CLINICAL STUDY PROTOCOL

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
Short Title:	CSL312 in COVID-19
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Protocol Version:	Amendment 3
Protocol Date:	16 September 2020
IND Number:	CCI [redacted]
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.

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator's Study File. This list will be updated by CSL Behring (or delegate) and provided to the study sites as needed.

REVISION HISTORY

Date	Version	Summary of Changes
19 May 2020	Original	Not applicable
11 July 2020	Amendment 1	1. Revised wording for indication to be studied. 2. Revised pharmacokinetic (PK) secondary endpoints to include area under the plasma concentration-time curve from time zero to the time of the last measureable concentration ($AUC_{0\text{-last}}$) rather than AUC from time zero up to a definite time ($AUC_{0\text{-t}}$) and add terminal half-life ($T_{1/2}$) 3. Revised prohibited therapies section to indicate that the use of any investigational product (IP) or investigational device according to a formal protocol for another clinical study is PROHIBITED during this study. 4. Revised study design, exclusion criteria, and prohibited/permitted therapies sections to indicate that off-label use of approved products (eg, antibodies against IL-6 [anti-IL-6]/antibodies against IL-6 receptors [anti-IL-6R]), administration of investigational product (IP) for which emergency use authorization has been granted (eg, remdesivir). Additionally, the use of IP for which expanded access for treatment use ("compassionate use") has been authorized (eg, convalescent plasma) is permitted during study participation. 5. Revised planned number and location of study sites to indicate the possibility of adding study sites in Latin America. 6. Revised inclusion criterion # 6 to specify that ≥ 1 of the respiratory parameters for severe COVID-19 disease must be met at Screening including within 24 hours before Screening.

		7. Revised the definition for the Pharmacokinetic Analysis Set to indicate the requirement for ≥ 1 blood sample available for CSL312 concentration measurement after administration of CSL312. Also, revised the definition to indicate that the PK analyses will only be performed for subjects treated with CSL312 and not for those treated with placebo. 8. Revised the definition of treatment effect of interest from "odds ratio of CSL312 + standard of care (SOC) versus placebo + SOC" to "proportion difference of CSL312 + SOC minus placebo + SOC", updated the primary efficacy analysis, and added citation and reference to support this evaluation. 9. Added details on Baseline comorbidities to be used as covariates in the statistical model. 10. Added details on analysis of secondary efficacy endpoints. 11. Added details on planned analysis of Sequential Organ Failure Assessment (SOFA) scores. 12. Added sensitivity analyses to assess the effect of missing data. 13. Added the definition of Baseline to be used in statistical analyses. 14. Minor corrections and clarifications, including word modifications and administrative changes.
25 August 2020	Amendment 2	1. Increased the number of potential sites from approximately 20 sites to approximately 25 sites (≥ 15 sites in the United States of America (USA) and up to 10 sites in Brazil). 2. Revised the temporary halting schedule for Independent Data Review Committee (IDMC) review such that enrollment will only be temporarily halted for review of safety data for the first 20 subjects. During subsequent IDMC reviews, enrollment will continue without pause. 3. Revised eligibility criteria to indicate that eligibility may be assessed at the time of hospital admission provided that the subject is randomized within 24 hours of Screening.

		4. Revised inclusion criteria to indicate that the SARS-CoV-2 infection must be determined using a molecular diagnostic test (reverse transcription polymerase chain reaction [RT-PCR] or equivalent) approved by regulatory authorities. 5. Revised inclusion criteria to indicate that the SARS-CoV-2 test may be repeated within the Screening Period if a false negative result is suspected. 6. Revised text regarding early hospital discharge to indicate the data to be obtained via weekly telephone call and by whom. 7. Defined the minimum laboratory results that are required to initiate randomization. 8. Revised study product administration to indicate that the intravenous infusion should be a slow injection, (ie, push of about 3 minutes). 9. Added assessment of outcome measures before dosing on Day 1, including the subject's use of supplemental oxygen; use of CPAP or BiPAP; use of HFNC; use of ECMO; intubation; and intensive care unit admission. 10. Revised Schedule of Assessments to indicate that pre-existing laboratory results may be used in lieu of repeating the assessments for Screening provided that the assessments were performed with 48 hours of randomization and the subject agrees to the use of those data in the inform consent form. 11. Added stratification by country variable (USA or Brazil) to the planned statistical analyses.
16 September 2020	Amendment 3	1. Revised the required duration of the use of acceptable forms of contraception to ≥ 90 days after the last administration of study drug. 2. Added the use a non-contact infrared thermometer to the methods of measuring body temperature.

Clinical Study Protocol Synopsis

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
Sponsor	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Development Phase	Phase 2
Study Product	CSL312 (Garadacimab, Factor XIIa Antagonist Monoclonal Antibody)
Indication	For the prevention of respiratory failure in patients with COVID-19
Study Summary and Overview	This is a prospective, phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety, PK, and efficacy of CSL312 administered intravenously, in combination with standard-of-care (SOC) treatment, in patients with Coronavirus disease 2019 (COVID-19).

	SOC treatment is defined as any written or established treatment protocol followed at the study site for patients with severe COVID-19 or complications associated with COVID-19, including off-label use of approved drugs (eg, antibodies against interleukin-6 [anti-IL-6]/antibodies against IL-6 receptors [anti-IL-6R]) or an investigational product (IP) for which administration under an emergency use authorization has been granted (eg, remdesivir). Administration of IP for which expanded access for treatment use ("compassionate use") has been authorized (eg, convalescent plasma) is also permitted during study participation. The study consists of a Screening Period of up to 2 days, and a Treatment Period of up to 28 days. Aggregate data from groups of subjects will be reviewed by an Independent Data Monitoring Committee (IDMC), both early and at predetermined intervals during the conduct of the study. For futility monitoring and sample size re-estimation, an interim analysis of unblinded primary endpoint data is planned after 62 subjects (50% of the target sample size) have completed primary endpoint assessment.
Primary Objective	The primary objective of the study is to assess the treatment benefit of CSL312 after intravenous (IV) infusion in patients with COVID-19.
Primary Endpoint	The primary endpoint is the incidence of tracheal intubation or death prior to tracheal intubation from randomization to Day 28.
Secondary Objectives	The secondary objectives of the study are: • To further assess the efficacy of CSL312 • To assess the safety of CSL312 • To assess the pharmacokinetics (PK) of CSL312

Secondary Endpoints	The secondary endpoints are: • All-cause mortality • Incidence of tracheal intubation • Clinical status as assessed on an 8-point National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale • Use of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) • Use of high-flow nasal cannula (HFNC) • Use of extracorporeal membrane oxygenation (ECMO) • Change in Sequential Organ Failure Assessment (SOFA) score • Length of hospital stay • Subjects experiencing the following safety events: o Adverse events (AEs) o Serious adverse events o Adverse events of special interest o CSL312-induced anti-drug antibodies o Clinically significant abnormalities in laboratory assessments reported as AEs • CSL312 PK in plasma: o Maximum plasma concentration (C_{max}) o Time to maximum plasma concentration (T_{max}) o Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration ($AUC_{0\text{-}last}$) o Terminal half-life ($T_{1/2}$)
Study Duration	The duration of an individual subject's study participation is expected to be up to 30 days. This estimate is based on: • A Screening Period of up to 2 days. • A Treatment Period of up to 28 days. The overall study duration (ie, first subject's Screening Visit to last subject's last study visit) will be approximately 6 months.
Number of Subjects	This study will enroll a total of approximately 124 subjects; 62 subjects in the CSL312 + SOC group and 62 subjects in the placebo + SOC group. After the first 62 subjects have completed the primary endpoint assessment, 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.

Study Population and Main Criteria for Eligibility

Inclusion criteria:

1. Capable of providing written informed consent. An individual legally permitted to make medical decisions on the subject's behalf can provide written informed consent.
2. Willing and able to adhere to all protocol requirements
3. Age ≥ 18 years at the time that informed consent is obtained
4. Positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as determined using a molecular diagnostic test (reverse transcription polymerase chain reaction [RT-PCR] or equivalent) approved by regulatory authorities (including Food and Drug Administration or Brazilian Health Regulatory Agency) or allowed under an emergency use authorization within 14 days before Screening. If a false negative result is suspected, the SARS-CoV-2 test may be repeated within the Screening Period.
5. Chest computed tomography (CT) scan or X-ray results confirming interstitial pneumonia
6. Severe COVID-19 disease as evidenced by ≥ 1 of the following criteria at Screening including within 24 hours before Screening:
   - Respiratory frequency > 30 breaths per minute
   - Saturation of peripheral (capillary) oxygen (SpO_2) ≤ 93% on room air
   - Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300
   - Arterial oxygen saturation (SaO_2)/FiO_2 ratio < 218 (if PaO_2/FiO_2 ratio is not available)
   - Radiographic lung infiltrates > 50%

Exclusion criteria:

1. Currently enrolled, planning to enroll, or participated, within the last 30 days, in a clinical study requiring administration of an IP, including expanded access or compassionate use with the only exception being administration of convalescent plasma. Administration of IP is permitted only if an emergency use authorization has been granted (eg, remdesivir). Additionally, off-label use of approved drugs (eg, anti-IL-6/anti-IL-6R) is also permitted.
2. Pregnant or breastfeeding (female subjects)
3. Intubated or requires mechanical ventilation (including ECMO) at the time of randomization
4. In the opinion of the investigator, the subject is expected to be intubated within the first 24 hours after IP administration

	5. Active Do-Not-Intubate (DNI) or Do-Not-Resuscitate (DNR) order 6. In the opinion of the investigator, the subject is not expected to survive for > 48 hours 7. Any of the following comorbid conditions prior to randomization and prior to SARS-CoV-2 infection: • Severe heart failure (New York Heart Association Class IV) • End-stage renal disease (Stage ≥ 4) or need for renal replacement therapy • Biopsy-confirmed cirrhosis, portal hypertension, or hepatic encephalopathy • Malignancy (Stage IV) • Chronic lung disease requiring the use of oxygen at home • Active tuberculosis disease 8. Active bleeding or current clinically significant coagulopathy (eg, international normalized ratio [INR] > 1.5) or clinically significant risk for bleeding (eg, recent intracranial hemorrhage or bleeding peptic ulcer within the last 4 weeks) 9. History of venous thrombosis, myocardial infarction, or cerebrovascular event within the last 3 months, or a prothrombotic disorder (eg, antithrombin III, protein C, or protein S deficiency) 10. Known or suspected Grade 3 or 4 infusion-related reaction or hypersensitivity (per Common Terminology Criteria for Adverse Events) to monoclonal antibody therapy, or hypersensitivity to the IP or any excipients of the IP [National Cancer Institute, 2009] 11. Currently receiving a therapy not permitted during the study 12. Female subject of childbearing potential or fertile male subject either not using or not willing to use an acceptable method of contraception to avoid pregnancy during the study and for 90 days after administration of IP 13. Any clinical or laboratory abnormality or other underlying conditions (eg, psychological disorders, substance abuse) that would render the subject unsuitable for participation in the study, in the opinion of the investigator
Study Product Dose, Dosing Regimen and Administration	CSL312 will be supplied as a sterile solution for injection containing 100 mg/mL of CSL312 in 2-mL vials. A single dose of 700 mg will be administered once, in an infusion volume of 7 mL, by slow IV injection (ie, push of about 3 minutes).

Comparator Product, Dose, Dosing Regimen and Administration	Placebo will be supplied as a sterile preservative-free solution for injection in 10-mL vials. The placebo is the same as the CSL312 formulation buffer, but does not contain the active substance (ie, CSL312). Placebo will be administered once, in an infusion volume of 7 mL, by slow IV injection (ie, push of about 3 minutes).
Efficacy Assessments	Outcome assessments will include the subject's use of supplemental oxygen; use of CPAP or BiPAP; use of HFNC; use of ECMO; intubation; extubation; clinical status on standardized scales; intensive care unit (ICU) admission and discharge; and hospital discharge or death.
Safety Assessments	Safety will be assessed through documentation of treatment-emergent adverse events, vital signs, physical examinations, respiratory parameters, clinical laboratory assessments, and anti-drug antibodies.
Pharmacokinetics	Blood samples will be collected for assessment of CSL312 PK in plasma.
CCI [redacted]	CCI [redacted]
Statistical Analyses	**Sample Size** There are limited data available 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 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, 62 subjects to placebo + SOC) in order to achieve 80% power to detect a treatment difference using a 2-group chi-square test. For the futility monitoring and sample size re-estimation, an interim analysis of unblinded primary endpoint data is planned after 62 subjects (50% of the target sample size) have completed primary endpoint assessment. Additional details on the interim analysis are provided in the body of the protocol.

Analyses of Primary Efficacy

The primary endpoint for this study is the incidence of tracheal intubation or death prior to tracheal intubation from randomization to Day 28. The proportion will be calculated as the number of subjects with tracheal intubation or death prior to tracheal intubation divided by the total number of subjects for each treatment group. Treatment effect of interest (ie, estimand) is defined as the proportion difference of tracheal intubation or death prior to tracheal intubation (CSL312 + SOC minus placebo + SOC) in the target population regardless of whether additional treatment is used or initial SOC has changed. The Intent-to-treat Analysis Set will be used for the primary efficacy analyses.

Firth logistic regression model including treatment group; age group as a continuous covariate; gender (male or female); country (USA or Brazil); and Baseline comorbidities (yes or no) as categorical covariates will be used to compare the rates between the 2 treatment groups. Comorbidities include hypertension, diabetes, and obesity (defined as body mass index $\geq$ 30 kg/m^2). A 2-sided p-value will be estimated from the model. The proportion difference and associated 95% confidence interval (CI) will be estimated using the method described by Ge at al [2011]. The mITT Analysis Set will be used for primary efficacy endpoint sensitivity analysis.

Sensitivity analyses to assess the effect of missing data will be conducted, for example, by performing tipping point analyses that vary assumptions about the missing outcomes in both study treatment groups.

Other Analyses

Details of the analyses of secondary efficacy, safety, PK, CCI are provided in the full clinical study protocol.

Schedule of Assessments

Study Period	Screening	Treatment Period												
Study Week	Week -1	Week 1							Week 2		Week 3		Week 4	
Study Day	Screening Visit[a] D-2 to D1[b]	D1				D2	D3 to D6	D7	D8 to D13	D14	D15 to D20	D21	D22 to D27	D28 EOS[d,e]
		Before Dosing	Dosing	After Dosing[c] 30 min	After Dosing[c] 6 h									
Visit Window	NA			± 15 min	± 2 h	NA	NA	NA	NA	NA	NA	NA	NA	± 2d
Written informed consent[f]	X													
Inclusion/exclusion criteria	X													
Confirm SARS-CoV-2 positive[g]	X													
Chest CT scan or X-ray[h]	X													
Medical history/demographics	X													
Physical examination[i]	X													X
Height and body weight[j]	X													
Vital signs[k]	X	X		←	—	—	—	—	—	—	—	—	—	→
Respiratory parameters[l]	X[u]	X		←	—	—	—	—	—	—	—	—	—	→
GCS for SOFA score	X	X				X		X		X		X		X
Arterial blood gas/PaO_2 for SOFA score[m]	X	X				X		X		X		X		X
NIAID 8-point ordinal scale		X				X		X		X		X		X
Urine collection for urinalysis[n]	X	X												X
Pregnancy test[n,o]	X													X
Hematology, biochemistry, coagulation[n,p]	X	X				X		X		X		X		X
Randomization		X												
Assignment to IP[q]		X												
Blood samples for PK and C assessments[r,s] CI		X		X	X	X		X		X		X		X
CCI														
Outcome assessments[t]		X		←	—	—	—	—	—	—	—	—	—	→
Administration of IP[q]			X											

Study Period	Screening	Treatment Period												
Study Week	Week -1	Week 1							Week 2		Week 3		Week 4	
Study Day	Screening Visit[a] D-2 to D1[b]	D1				D2	D3 to D6	D7	D8 to D13	D14	D15 to D20	D21	D22 to D27	D28 EOS[d,e]
		Before Dosing	Dosing	After Dosing[c] 30 min	After Dosing[c] 6 h									
Visit Window	NA			± 15 min	± 2 h	NA	NA	NA	NA	NA	NA	NA	NA	± 2d
AEs		←												→
Previous/concomitant medication and therapies	X	←												→

[redacted]; AE = adverse event; ANVISA = Brazilian Health Regulatory Agency; BiPAP = bi-level positive airway pressure; C1-INH = C1 esterase inhibitor; CPAP = continuous positive airway pressure: CT = computed tomography; β-hCG = beta human chorionic gonadotropin; eCRF = electronic case report form; ECMO = extracorporeal membrane oxygenation; EOS = End of Study; FDA = Food and Drug Administration; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; HFNC = high-flow nasal cannula; ICU = intensive care unit; ICF = informed consent form; IP = investigational product; INR = international normalized ratio; IV = intravenous; FXII = coagulation factor XII; NA = not applicable; NIAID = National Institute of Allergy and Infectious Diseases; PaO_2 = partial pressure of arterial oxygen; [redacted]; PK = pharmacokinetic; PT = prothrombin time; RT-PCR = reverse transcription polymerase chain reaction; SaO2 = arterial oxygen saturation; SARS-Co-V-2 = severe acute respiratory syndrome coronavirus-2; SOC = standard of care; SOFA = Sequential Organ Failure Assessment; SpO_2 = saturation of peripheral (capillary) oxygen; T_{max} = time to maximum plasma concentration; TT = thrombin time.

Notes for Schedule of Assessments:

a. If Screening occurs on Day 1, the assessments scheduled to occur at both Screening and before dosing on Day 1 may be performed only once (ie, do not need to be repeated).

b. Pre-existing laboratory results from assessments performed during the Screening Period, but before obtaining informed consent, may be used in lieu of performing the assessment at Screening (the same assessment does not need to be repeated/performed at Screening), if the subject agrees to the use of those data in the ICF. However, the assessments must have been performed with 48 hours of randomization.

c. Assessments to be performed after dosing will be done after the end of the infusion of IP (CSL312 or placebo), which should be done as a slow injection, (ie, push of about 3 minutes).

d. For subjects who are discharged from the hospital before Day 28, the EOS assessments will be performed on the day of discharge and subjects will be encouraged to return to the study site to complete the EOS Visit assessments on Day 28, but if a subject is not able to participate in the Day 28 (EOS) Visit in person, then the subject will be contacted by telephone to assess clinical status, AEs, and concomitant medications. For any subject who withdraws from the study before Day 28, attempts will be made to complete and document the Day 28 Visit (EOS) assessments.

e. For subjects who are discharged from the hospital before Day 28, a weekly telephone call will be made to assess clinical status, AEs, and concomitant medications. These subjects will be encouraged to return for the Day 28 (EOS) Visit.

f. Written informed consent must be obtained before any study-specific assessments or procedures are performed. An individual legally permitted to make medical decisions on the subject's behalf may provide written informed consent for study participation.

g. Positive for SARS-CoV-2 infection as determined using a molecular diagnostic test (RT-PCR or equivalent) approved by regulatory authorities (including the FDA and ANVISA) or allowed under an emergency use authorization within 14 days before Screening. If a false negative result is suspected, the SARS-CoV-2 test may be repeated within the Screening Period.

h. To be eligible for study participation, the subject's thoracic CT scan or X-ray (performed within the 24 hours prior to Screening) must show signs of interstitial pneumonia.

i. A physical examination will be conducted per the study site's standard procedure.
j. The subject's height and body weight will only be measured at Screening.
k. Vital sign assessments, including blood pressure (systolic and diastolic), heart rate, and body temperature, should be assessed and recorded in the eCRF at approximately the same time each day during study participation. Blood pressure and heart rate will be measured with the subject in a supine or seated position after resting for ≥ 5 minutes. Body temperature will be measured either sublingually or tympanically; body temperature may also be measured using a non-contact infrared thermometer. The method of measurement should be consistent throughout the study for a given subject.
l. Respiratory parameters: respiratory rate (breaths per minute), SpO_2 (%), and FiO_2 (natural air includes 21% oxygen, which is equivalent to FiO_2 of 0.21). Respiratory parameters should be measured once daily, ideally performed together with vital signs at the same time of the day.
m. PaO_2 should be measured only on days when the SOFA score is assessed. An indwelling arterial catheter should not be placed just to collect these samples. Although the PaO_2/FiO_2 ratio is preferable to calculate the SOFA score, if PaO_2 is not available, the SaO_2/FiO_2 ratio may be used instead.
n. These assessments will be performed at the local laboratory.
o. A urine test for β-hCG will be performed at the local laboratory for all female subjects of childbearing potential to rule out pregnancy during Screening and at the end of the Treatment Period. A serum pregnancy test will be performed by the site if urine result is inconclusive.
p. Blood samples will be analyzed for the laboratory parameters specified in Table 3.
q. IP will be either IV CSL312 +SOC or IV placebo +SOC.
r. Blood samples will be analyzed at the central laboratory for the PK parameters specified in Section 7.4 CCI [redacted] Analysis of the PK data will be performed by CSL (or delegate).
s. On Day 1, blood samples will be collected at 30 minutes and 6 hours after the end of the infusion of IP to perform PK assessments.
t. Outcome assessments include the subject's use of supplemental oxygen; use of CPAP or BiPAP; use of HFNC; use of ECMO; intubation; extubation; ICU admission and discharge; and hospital discharge or death.
u. Results from respiratory parameter assessments performed at the time of hospital admission may be used, without the requirement to repeat these assessments for the Screening Visit provided that the assessments were performed within 24 hours before Screening for this study.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Term
3F7	Parental antibody to CSL312
ACE-2	Angiotensin-converting enzyme 2
CCI	[redacted]
AE	Adverse event
AESI	Adverse event of special interest
Anti-IL-6	Antibodies against interleukin-6
Anti-IL-6R	Antibodies against interleukin-6 receptors
ANVISA	Brazilian Health Regulatory Agency
ARDS	Acute respiratory distress syndrome
aPTT	Activated partial thromboplastin time
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration
βFXIIa	Activated coagulation factor XII beta
BiPAP	Bi-level positive airway pressure
BK	Bradykinin
CI	Confidence interval
C_{max}	Maximum plasma concentration
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CP	Conditional power
CPAP	Continuous positive airway pressure
CSL	CSL Behring
CSL312	Factor XIIa antagonist monoclonal antibody
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTRA	Clinical Trial Research Agreement
CV%	Percent coefficient of variance
DABK	des-Arg^9 bradykinin
DIC	Disseminated intravascular coagulation
DNI	Do-not-intubate
DNR	Do-not-resuscitate

Abbreviation	Term
eCRF	Electronic case report form
ECMO	Extracorporeal membrane oxygenation
EOS	End of Study
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
FXII	Coagulation factor XII
FXIIa	Activated coagulation factor XII
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
HAE	Hereditary angioedema
HFNC	High-flow nasal cannula
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IP	Investigational product
INR	International normalized ratio
IP-10	Interferon gamma-induced protein 10
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
IV	Intravenous
KKS	Kallikrein-kinin system
KM	Kaplan-Meier
LMWH	Low molecular-weight heparin
LOS	Length of stay
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome

Abbreviation	Term
MIP-1α	Macrophage inflammatory protein 1-alpha
mITT	Modified intent-to-treat
NCPERE	Novel Coronavirus Pneumonia Emergency Response Epidemiology
NIAID	National Institute of Allergy and Infectious Diseases
NIV	Non-invasive ventilation
PaO_2	Partial pressure of arterial oxygen
CCI	[redacted]
PK	Pharmacokinetic
PT	Prothrombin time
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SaO_2	Arterial oxygen saturation
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SMT	Safety Management Team
SOC	Standard-of-care
SOFA	Sequential Organ Failure Assessment
SpO_2	Saturation of peripheral (capillary) oxygen
$T_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
T_{max}	Time to maximum plasma concentration
TNF-α	Tumor necrosis factor-alpha
USA	United States of America
WHO	World Health Organization

1 Introduction

1.1 Background

Coronavirus disease 2019 (COVID-19) is caused by a new coronavirus strain of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). According to the World Health Organization (WHO), the virus emerged in Wuhan, China [WHO Disease Outbreak News, 2020]. Since the first reports in December 2019, SARS-CoV-2 has spread rapidly with soaring numbers of confirmed cases globally [WHO COVID-19 Situation Report 65, 2020]. Symptoms elicited by SARS-CoV-2 include fever, dry cough, dyspnea, and fatigue. While most patients display a mild form of illness, a subset of infected individuals (~14%) develop severe disease, viral pneumonia, leading to hospitalization and the need for oxygen support, with approximately 5% of these patients requiring intensive care unit (ICU) admission [Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (NCPERE Team), 2020]. In severe cases, COVID-19 may be complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, multi-organ failure, and even death [Yang et al, 2020]. Risk factors associated with severe disease are age > 65 years and underlying comorbidities, such as obesity, diabetes mellitus, and other chronic disorders.

Emerging radiological evidence suggests that patients with COVID-19 pneumonia present with thoracic computed tomography (CT) imaging abnormalities [Shi et al, 2020]. The predominant pattern reported is ground-glass opacity, with ill-defined margins, air bronchograms, smooth or irregular interlobular or septal thickening, and thickening of the adjacent pleura. CT scan abnormalities appear to evolve from focal unilateral to diffuse bilateral ground-glass opacities and may progress to or co-exist with consolidations within 1 to 3 weeks. Evidence suggests that CT abnormalities are observed even in patients with mild symptoms. Overall, the reported imaging characteristics bear resemblance to those observed for other coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and are suggestive of vascular leakage and fluid accumulation in the lung tissue.

In a study by Huang et al, patients with COVID-19 had CT scan abnormalities that were associated with leukocytopenia and lymphopenia [Huang et al, 2020]. At the time of hospital admission, increased prothrombin time (PT) and D-dimer levels have been observed in patients that are eventually admitted to the ICU. Preliminary evidence further suggests that the non-survivors, at the time of admission, had higher levels of D-dimer and fibrin degradation product, longer PT, and activated partial thromboplastin time (aPTT) compared with survivors [Tang et al, 2020] During their hospital stays, 71.4% of non-survivors and 0.6% of survivors met the criteria for disseminated intravascular coagulation (DIC). Together, these data suggest that severe COVID-19 is associated with activation of the coagulation cascade. While DIC was initially thought to be a consequence of extrinsic activation of the coagulation system, more recent findings suggest that intrinsic activation may also play a role. Lastly, analysis of immune mediators in plasma showed increased concentrations of interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-alpha (MIP-1α), and tumor necrosis factor-alpha (TNF-α) in ICU patients compared with non-ICU patients [Huang et al, 2020].

Similar to SARS-CoV, the functional ligand of SARS-CoV-2 is angiotensin-converting enzyme-2 (ACE-2). Binding of SARS-CoV to ACE-2 has been reported to downmodulate ACE-2 expression. In addition to its role in the renin–angiotensin system, ACE-2 inactivates des-Arg^9 bradykinin (DABK), a potent vasodilative, vascular leakage, and proinflammatory mediator. Hence, we postulate that dysregulated ACE-2-dependent inactivation of DABK contributes to vascular leakage, fluid accumulation, and excessive tissue inflammation in COVID-19.

Coagulation factor XII (FXII) is the principal initiator of the plasma contact phase system. Upon contact with negatively-charged surfaces, FXII is converted to activated coagulation factor XII (FXIIa), leading to the production of bradykinin (BK) through the kallikrein-kinin pathway. Binding of BK to BK receptor type 2 and DABK to BK receptor type 1 activates various intracellular signaling pathways that dilate vessels, induce chemotaxis of neutrophils, and increase vascular permeability and fluid efflux. Further cleavage of FXIIa releases the light chain containing activated beta coagulation factor XII (βFXIIa), which can activate the classical complement pathway. Independent of kallikrein-kinin system (KKS) and complement activation, FXII induces expression of inflammatory mediators, including IL-8, IL-1β, and IL-6 on human fibroblasts and precision cut lung slices.

FXII activation to FXIIa also initiates the intrinsic coagulation pathway through cleavage and subsequent activation of coagulation factor XI. This pathway supports the formation of a stable thrombus but appears to have no critical function for fibrin formation during "normal" hemostasis at a site of injury. Specifically, patients with congenital deficiency of FXII do not exhibit a bleeding phenotype. Similarly, FXII knockout mice and rats maintain normal hemostasis despite FXII deficiency. Taken together, these findings show that FXII has potent proinflammatory and procoagulant activities.

To date, no targeted treatment for the COVID-19 associated pulmonary edema has been identified. Multiple potential therapeutic options, including immune modulation and antiviral combined with adjuvant therapies are currently under investigation. While the role of FXII in COVID-19 is currently not understood, indirect evidence, such as excessive fluid accumulation, DIC, and the observed cytokine storm may implicate this molecule in COVID-19. Of note, endothelial cell permeability during Hantavirus infection involved FXII-dependent activation of the KKS, implicating FXII in the pathobiology of viral infections [Taylor et al, 2013].

We hypothesize that FXII inhibition attenuates progression of SARS-CoV-2-related respiratory disease toward severe pneumonia and ARDS. Specifically, we hypothesize that FXII-targeted interventions will attenuate vascular leakage and expression of inflammatory mediators through inhibition of KKS-dependent BK generation. We further postulate that FXII inhibition will have a beneficial effect on DIC through attenuation of intrinsic coagulation-driven thrombosis.

According to feedback from treating physicians, in patients with disease progression, the time period from symptoms onset to development of dyspnea is reported to be between 5 to 10 days, and progression to severe leukocytopenic or lymphocytopenic pneumonia with or without ARDS occurs within 10 to 14 days. An estimated 15% to 18% of these patients will need mechanical ventilation, despite the use of non-invasive ventilation (NIV) support in the earliest phases of the disease. The probability of progression to end-stage disease is unpredictable, with the majority of these patients dying from multi-organ failure. Preventing disease progression to avoid the need for mechanical ventilation in patients with severe COVID-19 pneumonia should reduce morbidity and mortality and result in a decrease in the use of healthcare resources, ie, the need for mechanical ventilation and prolonged ICU stay.

1.2 Information on CSL312

CSL312 is a fully human immunoglobulin G4 (IgG4)/lambda, FXIIa antagonist, recombinant monoclonal antibody. CSL312 binds to the catalytic domain of FXIIa and potently inhibits the intrinsic coagulation cascade and BK production via inhibition of KKS [Cao et al, 2018]. Based on available nonclinical data, CSL312 may offer a novel therapeutic approach to prevent disease progression in patients with COVID-19.

CSL312 is a potent antithrombotic antibody in both mouse and rabbit thrombosis models involving FXII activation (without bleeding risk in either thrombosis or bleeding models). Pharmacologically, CSL312 treatment is accompanied by an expected increase in aPTT but without any increase in PT [Larsson et al, 2014]. CSL312 inhibits BK production in vitro and attenuates edema formation in vivo in BK-mediated edema models (ACE-inhibitor induced edema and acute anaphylaxis mouse models) [Cao et al, 2018]. CSL312 attenuates expression of inflammatory mediators. The parental antibody to CSL312, 3F7, attenuates bleomycin-induced lung fibrosis, renal fibrosis in a unilateral ureteral obstruction model, and liver fibrosis in mice. Based on available nonclinical data, CSL312 might offer a novel therapeutic approach to prevent disease progression in patients with COVID-19.

1.3 Study Overview

Study CSL312_COVID-19 is a prospective, phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of CSL312 administered intravenously in combination with standard-of-care (SOC) treatment in patients with COVID-19. The study will consist of a Screening Period of up to 2 days and a Treatment Period of up to 28 days. Eligible subjects will be randomly assigned to receive a single intravenous (IV) dose of either CSL312 or placebo in addition to SOC treatment (CSL312 + SOC or placebo + SOC) on Day 1. The primary endpoint for this study is the incidence of tracheal intubation or death prior to tracheal intubation from randomization to Day 28. A more detailed overview of the study is provided in Section 3.

1.4 Potential Risks and Benefits

CSL312 is a fully human monoclonal antibody that inhibits FXIIa activity. CSL312 is currently being developed for routine prophylaxis to prevent angioedema attacks in patients with hereditary angioedema (HAE). In the current study, CSL312 will be administered for the first time to subjects with COVID-19 with the aim of preventing disease progression (ie, the need for tracheal intubation or death).

CSL312 is currently only administered in the clinical study setting in accordance with the clinical study protocol (CSP). The maximum dose and the predicted corresponding maximum plasma concentration (C_{max}) in this study is equal to the highest administered dose and its corresponding C_{max} observed in the phase 1 study (CSL312_1001). Each subject who participated in Study CSL312_1001 received a single dose of CSL312; each subject who participates in the current study will receive a single dose of either CSL312 in addition to SOC treatment (CSL312 + SOC) or placebo in addition to SOC treatment (placebo + SOC).

Benefits

The benefits of CSL312, when provided in addition to SOC treatment, in patients with COVID-19 are unknown. Potential benefits are based on the mechanism of action of CSL312, ie, inhibition of FXIIa. The potential benefit is the prevention of disease progression in patients with COVID-19. Subjects randomly assigned to the placebo + SOC group, which is included for scientific rigor, are not expected to receive any additional benefits from placebo beyond the expected response to SOC treatment.

Risks

The following risks were not observed in the phase 1 study (CSL312_1001) but are potential risks based on the drug class and mechanism of action of CSL312:

- **Severe Hypersensitivity/Anaphylactic-type Reactions:** Administration of therapeutic proteins including monoclonal antibodies such as CSL312 is associated with the risk of hypersensitivity and anaphylactic reactions, some of which can be serious and life-threatening. Appropriate precautions will be taken when CSL312 is administered at the study site, with constant monitoring for potential anaphylactic reactions. The administration of CSL312 will be performed under medical supervision with immediate access to emergency equipment and medication for the treatment of severe hypersensitivity and anaphylaxis.
- **Exacerbation of Cytokine Release Syndrome:** Cytokine release syndrome is a symptom complex caused by the rapid release of pro-inflammatory cytokines from target immune cells which can be life-threatening [Stebbings et al, 2007; Stebbings et al, 2013]. Patients with severe COVID-19 are known to have an evolving cytokine release syndrome at the time of ICU admission. The administration of CSL312 will be performed under constant medical supervision and cytokine levels will be tested before and after dosing.

- **Bleeding and Thromboembolic Events:** By blocking FXIIa with CSL312, there may be a potential risk of bleeding or thromboembolic events (TEEs) due to altered hemostasis, unstable clot formation, or impaired clot breakdown. In addition, because of the pharmacological action of CSL312, a prolongation of aPTT is expected to be observed in a concentration-dependent manner. Clinical experience with CSL312 in healthy volunteers in the phase 1 study (CSL312_1001) and patients with HAE in the ongoing phase 2 study (CSL312_2001) did not show an effect on PT. This is consistent with the observation that patients who have congenital deficiency of FXII do not exhibit a bleeding phenotype, despite having a prolonged aPTT [Lammle et al, 1991; Ratnoff and Colopy, 1955]. In addition, nonclinical studies in mice and rabbits showed no impairment in hemostasis after inhibition of FXIIa [Larsson et al, 2014]. Currently, there is also no human experience with the administration of CSL312 in combination with other anticoagulant drugs. Coagulation parameters will be monitored throughout the study and subjects will be monitored carefully for any signs of bleeding or thrombosis.
- **Immunogenicity (Anti-drug Antibodies)**: All protein therapeutics are potentially immunogenic. Because CSL312 is a protein, it has the potential to cause the development of neutralizing and non-neutralizing anti-drug antibodies (ADAs). Subjects will be monitored for the development of immunogenicity throughout the study.

Given the potential benefit of CSL312 in patients with COVID-19, the favorable safety data from the phase 1 study (CSL312_1001) and the ongoing phase 2 study (CSL312_2001), and the implementation of procedures in the current study to closely monitor subject safety, the associated benefit-risk assessment is considered acceptable. Additional information on CSL312 can be found in the CSL312 Investigator's Brochure.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoints

2.1.1 Primary Objective

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

2.1.2 Primary Endpoint

Endpoint	Summary Measure
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

2.2 Secondary Objectives and Endpoints

2.2.1 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 pharmacokinetics (PK) of CSL312

2.2.2 Secondary Endpoints

Secondary Objectives	Endpoints	Summary Measures
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

Secondary Objectives	Endpoints	Summary Measures
1	Clinical status as assessed on an 8-point National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale (Appendix 3)	• 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
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 (Appendix 2)	• 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

Secondary Objectives	Endpoints	Summary Measures
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 (± SD) and geometric mean (geometric coefficient of variation percentage [CV%]) for all PK parameters except T_{max}. • Median (minimum, maximum) for T_{max}

2.3 CCI [redacted]

2.3.1 CCI [redacted]

CCI [redacted]

2.3.2 CCI

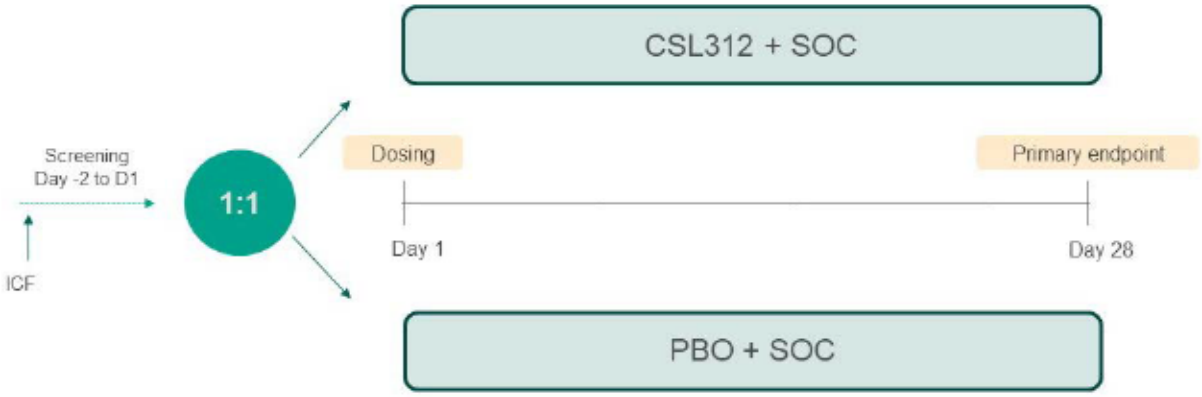
CCI

3 Study Design

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

SOC treatment is defined as any written or established treatment protocol followed at the study site for patients with severe COVID-19 or complications associated with COVID-19, including off-label use of approved drugs (antibodies against IL-6 [anti-IL-6]/antibodies against IL-6 receptors [anti-IL-6R]) or an IP for which administration under an emergency use authorization has been granted (eg, remdesivir). Administration of IP for which expanded access for treatment use ("compassionate use") has been authorized (eg, convalescent plasma) is also permitted during study participation.

Figure 1 Study Design



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

If Screening occurs on Day 1, the assessments scheduled to occur at both Screening and before dosing on Day 1 may be performed only once (ie, do not need to be repeated).

Study Type	Prospective/Interventional
Study Periods	The study will consist of a Screening Period of up to 2 days and a 28-day Treatment Period
Blinding Type	The study will be conducted in an double-blind manner
Study Configuration	Parallel group
Method of Assignment to Treatment	Eligible subjects will be randomized (1:1) on Day 1 of the Treatment Period to receive treatment with either CSL312 + SOC or placebo + SOC

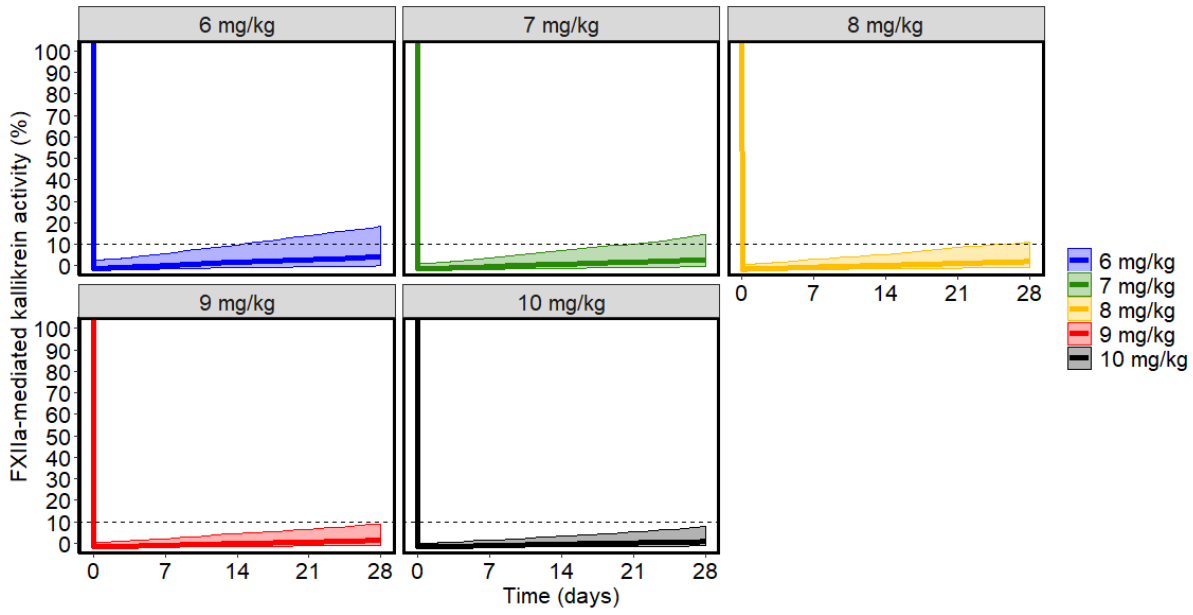
SOC = standard-of-care treatment.

Aggregate data from groups of subjects will be reviewed by an Independent Data Monitoring Committee (IDMC), both early and at predetermined intervals during the conduct of the study. The first 20 subjects will be enrolled, randomly assigned to treatment, and receive investigational product (IP). The 1st IDMC meeting will occur approximately 10 days after all 20 subjects have completed Day 3. The data for these subjects will be reviewed by an IDMC to determine whether there are any safety concerns before enrolling the next 20 subjects. Then the 2nd IDMC meeting will occur approximately 7 days after a total of 40 subjects have completed Day 3. The 3rd meeting will occur approximately 7 days after a total of 60 subjects have completed Day 3 and the 4th meeting will occur after a total of 80 subjects have completed Day 3. Additional details on the IDMC are provided in Section 8.

Dose Rationale

The dose of CSL312 to be used in this study was selected based on the observed safety, PK, CCI data obtained from the phase 1 single-ascending dose study (CSL312_1001) after administration of single IV and subcutaneous doses of CSL312 ranging from 0.1 to 10 mg/kg (7.75 to 1015 mg) in healthy volunteers. A population PK/CC model was developed to describe the time course of inhibition of FXIIa-mediated activity based on the observed data from the first in human study after single IV and SC doses of CSL312. Based on this PK/CC model, 700 mg (equivalent to 10 mg/kg for a subject with a body weight of 70 kg) of CSL312 is predicted to result in ≥ 90% inhibition of FXIIa-mediated kallikrein activity over 28 days. The simulated FXIIa-mediated kallikrein activity profiles at different doses (including 10 mg/kg) is presented in Figure 2.

Figure 2 **Predicted (Median + 95% PI) FXII-mediated Kallikrein Activity After Single Intravenous Doses of CSL312 (Including 10 mg/kg)**



FXIIa = activated factor XII; PI = prediction interval.
Solid line = median; shaded region = 95% PI.

3.1 Planned Number of Subjects

This study will enroll a total of approximately 124 subjects; 62 subjects in the CSL312 + SOC group and 62 subjects in the placebo + SOC group.

After the first 62 subjects have completed the primary endpoint assessment, 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. Additional details on the interim analysis are provided in Section 11.8.

3.2 Planned Study Duration

The duration of an individual subject's study participation is expected to be up to 30 days. This estimate is based on:

- A Screening Period of up to 2 days
- A Treatment Period of up to 28 days

The overall study duration (ie, first subject's Screening Visit to last subject's last study visit) will be approximately 6 months.

3.3 Planned Countries and Estimated Number of Sites

This study 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.

4 Study Interventions

4.1 Description of Investigational Product

4.1.1 CSL312

CSL312 will be supplied (2 mL per vial) as a sterile, preservative-free solution for injection, at pH 6.1 (Table 1). CSL312 is formulated in buffer containing 20 MM L-histidine, 150 nM arginine monohydrochloride, 140 nM L-proline, 0.02% w/v polysorbate 80, and hydrochloric acid. Each vial contains CSL312 at a concentration of 100 mg per 1 mL.

Table 1 Description of CSL312

Substance name	CSL312
Active substance	Fully human IgG4/lambda recombinant monoclonal antibody which specifically binds to the catalytic domain of FXIIa
INN	Garadacimab
Dosage form	Sterile solution for injection containing 100 mg/mL of CSL312 in 2-ml vials
Dose	700 mg
Dosing regimen	Single dose of CSL312 will be administered once during the Treatment Period as a slow IV injection, (ie, push of about 3 minutes
Infusion volume	7 mL (100 mg/mL)
Route of administration	Intravenous infusion
Anatomic location of administration	Peripheral vein

FXIIa = activated coagulation factor XII; IgG = immunoglobulin G; INN = international nonproprietary name; IV = intravenous.

CSL312 will be manufactured in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Manufacturing Practice (GMP) guidelines and local regulatory requirements.

Additional details related to the dosing and administration of the IP (ie, CSL312 or placebo), as well as the procedure used to prepare the study treatment before administration will be described in the IMP manual.

4.1.2 Placebo (CSL312 Diluent)

The placebo will be supplied (10 mL per vial) as a sterile, preservative-free solution for injection (Table 2). The placebo is the same as the CSL312 formulation buffer, but does not contain the active substance (ie, FXIIa antagonist monoclonal antibody).

Table 2 Description of Placebo

Substance name	Placebo
Active substance	Not applicable
Trade name	Not applicable
Dosage form	Sterile solution for injection in10-mL vial
Route of administration	Intravenous infusion

The placebo will be manufactured in accordance with ICH GMP guidelines and local regulatory requirements.

Additional details related to the dosing and administration of the IP (ie, CSL312 or placebo), as well as the procedure used to prepare the study treatment before administration will be described in the IMP manual.

4.1.3 Accountability and Destruction

All supplies of IP must be accounted for throughout the study. Records for the delivery of IP to the study site, inventory at the study site, the use by each subject, and the destruction or return of IP to CSL Behring (CSL; or delegate) must be maintained by the investigator (or delegate) using the interactive response technology (IRT) system. The investigator (or delegate) must provide reasons for any discrepancies in drug accountability using the IRT system.

Further details regarding accountability and destruction of IP are provided in the IMP manual.

4.1.4 Dose Modification

No modification of dose is planned for this study because subjects are only expected to receive 1 dose of IP (CSL312 + SOC or placebo + SOC) on Day 1 of the Treatment Period.

5 Allocation, Dosing, and Administration

5.1 Allocation to Treatment

5.1.1 Subject Assignment

After informed consent has been obtained, subjects will be assigned a study-level unique subject identification number, via an IRT system, which will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

5.1.2 Randomization Procedures

Randomization will be conducted using an IRT. The investigator will be supplied with a user guide for the 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.

5.1.3 Blinding Procedures

5.1.3.1 Blinding Method

Investigational site staff, including the investigators, will be blinded to treatment allocation. Subjects and CSL staff (or delegates) participating in the conduct of the study will also be blinded to treatment allocation (double-blind).

Unblinded study site personnel delegated by the investigator will prepare the IP, as assigned by the IRT. Unblinded study site personnel are not to administer the IP and will not be involved in conducting or recording any study assessment procedures (ie, in the care of the subject). Study site staff who will be conducting safety assessments, including the investigator, and subjects will be blinded to treatment allocation, the contents of the syringe and to kit number assignment (double-blind). Sponsor staff will also be blinded to treatment allocation, the contents of the syringe and kit number assignment, except as stated below.

A study-independent bioanalyst, statistician, and programming support responsible for the sample analysis and IDMC operations will be unblinded as well as a representative from Clinical Trial Supply and from IRT. Additionally, unblinded monitors may be assigned to sites. Designated unblinded personnel agree not to disclose the contents of the randomization list, the contents of the kit list or any subject kit number assignment. The safety-related data provided to the IDMC during the course of the study will be unblinded. All individuals will be placed under strict confidentiality to protect the integrity of the study.

All blood samples analyzed by the central laboratory will remain blinded until database lock. Blood samples analyzed by the local laboratory will be interpreted by personnel appointed by the investigator and defined in the site-specific blinding plan.

Study unblinding will take place following the locking of the database except in situations as outlined in Sections 5.1.3.2, 5.1.3.3, and 5.1.3.4.

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, as requested.

5.1.3.2 Breaking the Blind for an Emergency

The randomization code for individual subjects may be unblinded to a site during the study in emergency situations for reasons of subject safety, if knowing treatment assignment will change subject management. In case of an emergency situation for the reason of subject safety, the investigator should use the IRT to identify the treatment allocation for a subject. Whenever possible, the investigator should consult with CSL before unblinding the randomization code. The reason for unblinding the randomization code must be fully recorded in the subject's source documents, and the investigator must follow the defined procedures provided in the study reference manuals. The subject's treatment allocation should not be recorded in the subject's source document.

5.1.3.3 Planned Unblinding Procedures

Periodic unblinding safety reviews are planned for this study for the purposes of safety monitoring activities by the IDMC. With authorization by CSL, the IRT will provide the unblinded statistician performing analysis for the IDMC or the unblinded statistician with the randomization code or an IRT user account access to obtain the required information directly from the IRT.

An unblinded interim futility and sample size re-estimation analysis will also be performed by an IDMC. With authorization by CSL, the IRT will provide the unblinded statistician performing the analysis for the IDMC with the randomization code or an IRT user account access to obtain the required information directly from the IRT.

At the end of the study, CSL will authorize that the study be unblinded after database lock. The randomization codes will be provided to the study statistician (or delegate).

5.1.3.4 Ad-hoc Safety Unblinding

CSL Global Clinical Safety Pharmacovigilance personnel may, on an ad-hoc basis, unblind the randomization code directly in the IRT at any time during the study because of a safety concern. The purpose of the unblinded data review is to determine whether there is a risk to subject safety that would require further action either for the individual management of a study subject or for the ongoing conduct of the study. The need to unblind a subject or group of subjects may not necessarily arise because of an SAE. The need to unblind on an ad-hoc basis will be determined by CSL's Global Clinical Safety and Pharmacovigilance senior leadership.

6 Study Population and Main Criteria for Eligibility

6.1 Eligibility Criteria

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the investigator's study team before subjects are included in the study. Eligibility may be assessed at the time of hospital admission provided that the subject is randomized within 24 hours.

6.2 Inclusion Criteria

To be enrolled and randomized into the study, subjects must meet all of the following inclusion criteria:

1. Capable of providing written informed consent. An individual legally permitted to make medical decisions on the subject's behalf can provide written informed consent
2. Willing and able to adhere to all protocol requirements
3. Age ≥ 18 years at the time that informed consent is obtained

4. Positive for SARS-CoV-2 infection as determined using a molecular diagnostic test (reverse transcription polymerase chain reaction [RT-PCR] or equivalent) approved by regulatory authorities (including Food and Drug Administration [FDA] or Brazilian Health Regulatory Agency [ANVISA]) or allowed under an emergency use authorization within 14 days before Screening. If a false negative result is suspected, the SARS-CoV-2 test may be repeated within the Screening Period.
5. Chest computed tomography (CT) scan or X-ray results confirming interstitial pneumonia
6. Severe COVID-19 disease as evidence by ≥ 1 of the following criteria at Screening including within 24 hours before Screening:
    - Respiratory frequency > 30 breaths per minute
    - Saturation of peripheral (capillary) oxygen (SpO_2) ≤ 93% on room air
    - Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2 ratio) < 300
    - Ratio of arterial oxygen saturation to fraction of inspired oxygen (SaO_2/FiO_2 ratio) < 218 (if PaO_2/FiO_2 ratio is not available)
    - Radiographic lung infiltrates > 50%

6.3 Exclusion Criteria

Subjects must not be enrolled into the study or randomly assigned to treatment if they meet any of the following exclusion criteria:

1. Currently enrolled, planning to enroll, or participated, within the last 30 days, in a clinical study requiring administration of an IP, including expanded access or compassionate use with the only exception being the administration of convalescent plasma. Administration of IP is permitted only if an emergency use authorization has been granted (eg, remdesivir). Additionally, off-label use of approved drugs (eg, anti-IL-6/anti-IL-6R) is also permitted.
2. Pregnant or breastfeeding (female subjects)
3. Intubated and require mechanical ventilation (including ECMO) at the time of randomization

4. In the opinion of the investigator, the subject is expected to be intubated in the first 24 hours after IP administration

5. Active Do-Not-Intubate (DNI) or Do-Not-Resuscitate (DNR) order

6. In the opinion of the investigator, not expected to survive for > 48 hours after admission

7. Presence of any of the following comorbid conditions prior to randomization and prior to SARS-CoV-2 infection:
   - Severe heart failure (New York Heart Association Class IV)
   - End-stage renal disease (Stage ≥ 4) or need for renal replacement therapy
   - Biopsy-confirmed cirrhosis, portal hypertension, or hepatic encephalopathy
   - Malignancy (Stage IV)
   - Chronic lung disease requiring the use of oxygen at home
   - Active tuberculosis disease
8. Active bleeding or a current clinically significant coagulopathy (eg, international normalized ratio [INR] > 1.5) or clinically significant risk for bleeding (eg, recent intracranial hemorrhage or bleeding peptic ulcer within the last 4 weeks)
9. History of venous thrombosis, myocardial infarction, or cerebrovascular event within 3 months, or a prothrombotic disorder (eg, antithrombin III, protein C, or protein S deficiency)
10. Known or suspected Grade 3 or 4 infusion-related reaction or hypersensitivity (per Common Terminology Criteria for Adverse Events [CTCAE]) to monoclonal antibody therapy, or hypersensitivity to the IP or any excipients of the IP [National Cancer Institute, 2009]
11. Currently receiving a therapy not permitted during the study (see Section 9.1)
12. Female subject of childbearing potential or fertile male subject either not using or not willing to use an acceptable method of contraception to avoid pregnancy during the study and for 90 days after receipt of the last dose of IP. Note: Acceptable methods of contraception are defined in Section 9.3

13. Any clinical or laboratory abnormality or other underlying conditions (eg, psychological disorders, substance abuse) that would render the subject unsuitable for participation in the study, in the opinion of the investigator

6.4 Discontinuation of Study Treatment and Subject Withdrawal

6.4.1 Early Discharge from the Hospital

All subjects who maintain consent will remain in the study through Day 28 for all important safety and efficacy assessments. All Day 28 assessments will be conducted on the day of discharge from the hospital. For subjects who are discharged before Day 28, the investigator (or delegate) will contact them via weekly telephone calls. If the telephone call is performed by non-medical study personnel, the information on clinical status, AEs, and changes in concomitant medications need to be reviewed by the investigator or a medically trained delegate. These subjects will be scheduled for an in-person visit on Day 28 to perform the End of Study (EOS) Visit assessments including CCI and other laboratory parameters.

Every effort will be made to encourage both subject and investigators to continue study assessments via telephone following hospital discharge, unless the subject withdraws consent.

6.4.2 Discontinuation of Study Treatment

Subjects may discontinue study treatment with the IP at any time at their own request, or at the discretion of the investigator or CSL for safety, behavioral, or administrative reasons.

Subjects who discontinue treatment with the IP but remain in the study, will be asked to complete additional follow-up assessments or allow data collection as detailed in the Schedule of Assessments. If a subject discontinues IP and declines further study procedures/visit participation, the subject will be withdrawn from the study, and attempts will be made to complete and document the EOS Visit assessments.

6.4.3 Subject Withdrawal

Subjects may withdraw from the study at any time either at their own request or at the discretion of the investigator or CSL for safety, behavioral, or administrative reasons (eg, because of an AE, protocol deviation, subject noncompliance, or study termination). The investigator should record in the electronic case report form (eCRF) and in the subject's medical records the reason for and date of subject withdrawal.

In accordance with the ICH principles of Good Clinical Practice (GCP), the investigator always has the option to advise a subject to withdraw from the study if the subject's safety or well-being is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

6.4.4 Procedures for Handling Withdrawals

If a subject is withdrawn from the study, attempts will be made to complete and document the Day 28 (EOS) Visit assessments. If the subject is withdrawn from the study after receiving IP, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the investigator to complete other study assessments.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, CSL may retain and continue to use any data collected before such withdrawal of consent.

6.4.5 Replacement Policy

Subjects withdrawn from the study will not be replaced.

7 Study Assessments

7.1 Unscheduled Study Assessments and Additional Medical Data

Unscheduled study assessments are possible and can be documented in the unscheduled visit in the eCRF.

Additional data given to CSL may include any medical information from hospital records required by the study but not outlined in the study protocol. This information may be required to help scientific understanding of study data and might be collected even the completion of the study.

7.2 Efficacy Assessments

Outcome assessments will include the following:

- Use of supplemental oxygen
- Use of CPAP or BiPAP
- Use of HFNC
- Use of ECMO
- Intubation
- Extubation
- Clinical status on standardized scales (SOFA score and NIAID 8-point ordinal scale score)
- ICU admission and discharge
- Hospital discharge or death

7.3 Demographics and Safety Assessments

The clinical procedures to be conducted during this study related to the evaluation of safety are provided in Table 3. Some laboratory assessments may also be used for Screening. Clinical laboratory assessments are to be performed at time points as detailed in the Schedule of Assessments.

Table 3 Demographics and Safety Assessments

Assessment	Description
Demographics	• Year of birth/age • Sex • Race and ethnicity
Medical History	• Relevant medical history • Contraception method (if relevant) • Previous and concomitant medications and therapies • Smoking history
Pregnancy Test (local laboratory)	• Urine test for β-hCG will be performed for all female subjects of childbearing potential to rule out pregnancy at Screening and the end of the Treatment Period. A serum pregnancy test will be performed by the site if urine result is inconclusive.
Physical Examination	• As per the study site's standard procedure
Chest CT scan or X-ray	• Chest CT scan or X-ray results must show signs of interstitial pneumonia to confirm eligibility criteria at Screening.

Assessment	Description
Adverse Events	• Evaluation of all AEs (eg, causality/relatedness, severity, seriousness) • AESIs: ○ Abnormal bleeding events ○ TEEs ○ Severe hypersensitivity including anaphylaxis
Vital Signs	• Blood pressure (systolic and diastolic) • Body temperature • Heart rate • Height and weight
Respiratory Parameters	• Respiratory rate • FiO_2 • SpO_2 • PaO_2
Urinalysis (dipstick) (test kits provided for local laboratory)	**Mandatory review of all parameters indicated by * is required before randomization.** • Specific gravity • Ketones • pH • Bilirubin • Leukocyte esterase* • Urobilinogen • Occult blood* • Protein* • Nitrite • Glucose*
Hematology (local laboratory)	**Mandatory review of all parameters indicated by * is required before randomization.** • Hemoglobin* • Hematocrit* • Erythrocytes (RBC count)* • RBC indices: mean corpuscular volume; mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; erythrocyte distribution width • Platelets* • Leukocytes (WBC count)* • WBC differential (percentage or absolute): neutrophils; neutrophil band forms; lymphocytes; monocytes; eosinophils; basophils • Reticulocytes

Assessment	Description	
Biochemistry (local laboratory)	**Mandatory review of all parameters indicated by * is required before randomization.**	
	• Sodium*	• GGT*
	• Potassium*	• LDH*
	• Chloride*	• Total bilirubin*
	• Bicarbonate	• Direct bilirubin*
	• Carbon dioxide	• Magnesium*
	• Calcium	• Phosphate
	• Blood urea nitrogen*	• CRP*
	• Urea*	• Total cholesterol
	• Creatinine*	• Triglycerides
	• Glucose*	• HDL cholesterol
	• Total protein	• LDL cholesterol
	• Albumin	• Uric acid
	• Alkaline phosphatase*	• CK, CPK*
	• ALT*	• Ferritin
	• AST*	
Coagulation (central laboratory)	• CCI	• CCI
	• CCI	• CCI
Coagulation (local laboratory)	• CCI	• CCI
PK assessments (central laboratory)	• C_{max}	• $AUC_{0\text{-}last}$
	• T_{max}	• $T_{1/2}$
Cytokine Profile (central laboratory)	• Inflammatory cytokine panel	
CCI (central laboratory)	• CCI	

CCI; AESI = adverse events of special interest; ALT = alanine aminotransferase; CCI; AST = aspartate aminotransferase; $AUC_{0\text{-}last}$ = area under the plasma concentration-time curve from time zero to the time of the last measureable concentration; β-hCg = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CK/CPK = creatine kinase; C_{max} = maximum plasma concentration; CRP = C-reactive protein; FiO_2 = fraction of inspired oxygen; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PaO_2 = partial pressure of arterial oxygen; PT = prothrombin time; RBC = red blood cell; SpO_2 = saturation of peripheral (capillary) oxygen; $T_{1/2}$ = terminal half-life; TEE = thromboembolic event; WBC = white blood cell.

7.4 Pharmacokinetic Assessments

Blood samples will be collected before dosing and on Day 1 at 30 minutes and 6 hours after the end of the infusion of IP, Day 2, Day 7, Day 14, Day 21, and Day 28 for assessment of CSL312 PK in plasma. PK assessments will include C_{max}, T_{max}, $AUC_{0\text{-last}}$, and $T_{1/2}$.

Details related to the collection, preparation, and transfer of PK samples will be provided in the laboratory manual.

7.5 CCI

CCI

8 Study Oversight

8.1 Oversight and Monitoring Committees

An IDMC will be established to monitor the critical safety data generated during the study. The IDMC will consist of independent clinical specialists in internal medicine, pulmonology, intensive care, and statistics, who also have experience in clinical studies. The IDMC will review accumulating data from the ongoing study in an unblinded manner. Based on these reviews, the IDMC will advise on the further conduct of the study. CSL will continue the study unless a safety issue is confirmed that warrants study termination.

Review schedule for IDMC:

- 1st meeting after the initial 20 subjects (10 CSL312, 10 placebo)
- 2nd meeting after 40 subjects (20 CSL312, 20 placebo)
- 3rd meeting after 60 subjects (30 CSL312, 30 placebo)
- 4th meeting after 80 subjects (40 CSL312, 40 placebo)

The IDMC will also review the accumulating data in an unblinded manner to assess futility and the need for sample size increase based on an interim analysis. This committee will also review the data to make any necessary decisions on future drug supply and other investments.

Details on the composition, responsibilities, activities, timing of meetings, data required for each review, analyses, and the review and decision making processes for the IDMC will be described in detail in the IDMC charter.

8.2 Study Halting Criteria

The study will be halted (no recruitment or further dosing), pending review, if any of the following criteria are met:

- One subject develops an SAE that results in death and is considered by the investigator and/or CSL to be related to the administration of CSL312
- One subject develops any other serious event that is deemed to pose an unacceptable risk to other subjects in the study, and this event is considered by the investigator and/or CSL to be related to the administration of CSL312
- An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, CSL or IDMC consider associated with CSL312 and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety
- Three subjects with severe toxicity for the same parameter associated with study product

If any study halting rules are triggered, it will result in a TEMPORARY halt:

- CSL's Safety Management Team (SMT) will make a recommendation
- The SMT will conduct a safety assessment of the relevant safety observation to establish whether the study should be resumed or whether the temporary halt should continue and will further escalate to the Global Safety Committee
- If additional risk-benefit measures are warranted and modifications to the protocol are required to resume the study (including the addition of new risk mitigation measures), then a substantial protocol amendment will be submitted
- Regulatory authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be informed of a study halt and then its resumption

If safety concerns warrant a **PERMANENT** stop to the study:

- The SMT will conduct a risk assessment
- The SMT and Global Safety Committee are involved in recommending a stop, if it is has concluded that continued dosing poses an unacceptable risk to subjects and no further risk mitigation steps can be applied
- CSL's Global Benefit Risk Committee will ratify the decision to stop the study
- In case decision to stop study is not ratified, GBRC could recommend study continuation with implementation of additional risk-benefit measures (including addition of new risk mitigation measures); substantial protocol amendment will be submitted if modifications are required to continue the study

Regulatory authorities and IRBs/IECs will be notified in the case of a study stop.

8.3 Treatment Compliance

All doses of IP will be administered by IV infusion at the study site. Treatment compliance will be assessed using the administration details entered into the eCRF. A subject will be regarded as compliant with regard to IP administration if the subject received between ≥ 80% and ≤ 120% of the planned dose of IP.

9 Prohibited and Permitted Therapies

9.1 Prohibited Therapies

Because of the severity of the COVID-19 pneumonia pandemic, it is difficult to define in advance any contraindications to concomitant treatments (including antiviral drugs). Any medication that the subject is receiving at the time of study enrollment or that the subject receives during study participation will be recorded in the subject's eCRF along with the dates of administration (start date and end date), dosing information (dose and frequency), and reason for use.

The use of any IP or investigational device according to a clinical study protocol for another clinical study is PROHIBITED during this study and within ≤ 30 days before Screening or within 5 half-lives of the final dose of IP administered during the previous interventional study, whichever is longer. However, use of an IP with emergency use authorization is permitted (see Section 9.2).

Use of the following mediations is also PROHIBITED during this study:

- any therapeutic antibody other than CSL312
- anticoagulant therapy except low-molecular-weight heparin (LMWH)

9.2 Permitted Medications/Therapies

The following medications and therapies are PERMITTED at any time during the study:

- Prescribed medications required for the management of acute or chronic medical conditions including COVID-19, except those described in Section 9.1.
- Treatment considered SOC for COVID-19, defined as any written or established treatment protocol followed at the study site for the treatment of patients with severe COVID-19 or complications associated with COVID-19, including off-label use of approved drugs (eg, anti-IL-6/anti-IL-6R), an IP for which administration under an emergency use authorization has been granted (eg, remdesivir). Administration of IP for which expanded access for treatment use ("compassionate use") has been authorized (eg, convalescent plasma) is also permitted during study participation.
- Therapies to treat any AEs that the subject experiences during the study, including non-prophylactic aspirin (eg, to treat a headache).
- LMWH

9.3 Lifestyle Restrictions

Female subjects of childbearing potential and fertile male subjects must use a medically reliable form of contraception until 90 days after the last administration of study drug.

Childbearing potential is assumed in all female subjects except:

- Female subjects ages > 45 years with amenorrhea for ≥ 12 months without an alternative medical cause.
- Female subjects who are surgically sterile for ≥ 3 months before providing informed consent.

Acceptable methods of contraception are:

- Abstinence, where abstinence is the preferred and usual lifestyle of the subject, including refraining from heterosexual intercourse during the entire period of risk associated with the IP. Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable definitions of abstinence.
- Hormonal methods associated with inhibition of ovulation, if used at a stable dose during the 3 months before Screening with no plans to change dose during the study. Acceptable hormonal methods include: oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen/progestin vaginal ring, or contraceptive medication implant.
- Use of intrauterine device (placed > 3 months before providing informed consent).
- Surgical sterilization (> 3 months before providing informed consent) of subject or subject's partner.

9.4 Overdose

Overdose is defined as the infusion or ingestion of any dose (single or cumulative) of a product that is considered excessive. In this study, excessive is defined as any dose greater than the planned dose. The effects of any potential overdose with CSL312 have not been studied. In case of overdose, the subject should be closely monitored, and supportive treatment should be administered, as needed.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event

As per ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The period of observation for AEs extends from the time that informed consent is obtained until the EOS Visit (see Section 10.4 for further details).

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- A clinical event occurring after consent but before IP administration.
- Intercurrent illnesses with an onset after administration of IP.

Adverse events do not include:

- Events identified at Screening that meet exclusion criteria.
- Medical or surgical procedures (the condition that leads to the procedure is the AE).
- Situations where an untoward medical occurrence has not taken place. For example:
    - Planned hospitalizations due to pre-existing conditions, which have not worsened.
    - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).
    - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy).

- Overdose of IP or any concomitant therapy that does not result in any adverse signs or symptoms.

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must recorded in the eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Increases in aPTT will not be classified as AEs because CSL312 is expected to cause increase in these parameters.
- Laboratory parameters already beyond the reference range at Screening, unless a further increase/decrease can be considered an exacerbation of a pre-existing condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life or outside the measuring range).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE).

10.1.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.
- **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.

- **Requires in-patient hospitalization or prolongation of existing hospitalization** – CSL considers "hospitalization or prolongation of existing hospitalization" for ≥ 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- **Results in persistent or significant disability or incapacity**.
- **Is a congenital anomaly or birth defect.**
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

10.1.3 Adverse Event of Special Interest

There are several AEs that will be monitored closely as AESIs to enable an adequate risk-benefit evaluation of CSL312 during the study and additional data may be requested for these events. The AESIs will be:

- Bleeding events that are abnormal in the opinion of the investigator
- TEEs
  - Non-systemic thrombosis (eg, localized thrombosis associated with vascular access) is not considered an AESI
- Severe hypersensitivity including anaphylaxis

The reporting requirements for AESIs are detailed in Section 10.6.1.

10.2 Severity of Adverse Events

The severity of each AE (ie, nonserious and serious AEs) is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Severity Intensity Scale for Adverse Event Terminology.

10.3 Causality of Adverse Events

The causal relationship of an AE to IP **must always be assessed** by the investigator. All AEs will be classified as either **related** or **not related** to IP. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to the IP.

The degree of certainty with which an AE is attributed to the IP or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of the IP.
- Clinically and/or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor).
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with the IP, drug withdrawal or reproduced on rechallenge).

10.4 Observation Period for Adverse Events

The observation period for the reporting of AEs (and SAEs) for an individual subject will start at the time that informed consent is obtained for participation in the current study and end at the subject's final site visit.

If the investigator becomes aware of an SAE that has started after the EOS Visit and is considered by the investigator causally related to the IP, the event must be reported to CSL following the same timelines and procedures described for SAEs occurring during the study (see Section 10.6.1).

Such events are not entered into the eCRF.

10.5 Follow-up of Adverse Events

Every effort should be made to follow AEs until resolution or stabilization. Ongoing, nonserious AEs that have not resolved or stabilized will be followed until the subject completes the study. SAEs will be followed until the AE resolves, stabilizes, or the subject is lost to follow-up.

10.6 Adverse Event Reporting

10.6.1 Adverse Events

At each clinical evaluation, the investigator (or delegate) will determine whether any AEs have occurred. All AEs are to be recorded in the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an SAE is ongoing after the final study visit, the SAE will continue to be followed up until resolution, stabilization, or the subject is lost to follow-up.

If, during study participation, a subject presents with a pre-existing condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History eCRF.

10.6.2 Serious Adverse Events

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Foreign cross reporting will be ensured.

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the eCRF.

All SAEs that occur during the course of the study, whether or not causally related to the IP, must be entered into the eCRF immediately (within 24 hours of the investigator becoming aware of the event). An assessment of causality to the IP must be included.

AEs occurring in the period between the time that informed consent is obtained and the time of the first exposure to the IP that meets 1 or more of the seriousness criteria must be entered into the eCRF in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the final study visit and is considered by the investigator as causally related to the IP must be reported following the same timelines and reporting procedures described for SAEs occurring during the study. Such events are not entered into the eCRF.

The minimum reporting requirements for reporting of SAEs include:

- Subject identification number
- Suspected medicinal product and/or procedure
- Event term
- Reporting source identification

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.

In addition, the investigator must:

- Report all SAEs to the relevant IRB/IEC within the timeframe specified by the IRB/IEC.
- If the subject is an active participant in the study:
    - Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
    - Ensure that the causality assessment for all SAEs is entered in the eCRF
- If the subject is no longer participating in the study, report the follow-up information to CSL.

In cases of death, the investigator should supply CSL and the IRB/IEC (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

10.6.3 Adverse Events of Special Interest

AESIs must be reported as AEs in the subject's eCRF. Additional data might be requested in the eCRF for these events. Serious and nonserious AESIs must be reported following expedited reporting procedures, as described for SAEs (see Section 10.6.2).

10.6.4 Other Significant Events

Not applicable.

10.6.5 Overdose

Any overdose that occurs in association with an adverse sign or symptom must be entered into the eCRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 10.6.2).

Details (ie, volume infused, location of infusion, infusion start and stop times, and infusion rate) of overdose of IP (defined in Section 9.4) must be recorded in the Study Treatment Administration eCRF. Details of an overdose of any concomitant therapy must be recorded in the Concomitant Medication eCRF.

10.6.6 Pregnancy and Breastfeeding

A female subject or female partner of a male subject who becomes pregnant while participating in the study, or up to and including 90 days after the last dose of IP, must notify the investigator immediately.

If a female subject becomes pregnant during study participation, she may continue study procedures at the discretion of the investigator. If the subject withdraws from study participation, the procedure for discontinuation of a subject will be followed, as described in Section 6.4.3).

CSL must be notified within 5 days of the investigator becoming aware of the pregnancy.

Whenever possible, a pregnancy in a subject or in a female partner of a male subject exposed to the IP should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to CSL using a Pregnancy Reporting/Outcome Form.

10.7 Institutional Review Board/Independent Ethics Committee Reporting Requirements

The time frame within which an IRB/IEC must be notified of deaths and IP-related unexpected SAEs is stipulated by each IRB/IEC. It is the investigator's responsibility to comply with the requirements for IRB/IEC notification. CSL will provide investigators with all details of all SAEs reported to regulatory authorities.

11 Statistical Analyses

11.1 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 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) in order to achieve 80% power to detect a treatment difference using a 2 group chi-square test. For the sample size calculation, it is further confirmed using simulations performed in East® 6.5 software (Cytel, Inc.: Waltham, MA) that 80% power is maintained, accounting for the interim analysis for futility and sample size re-estimation.

11.2 Description of Study Analysis Sets

11.2.1 Screened Analysis Set

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

11.2.2 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.

11.2.3 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.

11.2.4 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 will be based on the actual treatment received.

11.2.5 Pharmacokinetic Analysis Set

The PK Analysis Set will comprise 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.

11.2.6 CCI

CCI

11.3 Analyses of Primary Efficacy

The primary endpoint for this study is the incidence of tracheal intubation or death prior to tracheal intubation from randomization to Day 28. The proportion will be calculated as the number of subjects with tracheal intubation or death divided by the total number of subjects for each treatment group. Treatment effect of interest (ie, estimand) is defined as the proportion difference of tracheal intubation or death prior to tracheal intubation (CSL312 + SOC minus placebo + SOC) in the target population regardless of whether additional treatment is used or initial SOC has changed. The ITT Analysis Set will be used for the primary efficacy analyses.

Firth logistic regression model including treatment group; age group as a continuous covariate; gender (male or female); country (USA or Brazil); and Baseline comorbidities (yes or no) as categorical covariates will be used to compare the rates between the 2 treatment groups. Comorbidities include hypertension, diabetes, and obesity (defined as body mass index ≥ 30 [kg/m^2]). A 2-sided p-value will be estimated from the model. The proportion difference and associated 95% confidence interval (CI) will be estimated using the method described by Ge at al [2011]. The mITT Analysis Set will be used for primary efficacy endpoint sensitivity analysis.

Sensitivity analyses to assess the effect of missing data will be conducted, for example, by performing tipping point analyses that vary assumptions about the missing outcomes in both study treatment groups.

11.4 Analyses of Secondary Efficacy

The following secondary efficacy endpoints will be summarized by treatment group using subject count and percentage:

- All-cause mortality
- Incidence of tracheal intubation from randomization to Day 28

- Proportions of subjects using CPAP or BiPAP
- Proportion of subjects using HFNC
- Proportion of subjects using ECMO

The same testing method used for the primary efficacy variable will also be used to compare the above secondary efficacy endpoints between the 2 treatment groups. The proportion differences, associated 95% CIs, and 2-sided p-values will be reported.

Clinical Status Assessed on an 8-Point NIAID Ordinal Scale

Frequency and proportion of subjects within each category of the 8-point NIAID ordinal scale will be summarized along with graphical displays for each treatment group. Frequency and proportion of subjects with an improvement from Baseline of ≥ 2 points will be analyzed using descriptive statistics.

Hospital Length of Stay

Hospital LOS is defined as the time interval from randomization to hospital discharge alive. In this analysis, for subjects who did not have hospital discharge (ie, no 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. 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 model including treatment group; age as a continuous covariate; gender (male or female), country (USA or Brazil); and comorbidities (yes or no) as categorical covariates in the model. Hazard ratio, its 95% CI and 2-sided Wald p-value for hypothesis-testing 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 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

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 by treatment group. Descriptive statistics for continuous variables will be reported. Median differences between treatment groups and 95% CIs using Hodges-Lehmann's method will be reported. Nonparametric Wilcoxon rank-sum test will be used to compare the 2 treatment groups. SOFA score components will also be summarized by treatment and visit using descriptive statistics.

The ITT Analysis Set and mITT Analysis Set will be used for the secondary efficacy endpoint analyses.

Baseline is defined as the most recent, non-missing value before randomization, if applicable, otherwise, the most recent non-missing value before administration of IP.

11.5 Analysis of Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 (or higher). A treatment-emergent adverse event (TEAE) is defined as an AE reported at or after the start of the first administration of study treatment. Only TEAEs will be summarized.

An overview summary of TEAEs, including counts and percentages of subjects with any TEAE; TEAEs related to study treatment; TEAEs leading to permanent discontinuation of study treatment; TEAE leading to dose modifications; serious TEAEs; serious TEAEs related to study treatment; fatal TEAEs; fatal TEAEs related to study treatment, TEAEs by severity, and TEAEs of special interest will be produced.

TEAEs will be summarized by system organ class and preferred term. TEAEs will also be summarized by causality and severity. All TEAE summaries will be provided for each treatment and overall.

Number and percentage of subjects with plasma anti-CSL312 antibodies will be summarized by treatment group and overall.

Laboratory evaluations (hematology, biochemistry, and urinalysis) will be summarized descriptively by treatment group.

Vital sign findings and respiratory parameters will be listed by subject and time point. The values and change from Baseline at each visit will be descriptively summarized by treatment group.

The Safety Analysis Set will be used for all safety analyses.

11.6 Analyses of Pharmacokinetics

The PK data for CSL312 plasma concentration will be summarized by nominal time point for each treatment group. The following descriptive statistics will be presented for plasma concentration summaries: n, arithmetic mean, SD, CV%, median, geometric mean, minimum, and maximum.

The PK parameters for CSL312, derived using a noncompartmental method, will be summarized descriptively by treatment group.

The following PK parameters will be derived and summarized:

- C_{max}
- $AUC_{0\text{-}last}$
- T_{max}
- $T_{1/2}$

The following descriptive statistics will be presented for all PK parameters, except for T_{max}, n, arithmetic mean, SD, CV%, median, geometric mean, minimum, and maximum. For T_{max}, n, median, minimum and maximum will be summarized.

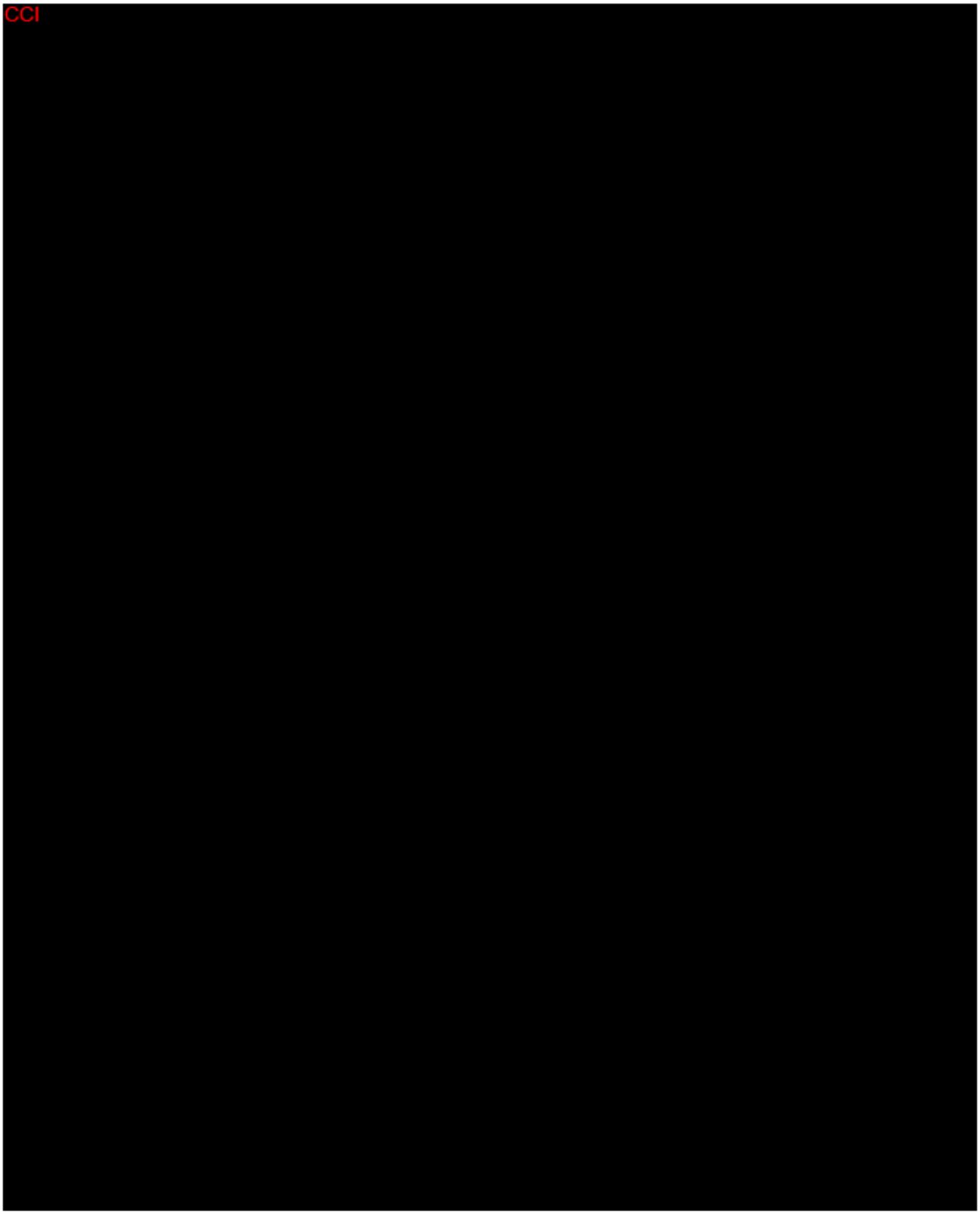
The PK Analysis Set will be used for all PK analyses.

11.7 CCI

CCI

[redacted]

CCI



CCI

[redacted]

11.8 Interim Analysis

An interim analysis of unblinded primary endpoint data is planned after 62 subjects (50% of the target sample size) have completed primary endpoint assessment. The interim analysis will be performed for the purpose of futility monitoring and sample size re-estimation.

At the interim analysis, the conditional power (CP) will be calculated assuming the data yet to be observed follow the current trend observed in the data available for the interim analysis. Chen et al [2004] showed that stopping a study early for futility or increasing the sample size when the interim result is promising will not inflate the Type I error rate. Thus, a statistical adjustment for multiplicity is not necessary to control the overall Type I error of the study. Mehta and Pocock [2011] have shown that the boundary for the promising interim result may be lowered to 0.36, if the maximum allowable sample size is restricted to 2 times the original sample size.

Based on the review of the interim analysis, early stopping for futility or sample size re-estimation may be recommended for implementation following these guidelines:

- Stop for futility if CP < 0.10 (futility zone)
- Continue to the planned completion if $0.10 \leq$ CP < 0.36 (unfavorable zone)
- Increase the sample size up to 200 if $0.36 \leq$ CP < 0.80 (promising zone)
- Continue to the planned completion if CP ≥ 0.80 (favorable zone)

Full details of the interim analysis, including the formula to calculate the CP will be specified in the IDMC statistical analysis plan. Although the statistical guidelines will be pre-specified, a number of factors must be considered thoroughly as part of the decision to modify or stop the study early. A recommendation to modify or terminate the study will not be based solely on statistical grounds.

12 Regulatory and Ethics Considerations

12.1 Regulatory Considerations

CSL or its agents will submit the appropriate documents to the local regulatory agencies and will await approval before commencement of the study.

This study will be conducted and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this CSP are designed to ensure that CSL and the investigator abide by the principles of the current ICH GCP guidelines on the conduct, evaluation, and documentation of this study, as described in ICH E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

12.2 Institutional Review Board/Independent Ethics Committee

The investigator must submit the CSP and informed consent forms (ICFs) for review by an authorized and properly constituted (according to local guidelines) IRB/IEC. Written approval must be received from the IRB/IEC before commencement of the study.

12.3 Subject Information and Informed Consent

Informed consent of study subjects according to the standards of GCP must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form and should be deemed appropriate by the IRB/IEC. Subjects, their relatives (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about the details of the study.

The subject (or if necessary, legally acceptable representatives) must be provided with a copy of the signed ICF.

Should there be any amendments to the CSP that would directly affect the subject's participation in the study (eg, a change in any procedures), then the ICF must be amended to incorporate this modification. Subjects must be informed of the change and they must sign the amended ICF indicating that they re-consent to participate in the study.

12.4 Subject Confidentiality

All subject names and contact details will be kept confidential. Subjects will be identified throughout documentation and evaluation by the subject number assigned to them during the study. Each subject will be told that all study findings will be handled in the strictest confidence.

The investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, phone number, and identity in the study) so that regulatory agencies or CSL may access this information should the need arise. These records should be retained in a confidential manner as long as legally mandated according to local requirements.

Subject medical records pertaining to the study may be inspected/audited at any time by CSL employees or their duly authorized representatives, a health authority or the IRB/IEC. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections/audits

12.5 Indemnity and Compensation

CSL has taken out insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding compensation and the obligations of the investigator/CSL are provided in the Clinical Trial Research Agreement (CTRA) for the study (Section 13.1).

13 Administrative Considerations

13.1 Clinical Trial Research Agreement

This study will be conducted under a CTRA between CSL (“Sponsor”) and the institutions representing the investigational study sites (“Authority”). Financial support to the investigational sites will be detailed in the CTRA. The CTRA will clearly delineate the responsibilities and obligations of the investigators and CSL, and will form the contractual basis under which the clinical study will be conducted. The CTRA may be executed by electronic signature (current provider DocuSign) in compliance with 21 Code of Federal Regulations Part 11 and simple or advanced electronic signature according to European Union Regulation No. 910/2014 – eIDAS.

13.2 Clinical Study Registration and Results Disclosure

CSL will provide the relevant CSP information in public databases before or at commencement of the study. CSL may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original CSP registration record.

13.3 Implementation of the Clinical Study Protocol and Amendments

With the exception of medical emergencies, no changes or deviations in the conduct of the signed CSP will be permitted without documented approval of the CSL Medical Monitor or designee and the IRB/IEC. In the event of a medical emergency, the investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the CSL Medical Monitor and the IRB/IEC.

Modifications to the CSP that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB/IEC.

Administrative changes to the CSP, defined as minor corrections and/or clarifications that have no effect on the way that the study is to be conducted, will not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information.

13.4 Protocol Deviations

All instances where the requirements of the CSP were not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of the investigator and/or CSL. CSP deviations arise when either subjects who have been entered in the study and/or the study sites deviate from the IRB/IEC-approved study protocol.

If a major protocol deviation (ie, a deviation that could have a significant effect on the subject's safety, rights, or welfare and/or on the integrity of the study data) occurs, the investigator must notify CSL and the appropriate IRB/IEC as soon as possible or as per local requirements.

13.5 Documentation and Record Keeping

13.5.1 Data Collection

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, or physical examinations, administration of IP or concomitant therapy, any AEs experienced, and other notes as appropriate. These records (electronic or paper) constitute source data.

An eCRF will be provided by CSL (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be backed up by source data unless the eCRF is considered source data. All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

13.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the eCRFs checked against the subject records for completeness and accuracy. The investigator must provide direct access to source data documents. CSL's study monitor will perform this function.

Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically and manually for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

13.5.3 Monitoring

The monitoring activities during the current COVID-19 pandemic will be primarily or exclusively be performed without peripheral visits. Remote monitoring will be performed through periodic, comprehensive connections through the internet or telephone with all participating study sites by CSL personnel or representatives.

13.5.4 Record Retention

The investigator must follow the principles for record retention outlined in the CTRA. An investigator study file prepared by CSL (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. All study documentation and materials maintained in the investigator study file must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the investigator study file at the study site must be available for inspection by CSL's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from CSL or a competent health authority.

Following completion of the study, the investigator is responsible for archiving the investigator's study file, the subject's records and the source data according to applicable regulatory requirements.

13.6 Study and Site Closure

CSL reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the CSL Study Monitor (or delegate) will discuss this with the investigator at each study site at that time and notify the investigators in writing. If the study is suspended or terminated for safety reasons, all investigators and the relevant regulatory agencies will be immediately notified of the action as well as the reason for the suspension/termination. The investigator at each study site will advise their IRB/IEC overseeing the study of the suspension/termination.

13.7 Clinical Study Report

A clinical study report (CSR) will be written after the completion of the study. CSL or its agent will write the CSR in consultation with the investigator or, if applicable, a nominated coordinating investigator (or delegate). CSL requires that the coordinating investigator will sign the CSR.

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

13.8 Use of Data and Publications

The rights and obligations of investigators and CSL concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the CTRA for the study.

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15 Appendices

Appendix 1 Signatures

Signature on Behalf of Sponsor

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

Protocol Number: CSL312_COVID-19

I have read the Clinical Study Protocol, dated 16 September 2020, titled "A Phase 2, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate CSL312 in Coronavirus Disease 2019 (COVID-19)" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

PPD

PPD

Date

Signature of Principal Investigator

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

Protocol Number: CSL312_COVID-19 **Site Number:**

I have read the Clinical Study Protocol, dated 16 September 2020, titled "A Phase 2, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate CSL312 in Coronavirus Disease 2019 (COVID-19)".

By signing this Clinical Study Protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the Clinical Study Protocol, the standards of Good Clinical Practice (as defined by the International Council on Harmonisation) and applicable regulatory requirements.

Changes to the Clinical Study Protocol will only be implemented after written approval is received from CSL Behring and the Institutional Review Board or Independent Ethics Committee (as appropriate) with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the Clinical Study Protocol.

_____ _____

(Signature) Date (DD MMM YYYY)

_____

(Printed name)

_____

(Title)

Appendix 2 Sequential Organ Failure Assessment (SOFA) Scale

	SOFA Score			
	1	**2**	**3**	**4**
Respiration[a]				
PaO_2/FiO_2 ratio (mmHg)	< 400	< 300	< 220	< 100
SaO_2/FiO_2 ratio (mmHg)	221-301	142-220	67-141	< 67
Coagulation				
Platelets × $10^3/mm^3$	< 150	< 100	< 50	< 20
Liver				
Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular[b]				
Hypotension	MAP < 70	Dopamine ≤ 5 or dobutamine (any)	Dopamine > 5 or norepinephrine ≤ 0.1	Dopamine > 15 or norepinephrine > 0.1
Central Nervous System				
Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal				
Creatinine (mg/dL) or urine output (mL/d)	1.2-1.9	2.0-3.4	3.5-4.9 or < 500	> 5.0 or < 200

FiO_2 = fraction of inspired oxygen; MAP = mean arterial pressure; PaO_2 = partial pressure of arterial oxygen; SaO_2 = 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: Jones et al, 2009.

Appendix 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 2019; ECMO = extracorporeal membrane oxygenation; NIAID = National Institute of Allergy and Infectious Diseases; NIV = non-invasive ventilation.
Source: NIAID, 2020.

Appendix 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.

Signature Page

CSL312_COVID-19 - Protocol Amendment - 3 - 16Sep2020

Signed By	Date (GMT)
PPD	17-Sep-2020 19:49:48
Approved-PPD Approval	
PPD	18-Sep-2020 06:58:54
Approved-Clinical Safety Physician Approval	
PPD	18-Sep-2020 12:08:03
Approved-PPD Approval	

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