 days of the Treatment Period (i.e., who discontinued from the study prematurely) and without documented intubation or death will be considered to not have progressed to tracheal intubation or died prior to tracheal intubation (see Section 10.1.3).

Firth logistic regression model including age as continuous covariate, treatment group, gender (male or female), country (USA or Brazil), and baseline comorbidities (yes or no) as categorical covariates in the model will be used to compare the risks of progression between the 2 treatment groups. Comorbidities will include hypertension, diabetes, and obesity (defined as BMI $\geq$ 30 kg/m^2). A 1-sided p-value will be estimated from the model and the null hypothesis (see Section 4.1.2) will be rejected if that p-value is < 0.025. The risk difference and associated 2-sided 95% confidence interval (CI) will be estimated using the method described by Ge et al [2011].

10.1.3 Sensitivity Analyses for Progression to Tracheal Intubation or Death Prior to Tracheal Intubation

The mITT Analysis Set will be used as sensitivity analysis for the primary analysis with the same endpoint and model as specified in Section 10.1.2.

The ITT Analysis Set will be used as sensitivity analysis for the primary analysis assuming that subjects with less than 28 days of the Treatment Period (i.e., who discontinued from the study prematurely) and without documented intubation or death progressed to tracheal intubation or died prior to tracheal intubation using the same model as specified in Section 10.1.2.

Another sensitivity analysis will be conducted where the subjects who started use of anti-COVID-19 drugs after randomization will be considered as having experienced progression to tracheal intubation or died prior to tracheal intubation using the same model as specified in Section 10.1.2.

For reference purpose, a complete-case analysis (i.e., including only subjects who completed Day 28 or who died) will also be done.

10.1.3.1 Tipping Point Analysis

Missing primary efficacy outcome is defined as subjects with less than 28 days of the Treatment Period and without documented tracheal intubation or death. Missing primary efficacy outcome will be imputed in a systematic way as having or not having experienced the event, where the event is progression to tracheal intubation or death prior to tracheal intubation.

The purpose of the tipping point analysis is to show which combination of imputed values for the missing primary efficacy outcome may alter the result of the primary efficacy comparison. Thus, the tipping point analysis will only be performed if the primary efficacy analysis indicates a significant treatment effect.

Analyses will be run for each possible combination of missing outcomes considering the subjects as not interchangeable: for each subject with missing outcome the two possible outcomes (1 = having experienced the event, 0 = not having experienced the event) will be imputed in combination with every other subject with missing outcome with the two possible outcomes of these subjects. This will result in 2^m possible combinations, with m being the number of subjects with missing outcome in both treatment group combined. All combinations of imputed data will be analyzed with the primary model as specified in Section 10.1.2.

The possible combinations will be derived as illustrated below for up to 4 subjects:

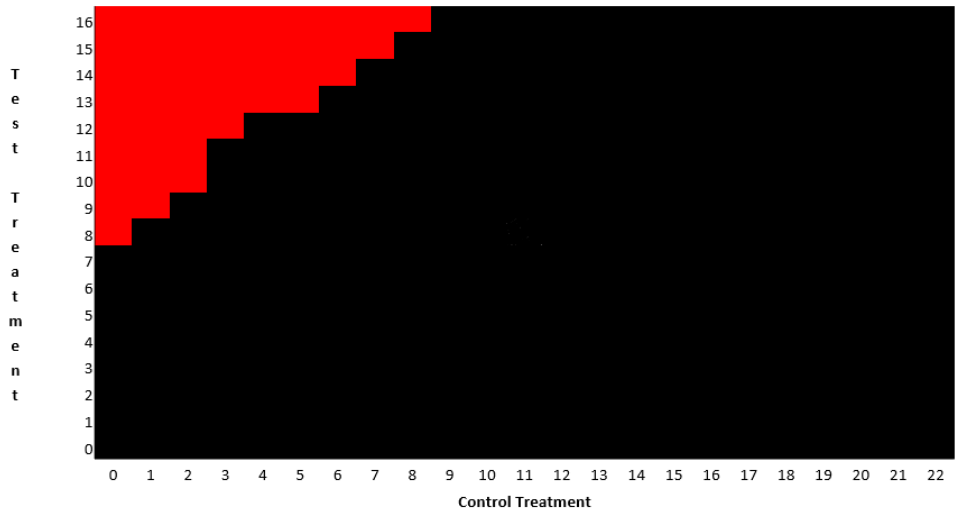
Number of Subjects With Missing Outcome	**Possible Combinations* (Number of Analyses)**	**Proportion of Subjects Experiencing the Event**
1	2 (0, 1)	0, 1
2	4 (00, 01, 10, 11)	0, 0.5 (twice), 1
3	8 (000, 001, 010, 011, 100, 101, 110, 111)	0, 0.33 (three times), 0.67 (3 times), 1
4	16 (0000, 0001, 0010, 0011, 0100, 0101, 0110, 0111, 1000, 1001, 1010, 1011, 1100, 1101, 1110, 1111)	0, 0.25 (4 times), 0.5 (6 times), 0.75 (4 times), 1

0 = subject did not experience the event, 1 = subject experienced the event

The treatment comparisons obtained from each combination will be classified into favorable (1-sided p-value < 0.025 symbolized by black color) and unfavorable (1-sided p-value ≥ 0.025 symbolized by red color) and depicted in a graph where the x-axis and y-axis will present the proportion of subjects with missing endpoint imputed as having experienced the event for CSL312 + SOC and placebo + SOC, respectively.

If each subject with missing outcome is combined with every other subject with missing outcome, there will be more than one combination with the same proportion of subjects having experienced the event if m > 1 as illustrated in the last column of the above table. The median p-value of the combinations with the same proportion of subjects having experienced the event will be used in the graph.

An example for such a graphical display could look like this (the axes represent the number of missing subjects in this graph, but maybe translated to the proportion of subjects having or not having experienced the event):



Red: 1-sided p-value ≥ 0.025, black: 1-sided p-value < 0.025

The number of subjects with missing outcome in this study is expected to be small. However, if the number of subjects with missing outcome is large and all possible 2^m combinations become too cumbersome for above described method to be implemented, an alternative method will be used (e.g., if appropriate, treating subjects as interchangeable, i.e., no covariates besides treatment will be included in the logistic regression model and there will

be (a+1)*(b+1) combinations for possible outcomes where a and b are the number of subjects with missing outcome in each treatment group, respectively).

10.1.4 Subgroup Analyses for Progression to Tracheal Intubation or Death Prior to Tracheal Intubation

Subgroup analyses by the variables defined in Sections 8.2.7.1, 8.2.7.2, 8.2.7.3, 8.2.7.4, and 8.2.7.5 will be performed using the ITT Analysis Set as described above in Section 10.1.2. The logistic regressions will not include the factor for the respective subgroup analysis as independent variable (if applicable), but they will include the other covariates as specified for the primary analysis.

A forest-plot will be provided for the estimated risk difference and 95% CIs for each subgroup level.

10.2 Analysis of Secondary Endpoints

Secondary Efficacy Endpoints are:

- All-cause mortality: calculated as number of deaths of any cause from randomization to Day 28 divided by the number of subjects in the treatment group. All deaths will be entered as SAEs in the AE CRF. Thus, the information will be obtained from the AE CRF as SAEs with outcome “Death Related to Adverse Event” and SAE end date (death date) occurring within the 28 days of the Treatment Period.
- Incidence of tracheal intubation from randomization to Day 28: calculated as number of subjects experiencing intubation from randomization to Day 28 divided by the number subjects in the treatment group. Tracheal intubation is defined as presence of a record for this procedure (“Endotracheal Intubation” ticked on the Respiratory Support CRF) with a start date during the 28 days of the Treatment Period.
- Proportions of subjects using CPAP or BiPAP: calculated as number of subjects using CPAP or BiPAP within 28 days of randomization divided by the number subjects in the treatment group. Use of CPAP or BiPAP is defined as presence of a record for this procedure (“CPAP” or “BiPAP” ticked on the Respiratory Support CRF) with a start date during the 28 days of the Treatment Period.
- Proportion of subjects using HFNC: calculated as number of subjects using HFNC within 28 days of randomization divided by the number subjects in the treatment group. Use of HFNC is defined as presence of a record for this procedure (“HFNC” ticked on the Respiratory Support CRF) with a start date during the 28 days of the Treatment Period.

- Proportion of subjects using ECMO: calculated as number of subjects using ECMO within 28 days of randomization divided by the number subjects in the treatment group. Use of ECMO is defined as presence of a record for this procedure ("ECMO" ticked on the Respiratory Support CRF) with a start date during the 28 days of the Treatment Period.
- Clinical status assessed on an 8-point NIAID ordinal scale as entered in the CRF.
- Length of hospital stay defined as time interval from randomization to hospital discharge alive. The information will be derived from the SARS-CoV-2 CRF along with the AE CRF for the survival status (no SAE with outcome "Death Related to Adverse Event" reported).
- Subject's maximum SOFA score, subject's maximum change from baseline in SOFA score, and subject's mean SOFA score during the study will be calculated.

10.2.1 Secondary Efficacy Analysis

The ITT and mITT Analysis Set will be used for the secondary efficacy analyses. Number and percentage of subjects will be presented by treatment for the following secondary efficacy endpoints:

- All-cause mortality;
- Incidence of tracheal intubation;
- Proportion of subjects using CPAP or BiPAP;
- Proportion of subjects using HFNC;
- Proportion of subjects using ECMO.

The same statistical model and testing methodology as used for the primary efficacy variable will be used to compare the above secondary efficacy endpoints between the 2 treatments. The risk differences, associated 95% CIs, and 1-sided p-values will be reported.

Subjects with less than 28 days of the Treatment Period and without documented secondary endpoints as defined above will be assumed as not having experienced the secondary endpoint.

Clinical Status Assessed on an 8-Point NIAID Ordinal Scale

Number and percentages of subjects within each category of the 8-point NIAID ordinal scale will be summarized by visit for each treatment group. Number and percentages of subjects with an improvement from baseline of ≥ 2 points will be analyzed by visit using descriptive statistics as specified in Section 7.

A bar chart showing the frequencies in each category of the scale in the segments of each bar for the two treatment groups by visit will be provided.

Hospital Length of Stay

Hospital LOS will be defined as the time interval from randomization to hospital discharge alive. Survival status will be obtained from the AE CRF as absence of an SAE with outcome "Death Related to Adverse Event". In this analysis, for subjects who did not have a recorded date of hospital discharge and did not die, the time to hospital discharge will be censored at the last known in-hospital date if the subject did not complete the 28-day Treatment Period (i.e., the date of premature study discontinuation). For subjects who do not have a hospital discharge event or censoring time within the 28 days after randomization or for subjects who have died, an administrative censoring will be applied at 28 days.

Hospital LOS will be analyzed using Cox proportional hazard model including age as a continuous covariate, treatment group, gender (male or female), country (USA or Brazil), and baseline comorbidities (yes or no) as categorical covariates in the model. The hazard ratio, its 95% CI and 1-sided Wald p-value will be estimated from the model. Cumulative event rates will be calculated using the Kaplan-Meier (KM) method. The effect over time will be illustrated with a plot of the complement (1 – KM) of the KM estimates. Event counts and percentages will be summarized. If ties occur, Efron's method will be used to adjust for ties.

Sequential Organ Failure Assessment

The SOFA score assesses organ failure. A subject who does not fall into grade 1 to 4 in any of the components will be assigned a grade 0, representing no organ failure. The SOFA score is calculated as the summation of the six components grades. For the component 'Respiration', the grade for partial pressure oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ratio (mmHg) will be used, if it is missing, the grade for peripheral arterial oxygen saturation (SaO_2)/FiO_2 ratio (mmHg) will be used.

Maximum SOFA score, maximum change from baseline in SOFA score, and mean SOFA score during the study will be calculated for each subject and summarized descriptively as specified in Section 7 by treatment group. Median differences in maximum SOFA score, maximum change from baseline in SOFA score, and mean SOFA score during the study between treatment groups and 95% CIs using Hodges-Lehmann's method will be reported. Non-parametric Wilcoxon rank-sum test will be used to compare the 2 treatment groups.

The SOFA score and its components will be summarized by treatment and visit using descriptive statistics as specified in Section 7 for the grades and change from baseline in the grades:

- Respiration;
- Coagulation;
- Liver;
- Cardiovascular;
- Central Nervous System;
- Renal.

The observed values of the laboratory tests, vital signs, respiratory, cardiovascular, or central nervous system assessments along with changes from baseline of the individual components which feed into the SOFA score will be summarized by treatment and visit using descriptive statistics as specified in Section 7 in the corresponding sections of the Safety analysis.

10.2.2 Subgroup Analyses for Secondary Efficacy Endpoints

Subgroup analyses by the variables defined in Sections 8.2.7.1, 8.2.7.2, 8.2.7.3, 8.2.7.4, and 8.2.7.5 will be performed using the ITT Analysis Set as described in Section 10.2.1 for the following secondary endpoints:

- All-cause mortality;
- Incidence of tracheal intubation from randomization to Day 28;
- Clinical status assessed on an 8-point NIAID ordinal scale.

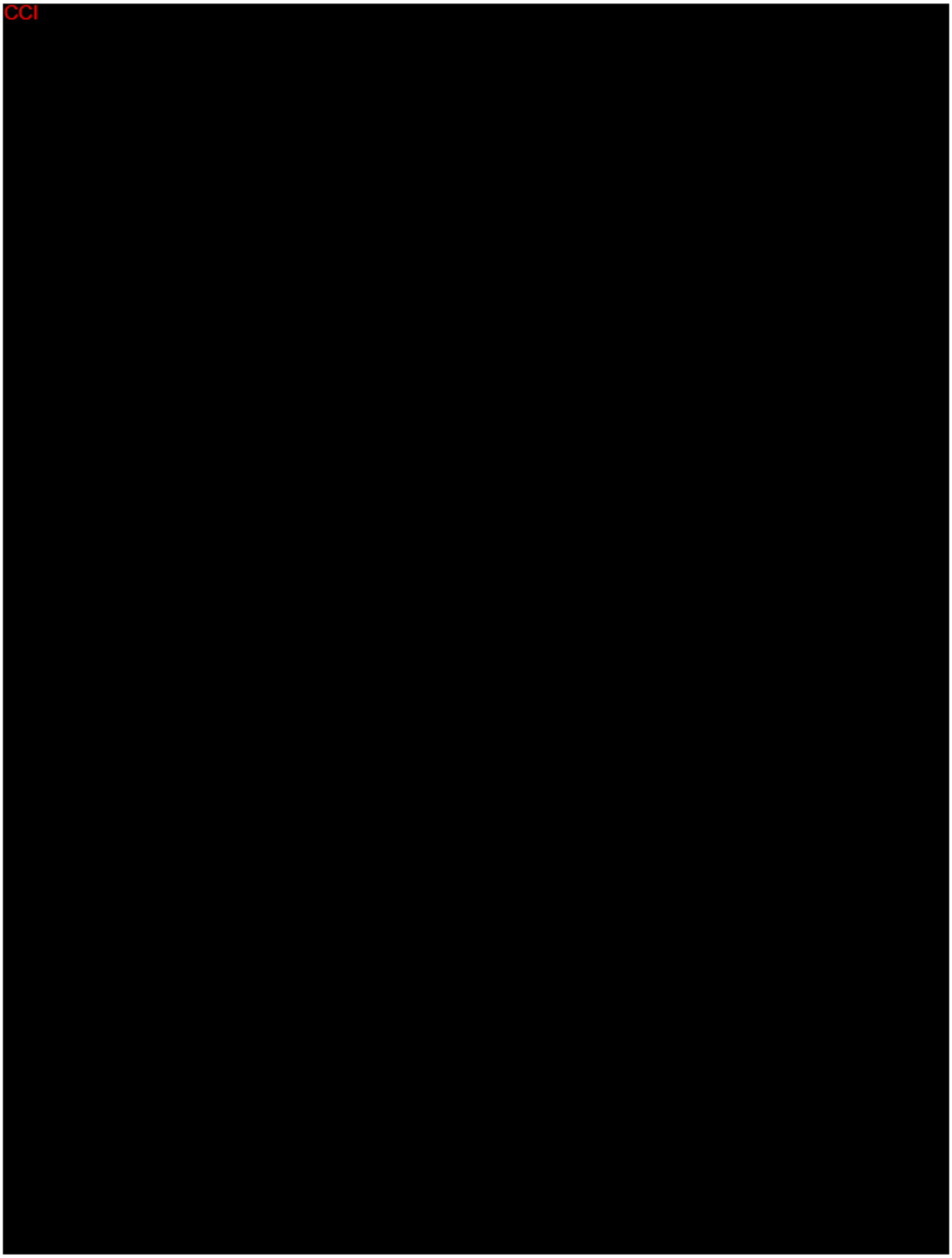
The logistic regressions will not include the factor for the respective subgroup analysis as independent variable (if applicable), but they will include the other covariates as specified for the primary analysis.

Forest-plots will be provided for the treatment comparison and 95% CIs for each subgroup level.

10.2.3 CCI

CCI [redacted]

CCI



CCI

[redacted]

10.3 Multiple Comparisons and Multiplicity

There will be 1 confirmatory test. All other statistical tests are meant to be descriptive. The sample size re-estimation at the interim analysis should not have an impact on the Type I error rate according to Chen et al [2004] and Mehta and Pocock [2011].

10.4 Missing Data and Imputation

For the primary efficacy analysis using the ITT Analysis Set, subjects with less than 28 days of the Treatment Period and without documented intubation or death will be considered as not having progressed to tracheal intubation or death prior to tracheal intubation in the primary analysis.

Sensitivity analyses as described in Section 10.1.3.1 will be performed to assess the impact of missing data on the primary efficacy results.

10.5 Treatment Compliance

Randomized subjects will receive 1 dose of IP administered by study personnel at the hospital. It is not expected that there will be any compliance issues.

11 Safety Analyses

The safety analyses will be based on the Safety Analysis Set as defined in Section 6 and on the treatment which the subject received.

11.1 Extent of Exposure

Subjects will receive 1 dose of IP. Duration of exposure is not relevant in this study. Duration of follow-up is of interest as this has an impact on the reporting of efficacy events and AEs.

Duration of follow-up will be descriptively summarized by treatment and total. The duration of follow-up is defined as:

$$\text{Subject's duration of follow-up (days)} = \text{EOS date} - \text{date of randomization} + 1,$$

where EOS date is either Day 28 or withdrawal date for subjects who discontinued.

A summary table will be provided with descriptive statistics as specified in Section 7 for:

- Duration of follow-up [days] per subject;
- Volume [mL] received per subject.

A by-subject listing will be provided based on the Safety Analysis Set including:

- Infusion date, start and end time, and duration (if start and end time is available);
- Volume administered [mL], location of infusion;
- Dose modified with reason.

11.2 Adverse Events

AEs will be coded using MedDRA. The version will be presented in the tables and listings. Treatment-emergent AEs (TEAEs), defined as AEs starting on or after the date (and time) of the administration of IP will be summarized. All AEs will be listed regardless of their start date.

Where AE start dates and/or times are missing or partially missing, AEs will be assumed to be treatment-emergent, except the partial dates and/or times or the AE end date and/or time indicate that the AE started before the first administration of IP:

Missing Elements of AE Start	Rule	Assignment
any	AE end date and time < IP start date and time	non-TEAE
any	AE end date and time ≥ IP start date and time	TEAE
otherwise		
all		TEAE
day and month	AE start year ≥ IP start year	TEAE
	AE start year < IP start year	non-TEAE
day	AE start month / year ≥ IP start month / year	TEAE
	AE start month / year < IP start month / year	non-TEAE
time	AE start date ≥ IP start date	TEAE
	AE start date < IP start date	non-TEAE

If AE start dates or end dates are missing or partially missing for an AE, duration will not be calculated. If for a TEAE the relationship to study treatment is missing the relationship to study treatment will be assumed to be “Yes” following a worst-case approach. No imputation

will be done in case of missing study treatment relationship for non-treatment emergent AEs. No other imputations for missing AE information will be done.

TEAEs occurring within 24 hours of IP administration will be defined as TEAEs with start date and time during IP administration or until 24 hours after the end of IP administration. AEs with missing start time will be assigned following the worst-case principle, i.e. when the start date of the TEAE is less or equal than the end date of the infusion + 1, the TEAE will be considered to having occurred within 24 hours after IP administration.

AEs fulfilling the definition of an AESI for this study will be ticked in the AE CRF. It will be ensured during data cleaning that the AESI recording on the AE CRF matches the AESI definition obtained by Standardized MedDRA Queries (SMQ):

- Hypersensitivity events corresponding to Hypersensitivity (SMQ) (broad);
- Anaphylactic reactions corresponding to Anaphylactic reaction (SMQ) (broad);
- Thromboembolic events (TEE) corresponding to Embolic and thrombotic events (SMQ);
- Bleeding events corresponding to Haemorrhages (SMQ).

All summary tables will be presented by actual treatment and total.

An overview summary table of TEAEs, including the number and percentage of subjects and the number of events will be provided for the following entries:

- Any TEAE;
- TEAEs related to study treatment;
- TEAEs occurring within 24 hours of IP administration;
- TEAEs leading to study discontinuation;
- TEAEs leading to dose modifications;
- Treatment-emergent AESIs;
- Treatment-emergent AESIs related to study treatment;
- Any serious TEAEs;
- Serious TEAEs related to study treatment;
- Serious TEAEs occurring within 24 hours of IP administration;
- Fatal TEAEs;
- Fatal TEAEs related to study treatment;
- TEAEs by intensity.

The following tables will be generated for TEAEs, including the number and percentages of subjects and the number of events. The tables will always be sorted by System Organ Class (for tables including System Organ Class) and Preferred Term within System Organ Class or Preferred Term alone (for the table not including System Organ Class). The order of the System Organ Class blocks or the order of the Preferred Terms alone or within System Organ Class block (if applicable) will be by descending frequency of number of subjects using the total column (in case of equal number of subjects sorting will be by descending frequency of number of events, in case of equal number of events sorting will be alphabetically).

- TEAEs by System Organ Class and Preferred Term;
- TEAEs by Preferred Term;
- TEAEs by System Organ Class, Preferred Term, and intensity;
- Related TEAEs by System Organ Class and Preferred Term;
- TEAEs occurring within 24 hours of IP administration by System Organ Class and Preferred Term;
- Fatal TEAEs by System Organ Class and Preferred Term;
- Treatment-emergent AESIs by System Organ Class and Preferred Term;
- Serious TEAEs by System Organ Class and Preferred Term.

The following by-subject listings based on the ITT Analysis Set will be provided including the information from the CRF:

- Deaths;
- Non-TEAEs;
- TEAEs;
- SAEs;
- AEs leading to study discontinuation;
- AESIs: hypersensitivity including anaphylactic reactions;
- AESIs: TEEs;
- AESIs bleeding events.

11.3 Clinical Laboratory Evaluations

The laboratory tests for hematology, biochemistry, and coagulation listed in the Schedule of Assessments of the protocol will be summarized (in the same sequence as in the protocol). Separate summary tables for hematology, biochemistry, and coagulation will be provided. Descriptive statistics as specified in Section 7 will be presented by treatment and total at scheduled visits for observed values and change from baseline. Number and percentage of

subjects will be presented for categorical tests by treatment and total at scheduled visits. The names and units of the laboratory tests will be used as provided in the data.

The following laboratory tests feeding into the SOFA score (see Section 10.2.1) will be indicated in the laboratory summary tables as SOFA score components: platelet count, bilirubin, creatinine. These tests will also be flagged in the listings as components of the SOFA score.

Laboratory values outside the normal range will be graded following Common Terminology Criteria for Adverse Events (CTCAE) 5.0 by clinical review. For laboratory tests with values outside normal range, the number and percentage of subjects in each grade will be presented.

For the definition of the baseline assessment see Section 8.2.3.

The denominator in percentage calculation at each scheduled visit will be based on the number of subjects with a non-missing value at each visit.

By-subject listings will be provided based on the ITT Analysis Set (date [and time] of sampling, test result, normal range, comments if applicable will be presented in a separate listing):

- Laboratory data for subjects with values outside the normal range;
- Hematology tests including flags for values outside the normal range and change from baseline;
- Biochemistry tests including flags for values outside the normal range and change from baseline;
- Coagulation tests including flags for values outside the normal range and change from baseline;
- Urinalysis tests.

11.4 Other Safety Measures

11.4.1 Vital Signs

Vital signs (blood pressure [systolic, diastolic], heart rate, respiratory rate) will be summarized by treatment and total at scheduled visits and time points. Descriptive statistics as specified in Section 7 will be presented for observed values and change from baseline.

For the definition of the baseline assessment see Section 8.2.3.

A by-subject listing will be provided based on the ITT Analysis Set (date [and time] of assessment, subject's position, location of body temperature measurement, test [blood pressure: systolic and diastolic; heart rate, respiratory rate, temperature, height and body weight at Screening], test result, change from baseline). Another by-subject listing will be provided for the hypotension assessment feeding into the SOFA score.

11.4.2 Respiratory Tests

Respiratory tests as entered in the Respiratory Parameter CRF (respiratory rate, peripheral oxygen saturation [SpO_2], FiO_2, PaO_2) will be summarized by treatment and total at scheduled visits and time points. Descriptive statistics as specified in Section 7 by treatment group will be presented for observed values and change from baseline. The respiratory component of the SOFA score, PaO_2/ FiO_2, will be analyzed in the same way as the other respiratory tests.

For the definition of the baseline assessment see Section 8.2.3.

A by-subject listing will be provided based on the ITT Analysis Set (date [and time] of assessment, test [respiratory rate, SpO_2, FiO_2, PaO_2, PaO_2/FiO_2], test result, change from baseline). PaO_2/FiO_2will be flagged in the listing as a component of the SOFA score.

11.4.3 Glasgow Coma Scale (SOFA Score Component)

Number and percentages of subjects in the response categories of the 3 features (eye opening, best verbal response, and best motor response) and descriptive statistics as specified in Section 7 for the total score will be presented by treatment group at scheduled visits.

A by-subject listing will be provided based on the ITT Analysis Set (date and time of the assessment, feature, scale response, score).

11.4.4 Physical Examination

Date and assessment performed for physical examination will be listed based on the ITT Analysis Set.

12 Pharmacokinetic Analyses

The PK analysis will be performed using the PK Analysis Set.

PPD will conduct the derivation of the PK parameters under the supervision of the CSL Behring Clinical Pharmacology department. All noncompartmental analyses will be

performed according to PK-GDL-01. PK parameters will be derived based on the CSL312 concentration after the administration of CSL312 on Day 1.

After data base lock, CSL will produce all SDTM domains needed for the PK analysis. The PC domain containing the CSL312 concentrations, nominal blood sampling times, actual sampling time relative to the start of the dose infusion, actual dosing and infusion durations and the PP domain containing the PK parameters will be provided. Any CSL312 plasma concentrations which will have been excluded from the derivation of the PK parameters will be flagged in the data.

PPD will produce the TFLs for the CSL312 plasma concentrations and the PK parameters as specified below.

12.1 Drug Concentration Measures

The handling and imputation of below limit of quantification (BLQ) values for PK parameter derivation is described in PK-GDL-01. The imputation rules below will be used for summary statistics of CSL312 plasma concentrations. The summaries will be given by planned time point.

- The sampling time of pre-dose samples relative to start of the dose infusion will be treated as zero;
- Concentration values below BLQ in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;
- Post-dose BLQ concentrations flanked by quantifiable concentrations will be set to missing;
- Post-dose BLQ concentrations after the last quantifiable point will be set to missing for summary statistics of plasma concentrations;
- The mean/median value at a time point where one or more samples have BLQ values will be reported (in tabular or graphical fashion) even if the mean/median value is BLQ of the assay;
- Zero mean or median values will be included in summary tables.

It should be noted that a high proportion of BLQ values may affect the summary statistics; if more than 50% of the values are imputed (i.e., BLQ), then the summary statistics (mean, SD, median, quartiles) will not be displayed.

Summary statistics for concentration-time data will include the percentage of BLQ values relative to the total N

> %BLQ = 100 * (number of subjects who have BLQ values / total number of subjects) at each time point.

Descriptive statistics will be provided as outlined in Section 7, and in addition the CV% and geometric mean.

Individual CSL312 plasma concentration plots (on log-linear scale) will be plotted versus actual sampling time. Multiple subject plots will be presented on 1 page.

Plots for mean (± SD) CSL312 plasma concentrations (on linear and on log-linear scales) versus nominal (planned) time will be provided. If more than 50% of the individual values are BLQ, the mean and SD will be set to missing in the plots.

Plasma concentrations excluded from the derivation of the PK parameters will also be excluded from the summary statistics and the mean plots. A footnote will indicate if plasma concentrations have been excluded from the analysis.

A by-subject listing of CSL312 plasma concentrations with the concentrations flagged that have been excluded from the derivation of the PK parameters based on the PK Analysis Set will support the summaries.

12.2 Deriving and Summarizing Pharmacokinetic Parameters

For subjects belonging to the PK Analysis Set, the PK parameters provided in Appendix 15.1 will be determined from the CSL312 plasma concentration-time data.

The PK parameter derivation including imputation of the values BLQ and missing data will be conducted in accordance to PK-GDL-01 which gives guidance on how to derive PK parameters in the presence of missing data.

PK parameters of CSL312 will be summarized with the following statistics being provided.

Variable	**Statistical Parameters:**
C_{max}, $AUC_{0\text{-last}}$, $T_{1/2}$	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
T_{max}	n, minimum, median, and maximum

The geometric CV% will be calculated as 100*sqrt(exp(ln(SD^2))-1).

A by-subject listing of CSL312 PK parameters based on the PK Analysis Set will be provided.

13 CCI [redacted]

CCI [redacted]

13.1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

14 References

Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. Statistics in Medicine. 2004;23(7):1023-1038.

Ge M, Durham LK, Meyer RD, Xie W, Thomas N. Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug Information Journal. 2011;45:481-493.

Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessments score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergent department presentation. Crit Care Med. 2009;37(5):1649-1654.

Mehta, C and Pocock, S. Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statistics in Medicine. 2011;30(28):3267-3284.

National Institute of Allergy and Infectious Diseases (NIAID). ClinicalTrials.gov. Adaptive COVID-19 Treatment Trial (ACTT). Available at: https://clinicaltrials.gov/ct2/show/NCT04280705. Accessed: May 05, 2020.

Newcombe RG. Confidence intervals for an effect size measure based on the Mann-Whitney statistic. Part 2: asymptomatic methods and evaluation. Statist. Med. 2006;25(4):559-573.

Novack V, Beitler JR, Yitshak-Sade M, Thompson BT, Schoenfeld DA, Rubenfeld G, et al. Alive and ventilator free: a hierarchical, composite outcome for clinical trials in the acute respiratory distress syndrome. Crit Care Med. 2020;48(2):158-166.

PK-GDL-01, Guideline on the Conduct of Non-compartmental Pharmacokinetic Analyses, CSL Behring.

Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol. 2014;13(8):844-854.

15 Appendices

15.1 PK Parameters

Term	Definition [unit]	Calculation method
$AUC_{0\text{-last}}$	Partial AUC from time point 0 to time point of the last measurable concentration [mass * time * volume^{-1}].	AUC from the time of dosing to a specified timepoint (t), using the linear up/log down trapezoidal rule.
C_{max}	The maximum (peak) observed plasma drug concentration [mass * volume^{-1}]	
$T_{1/2}$	The terminal half-life [time]	$t_{1/2} = \ln(2) / \lambda_z$
T_{max}	The time to reach maximum (peak) drug concentration in measured biological fluid [time]	

15.2 Sequential Organ Failure Assessment (SOFA) Scale

	SOFA Score				
	0	**1**	**2**	**3**	**4**
Respiration[a]					
PaO_2/FIO_2 (mmHg)	≥ 400	< 400	< 300	< 220	< 100
SaO_2/FIO_2 (mmHg)	> 301	221-301	142-220	67-141	< 67
Coagulation					
Platelets $\times 10^3/mm^3$	≥ 150	< 150	< 100	< 50	< 20
Liver					
Bilirubin (mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular[b]					
Hypotension	≥ 70	MAP < 70	Dopamine ≤ 5 or dobutamine (any)	Dopamine > 5 or norepi-nephrine ≤ 0.1	Dopamine > 15 or norepi-nephrine > 0.1
Central Nervous System					
Glasgow Coma Score	15	13-14	10-12	6-9	< 6
Renal					
Creatinine (mg/dL) or urine output (mL/d)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9 or < 500	> 5.0 or < 200

MAP = mean arterial pressure; SaO_2 = peripheral arterial oxygen saturation.

a. PaO_2/FIO_2 ratio is preferable. If not available, the SaO_2/FIO_2 ratio may be used.

b. Vasoactive medications administered for ≥ 1 hour (dopamine and norepinephrine µg/kg/min).

Source: Ge M, Durham LK, Meyer RD, Xie W, Thomas N. Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug Information Journal. 2011;45:481-493.

Jones et al, 2009.

15.3 National Institute of Allergy and Infectious Diseases (NIAID) 8-point Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day.

NIAID Score	Description
1	Death
2	Hospitalized, on invasive mechanical ventilation or ECMO
3	Hospitalized, on NIV or high-flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
6	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

COVID-19 = Coronavirus Disease 2019; ECMO = extracorporeal membrane oxygenation; NIAID = National Institute of Allergy and Infectious Diseases; NIV = non-invasive ventilation.

Source: NIAID, 2020.

15.4 Glasgow Coma Scale

Feature	Scale Responses	Score
Eye opening (E)	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response (V)	Oriented	5
	Sounds	4
	Words	3
	Confused	2
	None	1
Best motor response (M)	Obeying commands	6
	Localizing	5
	Normal flexion (withdrawal)	4
	Abnormal flexion	3
	Extension	2
	None	1
Total comma score		**3-15**

Source: Teasdale et al, 2014.

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Signed By	Date (GMT)
PPD	01-Sep-2020 05:59:05
Approved-PPD Approval	
PPD	31-Aug-2020 18:07:56
Approved-PPD Approval	

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