CLINICAL STUDY PROTOCOL

A Randomized, Double-blind, Placebo-controlled, Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of CSL312 in Subjects with Idiopathic Pulmonary Fibrosis

Study Number:	CSL312_2002
Study Product:	CSL312 (Garadacimab, Factor XIIa Antagonist Monoclonal Antibody)
Development Phase:	Phase 2a
Short Title:	CSL312 Safety, Pharmacokinetics, and Pharmacodynamics in Idiopathic Pulmonary Fibrosis
Sponsor:	CSL Behring, LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Protocol Version:	Amendment 3
EudraCT Number:	2021-003162-12
IND Number:	156 849
Protocol Date:	18 October 2022
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
07 June 2021	Original	Not applicable
15 November 2021	Amendment 1	For clarification regarding the process for breaking the blind in an emergency situation, the following statement has been removed from Section 6.3.2: “Whenever possible, the investigator should consult with CSL before unblinding the randomization code.”
18 January 2022	Amendment 2	Removed the word “prolonged” from the individual subject halting criterion for symptoms of severe hypersensitivity in Section 3.9.1.

18 October 2022	Amendment 3	1. Removed exclusion criterion #8 to allow administration of nonlive influenza virus vaccines or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccines before and during study participation. 2. Updated the Schedule of Assessments and Sections 4.1.2, 8.1.1, and 8.1.4 to clarify that: • International normalized ratio (INR) will be measured only at Screening and Baseline at the local laboratory. • Prothrombin time (PT) will not be measured in the local laboratory. • Both PT and INR will be measured in the central laboratory. 3. Revised wording in exclusion criterion #12 to clarify that standard of care medication is also prohibited during the Treatment and Observation Period up to Day 92. 4. Revised wording for subcutaneous (SC) administration regarding anatomical site of injection and the number of injections per dose. 5. Added an additional citation and reference for diffusing capacity of the lungs for carbon monoxide (DL_{CO}). 6. Low-dose aspirin now specifically mentioned in table of permitted therapies. 7. Revised wording on halting criteria due to electrocardiogram (ECG) prolongation for clarification. 8. Minor corrections and clarifications, including word modifications and administrative changes.

Clinical Study Protocol Synopsis

Title	A randomized, double-blind, placebo-controlled, study to investigate the safety, pharmacokinetics, and pharmacodynamics of CSL312 in subjects with idiopathic pulmonary fibrosis
Study Number	CSL312_2002
Sponsor	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Development Phase	Phase 2a
Study Product	CSL312 (Garadacimab, factor XIIa antagonist monoclonal antibody)
Indication	For the treatment of idiopathic pulmonary fibrosis
Study Summary and Overview	This is a prospective, phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of CSL312 in subjects with idiopathic pulmonary fibrosis (IPF). For all enrolled subjects, informed consent must be obtained at the Screening Visit before any study-specific assessments are performed. Screening can occur between 1 and 28 days before Day 1. For this study, Baseline is defined as before dosing on Day 1. Eligible subjects will be randomized to enter the Treatment and Observation Period for 14 weeks, during which subjects will receive an intravenous (IV) loading dose of CSL312 or placebo followed by 3 subcutaneous (SC) doses of CSL312 or placebo. A total of 12 study visits are planned (1 Screening Visit and 11 visits during the Treatment and Observation Period). A final safety check will be conducted by telephone approximately 90 days after the last administration of investigational product. The study will end when the last subject has completed the 14-week Treatment and Observation Period and the Follow-up Visit (Telephone Call).
Primary Objective	The primary objective of this study is to investigate the safety of CSL312 in subjects with IPF.

Primary Endpoint	The primary endpoints of this study are the subjects experiencing treatment-emergent adverse events (TEAEs) including: • Serious adverse events (SAEs) • Adverse events of special interest (AESIs) • CSL312-induced anti-CSL312 antibodies • Clinically significant abnormalities in laboratory assessments that are reported as adverse events (AEs)
Secondary Objectives	The secondary objectives of the study are: • To characterize the systemic PK of CSL312 in patients with IPF • To investigate the PD activity of CSL312 in patients with IPF
Secondary Endpoints	• Plasma PK parameters after SC administration of CSL312 at each SC dosing interval: o Trough plasma concentration (C_{trough}) o Maximum plasma concentration (C_{max}) (last SC dosing interval only) o Time to maximum plasma concentration (T_{max}) (last SC dosing interval only) o Area under the plasma concentration-time curve after 1 dose interval ($AUC_{0\text{-}tau}$) (last SC dosing interval only) • Plasma PK parameters after the IV dose of CSL312: o C_{max} o T_{max} o C_{trough} • Effect of treatment with CSL312 on FXIIa-mediated kallikrein activity
Study Duration	The duration of the study for an individual subject is expected to be approximately 6 months. This estimate is based on: • Screening / Washout Period of up 28 days • 14-week Treatment and Observation Period • Follow-up Telephone Call at 90 days after the last investigational product administration The overall study duration (ie, first subject's Screening Visit to last subject's Follow up Telephone call) will be approximately 17 to 19 months.

Number of Subjects	This study will enroll approximately 80 subjects to achieve a total of 70 evaluable subjects by Week 14; 35 subjects in the CSL312 group and 35 subjects in the placebo group. The estimated dropout rate is approximately 12%.
Study Population and Main Criteria for Eligibility	Inclusion criteria: 1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements. 2. Male or female patients, ≥ 40 years of age at the time of providing written informed consent. 3. Documented diagnosis of IPF according to the investigator using the criteria from the 2018 Clinical Practice Guideline of the American Thoracic Society (ATS) / European Respiratory Society (ERS) / Japanese Respiratory Society (JRS) / Latin American Thoracic Association (ALAT) for the diagnosis of IPF [Raghu et al, 2018] at the time of Screening. 4. Forced vital capacity (FVC) ≥ 45% of predicted normal at Screening. 5. Diffusing capacity of the lungs for carbon monoxide (DL_{CO}, corrected for hemoglobin) ≥ 30% of predicted normal at Screening. 6. Forced expiratory volume in 1 second (FEV_1) / FVC ratio ≥ 0.7 at Screening. 7. Investigator believes that the subject (or the subject's legally acceptable representative) understands the nature, scope, and possible consequences of the study.

Exclusion criteria:

1. History of clinically significant cardiovascular disease, including myocardial infarction, unstable ischemic heart disease, congestive heart failure, or angina during the 6 months before Screening.
2. Resting pulse < 50 beats per minute, sinoatrial or atrioventricular block, uncontrolled hypertension, or QT interval corrected using the Fridericia formula (QTcF) > 450 milliseconds.
3. 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 4 weeks before Screening).
4. History of venous thrombosis or cerebrovascular event within the 3 months before Screening, or a prothrombotic disorder (eg, antithrombin III, protein C, or protein S deficiency or antiphospholipid syndrome).
5. Known or suspected severe infusion-related reaction or hypersensitivity to monoclonal antibody therapy, or hypersensitivity to the investigational product or any excipients of the investigational product.
6. Major surgery scheduled to occur during the study or up to 90 days after the last administration of investigational product.
7. Lung transplantation anticipated during the study or within 90 days after the last administration of investigational product.
8. *Removed per Amendment #3*
9. Any other condition which, in the opinion of the investigator, may pose an additional risk to the study participant after the administration of investigational product.
10. Received any investigational therapy within 28 days, or 5 drug half-lives whichever is longer, before randomization or intends to take an investigation therapy other than CSL312 during the study.
11. Previously administered CSL312 in another interventional clinical study.
12. Use of nintedanib or pirfenidone within 28 days before randomization and during the 14-week Treatment and Observation Period up to and including the End of Treatment Visit (Day 92).
13. Pregnant at Screening or breastfeeding at Screening and not willing to cease breastfeeding.

	14. Female subject of childbearing potential or fertile male subject either not using or unwilling to use an acceptable method of contraception to avoid pregnancy during the study and for up to 90 days after the last administration of investigational product. Acceptable methods of contraception. All female subjects are assumed to be of childbearing potential except: • Subjects > 60 years of age. • Subjects between the ages of 45 to 60 years, inclusive, with amenorrhea for ≥ 1 year with documented evidence of follicle-stimulating hormone (FSH) level > 30 IU/L. If the FSH level is not available before randomization, a serum pregnancy test is required at Screening. Urine pregnancy tests will also be required at the time points indicated in the Schedule of Assessments. • Subjects who are surgically sterile for ≥ 3 months before providing informed consent. All male subjects are assumed fertile except subjects who are surgically sterile for ≥ 3 months before providing informed consent. 15. Clinical evidence of active infection, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). 16. Current alcohol, drug, or medication abuse. 17. Currently receiving a therapy not permitted during the study. 18. Involved in the planning and / or conduct of the study (applies to CSL staff, staff at the study site, and third-party vendors).
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. On Day 1, an IV loading dose of 300 mg will be administered in an infusion volume of 3 mL, by IV injection (ie, push over approximately 3 minutes). The second dose of 600 mg will be administered SC 7 days later. Doses 3 and 4 of 600 mg will be administered SC 28 days after doses 2 and 3, respectively.
Comparator Product, Dose, Dosing Regimen and Administration	Placebo will be supplied as a sterile, preservative free solution for injection in 2-mL vials. The placebo is the same as the CSL312 formulation buffer, but does not contain the active substance (ie, CSL312). IV and SC administered placebo will match the volume used for CSL312 to maintain the blind. The first dose of placebo will be administered IV (on Day 1) and the other 3 doses will be administered SC using the same dosing regimen as for CSL312.

Efficacy Assessments	Efficacy will be assessed using spirometry.
Safety Assessments	Safety will be assessed through documentation of treatment-emergent adverse events, vital signs, physical examinations, respiratory parameters, clinical laboratory assessments, and antidrug antibodies (ADAs).
Pharmacokinetics	Blood samples will be collected for assessment of CSL312 PK in plasma.
Pharmacodynamics	Plasma samples will be collected and analyzed for the following parameters: • Activated factor XII (FXIIa)-mediated kallikrein activity • Factor XII (FXII) concentration • Activated partial thromboplastin time (aPTT)

Biomarker Assessments	Additional biomarkers will explore the proposed mechanism of action of CSL312 in IPF including biomarkers of coagulation, inflammation, tissue modeling, and fibrosis, together with disease biomarkers of alveolar epithelial cell damage. The following biomarkers will be measured: pF1+2, fibrinogen, D-dimer, aPTT, high-sensitivity C-reactive protein (hs-CRP), and monocytes. Samples will be collected at Screening, before administration of the IV loading dose of investigational product on Day 1, and on Days 8, 36, 64, and 92. hs-CRP will be assessed at all study visits, including Screening, before administration of the IV loading dose investigational product and immediately after the end of the infusion (EOI) on Day 1. The following biomarkers will be measured at Screening, before administration of the IV loading dose of investigational product on Day 1, and on Days 8, 36, 64, and 92: FXII (free vs. total), C3a, C5a, interleukin (IL)-8, IL-10, C-C motif chemokine ligand (CCL)-2, C-X-C motif chemokine ligand (CXCL)-1, CCL-18, plasminogen activator inhibitor 1 (PAI-1), surfactant protein A (SP-A), surfactant protein D (SP-D), YKL-40, tenascin-C (TN-C), thrombospondin-1 (TSP-1), vascular endothelial growth factor (VEGF), neo-epitope of matrix metalloproteinase-mediated degradation of citrullinated vimentin (VICM), neo-epitope of matrix metalloproteinase-mediated degradation of C-reactive protein (CRPM), Pro-Fib (biomarker specifically targeting the thrombin-mediated conversion of fibrinogen into fibrin), neo-epitope of calprotectin generated by human neutrophil elastase (CPa9-HNE), and collagen synthetic and degradation neo-epitopes (pro-C3/4/6 and C1/3/4/6M). The following PD parameters and biomarkers will be assessed at all study visits at which PK is being assessed, including before administration of the IV loading dose of investigational product and immediately after the EOI on Day 1: FXIIa-mediated kallikrein activity, FXII concentration, IL-6, and hs-CRP. Additionally, hs-CRP will also be assessed at Screening. **Blood transcriptomics:** Blood will be collected for RNA sequencing to investigate changes in gene expression at Screening, before administration of the IV loading dose of investigational product on Day 1, and on Days 8, 36, 64, and 92. **Proteomic analysis:** Blood will be collected to characterize the plasma proteome at Screening, before administration of the IV loading dose of investigational product on Day 1, and on Days 8, 36, 64, and 92.

Statistical Analyses	The sample size for this study was determined based on feasibility, not based on a power calculation. It was estimated that enrolling approximately 80 subjects (40 in each treatment group), and taking into account a 12% dropout rate, a total of 70 evaluable subjects (35 in each treatment group), would be considered sufficient for assessment of safety, PK, and biomarker profiles. The primary endpoints of this study are subjects experiencing TEAEs including SAEs, AESIs, CSL312-induced ADAs, and clinically significant abnormalities in laboratory assessments that are reported as AEs. The summary measures will be the number and proportion of subjects experiencing these safety events after treatment with investigational product (CSL312 or placebo). TEAEs will be summarized by the number and percentages of subjects experiencing ≥ 1 TEAE and the number of events. TEAEs will be summarized by system organ class and preferred term and also by causality and severity. More detailed information on the analyses of efficacy, safety, PK, PD, and biomarkers are provided in the full clinical study protocol.

Schedule of Assessments

Study Period		Screening/ Washout Period[A]	Treatment and Observation Period													FU Visit (Phone Call)[B]
Study Week		-4	1			2	3	6	7	10		11	12	13	EOT/EW 14[C]	22
Study Day		-28	1			8	15	36	43	64	67	71	78	85	92	154
Time (Hours)[D]			Baseline Predose	0	EOI[D]											
Visit Window (Days)						±1	±1	±2	±1	±1	±1	±1	±2	±2	±2	±5
Informed consent[E]		X														
Inclusion / exclusion criteria		X	X													
Medical history and demographics		X														
Randomization via IRT			X													
Treatment assignment via IRT			X			X		X		X						
Administration of investigational product				IV		SC		SC		SC						
12-lead ECG		X	X			X		X		X					X	
Pregnancy test[F]		X	X			X		X		X					X	
Physical examination		X	X			X		X		X					X	
Vital signs[G]		X	X			X		X		X					X	
Urine sample for urinalysis (central laboratory)		X	X			X		X		X					X	
Blood Samples (central laboratory)	Hematology[H], biochemistry[I,J], and coagulation[K]	X	X			X		X		X					X	
	Retention sample for virology[L]		X													
	PD and biomarkers[M,N,O]	X[N]	X[M,N,O]		X[O]	X[M,N,O]	X[O]	X[M,N,O]	X[O]	X[M,N,O]	X[O]	X[O]	X[O]	X[O]	X[N,O]	
	PK		X[M]		X	X[M]	X	X[M]	X	X[M]	X	X	X	X	X	
	RNA Seq / proteomics	X	X[M]			X[M]		X[M]		X[M]					X	
INR and D-dimer (local laboratory)		X	X													
Immunogenicity (ADAs; central laboratory)[P]			X					X							X	
Spirometry at site (local laboratory)[Q]		X	X			X		X		X					X	
DL_{CO} (local laboratory)[Q]		X	X												X	
AEs[R]		←	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Prior / concomitant therapies[R]		←	—	—	—	—	—	—	—	—	—	—	—	—	—	→

ADA = antidrug antibody; AE = adverse event; ALT= alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BMI = body mass index; CCL = C-C motif chemokine ligand; CK = creatinine kinase; CPa9-HNE = neo-epitope of calprotectin generated by human neutrophil elastase; CPK = creatinine phosphokinase; CRPM = neo-epitope of matrix metalloproteinase-mediated degradation of C-reactive protein; CSL = CSL Behring; CXCL = C-X-C motif chemokine ligand; DL_{CO} = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; EOI = end of the infusion; EOT = end of treatment; EW = early withdrawal; FU = follow-up; GGT = gamma glutamyltransferase; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; IPF = idiopathic pulmonary fibrosis; IL-interleukin; INR = international normalized ratio; IRT = interactive response technology; IV = intravenous; LDH= lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PAI-1 = plasminogen activator inhibitor 1; PD = pharmacodynamic; pF1+2 = prothrombin fragment; PFT = pulmonary function test; PK = pharmacokinetic; Pro-Fib = biomarker specifically targeting the thrombin-mediated conversion of fibrinogen into fibrin; PT = prothrombin time; RBC = red blood cell; RDW = red cell (erythrocyte) distribution width; RNA seq = ribonucleic acid sequencing; SC = subcutaneous; SP-A = surfactant protein A; SP-D = surfactant protein D; TN-C = tenascin-C; TSP-1 = thrombospondin 1; VEGF = vascular endothelial growth factor; VICM = neo-epitope of matrix metalloproteinase-mediated degradation of citrullinated vimentin; WBC = white blood cell.

Notes for the Schedule of Assessments:

A. Eligible subjects must discontinue all prohibited medications ≥ 28 days (or 5 half-lives) before randomization.
B. The Follow-up Visit will be a telephone call conducted on Day 154 (± 5), approximately 90 days after the last administration of investigational product, to collect data on AEs (including acute exacerbations of IPF) and concomitant medications since the previous study visit.
C. EOT / EW Visit. If a subject withdraws from the study before the Week 14 Visit, the subject will be asked to return to the study site to complete the EOT assessments.
D. Postdose assessments should be performed immediately after the EOI of investigational product for the IV loading dose. Subjects should remain at the site for 15 to 30 minutes after the EOI for the IV loading dose of investigational product.
E. For all potential subjects, informed consent must be obtained before performing any study-specific screening assessments.
F. For female subjects of childbearing potential only: a serum pregnancy test will be performed at Screening (local laboratory). At all other time points, a urine pregnancy test will be used. If the results of the urine pregnancy test are inconclusive, a serum pregnancy test will be performed by the site (local laboratory). Urine pregnancy test kits will be provided by the Sponsor.
G. Vital signs include supine systolic and diastolic blood pressure, heart rate, and respiratory rate after resting for 5 (± 3) minutes, as well as body temperature, height, body weight, and BMI. Height will only be measured and recorded at Screening.
H. **Hematology parameters:** hematocrit, hemoglobin, platelets, reticulocytes, erythrocytes (RBC count), RBC indices (MCHC, MCH, MCV, RDW), leukocytes (WBC count), differential (percentage and absolute): neutrophils, neutrophil band forms, lymphocytes, monocytes, eosinophils, and basophils.
I. **Biochemistry parameters:** sodium, potassium, chloride, bicarbonate, calcium, bun, urea, creatinine, glucose, protein – total, albumin, alkaline phosphatase, ALT, AST, LDH, GGT, bilirubin – total, direct bilirubin, magnesium, phosphate, hs-CRP, cholesterol – total, triglycerides, HDL cholesterol, LDL cholesterol, urate (uric acid), and CK / CPK.
J. hs-CRP will be assessed at all study visits, including at Screening and **before administration of the IV loading dose investigational product** and immediately after the EOI on Day 1.
K. **Coagulation:** aPTT, PT and INR, pF1+2, fibrinogen (Clauss assay), and D-dimer.
L. An additional blood sample will be obtained on Day 1, **before administration of investigational product**, for potential virus testing in the future. This retention sample will be stored at the central laboratory and will be analyzed only if there is a suspicion of viral infection.
M. On the days when investigational product is administered (Days 1, 8, 36, and 64), blood samples for PK and PD assessments, biomarker assessments, proteomics, and RNA sequencing should be collected **before administration of investigational product**.
N. The following biomarkers will be measured at Screening, **before administration of the IV loading dose of investigational product** on Day 1, and on Days 8, 36, 64, and 92: FXII (free vs. total), C3a, C5a, IL-8, IL-10, CCL-2, CXCL-1, CCL-18, PAI-1, SP-A, SP-D, YKL-40, TN-C, TSP-1, VEGF, VICM, CRPM, Pro-Fib, CPa9-HNE, and collagen synthetic and degradation neo-epitopes (pro-C3/4/6 and C1/3/4/6M).
O. The following PD parameters and biomarkers will be assessed at all study visits, except Screening, including before administration of the IV loading dose of investigational product and immediately after the EOI on Day 1: FXIIa-mediated kallikrein activity, FXII concentration, IL-6, and hs-CRP. Additionally, hs-CRP will also be assessed at Screening.
P. Blood samples for assessment of ADAs will be obtained **before administration of investigational product**.
Q. PFTs including spirometry and DL_{CO} will be performed before administration of investigational product. Bronchodilator therapies, if used, must be washed out before PFTs are performed (8 hours for short-acting bronchodilators and 24 hours for long-acting bronchodilators). CSL will provide the device to be used for spirometry.
R. For each study visit, the investigator (or delegate) will review AEs and concomitant medications with the subject, which can be done in person or by telephone.

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List of Abbreviations

Abbreviation	Term
3F7	Parental antibody to garadacimab
%BLQ	Percent below the limit of quantitation
%CV	Percent coefficient of variance
β-FXIIa	Activated coagulation factor XII beta
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALAT	Latin American Thoracic Society
aPTT	Activated partial thromboplastin time
ATS	American Thoracic Society
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}tau}$	Area under the concentration-time curve in 1 dosing interval
BMI	Body-mass index
C1-INH	C1-esterase inhibitor
CCl4	Carbon tetrachloride
CCL	C-C motif chemokine ligand (CCL-2, CCL-18)
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CPa9-HNE	Neo-epitope of calprotectin generated by human neutrophil elastase
CRPM	Neo-epitope of matrix metalloproteinase-mediated degradation of C-reactive protein
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
C_{trough}	Trough plasma concentration
$C_{trough,ss}$	Trough plasma concentration at steady-state
CXCL	C-X-C motif chemokine ligand (CXCL-1, CXCL-5, CXCL-10)

Abbreviation	Term
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EOI	End of the infusion
EOT	End of treatment
ERS	European Respiratory Society
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
FVIII	Coagulation factor VIII
FXa	Activated coagulation factor X
FXII	Coagulation factor XII
FXIIa	Activated coagulation factor XII
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GERD	Gastroesophageal reflux disease
GMP	Good Manufacturing Practice
Gro-α	Growth-regulated oncogene-alpha (same as CXCL-1)
HAE	Hereditary angioedema
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IgG	Immunoglobulin G
IL	Interleukin (IL-1β, IL-6, IL-8, IL-10)
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International normalized ratio

Abbreviation	Term
IP	Investigational product
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional review board
IRT	Interactive response technology
IV	Intravenous
JRS	Japanese Respiratory Society
LIF	Leukemia inhibitory factor
MCP-1	Monocyte chemoattractant protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteinase
MMRM	Mixed-model repeated measure
mRNA	Messenger ribonucleic acid
PAI-1	Plasminogen activator inhibitor 1
PAR-1	Protease activated receptor 1
PD	Pharmacodynamic
pF1+2	Prothrombin fragment
PFT	Pulmonary function test
PK	Pharmacokinetic
Pro-Fib	Biomarker specifically targeting the thrombin-mediated conversion of fibrinogen into fibrin
PT	Prothrombin time
Q	Quartile
Q4W	Every 4 weeks
QTcF	QT interval corrected using the Fridericia formula
RNA	Ribonucleic acid
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SC	Subcutaneous
SD	Standard deviation
SOP	Standard operating procedure
SP-A	Surfactant protein A

Abbreviation	Term
SP-D	Surfactant protein D
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
TGF-β	Transforming growth factor-beta
T_{max}	Time to reach maximum observed plasma concentration
TNF	Tumor necrosis factor
TSP-1	Thrombospondin-1
USA	United States of America
VEGF	Vascular endothelial growth factor
VICM	Neo-epitope of matrix metalloproteinase-mediated degradation of citrullinated vimentin

1 Introduction

1.1 Background

Idiopathic pulmonary fibrosis (IPF) is a form of chronic, progressive, fibrosing interstitial pneumonia of unknown etiology that occurs primarily in older adults and is limited to the lungs. IPF is associated with the histopathological and / or radiological pattern of usual interstitial pneumonia [Raghu et al, 2011; Raghu et al, 2018]. A pattern of usual interstitial pneumonia typically shows basal honeycombing as a distinguishing feature with or without peripheral traction bronchiectasis or bronchiolectasis. In addition, subpleural, basal-predominant reticular abnormalities and ground-glass opacification are often present [Raghu et al, 2018].

Previously, IPF was considered to be a predominantly an inflammatory disease [Scadding et al, 1967; Katzenstein et al, 1998; Crystal et al, 1984; Ryu et al, 1998]. However, recently there has been a shift in thinking regarding IPF pathogenesis from an inflammatory driven process to a primarily fibrotic one, in which fibrogenesis results from repetitive local micro-injuries to an aging alveolar epithelium. These micro-injuries initiate aberrant epithelial-fibroblast communication, the induction of matrix-producing myofibroblasts, and extracellular matrix accumulation and remodeling of the lung interstitium [Richeldi et al, 2017; Sgalla et al, 2018; Martinez et al, 2017]. Nevertheless, inflammation appears to be a prominent feature in the lungs of patients with IPF [Bringardner et al, 2008] and may contribute the rate of disease progression [Balestro et al, 2016; Kahloon et al, 2013]. A severe innate and adaptive inflammatory infiltrate is observed in rapidly progressing patients with IPF that is markedly increased compared with slow progressors and is similar to that observed in patients experiencing an acute exacerbation [Balestro et al, 2016]. Differences in the expression of inflammatory markers and autoantibodies have been shown to be associated with different clinical outcomes in patients with IPF [Kahloon et al, 2013; Gilani et al, 2010; Prasse et al, 2009; Shinoda et al, 2009; Collard et al, 2007; dePianto et al, 2015; Nicholson et al, 2002; Moore et al, 2014; Taille et al, 2011].

IPF is one of the most common forms of idiopathic interstitial lung disease (ILD) [Kim et al, 2015] and several genetic and environmental risk factors for the disease have been identified. These include male sex, older age, cigarette smoking, environmental exposures such as metal and wood dusts, gastroesophageal reflux disease (GERD), chronic viral infections such as Epstein-Barr virus and hepatitis C, and a family history of ILD [Raghu et al, 2011; Raghu et al, 2018; Sgalla et al, 2018].

Patients with IPF typically present with nonspecific symptoms of exertional dyspnea with or without dry cough. On physical examination, fine, high-pitched bibasilar inspiratory crackles are usually heard, and digital clubbing is present in approximately 30% of patients [Richeldi et al, 2017; Raghu et al, 2018]. The natural history of IPF is highly variable and the course of disease in an individual patient is difficult to predict [Kim et al, 2015]. For some patients, disease progress occurs relatively slowly; others have a rapid decline in lung function leading to death; and a portion of patients suffer a stepwise loss of lung function with periods of relative stability [Kim et al, 2015]. Progression of IPF is characterized by a decline in lung function, worsening symptoms of dyspnea and cough, and deterioration in quality of life [Quinn et al, 2019]. For patients with IPF, acute exacerbations in respiratory function usually result in hospitalization and are associated with high mortality [Collard et al, 2016]. The evidence suggests that up to 46% of deaths in patients with IPF are preceded by an acute exacerbation, with a median survival of approximately 3 to 4 months in these patients [Collard et al, 2016]. Although the course of IPF may be variable, its overall prognosis is poor, with a median survival after diagnosis of only 3 to 4 years in patients who do not receive antifibrotic therapy or undergo lung transplant [Quinn et al, 2019].

Many patients with IPF have comorbid conditions including chronic obstructive pulmonary disease, lung cancer, pulmonary hypertension, obstructive sleep apnea, anxiety, depression, GERD, and ischemic heart disease [Caminati et al, 2019; Raghu et al, 2015a]. Comorbid conditions may affect the disease course in patients with IPF [Raghu et al, 2011], although in most of these patients the cause of death is IPF itself (ie, respiratory failure) [Kim et al, 2015].

Two antifibrotic medications, nintedanib and pirfenidone, are approved in most countries for the treatment of IPF. These drugs received conditional recommendation for use in the latest international treatment guideline for IPF [Raghu et al, 2015b]. Both drugs reduce the rate of decline in forced vital capacity (FVC) compared with placebo over time, consistent with slowing the progression of the disease [Raghu et al, 2015a; Quinn et al, 2019]. However, neither drug significantly improves the patient's quality of life [Quinn et al, 2019; Graney and Lee, 2018].

Hypercoagulation coupled with decreased antifibrinolytic activities have been reported in IPF and other ILDs. This claim is supported by several studies reporting increased deposition of platelets, tissue factor, coagulation factor VIII (FVIII), and plasminogen activator inhibitor-1 (PAI-1) within animal models of lung fibrosis and in patients with IPF [Fujimoto et al, 2003; Navaratnam et al, 2014; Crooks and Hart, 2015]. Significantly, patients with IPF who experience acute exacerbations have correlating elevated levels of D-dimer, fibrinogen, and homocysteine have been reported in both subjects with stable IPF and subjects with acute exacerbations of IPF compared with healthy control subjects [Bargagli et al, 2014].
Fibrin-rich wound clots are the result of the activated coagulation cascade. The clot can serve as a scaffold for fibroblast accumulation and synthesis of extracellular matrix [Schuliga et al, 2018]. Furthermore, various proteins from the coagulant and fibrinolytic pathways have been implicated in the pathogenesis of pulmonary fibrosis. Procoagulant proteins, thrombin, and activated coagulation factor X (FXa) have direct profibrotic activities on lung fibroblasts through activation of protease activated receptor 1 (PAR-1) and direct inhibition of these proteins attenuated lung fibrosis in vivo [Howell et al, 2005; Chiu et al, 2008; Scotton et al, 2009; Shea et al, 2017]. Dabigatran, the direct thrombin inhibitor, was able to inhibit fibroblast differentiation, profibrotic cytokine, collagen production [Bogatkevich et al, 2009]. It also ameliorated the development of bleomycin-induced pulmonary fibrosis in vivo and demonstrated a good safety profile in a phase 1 clinical study for patients with systemic sclerosis-interstitial lung disease [Bogatkevich et al, 2011; Silver et al, 2019]. In the fibrinolytic system, PAI-1 and plasmin drive excess fibrin accumulation and activation of profibrogenic actions of fibroblasts, respectively [Hattori et al, 2000; Senoo et al, 2010; Schuliga et al, 2017]. Overall, the evidence suggests that targeting the coagulation, inflammatory, and fibrinolytic pathways may be a potentially viable strategy for treating patients with IPF.

1.2 Information on CSL312

1.2.1 Overview

The coagulation factor XII (Hageman factor, FXII) is produced in the liver and is secreted into the plasma where the glycosylated 80 kDa zymogen circulates with a concentration of ~30 µg/mL and a half-life of 50 to 70 hours [Bjorkqvist et al, 2014]. FXII can be activated to a 2-chain active form, FXIIa (also 80 kDa), following binding to negatively charged artificial or biologic surfaces [Maas and Renne, 2018]. Further cleavage of FXIIa releases the 30 kDa light chain containing the catalytic domain (FXIIa-β), which can activate the classical complement pathway [Ghebrehiwet et al, 1981]. FXIIa initiates coagulation via the fibrin-forming intrinsic pathway and promotes inflammation via the bradykinin-producing kallikrein-kinin system [Renne and Stavrou, 2019; Maas and Renne, 2018]. Binding of bradykinin to the kinin B2 receptor activates proinflammatory signaling pathways that dilate vessels, induce chemotaxis of neutrophils, and increase vascular permeability [Renne et al, 2012]. FXIIa may also modulate components of the complement and fibrinolytic systems. However, to date, these activities have only been demonstrated in vitro [Renne and Stavrou, 2019]. Studies have shown that FXII deficient animals are protected from thrombosis without impaired hemostasis [Renne et al, 2005; Kleinschnitz et al, 2006; Matafonov et al, 2014]. Similarly, pharmacological targeting of FXII or FXIIa provides protection from thrombosis without an increased incidence of bleeding [Larsson et al, 2014; Revenko et al, 2011]. CSL312, an affinity matured antibody targeting the catalytic domain of FXII, effectively reduced edema in in vivo models and prevented bradykinin formation following contact activation of normal and kallikrein-defective plasma samples [Cao et al, 2018].

1.2.1.1 Evidence for FXII and the Contact System in Lung Fibrosis

Emerging evidence has shown an increased expression and local activation of FXII in the lungs of patients with IPF that is associated with fibroblasts / myofibroblasts [Wygrecka et al, 2015]. FXII binds to lung fibroblast through heparan sulfate proteoglycan and induces proliferation, fibroblast differentiation and extracellular matrix production [Wujak et al, 2015; Hess et al, 2017]. Moreover, transforming growth factor-beta (TGF-β) was found to induce p-JNK and translocation of SMAD-3 to the nucleus to upregulate FXII expression [Jablonska et al, 2010]. Genetic ablation or pharmacological blockade of FXII activity abrogated fibrogenesis in a bleomycin lung injury model in mice [Wygrecka et al, 2015]. FXII was reported to induce the production and release of interleukin (IL)-8, IL-1β, IL-6, leukemia inhibitory factor (LIF), CXCL motif chemokine ligand 5 (CXCL-5), and tumor necrosis factor (TNF) in human precision-cut lung slides in a kallikrein kinin-independent manner [Hess et al, 2017]. FXII also has direct effects on endothelial cell proliferation, vascular smooth muscle cells, neutrophil activation, monocyte / macrophage activation and associated M2 phenotype induction [Mahdi et al, 2002; Fernando et al, 2005; LaRusch et al, 2010; Wang et al, 2010; Vorlova et al, 2017; Stavrou et al, 2018]. These cells types have been implicated in fibrogenesis. Lung epithelial cells support the assembly and activation of plasma kallikrein kinin system. The resulting bradykinin production may potentiate inflammation in lung disease [Varano Della Vergiliana et al, 2010]. Bradykinin can also induce fibroblast cytokine expression and activation [Hayashi et al, 2000; Sabatini et al, 2013]. Thus, inhibition of FXII and the contact protein functions may have a therapeutic effect in IPF patients.

CSL312 is a fully human, recombinant, immunoglobulin G4 (IgG4) monoclonal antibody which binds to activated human FXII and potently inhibits its catalytic activity. CSL312 is an affinity-matured variant of the parental antibody 3F7, which was isolated from a Fab-based phage display library following screening against the active catalytic fragment of FXII (β-FXIIa). CSL312 is expressed in Chinese hamster ovary cells and has a structure typical of IgG4 monoclonal antibodies consisting of 2 heavy and 2 light chains, joined by disulphide bridges. CSL312 has a molecular weight of ~148 kDa. The CSL312 drug product is a sterile liquid formulation presented in 2-mL single-use glass vials, which is suitable for intravenous (IV) and subcutaneous (SC) administration to humans. CSL312 is manufactured according to Good Manufacturing Practice (GMP), in GMP-compliant facilities. A comprehensive manufacturing strategy that employs a combination of virus testing, the use of animal / human component-free growth media and excipients, and the incorporation of 2 dedicated virus removal / inactivation steps, ensures that the final product has a high level of virus safety.

A detailed description of the chemistry, pharmacology, efficacy, and safety of CSL312 is provided in the CSL312 Investigator's Brochure (IB).

1.2.2 Nonclinical Evaluation

For the ILD / IPF indication, in vitro studies were performed to support the role of FXII in lung fibrogenesis. FXII protein levels were found to be elevated in the lungs of patients with IPF when compared with non-disease control lungs. Whole lung RNA sequencing and published single cell RNA sequencing datasets have confirmed that FXII is not made in the lungs or the lung fibroblasts. Collectively, these data suggest that FXII is not produced in the lungs and is found when the lung is damaged, causing activation of the pulmonary endothelium, increased vascular permeability and increased perfusion into the lung tissue. FXII was found to be significantly elevated the blood of a subset of patients with IPF displaying a progressive decline in lung function. IL-6 has been implicated in the pathogenesis of lung fibrosis [Saito et al, 2008; Le et al, 2014; Kobayashi et al, 2015]. Activated β-FXIIa-induced IL-6 mRNA expression and protein production from human lung fibroblasts and CSL312 inhibited this function in a dose-dependent manner [Wong et al, 2017]. This process was found to be mediated through PAR-1 and NF-κB signalling pathways. Aside from IL-6, β-FXIIa also significantly increased the release of pro-fibrotic cytokines / chemokines (CXCL-1 / growth regulated oncogene-alpha [Gro-α], monocyte chemoattractant protein 1 [MCP-1 / C-C motif chemokine ligand (CCL-2)], IL-8, PAI-1, and latent TGF-β from lung fibroblasts a dose-dependent manner. Correspondingly, CSL312 inhibited CXCL-1, MCP-1, IL-6, IL-8, and PAI-1. β-FXIIa significantly induced the proliferation of IPF fibroblasts. β-FXIIa induced the transition of primary M0 macrophages to an M2 phenotype, and IL-6 induced hyperpolarization of M2 macrophages and also stimulated Type II cytokine (CCL-18, IL-10, and vascular endothelial growth factor [VEGF]) release from naïve and M2 macrophages. Excessive M2-associated responses are an important part of many fibrotic diseases and are implicated in the aberrant wound-healing cascade during fibrosis [Zhang et al, 2018]. CSL312 inhibited the β-FXIIa-mediated migration of primary lung fibroblasts in a dose-dependent manner.

Bradykinin, a downstream product of FXII activation is involved in vasodilation and inflammation during tissue injury. CSL312 can effectively inhibit bradykinin formation in human plasma following potent FXII activation. Preliminary studies have confirmed that bradykinin induces IL-6 in lung fibroblasts, which is mediated through the bradykinin receptor-2 subtype.

Bioinformatics methods utilizing the transcriptome of in vitro FXII and CSL312-stimulated fibroblasts revealed processes regulated by CSL312, leading to the identification of a FXII / CSL312 gene signature. Preliminary results demonstrate an enrichment of this gene signature in patient samples of several ILD subtypes (IPF, nonspecific interstitial pneumonia, systemic sclerosis-ILD, and hypersensitivity pneumonitis) when compared with healthy / non-fibrotic controls. Stratification of ILD patients based on the FXII signature and clinical data showed that it correlated with declining lung function (increased disease severity). These preliminary findings may provide the potential to guide selection and stratification of ILD patients for treatment with CSL312. Further work is underway to validate and refine the FXII gene signature, examine the signature enrichment in larger ILD cohorts, and evaluate whether it can be translated into blood to select for CSL312-responsive patients.

In vivo evaluation of 3F7, the parental antibody to CSL312, was assessed in the murine bleomycin lung model of pulmonary fibrosis. The prophylactic or therapeutic administration of 3F7 significantly ameliorated bleomycin-induced pulmonary fibrosis, as evident by the preserved lung structure, improved lung function, and reduced expression extracellular matrix proteins. Additionally, 3F7 inhibited bleomycin-induced pulmonary fibrosis similarly to anti-TGF-β monoclonal antibody in benchmarking studies. 3F7 also significantly inhibited carbon tetrachloride (CCl4)-induced liver fibrosis and unilateral ureteral obstruction-induced renal fibrosis in these mouse models.

Within the framework of the hereditary angioedema (HAE) project the pharmacology program was structured to characterize the interaction between CSL312 and FXII zymogen and its active forms, as well as the ability of CSL312 to specifically inhibit FXIIa-mediated biological activities both in vitro and in vivo using relevant animal species, ie, mice, rabbits and cynomolgus monkeys.

The pharmacokinetic (PK) studies and the toxicology program supporting the clinical development of CSL312 in IPF were performed according to international standards outlined in International Council for Harmonisation (ICH) guidelines.

Two single-dose PK / pharmacodynamics (PD) studies with CSL312 after IV and / or SC administration in cynomolgus monkeys showed prolongation of activated partial thromboplastin time (aPTT) confirming pharmacological activity of CSL312. Throughout both studies, terminal half-life ($T_{1/2}$) after IV administration was between 9 and 11 days. After SC administration, $T_{1/2}$ was between 12 and 14 days and bioavailability was calculated to be approximately 66%. A single-dose PK study comparing formulations of 100 mg/mL and 170 mg/mL of CSL312 in rabbits at a SC dose of 20 mg/kg demonstrated a similar PK profile for both formulations.

The CSL312 safety pharmacology and toxicological program demonstrated that at doses of up to 100 mg/kg IV and 200 mg/kg SC, CSL312 was well tolerated and had no adverse treatment-related effects on safety in mice or cynomolgus monkeys at up to 26 weeks. In the 4-week repeat-dose toxicity study in mice lower IV doses (3 to 30 mg/kg) revealed adverse treatment-related clinical signs and mortality after repeat dosing due to an immunological reaction to the human protein CSL312, which has limited predictive value for the clinical situation. In a local tolerance study in rabbits, CSL312 was well tolerated at the injection site. In addition, no adverse treatment-related effects were observed in the embryo-fetal development, in the fertility studies (1 study for each sex), and in a prenatal and postnatal development study in rabbits. Moreover, tissue cross-reactivity was observed on various human and cynomolgus monkey tissues; however, no related safety findings were observed in cynomolgus monkey repeat-dose toxicity studies.

Carcinogenicity assessments based on abovementioned published literature and available nonclinical and clinical data concluded that CSL312 has no carcinogenic potential when administered to patients.

In conclusion, nonclinical experiments demonstrate increased FXII protein expression in the damaged IPF lung and contribution to lung fibrogenesis by enhancing in vitro fibroblast proliferation, migratory capacity and pro-inflammatory / profibrotic cytokine / chemokine release. CSL312 inhibited these FXIIa-β-mediated processes. Anti-FXIIa monoclonal antibody 3F7 also demonstrated efficacy in ameliorating lung fibrosis in the murine bleomycin model of lung fibrosis in the prophylactic and therapeutic setting. CSL312 safety, PD, and toxicology studies demonstrated an adequate safety profile supporting a phase 2 clinical study. Since immunological reactions are principally expected after repeat-dosing of heterologous proteins (ie, human proteins in animal species), respective findings observed in

repeat-dose toxicological studies are considered not predictive for the clinical situation, which is in line with the ICH S6(R1) guideline.

Further details on nonclinical data for CSL312 are available in the CSL312 IB.

1.2.3 Clinical Experience

CSL312 is currently being developed for 2 target indications: IPF and HAE. Additionally, CSL312 had been under evaluation for the prevention of respiratory failure in patients with Coronavirus disease 2019 (COVID-19), but based on the results from a proof-of-concept study, development was discontinued (refer to the CSL312 IB for additional details).

1.2.3.1 Healthy Subjects

In healthy subjects, a phase 1 study has been completed and another is ongoing.

Study CSL312_1001, a phase 1, randomized, double-blind, placebo-controlled, single-ascending dose study was conducted in healthy volunteers. During this study, the safety, tolerability, and PK of escalating doses of CSL312 were assessed after single IV or SC injections of up to 10 mg/kg in healthy male subjects. CSL312 had an acceptable safety and tolerability profile. During the study there were no serious adverse events (SAEs); no withdrawals due to adverse events (AEs); no thromboembolic events (TEEs), bleeding events, or cases of anaphylaxis; no clinically significant abnormal trends in hematology or clinical chemistry assessments. After SC doses, the time to reach maximum observed plasma concentration (T_{max}) was approximately 7 days. The majority of the AEs were of mild severity. Injection site reactions were more common with SC CSL312 than SC placebo, but there was no apparent dose dependence. Additionally, CSL312 exhibited linear PK with a $T_{1/2}$ of approximately 18 days after the SC injection. The study results are described in greater detail in the CSL312 IB.

Additionally, a phase 1, single ascending dose study to investigate the PK, PD, safety, and tolerability of CSL312 in healthy Japanese and Caucasian subjects (CSL312_1003) is ongoing. Preliminary data from this study are not yet available.

1.2.3.2 Subjects with Idiopathic Pulmonary Fibrosis

Study CSL312_2002 will be the first CSL-sponsored clinical study evaluating CSL312 in patients with IPF.

1.2.3.3 Subjects with Hereditary Angioedema

Three clinical studies assessing CSL312 are currently ongoing in subjects with HAE; one phase 2 study and two phase 3 studies.

Study CSL312_2001

CSL312_2001 is an ongoing multicenter, randomized, placebo-controlled, parallel-arm, phase 2 dose-ranging (75, 200, and 600 mg) study to investigate the efficacy, PK, and safety of CSL312 SC administered every 4 weeks (Q4W) as prophylaxis to prevent HAE attacks in subjects with C1-esterase inhibitor (C1-INH) HAE or FXII / plasminogen HAE. The study consists of a Screening Period, a Run-in Period, 2 treatment periods (Treatment Period 1 [2 parts: 1 double-blind portion and 1 open-label portion] and open-label Treatment Period 2), and a Follow-up Period. After the Run-in Period, eligible subjects with C1-INH HAE were randomized to 1 of 4 treatment groups (placebo, or 75, 200, or 600 mg CSL312) in double-blind Treatment Period 1. Subjects received a single IV loading dose of investigational product followed 1 week later by a single SC injection of investigational product Q4W for 12 weeks (for a total of 13 weeks). In the open-label portion (Treatment Period 2), subjects receive a single SC injection of CSL312 at a dose of either 200 or 600 mg Q4W. The study is currently ongoing and the randomized, double-blinded portion of Treatment Period 1 has been completed.

A total of 32 patients with C1-INH (type 1 or type 2) HAE were enrolled in the randomized double-blind treatment groups of Treatment Period 1 at 20 study sites across 5 countries. Interim results from Treatment Period 1 demonstrate that CSL312 is safe and well tolerated at all 3 doses and has an overall favorable safety profile. All 3 dosages of CSL312 SC Q4W achieved clinically meaningful reductions in the HAE attack rate compared with placebo. The most frequent AEs were nonserious injection site reactions (ie, injection site erythema, pruritus, swelling, and discomfort) that were mild or moderate in severity. No related SAEs or adverse events of special interest (AESIs; TEEs, abnormal bleeding, or severe hypersensitivity and anaphylaxis events) were reported.

No difference in the PK of CSL312 was noted between healthy subjects in Study CSL312_1001 and subjects with HAE in Study CSL312_2001.

All subjects who successfully complete Study CSL312_2001 will be eligible to participate in the open-label, long-term safety study (CSL312_3002).

Study CSL312_3001

Study CSL312_3001 is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study designed to investigate the efficacy and safety of a single dose of CSL312 administered SC once a month as prophylaxis to prevent HAE attacks in adolescent (12 to 17 years, inclusive) and adult subjects with HAE. This study was recently initiated and, therefore no preliminary data from this study are available.

Study CSL312_3002

A multicenter, open-label study designed to investigate the long-term safety and efficacy of SC administered CSL312 in the prophylactic treatment of subjects with HAE is currently ongoing. Preliminary data from this study are not yet available.

1.2.3.4 Subjects with Coronavirus Disease 2019

A phase 2, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted to assess the safety, PK, and efficacy of IV administration of CSL312, administered in combination with standard-of-care treatment in patients with COVID-19 (CSL312_COVID19). Of the 124 patients randomized, 117 subjects were administered a single IV dose of investigational product (CSL312 or placebo).

The primary endpoint of the study was the incidence of progression to tracheal intubation or death prior to tracheal intubation. Although the incidence of progression to tracheal intubation or death prior to tracheal intubation was lower for subjects in the CSL312 group compared with the placebo group, the difference was not statistically significant ($p = 0.274$).

During the study, nearly two-thirds of subjects experienced ≥ 1 TEAE (64.1% [75 / 117] subjects, 303 events); a smaller percentage in the CSL312 group experienced TEAEs compared with the placebo group (60.3% vs. 67.8%). Few TEAEs were considered treatment-related (5 events in 4 subjects [3.4%]) and the percentages were similar for the CSL312 and placebo groups (3 events in 2 subjects [3.4%] vs. 2 events in 2 subjects [3.4%]). All 3 related TEAEs in the CSL312 group (1 patient experienced 2 AEs of ALT increased and AST increased and 1 patient experienced 1 AE of hemiparesis [left-sided weakness]) were non-serious, mild in intensity and resolved within one day after onset.

One-third of subjects (33.3%; 39 /117) experienced SAEs (83 events). The percentage of subjects with SAEs was similar for the CSL312 and placebo groups (34.5% vs. 32.2%), although the number of reported SAEs was lower for the CSL312 group (38 vs. 45 events). Only 1 subject, who was in the placebo group, experienced a treatment-related SAE of bilateral deep vein thrombosis (DVTs) that was reported as a suspected unexpected serious adverse reaction (SUSAR) and also as an AESI.

During the study, 11 subjects experienced a total of 19 AESIs; 10 subjects with 15 TEEs and 1 subject with 4 bleeding events. A total of 4 bleeding events were reported for 1 subject, who was in the placebo group. The percentage of subjects with TEEs and number of events was similar for the CSL312 group (5 / 58 subjects [8.6%], 8 events) and the placebo group (5 / 59 subjects [8.5%], 7 events). All AESIs except the previously described SUSAR case were considered as not related to the investigational product.

In total, 23 subjects had fatal TEAEs (23 / 117 subjects [19.7%]). The percentage of subjects with fatal events was similar for the CSL312 and placebo groups (20.7% vs. 18.6%). None of the deaths were considered related to investigational product.

Only 1 subject, who was in the CSL312 group, discontinued study treatment because of a TEAE.

1.3 Study Overview

Study CSL312_2002 is designed to explore the treatment effect of CSL312 600 mg on safety, PK, and biomarkers in subjects with IPF over a 14-week Treatment and Observation Period. Subjects will be randomized to 1 of 2 treatment groups:

- CSL312 600 mg SC Q4W
- Placebo SC Q4W

One week before the first SC dose of investigational product, an IV loading dose that is half of the SC maintenance dose will be administered and the date of the IV loading dose will be considered Day 1 of study.

The overall objective of the study is to establish a proof of mechanism and generate additional human data to support decision-making for further development of CSL312 for the treatment of patients with IPF.

The study has the following specific objectives:

- To investigate the safety of CSL312 in patients with IPF
- To characterize the systemic PK of CSL312 in patients with IPF
- To investigate the effect of CSL312 on FXII-related pathways and on a validated clinical endpoint (FVC) in patients with IPF
- To further investigate the association of FXII-related anti-fibrotic pathways (contact / coagulation, inflammation, and fibroblast function) with IPF clinical features and biomarkers of lung structural damage and IPF pathogenesis

1.4 Potential Risks and Benefits

1.4.1 Potential Benefits

This is a 26-week clinical study that includes a 28-day Screening Period, a 14-week Treatment and Observation Period, and a Follow-up Telephone call at 90 days after the last administration of investigational product. The benefits of treatment with CSL312 in patients with IPF are unknown. Subjects randomly assigned to the placebo group are not expected to receive any benefits related to their IPF disease from participating in this study.

1.4.2 Potential Risks

Potential risks associated with CSL312 have been considered based on the anticipated effects of the proposed mechanism of action and known risks associated with drugs of the same or similar class. The following events constitute potentially important medical risks:

- **Severe hypersensitivity including anaphylaxis:** Administration of therapeutic proteins including monoclonal antibodies such as CSL312 may be associated with the risk of hypersensitivity and anaphylactic reactions, some of which can be serious and life-threatening. To date, no severe hypersensitivity or anaphylactic-type reactions have been observed after repeated administration of CSL312 in the completed or ongoing clinical studies. Nevertheless, administration of CSL312 will be performed at the study site under medical supervision, with immediate access to emergency equipment and medication for the treatment of severe hypersensitivity, including anaphylaxis. Subjects will be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis, and will be encouraged to report any symptoms to site personnel.
- **Abnormal bleeding and thromboembolic events:** By blocking FXIIa, CSL312 may be associated with a potential risk of bleeding or TEEs, due to altered hemostasis, unstable clot formation, or impaired clot breakdown. In addition, due to the pharmacological action of CSL312, a concentration-dependent prolongation of aPTT was observed with dosages similar to those proposed in this study. Clinical experience with CSL312 in study CSL312_1001 and CSL312_2001 did not show an effect on prothrombin time (PT). This is consistent with the observation that patients who have a 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]. Nevertheless, subjects will be monitored carefully for any signs of thrombosis or bleeding during the study.
- **Immunogenicity (anti-drug antibodies):** All protein therapeutics are potentially immunogenic. Because CSL312 is a protein, it has the potential to cause the development of ADAs. During the study, investigators will monitor subjects for the development of ADAs for clinical evaluation of any signs of immunogenicity.

Given the acceptable safety profile of CSL312 observed in the phase 1 study (CSL312_1001) and the two phase 2 studies (CSL312_2001 and CSL312_COVID-19), and taking into account the implementation of procedures in the current study to closely monitor subject safety, the associated benefit-risk assessment is considered to be acceptable. Additional information on CSL312 can be found in the CSL312 IB.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoint

2.1.1 Primary Objective

The primary objective of this study is to investigate the safety of CSL312 in subjects with IPF.

2.1.2 Primary Endpoints

Endpoints	Summary Measure
Subjects experiencing treatment-emergent adverse events (TEAEs) including: • SAEs • AESIs • CSL312-induced ADAs • Clinically significant abnormalities in laboratory assessments that are reported as AEs	Number and proportion of subjects experiencing the specified safety events after treatment with investigational product (CSL312 or placebo)

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of the study are:

1. To characterize the systemic PK of CSL312 in patients with IPF.

2. To investigate the pharmacodynamics (PD) activity of CSL312 in patients with IPF.

2.2.2 Secondary Endpoints

The secondary endpoints of the study are:

Secondary Objective	Endpoints	Summary Measures
1	Plasma PK parameters after SC administration of CSL312 at each SC dosing interval: • Trough plasma concentration (C_{trough}) • Maximum plasma concentration (C_{max}) (last SC dosing interval only) • T_{max} (last SC dosing interval only) • Area under the plasma concentration-time curve after the first dose interval ($AUC_{0\text{-}tau}$) (last SC dosing interval only)	• Mean (standard deviation [SD]) and geometric mean (geometric percent coefficient of variation [%CV]) for all PK parameters except for T_{max} • Median (minimum, maximum) for T_{max}
1	Plasma PK parameters after the IV dose of CSL312: • C_{max} • T_{max} • C_{trough}	• Mean (SD) and geometric mean (geometric %CV) for all PK parameters except for T_{max} • Median (minimum, maximum) for T_{max}
2	Effect of treatment with CSL312 on FXIIa-mediated kallikrein activity	• Mean (SD) change from Baseline in FXIIa-mediated kallikrein activity by treatment • Mean percentage of Baseline in FXIIa-mediated kallikrein activity by treatment

2.3 Exploratory Objectives and Endpoints

2.3.1 Exploratory Objectives

The exploratory objectives of this study are:

1. To investigate the potential effect of CSL312 on FXII-related pathways in patients with IPF

2. To investigate the effect of CSL312 on lung function in patients with IPF

2.3.2 Exploratory Endpoints

The exploratory endpoints of the study are:

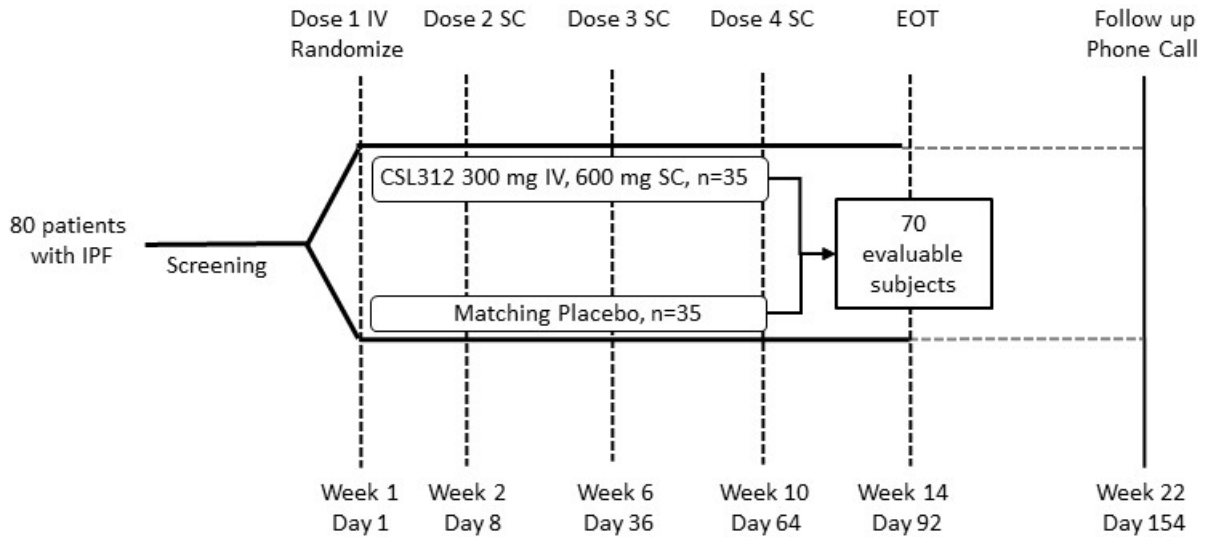
Exploratory Objective	Endpoints	Summary Measures
1	Concentration of PD and biomarkers in blood	• Mean (SD) change from Baseline in PD and biomarkers by treatment • Mean percent change from Baseline in PD and biomarkers by treatment
2	Change in FVC	• Absolute change from Baseline in FVC at 14 weeks (expressed in mL) • Absolute change from Baseline in FVC percent predicted at 14 weeks • Number and proportion of subjects with ≥ 5% or ≥ 10% absolute or relative decline in FVC percent predicted at 14 weeks

3 Study Design and Oversight

3.1 Overall Design

This is a prospective, randomized, double-blind, placebo-controlled study to investigate the safety, PK, and PD of CSL312 in patients with IPF (Figure 1). Approximately 80 patients with a confirmed diagnosis of IPF will be enrolled and randomized to treatment in a 1:1 ratio; to achieve a total of 70 evaluable subjects by Week 14; 35 subjects in the CSL312 600 mg group and 35 subjects in the placebo group.

Figure 1 Study Design Schematic



EOT = End-of-Treatment Visit; IPF = idiopathic pulmonary fibrosis; IV = intravenous; n = number of subjects in the treatment group; SC = subcutaneous.

For all enrolled subjects, informed consent must be obtained at the Screening Visit before any study-specific assessments are performed. Screening can occur between 1 and 28 days before Day 1. For this study, Baseline is defined as before dosing on Day 1.

Eligible subjects will be randomized to enter the Treatment and Observation Period for 14 weeks, during which subjects will receive an IV loading dose of CSL312 or placebo followed by 3 SC doses of CSL312 or placebo. A total of 12 study visits are planned (1 Screening Visit and 11 visits during the Treatment and Observation Period). A final safety check will be conducted by telephone approximately 90 days after the last administration of investigational product (see the Schedule of Assessments). The study will end when the last subject has completed the 14-week Treatment and Observation Period and the Follow-up Visit (Telephone Call).

Table 1 Overview of Study Design

Study Type:	Prospective / Interventional
Study Periods:	The study will consist of a Screening / Washout Period, a Treatment and Observation Period, and a Follow-up Period
Blinding Type:	The study will be conducted in a double-blind manner
Study Configuration:	Parallel group
Method of Assigning Subjects to Treatment:	Eligible subjects will be randomized to treatment at the first study visit on Day 1 during the Treatment and Observation Period

3.2 Dose and Dosing Regimen

Investigational product will be administered as an IV loading dose followed by 3 subsequent SC injections at the following doses based on treatment group:

- **CSL312 Group:** IV loading dose of CSL312 at 300 mg followed by a second dose of 600 mg administered SC 7 days later (Week 2). Doses 3 and 4 of 600 mg will be administered SC at Weeks 6 and 10, respectively.
- **Placebo Group:** IV loading dose of placebo followed by a second dose of placebo (formulation buffer) administered SC 7 days later (Week 2). Doses 3 and 4 of placebo will be administered SC at Weeks 6 and 10, respectively.

On Day 1, subjects will be asked to remain at the site for observation for 15 to 30 minutes after the end of the infusion (EOI) for the IV loading dose of investigational product.

3.3 Scientific Rationale

3.3.1 Study Design Rationale

Data have shown that FXII contributes to lung fibrosis by modulating markers that are implicated in the mechanistic pathways of IPF [Wong et al, 2017]. In vitro studies conducted in human lung fibroblasts showed that CSL312 inhibited β-FXIIa-mediated IL-6 production, fibroblast migration, and bradykinin generation at the highest concentration tested. Furthermore, repeat administration of 3F7, the parental antibody to CSL312, at 20 mg/kg as either a prophylactic or a therapeutic treatment regimen significantly ameliorated bleomycin-induced pulmonary fibrosis in mice. Taken together, these results support the rationale to develop CSL312 as a therapeutic option for the treatment of IPF. Although it is known that IPF is a multi-factorial disease, it is assumed that inhibiting FXIIa-mediated kallikrein activity to a particular percent target inhibition may inhibit inflammatory and fibrotic mediators involved in the disease process in IPF.

3.3.2 Dose Rationale

The proposed dose of CSL312 to be administered in this study is 600 mg SC Q4W. One week before the first SC dose, an IV loading dose that is half of the SC maintenance dose will be administered.

Dose selection was based on the safety, PK, and PD data obtained from the phase 1 study in healthy volunteers (CSL312_1001) and the phase 2 study in subjects with HAE (CSL312_2001). Results from previous clinical studies in healthy volunteers and subjects with HAE showed that a single administration of CSL312 at a dose of up to 10 mg/kg both IV and SC (CSL312_1001) and repeated SC administration of CSL312 at doses of up to 600 mg (CSL312_2001) were safe and well tolerated. In Study CSL312_1001, CSL312 exhibited linear PK when administered as a single IV infusion or SC injection with an absolute bioavailability of approximately 50%, and a $T_{1/2}$ of approximately 18 days after the SC injection. Dose-dependent PK was observed in C_{max} and area under the plasma concentration-time curve (AUC) after repeated SC administration in Study CSL312_2001. To date, no difference in the PK of CSL312 was noted between healthy volunteers and subjects with HAE.

A PK / PD model was developed to quantify the relationship between CSL312 plasma concentrations and FXIIa-mediated kallikrein activity from Studies CSL312_1001 (healthy volunteers) and CSL312_2001 (patients with HAE). The modeled relationship showed an increase in inhibition of FXIIa-mediated kallikrein activity with increasing concentrations of CSL312.

The IV loading dose was considered for this study to immediately achieve and maintain approximate steady-state exposures (ie, C_{max}, C_{trough}, AUC) during the proposed 3-month Treatment and Observation Period. With an IV loading dose, 73% of patients are projected to be above the median steady-state C_{trough} ($C_{trough,ss}$) at the end of the first SC dosing interval.

Simulations from the final healthy volunteer / HAE patient PK / PD model showed that a fixed dose of 600 mg SC Q4W would achieve a median percent inhibition of FXIIa-mediated kallikrein activity of ≥ 90% at the nadir during the SC dosing interval.

3.4 Planned Study Duration

The duration of the study for an individual subject is expected to be up to 6 months. This estimate is based on:

- Screening / Washout Period of up to 28 days
- 14-week Treatment and Observation Period
- Follow-up Telephone Call at 90 days after the last investigational product administration

The overall study duration (ie, first subject's Screening Visit to last subject's Follow-up Telephone call) will be approximately 17 to 19 months.

3.5 Planned Number of Subjects

The study will enroll approximately 80 subjects to achieve a total of 70 evaluable subjects by Week 14; 35 subjects in the CSL312 group and 35 subjects in the placebo group. The estimated dropout rate is approximately 12%.

A subject is considered enrolled in the study once they have signed the informed consent and are considered eligible for the study (ie, have met all inclusion criteria and none of the exclusion criteria; see Section 4.1).

3.6 Definition of Start of the Clinical Study

The start of the clinical study is defined as the date of the first subject's signed consent form (ICF).

3.7 Definition of End of the Clinical Study

The end of the clinical study (ie, completion of the study at all participating study sites) is defined as the date of the last contact with the last subject.

3.8 Study Oversight

3.8.1 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be established to monitor the critical safety data generated during the study. The IDMC will consist of at least 3 members including at least 1 independent clinical specialist in pulmonology, who also has experience in clinical studies. The IDMC will review accumulating safety data from the ongoing study in an unblinded manner. Based on these reviews, the IDMC will advise on further conduct of the study. CSL will continue the study unless a safety issue is confirmed that warrants study termination.

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 the IDMC charter.

3.9 Stopping / Halting Criteria

For the purpose of this study, the study stopping criteria and study halting criteria are the same.

If any halting criteria are met and the study is halted per IDMC recommendation, the CSL Global Safety Committees will conduct a safety assessment to establish whether the study should be resumed or whether the temporary halt should continue. The study can be resumed on the recommendation of CSL's Global Safety Committees, in agreement with the IDMC, if the safety assessment concludes that no further study modifications, protocol amendments, or risk mitigation measures are necessary, and that it is safe to resume the study. Regulatory authorities and the institutional review board (IRB) will be notified of the temporary halt and subsequent resumption of the study. A substantial protocol amendment will be submitted to the regulatory authorities and the IRB for approval if the safety assessment concludes that modifications to the clinical study protocol (CSP), including addition of new risk mitigation measures, are required to resume the study. If necessary, ad-hoc unblinding procedures may be initiated according to CSL's standard operating procedures (SOPs) for further safety assessment. If the risk assessment concludes that continued dosing poses an unacceptable risk to subjects and no further risk mitigation steps can be applied, the CSL Global Safety Committees will be involved in recommending a study stop. Regulators and the independent ethics committee (IEC) will be notified of a study stop.

3.9.1 Individual Subject Halting Criteria

If a subject meets any of the following criteria, then further administration of CSL312 to that subject will be halted (ie, temporarily paused) until an assessment of that subject's safety is completed:

- Symptoms of severe hypersensitivity considered by the investigator and / or CSL to be related to CSL312 administration.
- Prolongation of the QT interval corrected using the Fridericia formula (QTcF) interval of > 500 milliseconds.
- Prolongation of the QT interval corrected using the QTcF interval of > 60 milliseconds compared with the baseline measurement.
- A confirmed diagnosis of TEE or a clinically significant abnormal bleeding event, irrespective of CSL312 causality.
- Any event or laboratory abnormality that is considered by the investigator and / or CSL to pose an unacceptable risk to the subject in the study.

3.9.2 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 develops that the medical monitor, CSL, or IDMC considers to be associated with CSL312 and that may appear minor in terms of individual events, but that collectively may represent a serious potential concern for safety.

4 Selection and Withdrawal of Subjects

4.1 Eligibility Criteria

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. 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.

4.1.1 Inclusion Criteria

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

1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements.
2. Male or female patients, ≥ 40 years of age at the time of providing written informed consent.

3. Documented diagnosis of IPF according to the investigator using the criteria from the 2018 Clinical Practice Guideline of the American Thoracic Society (ATS) / European Respiratory Society (ERS) / Japanese Respiratory Society (JRS) / Latin American Thoracic Association (ALAT) for the diagnosis of IPF [Raghu et al, 2018] at the time of Screening.
4. FVC ≥ 45% of predicted normal at Screening.
5. Diffusing capacity of the lungs for carbon monoxide (DL_{CO}, corrected for hemoglobin) ≥ 30% of predicted normal at Screening.
6. Forced expiratory volume in 1 second (FEV_1) / FVC ratio ≥ 0.7 at Screening.
7. Investigator believes that the subject (or the subject's legally acceptable representative) understands the nature, scope, and possible consequences of the study.

4.1.2 Exclusion Criteria

Subjects must not be enrolled into the study if they meet any of the following exclusion criteria:

1. History of clinically significant cardiovascular disease, including myocardial infarction unstable ischemic heart disease, congestive heart failure, or angina during the 6 months before Screening.
2. Resting pulse < 50 beats per minute, sinoatrial or atrioventricular block, uncontrolled hypertension, or QTcF > 450 milliseconds.
3. 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 4 weeks before Screening).
4. History of venous thrombosis or cerebrovascular event within the 3 months before Screening, or a prothrombotic disorder (eg, antithrombin III, protein C, or protein S deficiency or antiphospholipid syndrome).
5. Known or suspected severe infusion-related reaction or hypersensitivity to monoclonal antibody therapy, or hypersensitivity to the investigational product or any excipients of the investigational product.
6. Major surgery scheduled to occur during the study or up to 90 days after the last administration of investigational product.

7. Lung transplantation anticipated during the study or within 90 days after the last administration of investigational product.
8. *Removed per Amendment #3*
9. Any other condition which, in the opinion of the investigator, may pose an additional risk to the study participant after the administration of investigational product.
10. Received any investigational therapy within 28 days, or 5 drug half-lives whichever is longer, before randomization or intends to take an investigation therapy other than CSL312 during the study.
11. Previously administered CSL312 in another interventional clinical study.
12. Use of nintedanib or pirfenidone within 28 days before randomization and during the 14-week Treatment and Observation Period up to and including the End of Treatment Visit (Day 92).
13. Pregnant at Screening or breastfeeding at Screening and not willing to cease breastfeeding.
14. Female subject of childbearing potential or fertile male subject either not using or unwilling to use an acceptable method of contraception to avoid pregnancy during the study and for up to 90 days after the last administration of investigational product. Acceptable methods of contraception are defined in Section 7.4.

    All female subjects are assumed to be of childbearing potential except:

    - Subjects > 60 years of age.
    - Subjects between the ages of 45 to 60 years, inclusive, with amenorrhea for ≥ 1 year with documented evidence of follicle-stimulating hormone (FSH) level > 30 IU/L. If the FSH level is not available before randomization, a serum pregnancy test is required at Screening. Urine pregnancy tests will also be required at the time points indicated in the Schedule of Assessments.
    - Subjects who are surgically sterile for ≥ 3 months before providing informed consent.

    All male subjects are assumed fertile except subjects who are surgically sterile for ≥ 3 months before providing informed consent.
15. Clinical evidence of active infection, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

16. Current alcohol, drug, or medication abuse.
17. Currently receiving a therapy not permitted during the study, as defined in Section 7.3.
18. Involved in the planning and / or conduct of the study (applies to CSL staff, staff at the study site, and third-party vendors).

4.2 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical study but who do not meet the eligibility criteria for participation in the study (see Section 4.1). A minimal set of information including demography, eligibility criteria, laboratory results, screening failure details, and any SAE should be recorded for all individuals considered screen failures.

Subjects who do not meet the inclusion / exclusion criteria within the specified time limit of 28 days and fail to complete screening assessments, may be re-screened but only once, if approved by the Sponsor's medical monitor.

Subjects who are not eligible for enrollment because laboratory test results do not meet the inclusion / exclusion criteria may have laboratory testing repeated, but once only, if the results are thought to represent a laboratory error or a reversible or a clinically insignificant intermittent condition. If testing is repeated, all Screening assessments will need to be repeated with the exception the 12-lead ECG, which may be repeated separately from other assessments, as necessary. The Sponsor's medical monitor may also grant permission for tests to be repeated separately from other tests as necessary. If inclusion / exclusion criteria are not met based on the results of the repeated tests, the subject should be considered a screen failure and not be enrolled in the study. Repeat tests should be conducted and the results available within 28 days before Baseline.

If the subject is re-screened, the subject will be asked to sign a new ICF.

4.3 Discontinuation of Study Treatment and Subject Withdrawal

4.3.1 Discontinuation of Study Treatment

Subjects may discontinue study treatment with investigational product 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 investigational product 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 investigational product 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 Withdrawal Visit assessments. Refer to Section 4.3.2 and Section 4.3.3 for details on handling subject withdrawals.

4.3.2 Subject Withdrawal

Subjects may withdraw from the study at any time 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, loss to follow-up, subject noncompliance, study termination). The investigator should record in the electronic case report form (eCRF), and in the subject's medical records, the reason 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 wellbeing 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.

4.3.3 Procedures for Handling Withdrawals

If a subject is withdrawn from the study, attempts will be made to complete and document the End-of-Treatment (EOT) Visit assessments. If the subject is withdrawn from the study after receiving investigational product, 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.

Publicly available records will be used to establish the vital status of subjects who withdraw from the study and withdraw consent for disclosure of future information.

4.3.4 Subjects Lost to Follow-up

If a subject repeatedly fails to return for scheduled visits, the site must attempt to contact the subject and counsel the subject on the importance of maintaining the assigned visit schedule and to ascertain whether or not the subject wishes to and / or should continue in the study. All attempts to contact the subject should be documented in the subject's medical record.

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Subjects lost to follow-up will be considered to have withdrawn from the study.

4.3.5 Replacement Policy

Subjects withdrawn from the study will not be replaced.

5 Study Interventions

5.1 Investigational Products

5.1.1 Description of CSL312

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

Table 2 Description of CSL312

Substance name:	CSL312
Active substance:	Fully human IgG4 / lambda recombinant monoclonal antibody that binds specifically to the catalytic domain of FXIIa
INN:	Garadacimab
Trade name:	Not applicable
Dosage form:	IV CSL312: Sterile solution for injection containing 100 mg/mL of CSL312 in 2-mL vials SC CSL312: Sterile solution for injection containing 100 mg/mL of CSL312 in 2-mL vials
Dose:	CSL312 300 mg IV; CSL312 600 mg SC
Dosing regimen:	The first dose of CSL312 will be administered as an IV loading dose of 300 mg. The second dose of 600 mg will be administered 7 days later by the SC route. Doses 3 and 4 of 600 mg will be administered SC 28 days after doses 2 and 3, respectively.
Injection volume:	IV 3 mL; SC 6 mL
Mode of administration:	IV loading dose followed by 3 SC doses
Anatomic location of administration:	IV CSL312: Left or right arm contralateral to the PK / PD sampling site SC CSL312: Abdomen is the preferred site of injection. If injection into the abdomen is not possible, injection can be into the thigh.

FXIIa = activated coagulation factor XII; IgG = immunoglobulin G; INN = international nonproprietary name; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous.

CSL312 will be manufactured by CSL in accordance with ICH GMP guidelines and local regulatory requirements.

5.1.2 Description of Placebo

The placebo (formulation buffer) will be supplied (2 mL per vial) as a sterile, preservative-free solution for injection (Table 3). The placebo is the same as the CSL312 formulation buffer, but does not contain the active substance (ie, FXIIa antagonist monoclonal antibody).

Table 3 Description of Placebo (Formulation Buffer)

Substance name:	Placebo
Active substance:	NA
INN:	NA
Trade name:	NA
Dosage form:	IV placebo: formulation buffer in 2-mL vials SC placebo: formulation buffer in 2-mL vials
Dose:	NA
Dosing regimen:	IV and SC administered formulation buffer using the same dosing regimen as for CSL312
Injection volume:	IV and SC administered formulation buffer will match the volume used for CSL312 to maintain the blind
Mode of administration:	IV loading dose followed by 3 SC doses
Anatomic location of administration:	IV: Left or right arm contralateral to the PK / PD sampling site SC: Abdomen is the preferred site of injection. If injection into the abdomen is not possible, injection can be into the thigh.

INN = international nonproprietary name; IV = intravenous; NA = not applicable; PD = pharmacodynamics; PK = pharmacokinetic; SC = subcutaneous.

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

Additional details related to the dosing and administration of the investigational product (CSL312 or placebo), as well as the procedure used to prepare the study treatment before administration, will be described in the Site Investigational Medicinal Product (IMP) manual.

5.1.3 Dosing and Administration of Investigational Product

The investigator (or delegate) will administer or dispense investigational product (CSL312 or placebo) only to subjects included in this study following the procedures set out in this CSP. Information on the dosing characteristics of investigational product is provided in Table 4.

Investigational product (CSL312 or placebo) will be administered by the investigator at the study site during Week 1 (IV loading dose on Day 1) and SC maintenance dose at Week 2, Week 6, and Week 10 (see Schedule of Assessments).

Table 4 Investigational Product Dosing Characteristics

Administration Parameter	CSL312	Placebo
Dose	CSL312 300 mg IV; CSL312 600 mg SC	NA
Route	IV loading dose followed by 3 SC doses	IV loading dose followed by 3 SC doses
Anatomic Location of Administration	IV: Left or right arm contralateral to the PK / PD sampling site SC: Abdomen is the preferred site of injection. If injection into the abdomen is not possible, injection can be into the thigh. Note that if IP is being administered as 2 injections of 3 mL each or 3 injections of 2 mL each, then all injections must be administered to the same anatomical site in a given subject (ie, abdomen)	IV: Left or right arm contralateral to the PK / PD sampling site SC: Abdomen is the preferred site of injection. If injection into the abdomen is not possible, injection can be into the thigh. Note that if IP is being administered as 2 injections of 3 mL each or 3 injections of 2 mL each, then all injections must be administered to the same anatomical site in a given subject (ie, abdomen)
Total Infusion Volume	IV 3 mL; SC 2 mL × 3 (6 mL) that may be administered as 1 injection of 6 mL or 2 injections of 3 mL each or 3 injections of 2 mL each	IV and SC administered formulation buffer using the same volume and number of injections as CSL312
Infusion / Injection Duration	Approximately 3 minutes	Approximately 3 minutes

IP = investigational product; IV = intravenous; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous.

Detailed information on the preparation and administration of the investigational product is provided in the Site IMP Manual.

5.1.3.1 Dosing Modification

No dose modifications are permitted during the study.

5.1.3.2 Treatment Compliance

All doses of investigational product will be administered at the study site. Treatment compliance will be assessed using the administration details entered into the eCRF.

5.1.3.3 Overdose

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

See Section 9.6.5 for overdose reporting requirements.

5.1.4 Description of Investigational Medical Device Constituents

Not applicable.

5.1.5 Packaging, Labeling, Supply and Storage

5.1.5.1 Packaging and Labeling

The investigational product will be packaged and labeled according to current ICH GMP and GCP guidelines, and national legal requirements.

5.1.5.2 Supply and Storage

The investigational product (CSL312 and placebo) will be supplied to the study sites by CSL or delegate.

The investigational product must be stored under temperature-controlled and access-monitored conditions from +2°C to +8°C in a secure storage area as specified in the Site IMP Manual.

5.2 Accountability and Destruction

The investigational product must be used only as directed in the CSP.

The investigator or delegate will confirm receipt of all shipments of investigational product in the interactive response technology (IRT) system.

All supplies of investigational product must be accounted for throughout the study.

Records for the delivery of investigational product to the study site, the inventory at the study site, the use by each subject, and the destruction or return of investigational product to CSL (or designee) must be maintained by the investigator (or delegate) using the IRT system.

The investigator (or delegate) must provide reasons for any discrepancies in drug accountability in the IRT.

Further details regarding receipt, packaging, and labeling, storage accountability and destruction of investigational product are provided in the Site IMP Manual.

5.3 Treatment for Acute Exacerbation or Disease Progression

At each study visit, subjects will be evaluated for symptoms of acute IPF as defined in Section 8.1.2.

If a subject experiences an acute IPF exacerbation or disease progression, medications or other therapy, including but not limited to antifibrotic agents (nintedanib or pirfenidone), may be administered at the investigator's discretion, at any time during the study.

6 Allocation to Treatment

6.1 Subject Assignment

After providing written informed consent, the subject will be issued with a study-level unique subject identification number using an IRT system. The subject identification number will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

6.2 Randomization Procedures

Subjects will be randomized in a ratio of 1:1 to either CSL312 600 mg or placebo group by means of the IRT. A centralized randomization schedule will be used.

The IRT external service provider will prepare the study randomization code according to approved specifications. The IRT external service provider will keep the randomization code on file.

At Screening, subjects will be assigned a unique subject number via the IRT system.

6.3 Blinding Procedures

6.3.1 Blinding Method

Investigational site staff, including the investigators, will be blinded to treatment allocation. Subjects and CSL staff / designates participating in the conduct of the study, with the exception of IRT and Clinical Trial Supply staff at CSL, will also be blinded to treatment allocation (double-blind).

To maintain the blind, all doses of investigational product administered during the Treatment and Observation Period will be volume normalized (see Section 5). Volume normalization will permit administration of the same volume of investigational product to be administered to each subject, regardless of their treatment assignment.

After preparation of the investigational product and before the investigational product is delivered to the subject for administration, a physical blind (eg, opaque or colored syringe) will be employed so that other site staff and study subjects are unable to detect any differences between CSL312 and placebo.

Unblinded study site personnel delegated by the investigator will prepare the investigational product, as assigned by the IRT. The unblinded study site personnel will also ensure the contents remain blinded to the subject and the blinded study site personnel who will be conducting assessments. Unblinded study site personnel are not to administer the investigational product and will not be involved in conducting or recording any study assessment procedures (ie, in the care of the subject).

All 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 locking of the study database except in the situations as outlined in Section 6.3.2, Section 6.3.3, and Section 6.3.4.

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.

The bioanalyst and pharmacokineticist responsible for the sample analysis and pharmacokinetic evaluation will be unblinded. However, they will agree not to disclose the randomization schedule.

6.3.2 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 reasons of subject safety, the investigator should use the IRT to identify the treatment allocation for a subject. 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.

6.3.3 Planned Unblinding Procedures

Periodic unblinded 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 either the unblinded statistician performing analyses for the IDMC with the randomization code or an IRT user account 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).

6.3.4 Ad-hoc Safety Unbinding

CSL's Global Clinical Safety and Pharmacovigilance (GCSP) 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 if 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 GCSP senior leadership.

7 Contraindications, Permitted Therapies and Prohibited Therapies

7.1 Contraindications and Precautions to Further Dosing

There are no contraindications or precautions associated with CSL312 administration.

The administration of investigational product (CSL312 or placebo) to any subject not meeting the eligibility criteria for this study, or to any patient not enrolled in this study, is prohibited.

7.2 Permitted Therapies

The medications and therapies that are PERMITTED during participation in the study are detailed in Table 5. Note: This list is not intended to be all inclusive.

Table 5 Permitted Medications / Therapies

Medication / Therapy	Dose	Permitted Period of Use
Corticosteroids for acute exacerbations of IPF during study participation	No dose restriction for IPF exacerbation	Treatment duration for acute IPF exacerbation at the investigator's discretion
Antifibrotic therapy (pirfenidone or nintedanib) for disease progression during study participation	According to approved prescribing information	Antifibrotic therapy (pirfenidone or nintedanib) is not permitted during this study as per exclusion criterion #12. However, in the event of disease progression during the study and if, in the investigator's judgment, the subject will benefit from this medication, the subject may receive antifibrotic treatment.
Bronchodilators	According to approved prescribing information	Bronchodilator therapies must be washed out before all PFTs as follows: Short-acting bronchodilators: 8 hours Long-acting bronchodilators: 24 hours
Anticoagulant therapy with LMWH	According to approved prescribing information	Treatment at the investigator's discretion
Low dose aspirin	75 to 100 mg	Treatment at the investigator's discretion
Nonlive influenza virus vaccines and SARS-CoV-2 vaccines	According to prescribing information	Administered at the discretion of the subject's treating physician

IPF = idiopathic pulmonary fibrosis; LMWH = low molecular-weight heparin; PFT = pulmonary function test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

7.3 Prohibited Therapies

The medications and therapies that are NOT PERMITTED during participation in the study are detailed in Table 6. Note: This list is not intended to be all inclusive.

Table 6 Prohibited Medications / Therapies

Prohibited Medication / Therapy	Prohibited Period of Use
Cytotoxic, immunosuppressive, or cytokine-modulating medication (ie, cyclophosphamide, cyclosporine, methotrexate, etanercept, TNF inhibitors, iloprost, tacrolimus, mycophenolate mofetil)	Within 28 days before randomization (at any time, for any duration, and for any reason) or during the 14-week Treatment and Observation Period
Antifibrotic therapy (nintedanib and pirfenidone)	Within 28 days before randomization and during the 14-week Treatment and Observation Period up to and including the End of Treatment Visit (Day 92) unless administered at the investigator's discretion for disease progression
Anticoagulant therapy other than LMWH	Within 28 days before randomization and during the 14-week Treatment and Observation Period up to and including the End of Treatment Visit (Day 92)
Any investigational therapy other than investigational product	Within 28 days before randomization, or 5 drug half-lives before randomization, whichever is longer During the 14-week Treatment and Observation Period During the 90 days after the last administration of investigational product
Lung transplantation	Planned to occur during study participation

LMWH = low molecular-weight heparin; TNF = tumor necrosis factor.

Subjects should not be enrolled into the study if they receive any prohibited therapy.

If administration of any prohibited therapy becomes necessary during the study for medical reasons, the subject may be withdrawn from further study participation.

7.4 Lifestyle Restrictions

Female subjects of childbearing potential or male subjects must use a medically reliable form of contraception until 90 days after the last administration of the investigational product. 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 investigational product. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable definitions of abstinence.
- Hormonal methods associated with inhibition of ovulation. 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).
- Bilateral tubal occlusion of female subjects (≥ 3 months before providing informed consent).
- Vasectomy of male subjects (≥ 3 months before providing informed consent).

8 Study Procedures and Visit Schedule

8.1 Clinical Procedures

The timing and frequency of the clinical procedures described in the following sections are detailed in the Schedule of Assessments. More frequent assessments may be performed, if clinically indicated, at the discretion of the investigator. Refer to the provided study manual for detailed instructions on how the assessments should be performed.

8.1.1 Demographics and Safety Assessments

Subject demographics and safety assessments to be conducted during this study are provided in Table 7. Clinical laboratory assessments are to be performed at the time points indicated in the Schedule of Assessments.

Table 7 Study Procedures: Demographics and Safety Assessments

Assessment	Description	
Demographics	• Year of birth • Sex	• Age • Race and ethnicity (where permitted)
Medical history	• Relevant medical history • Diagnosis and disease status • Contraception method (if relevant)	• Previous (within 6 months before Screening) and concomitant medications and therapies
Pregnancy test (local laboratory)	A serum test for β-hCG will be performed for all female subjects of childbearing potential to rule out pregnancy at Screening. At all other study visits, a urine pregnancy test will be performed. If the results from the urine pregnancy test are inconclusive, the site will perform a serum pregnancy test.	
Physical examination	As per the site's standard procedure, including assessment of unilateral pain and / or swelling of the lower extremities for the purposes of screening for DVTs.	
12-lead ECG (Performed and analyzed locally)	• Heart rate • PR interval • QRS duration • Interpretation (investigator's overall interpretation)	• QT interval • QTcB interval • QTcF interval
PFTs	• Spirometry including FVC and FEV_1	• DL_{CO}

AEs	• Evaluation of all AEs (eg, causality / relatedness, severity, seriousness)
	• AESIs:
	  ○ Abnormal bleeding events
	  ○ TEEs
	  ○ Severe hypersensitivity including anaphylaxis
	The description of AEs and reporting requirements are detailed in Section 9.	

Vital signs	• Blood pressure (systolic and diastolic) • Respiratory rate • Heart rate	• Body temperature • Height (Screening only) • Weight and BMI
Urinalysis (dipstick) (central laboratory)	• Specific gravity • pH • Nitrite • Ketones • Protein • Glucose	• Occult blood • Leukocyte esterase • Erythrocytes • Bilirubin • Urobilinogen

Assessment	Description	
Hematology (central laboratory)	• Hematocrit • Platelets • Erythrocytes (RBC count) • RBC indices (MCHC, MCH, MCV, RDW)	• Hemoglobin • Reticulocytes • Leukocytes (WBC count) • Differential (percentage and absolute): neutrophils, neutrophil band forms, lymphocytes, monocytes, eosinophils, basophils
Biochemistry (central laboratory)	• Sodium • Potassium • Chloride • Bicarbonate • Calcium • BUN • Urea • Creatinine • Glucose • Protein – total • Albumin • Alkaline phosphatase • ALT • AST	• LDH • GGT • Bilirubin – total • Direct bilirubin • Magnesium • Phosphate • hs-CRP • Cholesterol – total • Triglycerides • HDL cholesterol • LDL cholesterol • Urate (Uric Acid) • CK / CPK
Coagulation for safety assessments (local laboratory)	• INR	D-dimer
Coagulation for biomarker assessments (central laboratory)	• aPTT • pF1+2 • D-dimer	• PT and INR • Fibrinogen (Clauss assay)
Immunogenicity (ADAs) (central laboratory)	Plasma analyzed for the presence of binding antibodies (neutralizing and non-neutralizing) specific to FXIIa antagonist monoclonal antibody (anti-CSL312).	

β-hCG = beta-human chorionic gonadotropin; ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen; CK = creatinine kinase; CPK = creatinine phosphokinase; DL_{CO} = diffusing capacity of the lungs for carbon monoxide; DVT = deep vein thrombosis; ECG = electrocardiogram; FEV_1 = Forced expiratory volume in 1 second; FVC = forced vital capacity; FXIIa = activated coagulation factor XII; GGT = gamma glutamyl transferase; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; pF1+2= prothrombin fragment; PFT = pulmonary function tests; PT = prothrombin time; QTcB = Bazett's correction formula; QTcF = Fridericia's correction formula; RBC = red blood cell; RDW = red cell (erythrocyte) distribution width; TEE = thromboembolic event; WBC = white blood cell.

Results of laboratory tests (hematology, coagulation, biochemistry, and urinalysis) completed at the central laboratory should be signed and dated and retained at the study site as source data. The investigator should make an evaluation of the available safety-assessment results with regard to clinically relevant abnormalities. Refer to Section 9 for information on how AEs based on laboratory tests should be assessed and reported.

Laboratory Parameters

Details related to the collection, preparation, storage, and transfer of blood and urine samples for laboratory assessments will be provided in the Laboratory Manual.

Refer to Section 9.1.1 for assessment of abnormal laboratory values. Tests resulting in abnormal laboratory values during the study period that have been classified by the investigator as clinically significant should be followed up after receiving the laboratory report, and may include an unscheduled repeat safety sampling at the discretion of the investigator.

Vital Signs

Blood pressure and heart rate will be measured with the subject in a supine or seated position after resting for 5 (± 3) minutes. Body temperature will be measured either sublingually or tympanically, and the method of measurement should be consistent throughout the study for a given subject.

8.1.2 Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Data on acute exacerbations will be collected. An acute exacerbation of IPF is an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality [Collard et al, 2016]. The median survival of patients with IPF who experience an acute exacerbation is approximately 3 to 4 months [Collard et al, 2016]. Acute exacerbation has been shown to increase the risk of death more profoundly than an absolute decline in FVC percent predicted of ≥ 15% [Paterniti et al, 2017; Ley et al, 2017].

The diagnostic criteria for acute exacerbation of IPF in this study will be as follows [Collard et al, 2016]:

- Previous or concurrent diagnosis of IPF
- Acute worsening or development of dyspnea typically < 1 month in duration

- Computed tomography (CT) scan results with new bilateral ground-glass opacity and / or consolidation superimposed on a background pattern consistent with a pattern for usual interstitial pneumonia. (If no previous CT scan results are available, the qualifier "new" can be dropped)
- Deterioration not fully explained by cardiac failure or fluid overload

Note: Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet all 4 diagnostic criteria because of missing CT data should be termed "suspected acute exacerbations."

8.1.3 Pharmacokinetic and Pharmacodynamic Assessments

PK and PD assessments to be conducted during the study are provided in Table 8. Details related to the collection, preparation, and transfer of PK / PD samples will be provided in a Laboratory Manual.

Table 8 Clinical Procedures: Pharmacokinetic and Pharmacodynamic Assessments

Procedure	Description
PK evaluations (central laboratory)	Plasma samples will be collected for assessment of CSL312 concentration.
PD evaluations (central laboratory)	Plasma samples will be collected for assessment of the following parameters: • FXIIa-mediated kallikrein activity • FXII concentration • aPTT

aPTT = activated partial thromboplastin time; FXII = factor XII; FXIIa = activated factor XII; PD = pharmacodynamic; PK= pharmacokinetic.

8.1.4 Biomarker Assessments

The proposed mechanism of action of CSL312 in IPF will be explored using biomarkers of coagulation, inflammation, alveolar epithelial cell damage, tissue modeling, and fibrosis, such as but not limited to, those detailed below.

The following biomarkers will be measured: pF1+2, fibrinogen, D-dimer, aPTT, high-sensitivity C-reactive protein (hs-CRP), and monocytes. Samples will be collected at Screening, before administration of the IV loading dose of investigational product on Day 1, and on Days 8, 36, 64 and 92. hs-CRP will be assessed at all study visits, including Screening, before administration of the IV loading dose investigational product and immediately after the EOI on Day 1.

The following biomarkers will be measured at Screening, before administration of the IV loading dose of investigational product on Day 1, and on Days 8, 36, 64, and 92: FXII (free vs. total), C3a, C5a, IL-8, IL-10, CCL-2, CXCL-1, CCL-18, PAI-1, surfactant protein A (SP-A), surfactant protein D (SP-D), YKL-40, tenascin-C (TN-C), thrombospondin-1 (TSP-1), VEGF, neo-epitope of matrix metalloproteinase-mediated degradation of citrullinated vimentin (VICM), neo-epitope of matrix metalloproteinase-mediated degradation of C-reactive protein (CRPM), pro-Fib, neo-epitope of calprotectin generated by human neutrophil elastase (CPa9-HNE), and collagen synthetic and degradation neo-epitopes (pro-C3/4/6 and C1/3/4/6M).

The following PD parameters and biomarkers will be assessed at all study visits at which PK is being assessed, including before administration of the IV loading dose of investigational product and immediately after the EOI on Day 1: FXIIa-mediated kallikrein activity, FXII concentration, IL-6, and hs-CRP. Additionally, hs-CRP will also be assessed at Screening.

Blood transcriptomics: Blood will be collected for RNA sequencing to investigate changes in gene expression at Screening, before administration of the IV loading dose of investigational product on Day 1, and on Days 8, 36, 64, and 92.

Proteomic analysis: Blood will be collected to characterize the plasma proteome at Screening, before administration of the IV loading dose of investigational product on Day 1, and on Days 8, 36, 64, and 92.

Details related to the collection, preparation, transfer, and storage of biomarker samples will be provided in the laboratory manual. Blood sampling time points for biomarker assessment are indicated in the Schedule of Assessments.

8.1.5 Pulmonary Function Tests

Pulmonary function tests (PFTs) will be performed at the time points indicated in the Schedule of Assessments. The time windows for each type of assessment are detailed in Section 8.5.1.

PFTs, including spirometry and DL_{CO}, will be performed at the study site by the investigator or qualified designee according to the site's SOPs and conducted in accordance with criteria published by the American Thoracic Society (ATS) / ERS [Graham et al, 2017; Graham et al, 2019]. FVC reference ranges will be those established by the Global Lung Function Initiative [Cooper et al, 2017; Quanjer et al, 2012].

Before spirometry and measurement of DL_{CO}, long-acting bronchodilators must be washed out for 24 hours and short-acting bronchodilators for 8 hours. Approximately 1 in 10 patients with IPF shows physiological evidence of reversible airflow limitation, and bronchodilator use in these patients may improve the assessment of disease progression based on FVC change over time. Bronchodilator use does not appear to meaningfully affect the precision of FVC as an endpoint in clinical studies [Assayag et al, 2015].

The decline in FVC is an accepted measure of disease course and reliably predicts mortality in patients with IPF [Paterniti et al, 2017; Zappala et al, 2010; Flaherty et al, 2003; Collard et al, 2003; Quinn et al, 2019]. A decline in FVC of ≥ 10% has been correlated with worse survival time in patients with IPF [Paterniti et al, 2017; Zappala et al, 2010; Flaherty et al, 2003; Collard et al, 2003] and recent evidence-based guidelines state that an absolute decrease in FVC of ≥ 10% over time is an acceptable method for assessing disease progression and estimate risk of future mortality in patients with IPF [Raghu et al, 2011]. Some studies suggest that an FVC decline ≥ 5% may also be clinically significant [Zappala et al, 2010; du Bois et al, 2011]. Using a relative (rather than an absolute) change in FVC has been shown to maximize the chance of identifying a ≥ 10% decline without sacrificing prognostic accuracy [Richeldi et al, 2012]. The change in FVC has been used as the primary endpoint in several randomized controlled studies in subjects with IPF [Raghu et al, 2008; Raghu et al, 2012] including those for the approved drugs nintedanib and pirfenidone [Richeldi et al, 2014; Noble et al, 2011].

This study is a 14-week, placebo-controlled study. In both the INPULSIS studies and the INBUILD study with nintedanib in patients with IPF and progressive fibrosing interstitial lung diseases, respectively, a clear difference in the mean change in FVC from Baseline between the nintedanib groups and the placebo group is apparent at 12 weeks [Richeldi et al, 2014 (INPULSIS 1 and INPULSIS 2); Flaherty et al, 2019 (INBUILD)]. Similarly, a treatment effect is evident at Week 13 in the ASCEND study with pirfenidone in patients with IPF [King et al, 2014]. This study will determine if the FVC is altered by treatment with CSL312 over a 14-week period in patients with IPF.

As a safety parameter, single-breath DL_{CO} will be assessed at Screening, before administration of investigational product on Day 1 (Baseline), and at Week 14 (EOT / EW Visit). DL_{CO} will be assessed at the study site by the investigator or a qualified designee according to the site's SOPs, and conducted in accordance with criteria published by ATS / ERS [Graham et al, 2017]. The DL_{CO} reference ranges used will be those established by the Global Lung Function Initiative [Stanojevic et al, 2017]. DL_{CO} will be corrected for hemoglobin retrospectively using a blood sample collected on the same day as the DL_{CO} measurement, if available.

8.2 Blood Samples

During the study, blood will be taken from each subject for laboratory safety assessments, PK, and relevant PD and exploratory biomarkers. Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

Information on the volume of blood to be collected for each visit will be available in the informed consent form (ICF).

Refer to the Laboratory Manual for details about the volume, collection, storage, handling and processing of blood samples.

8.3 Retention of Samples

Refer to the Laboratory Manual for further details about the storage and destruction of **r**etention samples.

8.3.1 Retention Samples for Exploratory Biomarkers

Residual blood samples from the exploratory biomarker samples obtained during the Treatment and Observation Period at the time points indicated in the Schedule of Assessments, including the EOT Visit (Day 92) will be stored for potential testing of IPF biomarker and assay development and will be destroyed within 15 years or according to regional or local regulatory requirements after the completion of the study.

8.4 Concomitant Therapies

All drugs and procedures currently being administered to a subject at the time of signing informed consent, and which continue to be taken in addition to investigational product during study participation, are regarded as concomitant therapies.

8.5 Visit Schedule

8.5.1 Assessment Time Windows

The timing and frequency of the study visits, as well as time windows, are described in the Schedule of Assessments.

8.5.2 Screening Period

All subjects (or the subject's authorized representative) must provide written informed consent before any study-specific assessments or procedures are performed. Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of study eligibility.

A screening examination should be performed within 28 days before the intended date of dosing (Day 1). If a potential subject was not enrolled into the study within 28 days of the first Screening Visit, the potential subject may attend a second Screening Visit (for a maximum of 2 Screening Visits per subject). In the event that a potential subject is screened twice, all screening assessments must be repeated at the second Screening Visit, with the exception the 12-lead ECG, which may be repeated separately from other assessments, as necessary. The Sponsor's medical monitor may also grant permission for tests to be repeated separately from other tests as necessary.

If the subject is not eligible for the study (ie, the subject is a screen failure), all eligibility criteria that are not met will be recorded in the eCRF.

8.5.3 Treatment and Observation Period

On Day 1 (Baseline), subjects who complete all screening assessments and who fulfill the eligibility criteria (ie, eligible subjects) will be enrolled into the study and randomized to investigational product on Day 1 (Baseline).

Subjects will continue participation in the study for the 14-week Treatment and Observation Period. Subjects will be asked to return to the site for safety, PK, and efficacy assessments at the time points indicated in the Schedule of Assessments. Subjects will be contacted by telephone on Day 154 (± 5 days) for safety follow-up.

An IV loading dose of investigational product (CSL312 or placebo) will be administered on Day 1. Subjects subsequently will receive 3 doses of investigational product administered SC. The first SC dose will be administered 7 days after the IV loading dose and the second and third SC doses will be administered every 4 weeks (Q4W; on Day 36 and Day 64).

8.5.4 Unscheduled Study Visit

Unscheduled study visits are possible and all assessments performed should be documented in the unscheduled visit page 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 after the completion of the study

8.5.5 End-of-Treatment Visit

The scheduled end of study participation for an individual subject occurs with completion of the EOT Visit on Day 92 ± 2 days, after which no further study-related procedures will be performed.

8.5.6 Follow-up Telephone Call

On Day 154 (± 5 days), the investigator (or delegate) will contact the subject by telephone to collect data on AEs (including acute exacerbation of IPF symptoms) and concomitant medications. The Follow-up Telephone Call should be scheduled to occur 90 days after the last administration of investigational product.

8.5.7 Withdrawal

If a subject is withdrawn from the study before the Week 14 Visit (EOT Visit), the investigator should make every effort to perform the assessments during the subjects last study visit or, if possible, encourage the subject to return to the study site for EOT assessments.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

As per the ICH Topic 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 it is considered related to the medicinal (investigational) product.

The period of observation for AEs extends from the time the subject gives informed consent until the end of study (see Section 9.4 for further details).

AEs 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 investigational product administration.
- Intercurrent illnesses with an onset after administration of investigational product.

AEs 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 that 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 investigational product 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 to be 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 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).

9.1.2 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 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.

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

9.1.3 Adverse Event of Special Interest

There are several AEs that will be monitored closely as AEs of special interest (AESIs) to allow for an adequate risk-benefit evaluation of CSL312 during the study. Additional data may be requested for these events.

The AESIs for this study are:

- 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 9.6.2

9.2 Severity of Adverse Events

The severity of each AE (ie, nonserious and serious AEs) is to be assessed by the investigator as shown in Table 9.

Table 9 Severity of Adverse Events

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 posing 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.

AE = adverse event; CDISC SDTM Severity Intensity Scale for Adverse Event Terminology.

9.3 Causality of Adverse Events

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

The degree of certainty with which an AE is attributed to investigational product 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 investigational product.
- 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 investigational product, drug withdrawal, or reproducible on rechallenge).

9.4 Observation Period for Adverse Events

The observation period for the reporting of AEs and SAEs for an individual subject will start at the time at which written informed consent for participation in the current study is obtained and ends with the Follow-up Telephone Call.

If the investigator becomes aware of an SAE that started after the observation period has finished, and there is at least a possible causal relationship with the investigational product, the event must be reported to CSL (see Section 9.6.3).

9.5 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.

9.6 Adverse Event Reporting

9.6.1 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, laboratory findings, and / or symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the Follow-up Visit, the AE will continue to be followed until resolution, stabilization, or the subject is lost to follow-up.

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

9.6.2 Adverse Events of Special Interest

Adverse event of special interest must be reported as AEs in the subject's eCRF. Additional data may be requested in the eCRF for these events. Serious and nonserious AESIs must be reported following the procedures for expedited reporting as described for SAEs (see Section 9.6.3).

9.6.3 Serious Adverse Events

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

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 investigational product, **must be entered into the eCRF immediately (within 24 hours of the investigator's becoming aware of the event). Assessment of causality to the investigational product must be included.**

AEs occurring in the period between the time when the subject gave written informed consent and the first exposure to investigational product, and that meet 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 EOT Visit that is considered to be causally related to investigational product must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSL.** 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).

9.6.4 Other Significant Events

Not applicable.

9.6.5 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 9.6.3).

Details (ie, volume, location of infusions, infusion rate) of overdose of investigational product (defined in Section 5.1.3.3) must be recorded in the study treatment administration eCRF. Details of overdose of any concomitant therapy must be recorded in the Concomitant Medication eCRF.

9.6.6 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 administration of investigational product, must notify the investigator immediately.

If a female subject becomes pregnant, she must discontinue treatment with investigational product, but may continue other study procedures at the discretion of the investigator. If the female subject is in the active treatment period of the study, her participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in Section 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 investigational product 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.

9.7 Institutional Review Board / Independent Ethics Committee Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and investigational product-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 health authorities.

10 Statistics

10.1 Sample Size Estimation

The sample size for this study was determined based on feasibility, not based on a power calculation. It was estimated that enrolling approximately 80 subjects (40 in each treatment group), and taking into account a 12% dropout rate, a total of 70 evaluable subjects (35 in each treatment group), would be considered sufficient for assessment of safety, PK, and biomarker profiles.

10.2 Description of Study Analysis Sets

10.2.1 Screened Analysis Set

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

10.2.2 Safety Analysis Set

The Safety Analysis Set comprises all subjects who receive any portion of an IV infusion or SC injection of CSL312 or placebo, and analyses will be based on the actual treatment received.

10.2.3 Pharmacokinetic Analysis Set

The PK Analysis Set is defined as subjects in the Safety Analysis Set who receive ≥ 1 dose of CSL312 with ≥ 1 measurable concentration of CSL312 after administration.

10.2.4 Pharmacodynamic Analysis Set

The PD Analysis Set is defined as subjects in the Safety Analysis Set for whom analysis results are obtained for ≥ 1 of the exploratory biomarkers of interest.

10.3 Statistical Analyses and Methods

10.3.1 General Considerations

A complete description of the statistical analyses and methods will be provided in the statistical analysis plan (SAP), which will be finalized before database lock. In general, continuous variables will be summarized using descriptive statistics (number of observations [n], mean, SD, median, minimum and maximum. Categorical variables will be described using frequencies and percentages. For repeated observations of continuous variables, the change from Baseline will also be summarized.

All statistical tests will be 2-sided and will be performed at the 5% level of significance. Since no type I error adjustment will be performed for this study, all p-values will be considered nominal.

If not specified otherwise, Baseline refers to the last nonmissing measurement before the first administration of investigational product (CSL312 or placebo).

10.3.2 Subject Disposition and Characteristics

10.3.2.1 Subject Disposition

Summary tables by treatment group and total population will present:

- The number of subjects enrolled into the study (ie, signed the ICF).
- The number of subjects who prematurely discontinued investigational product.
- The number of subjects who were withdrawn from the study.
- The number of subjects who completed the study.

Reasons for discontinuing the investigational product and withdrawing a subject from the study will be listed by subject.

10.3.2.2 Subject Characteristics

At minimum, subject characteristics will be presented in summary tables. Descriptive statistics will be presented for continuous data and categorical data as described above. Age will be described as both a continuous and a discrete variable. Supportive data will be listed by subject.

10.3.3 Safety Analyses

TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 (or higher). A 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 of the following events, will be produced:

- TEAEs
- TEAEs related to study treatment
- TEAEs leading to permanent discontinuation of study treatment
- Serious TEAEs
- Serious TEAEs related to study treatment
- Fatal TEAEs

- Fatal TEAEs related to study treatment
- TEAEs by severity
- Treatment-emergent AESIs

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 group and overall.

The 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.

Change from Baseline in DL_{CO} will be summarized using descriptive statistics by treatment group.

The Safety Analysis Set will be used for the safety analyses unless indicated otherwise.

10.3.4 Pharmacokinetics Analyses

Plasma concentrations of CSL312 will be summarized by nominal time point. The following descriptive statistics will be presented for plasma concentration summaries: number of observations (n), arithmetic mean, SD, %CV, median, geometric mean, geometric CV, minimum, and maximum.

The following PK parameters will be derived using non-compartmental PK analyses and will be summarized after SC administration of CSL312 at each SC dosing interval:

- C_{trough}
- C_{max} (last SC dosing interval only)
- T_{max} (last SC dosing interval only)
- $AUC_{0\text{-}tau}$ (last SC dosing interval only)

The following PK parameters will be derived and summarized after the IV administration of CSL312:

- C_{max}
- T_{max}
- C_{trough}

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

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

Additional information on the analysis of PK parameters will be provided in the SAP.

10.3.5 Pharmacodynamic Analyses

10.3.5.1 FXIIa-mediated Kallikrein Activity

Change from Baseline in FXIIa-mediated kallikrein activity over time will be calculated for each subject. The comparison of primary interest is the change from Baseline at Week 14. If the data are not normally distributed by visual inspection or statistical testing, an appropriate data transformation may be done. The data (or transformed data) will be compared between CSL312 and placebo using mixed-model repeated measure (MMRM), with treatment group and visit as fixed effects, and Baseline as a covariate. Analyses will be implemented using SAS PROC MIXED. Interactions with visit will be included for treatment group and Baseline. A restricted maximum likelihood (REML) approach will be used. An unstructured variance-covariance structure will be used to model the within-subject errors. This variance-covariance matrix will be estimated across treatment groups. If the model fails to converge, a heterogeneous Toeplitz structure (the TOEPH option in SAS PROC MIXED) will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors.

FXIIa-mediated kallikrein activity will be summarized by nominal time point with the following descriptive statistics: n, mean, SD, %CV, minimum, first quartile (Q1), median, third quartile (Q3), maximum, geometric mean, geometric %CV, and percent below the limit of quantitation (%BLQ). Individual FXIIa-mediated kallikrein activity-time profiles will be plotted using actual sampling times. Mean (± SD) FXIIa-mediated kallikrein activity profiles will also be plotted using nominal (planned) time points.

Observed change from Baseline and percentage of Baseline values of FXIIa-mediated kallikrein activity over time will also be summarized using descriptive statistics and presented graphically by treatment group.

A nonparametric Jonckheere-Terpstra test may be performed as appropriate to test the trend over time for each treatment group.

The PD Analysis Set will be used for this analysis. Additional information on the analyses of FXIIa-mediated kallikrein activity will be provided in the SAP.

10.3.6 Pharmacokinetic / Pharmacodynamic Relationships

Population PK and PK / PD modelling will be explored, as feasible, for further time-dependent characterization of PK versus PD endpoints and / or safety and efficacy endpoints.

Population PK and PK / PD modeling will be specified in a separate PK modelling SAP and the results will be reported separately.

10.3.7 Analysis of Exploratory Endpoints

10.3.7.1 Biomarker Analyses

All PD and biomarker data change from Baseline and percent change from Baseline in the blood will be analyzed using the same methodologies as described for FXIIa-mediated kallikrein activity (see Section 10.3.5.1). In addition, correlations between the change from Baseline for each PD and biomarker at Week 14 and each spirometry measurement of FVC (change from Baseline in FVC [mL] and in FVC percent predicted) measured at Week 14 may be investigated using a scatter plot, Pearson correlation coefficient and Spearman correlation coefficient by treatment group. All PD and biomarker data will be summarized and analyzed using the PD Analysis Set. Additional information on PD analyses will be provided in the SAP.

Additional exploratory biomarker analyses will be reported separately from the clinical study report (CSR).

10.3.7.2 Pulmonary Function Data Analyses

Change from Baseline including absolute and percent predicted in FVC over time will be summarized using the same MMRM, with treatment group, and visit as fixed effects, and Baseline as a covariate. Interactions with visit will be included for treatment group and Baseline. Mean difference and its 95% confidence interval will be provided at each time point, assuming that the data is normally distributed. A plot of these variables over time will also be provided by treatment group. The number and proportion of subjects with ≥ 5% or ≥ 10% absolute or relative decline in FVC percent predicted at 14 weeks will be presented. The Safety Analysis Set will be used for this analysis.

10.3.8 Interim Analysis

No interim analysis is planned for this study.

11 Quality Assurance

The study may be subject to an audit by CSL, an authorized representative of CSL or inspections by an authorized health authority (eg, USA Food and Drug Administration [FDA]). Health authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSL will notify the investigator of any upcoming audit / inspection.

In the event of an audit, all pertinent study-related documentation must be made available to the auditors. If an audit or inspection occurs, the investigator at each study site will permit the auditor / inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

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 study start.

This study will be conducted under an FDA investigational new drug application as well as clinical trial applications in multiple countries 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 guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic 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 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 details of the study.

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

Should there be any amendments to the CSP that would directly affect the subject's participation in the study (eg, a change in any procedure), 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 number allotted 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 (see 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 must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and CSL, and will form the contractual basis under which the clinical study will be conducted. CTRAs 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 (EU) 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 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. Protocol deviations arise when either subjects who have been entered in the study and / or the study sites deviate from the IRB / IEC-approved CSP.

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 investigational product or concomitant therapy, any AEs experienced, and other notes as appropriate. These records (electronic or paper) constitute source data.

Electronic CRF entries will be considered source data if the eCRF is the site of the original recordings (ie, there is no other written or electronic record of the 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 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 Record Retention

The investigator must follow the principles for record retention outlined in the Clinical Trial Research Agreement. 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 CSR will be written after the completion of the study. CSL or its agent will write the report 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 Randomized, Double-blind, Placebo-controlled, Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of CSL312 in Subjects with Idiopathic Pulmonary Fibrosis

Protocol Number: CSL312_2002

I have read the clinical study protocol titled "A Randomized, Double-blind, Placebo-controlled, Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of CSL312 in Subjects with Idiopathic Pulmonary Fibrosis," dated 18 October 2022, and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

PPD

Date (DD MMM YYYY)

PPD

(Printed name)

PPD

(Title)

Signature of Principal Investigator

Study Title:	A Randomized, Double-blind, Placebo-controlled, Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of CSL312 in Subjects with Idiopathic Pulmonary Fibrosis
Protocol Number:	CSL312_2002 Site Number:

I have read the clinical study protocol titled "A Randomized, Double-blind, Placebo-controlled, Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of CSL312 in Subjects with Idiopathic Pulmonary Fibrosis," dated 18 October 2022.

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)

Signature Page

CSL312_2002 - Protocol Amendment - 3 - 18Oct2022

Signed By	Date (GMT)
PPD	24-Oct-2022 16:29:28
Approved-PPD Approval	
PPD	24-Oct-2022 17:21:52
Approved-PPD Approval	
PPD	24-Oct-2022 18:42:50
Approved-PPD Approval	

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