STATISTICAL ANALYSIS PLAN (SAP)

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

Study Number:	CSL312_2002
Study Product:	CSL312 (Garadacimab, Factor XIIa Antagonist Monoclonal Antibody)
Development Phase:	Phase 2a
Sponsor:	CSL Behring, LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Version:	Final 1.0
Version Date:	28Apr2022
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

COMMERCIAL IN CONFIDENCE

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1 Modification History

Version	Effective Date	Author of Modification	Summary of Change
1.0	28Apr2022	PPD	N/A – First Version

2 List of Abbreviations

Abbreviation	Term
%CV	Percent coefficient of variation
ADA	Antidrug antibody
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}tau}$	Area under the plasma concentration-time curve during a dosing interval
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BLQ	Below the limit of quantification
BUN	Blood urea nitrogen
C3M	neo-epitope of MMP-9 mediated degradation of type III collagen
C6M	neo-epitope of MMP-2 mediated degradation of type VI collagen
CCL-18	C-C motif chemokine ligand 18
CDG	Customized drug grouping
CDISC	Clinical data interchange standards consortium
C_{max}	Maximum plasma concentration
CK	Creatine kinase
CMQ	Custom MedDRA Query
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
eCRF	Electronic case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTMS	Clinical trial management system
C_{trough}	Trough plasma concentration
CV	Coefficient of variation
DBL	Database lock

Abbreviation	Term
DLCO	Diffusing capacity of the lungs for carbon monoxide
ECG	Electrocardiogram
EOT	End of treatment
eCRF	Electronic case report form
FVC	Forced vital capacity
FXIIa	Activated coagulation factor XII
GGT	Gamma-Glutamyl-Transferase
hs-CRP	High sensitivity-C reactive protein
HDL	High density lipoprotein
IDMC	Independent data monitoring committee
ICH	International council for harmonisation
ICF	Informed consent form
INR	International normalized ratio
IP	Investigational product
IPF	Idiopathic pulmonary fibrosis
IRT	Interactive response technology
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLN	Lower limit of normal
LLOQ	Lower level of quantification
LSMean	Least square mean
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-model repeated measure
MSAP	Modeling and simulation analysis plan
PAI-1	plasminogen activator inhibitor 1
PD	Pharmacodynamic
PK	Pharmacokinetic
PROC3	released N terminal pro-peptide of type III collagen
PROC6	C terminal of released C5 domain of type VI collagen

Abbreviation	Term
PT	Prothrombin time
RDW	Red cell (erythrocyte) distribution width
REML	Restricted maximum likelihood
Q1	First quartile
Q3	Third quartile
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDG	Standardized drug grouping
SDTM	Study data tabulation model
SI units	International system of units
SMQ	Standard MedDRA query
SP-A	surfactant protein A
SP-D	surfactant protein D
SOC	System organ class
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
T_{max}	Time to reach maximum plasma concentration
ULN	Upper limit of normal
WBC	White blood cell count
WHO	World health organization
WHO-DDE	World health organization drug dictionary enhanced

3 Purpose

This statistical analysis plan (SAP) provides a detailed and complete description of the planned statistical analyses of the data for the study CSL312_2002 "A Randomized, Double-blind, Placebo-controlled, Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of CSL312 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)".

This SAP complies with the International Council for Harmonisation (ICH) E9 'Statistical Principles for Clinical Trials' and is based upon the following study documents:

- CSL312_2002 Clinical Study Protocol (CSP), Original (dated 07 June 2021);
    - CSP Amendment 1 (dated 15 November 2021);
    - CSP Amendment 2 (dated 18 January 2022);
- CSL312_2002 electronic Case Report Form (eCRF), Version 1.0 (dated 08 February 2022).

All decisions regarding the final analysis of the study results, as defined in this SAP, will be made before database lock (DBL) of the study data.

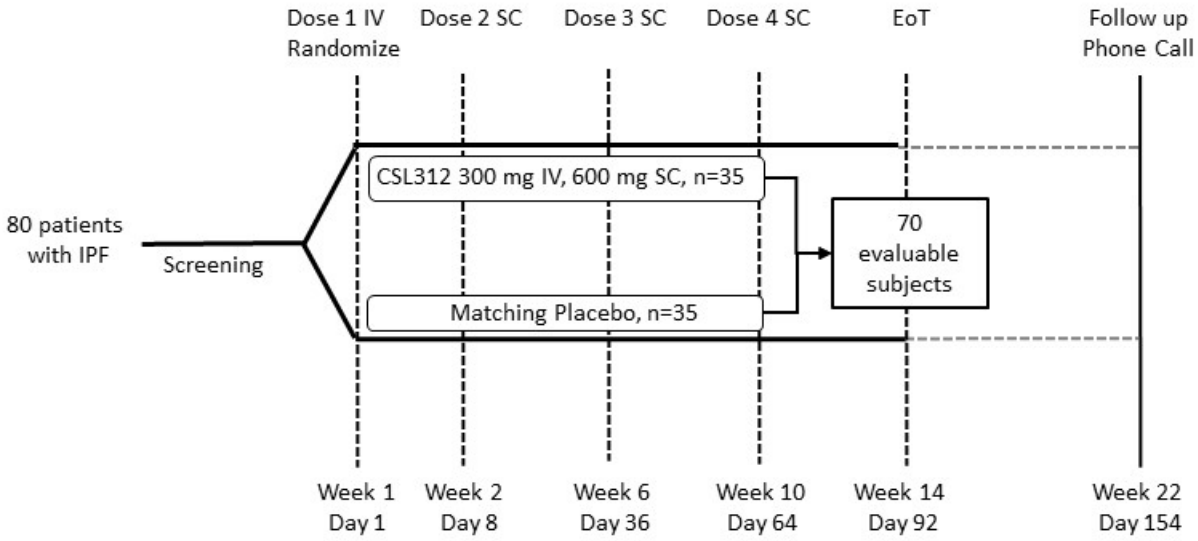
Deviations from the analyses in this SAP will be detailed in the clinical study report (CSR).

4 Study Design

This is a prospective, randomized, double-blind, placebo-controlled study to investigate the safety, PK, and pharmacodynamic (PD) of CSL312 in patients with IPF (Figure 1). Approximately 80 patients with a confirmed diagnosis of IPF will be enrolled and randomized in a 1:1 ratio; to achieve a total of 70 evaluable subjects by Week 14 (Day 92); 35 subjects in the CSL312 600 mg group and 35 subjects in the placebo group. It is expected that the dropout rate is approximately 12%.

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 (IP) (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).

Figure 1 Study Design Schematic



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

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.

4.1 Objectives and Endpoints

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

The secondary objectives of the study are:

1. To characterize the systemic PK of CSL312 in patients with IPF.
2. To investigate the PD activity of CSL312 in patients with IPF.

The exploratory objectives of the 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.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints and /or Estimand	Summary Measure(s)
Primary	Subjects experiencing treatment-emergent adverse events (TEAEs) including: • Serious adverse events (SAEs) • Adverse events of special interest (AESIs [bleeding events, thromboembolic events (TEE), severe hypersensitivity]) • CSL312-induced antidrug antibodies (ADAs) • Clinically significant abnormalities in laboratory assessments that are reported as adverse events (AEs)	Number and proportion of subjects experiencing the specified safety events after treatment with IP (CSL312 or placebo)
Secondary		
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) • Time to reach maximum plasma concentration (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 (SD) and geometric mean (geometric percent coefficient of variation [geometric %CV]) for all PK parameters except for T_{max} • Median (minimum, maximum) for T_{max}

Objectives	Endpoints and /or Estimand	Summary Measure(s)
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 activated coagulation factor XII (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
Exploratory		
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 forced vital capacity (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

4.1.1 Primary Study Hypotheses

There is no primary study hypothesis for this study.

Methods to control for multiplicity are not required.

4.2 Study Treatments

IP 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. The drug will be provided as a sterile solution for injection containing 100 mg/mL of CSL312 in 2-mL vials.
- Placebo Group: IV loading dose of placebo (formulation buffer) followed by a second dose of placebo administered SC 7 days later (Week 2). Doses 3 and 4 of placebo will be administered SC at Weeks 6 and 10, respectively. The drug will be provided as a sterile solution for injection containing a formulation buffer in 2-mL vials.

4.3 Randomization Procedures and Blinding

Subjects will be randomized in a ratio of 1:1 to either CSL312 600 mg or placebo group by means of the interactive response technology (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.

4.4 Determination of the Sample Size

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.

4.5 Planned Interim Analyses and Sample Size Re-estimation

No formal interim analyses and no sample size re-estimation is planned for this study.

4.5.1 Independent Data Monitoring Committee

The roles and responsibilities of the independent data monitoring committee (IDMC) and the safety data review schedules are described in the IDMC charter. Operationally, since the IDMC is ad-hoc and can be triggered before SAS programming can be done to generate summary output, in this case, only data dump listings will be generated. Otherwise, those summary tables will be provided for the following (along with their supporting listings):

- Demographics;
- Treatment and exposure;
- AE overall summary, SAEs, AEs, AESIs.

Other safety analysis output as listed below, will be provided as data listings:

- Vital signs, physical exams and respiratory tests;
- Safety laboratory parameters / urinalysis;
- ECG;
- Medical history;
- Concomitant medication;
- Spirometry.

Please refer to Sections 9, 10, and 11 of this SAP for descriptions of the analysis listed above.

5 Changes from the Protocol Planned Analyses

There are no changes to the planned analyses as previously documented in the CSP.

The definition of screened analysis set was slightly modified, please refer to Section 6.1.

6 Study Analysis Sets

6.1 Screened Analysis Set

The Screened Analysis Set comprises all subjects who provide written informed consent.

Section 10.2.1 of the CSP had previously included a more narrow definition for the Screened Analysis Set, which read as follows: “The Screened Analysis Set comprises all subjects who provide written informed consent and who complete all of the Screening procedures.

6.2 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.

6.3 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.

6.4 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.

7 General Considerations

Datasets will be created according to clinical data interchange standards consortium (CDISC) standards. Study data will be provided in study data tabulation model (SDTM) format. Analysis data will be provided in analysis data model (ADaM) format.

SAS version 9.4 or higher will be used to perform all data analyses.

Summaries of continuous variables will be in terms of the number of observations, mean, SD, median, first quartile (Q1), third quartile (Q3), minimum and maximum. Other descriptive statistics (eg, standard error, CV) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics identified with the analysis in the applicable SAP section.

7.1 COVID-19 Impact

During the course of this study, the global coronavirus disease 2019 (COVID-19) pandemic is expected to continue. This might impact the study in a variety of ways. This section describes how the potential impact of COVID-19 will be reported.

Subject Disposition: Study Treatment Discontinuation or Study Discontinuation

Subjects who experience either study treatment discontinuation or study discontinuation due to COVID-19 will have the reason captured in the eCRF. On the appropriate eCRF form to record either study medication discontinuation (“End of Treatment” form) or study

discontinuation ("Conclusion of Subject Participation" form), a reason will be selected which includes a field for descriptive text. The reason can be either "Withdrawal by Subject," "Physician Decision," or "Other". The associated free text field entry will include "COVID-19". When either treatment or the study is discontinued due to an AE or death, the specific corresponding AE is collected. Discontinuations due to COVID-19 related AEs will then be identified based on whether the medical dictionary for regulatory activities (MedDRA) code for the AE is included in standardised MedDRA Query (SMQ): COVID-19 (SMQ (broad)).

Cases of study treatment discontinuation or study discontinuation due to COVID-19 will be included in the summary of subject disposition.

Concomitant Medications

For concomitant medications which are linked to specific AEs, the eCRF collects information to identify the specific AE. As described in the Adverse Events section, relevant AEs will be identified by standardised MedDRA Query (SMQ): COVID-19 (SMQ (broad)). Concomitant medications used to treat COVID-19 associated AEs will be summarized.

Concomitant medications used to treat COVID-19 associated AEs will be flagged in the by-subject listing of prior and concomitant medications.

Adverse Events

AEs associated with COVID-19, which can include a clinically significant laboratory finding, will be reported by investigators following reporting requirements outlined in the CSP. COVID-19 associated AE are identified via MedDRA coding. Relevant AEs will be identified for reporting by standardised MedDRA Query (SMQ): COVID-19 (SMQ (broad)). All COVID-19 associated AEs will be included in standard AE tables.

An overview summary table of COVID-19 associated TEAEs, including number and percentages of subjects as well as the number of events, will be provided for the following:

- Any TEAE (related/not related);
- Serious TEAE (related/not related);
- TEAE resulting in death (related/not related);
- TEAE leading to discontinuation of study treatment (related/not related);
- TEAE leading to dose interruptions (related/not related);

- TEAE leading to study withdrawal (related/not related);
- TEAE by maximum severity (mild, moderate, severe, missing).

A by-subject listing showing all COVID-19 associated AEs will be provided.

Visit Modality, Missed Visits and Missing Assessments

Changes to subjects' visits caused by the COVID-19 pandemic will be captured for each subject in the eCRF, on the "Visit Status" form. The eCRF page includes different options for the primary visit modality, as well as whether the missed visit/alternate visit modality is due to COVID-19. Changes to visit modality may be a protocol deviation, or could be permitted via a contingency amendment; in either case, this data is captured. Since assessments (eg, vital signs, laboratory data) collected at each visit are known, the data missing due to COVID-19 can be determined.

Assessments that were missed or required alternate visit modality (eg, televisits or home health visits) due to COVID-19 will be summarized. In addition, the number of subjects with missed visits or alternate visit modality, by visit, will be summarized. Data will be listed.

Protocol Deviations

Protocol deviations due to the COVID-19 pandemic will be collected in the Clinical Trial Management System (CTMS) per the study specific Protocol Deviation plan.

When a protocol deviation within the CSL CTMS, such as when a subject is outside of the visit window due to COVID-19 restriction, is detected, the protocol deviation captured would be with reason of 'due to COVID-19 restrictions.

COVID-19-related protocol deviations will be summarized as sub-categories under existing categories of protocol deviations (refer to Section 9.2). All COVID-19 related protocol deviations will appear in the by-subject listing of protocol deviations and will be flagged.

COVID-19 Vaccinations

COVID-19 vaccinations are not allowed in this study as 1 of the exclusion criteria. In case it does occur, it is a protocol deviation. Sites will be prompted to inquire whether a subject has received a COVID-19 vaccination and to record each dose of the vaccine on the concomitant medications form along with the exact date of administration and manufacturer of the vaccine. Customized drug grouping (CDG) from World Health Organization (WHO) Drug

Dictionary will be utilized to identify COVID-19 vaccines. Any vaccination related AEs experienced by study participants will be recorded on the AE/SAE eCRF page. As a mechanism to assess potential TEAEs associated with the COVID-19 vaccines, those TEAEs occurring within 7 days after COVID-19 vaccine administration will be listed.

The following by-subject listings will be provided:

- Listing of all subjects receiving COVID-19 vaccine during the study (included in protocol deviation listing and respectively flagged).

Overview of COVID-19 Impact

Number and percentages of subjects with ≥ 1of the following due to COVID-19 will be summarized in an overview table:

- Subjects with Any COVID-19 Impact
- Protocol Deviations;
- Missing assessment;
- Missing Visit;
- Alternate Visit Modality;
- Study Treatment Discontinuation;
- Study Discontinuation;
- Any AEs/TEAEs;
- Any Serious AEs/TEAEs.

8 Data Handling Conventions

8.1 Missing Data

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

Because of the design and duration of the study, missing data are inevitable. The details of handling missing data are presented in the corresponding sections of this SAP for respective analyses (eg, primary and secondary endpoints, safety analyses).

8.2 General Derived Variables

8.2.1 Reference Dates and Study Days

Reference dates are used to assign study periods relative to treatment (Section 8.4).

- The safety reference date is the treatment start date, and will be used to calculate study day for safety measures.

The respective study day will be calculated as (date of interest - reference date) + 1 if the date of interest occurs on or after the reference date. If the date of interest occurs before the reference date, then the study day will be calculated as (date of interest – reference date). There will be no study day zero.

8.2.2 Durations

Durations (eg, the duration of an AE) are calculated in days as:

- Event end date – event start date + 1, if end time or start time not available;
- Event end date / time – event start date / time, if both end time and start time available.

Thus, there will be no duration of 0 if end time or start time are not available. If an AE has missing or partially missing start or end date, no duration will be calculated.

To transform durations or elapsed times, which are calculated in days into weeks, divide the number of days by 7; to report in months, divide the number of days by 30.4375; to report in years, divide the number of days by 365.25. These algorithms return decimal numbers, and ignore the actual numbers of days in the months or years (the calendar days) between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one-twelfth of that year.

8.2.3 Baseline Definition

Baseline is defined as the most recent, non missing value before the first IP administration (including unscheduled visits) for all assessments unless otherwise stated.

8.2.4 Change from Baseline

Change from baseline is calculated as:

- Visit value – baseline value.

Percentage change from baseline is calculated as:

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

The percent of baseline is calculated as:

- (Visit value / baseline value) * 100.

If either the baseline or visit value is missing, the change and percent change from baseline is missing.

8.2.5 Multiple Assessments

All data will be reported according to the nominal visit date for which they were reported (that is, no visit windows will be applied during dataset creation and the visit will not be re-allocated if the actual visit date deviates from the planned date according to the visit schedule in the protocol). Unscheduled data will not be included in by-visit summaries, but will appear chronologically in by-subject listing. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in by-subject listing.

8.2.6 Actual Treatment

The subjects' actual treatment will be derived from exposure data. If a subject receives a study treatment that is different from the planned treatment for the entire time of treatment, then actual treatment is the treatment actually received. In the event that a subject receives both CSL312 and placebo, the subject will be included in the CSL312 group for this analysis set. Subjects receiving only placebo will be included in the placebo group.

8.3 Stratification

The study design does not include any stratification factors. There are no formal plans for investigating any covariates.

8.4 Study Periods Relative to Treatment

All data will be assigned to 1 of the 3 study time periods defined below.

- **Pre treatment** is defined as the time before the subject's first date / time of IP (Day 1).
- **On-treatment** (Treatment and Observation Period) is defined as the time from first date / time of IP up to Week 14 (Day 1 to Day 92).
- **Post treatment** begins after the end of the Treatment and Observation Period (Day 92) and continues through the Follow-up visit (follow-up telephone call) (Day 154).

9 Study Population

Unless otherwise stated, all tables and listings in this section will be based on the Safety Analysis Set.

9.1 Subject Disposition

The following summaries will be provided for the Screened Analysis Set by CSL312 group, placebo group, and total population for:

- Subjects who underwent Screening – only total;
- Subjects who are re screened – only total;
- Screening failures with reason for failure – only total;
- Subjects eligible for randomization – only total;
- Subjects randomized – by treatment and total;
- Subjects randomized but not treated – by treatment and total;
- Subjects treated – by treatment and total;
- Subjects treated who completed treatment through Day 64 – by treatment and total;
- Subjects treated who completed the Treatment and Observation Period (Day 92) – by treatment and total;
- Subjects treated who discontinued from the study before end of treatment (Day 64) with reason (including discontinuation due to COVID-19) – by treatment and total;

- Subjects treated who discontinued from the study before end of Treatment and Observation Period (Day 92) with reason (including discontinuation due to COVID-19) – by treatment and total;
- Subjects treated who completed the study through the Follow-up Visit – by treatment and total;
- Subjects treated who discontinued from the study before the Follow-up Visit with reason (including discontinuation due to COVID-19) – by treatment and total;
- Subjects in each of the analysis sets described in Section 6.

Reasons for study withdrawal and study treatment discontinuation will be presented in the order they are displayed in the eCRF.

By-subject listing will be provided for disposition status for each subject. This will include:

- Randomization scheme based on the randomized treatment;
- Subjects treatment used in safety analysis;
- Subject disposition with date of screening (in case of re-screening, all screening records will be listed), date (and time) of randomization, date (and time) of first IP administration, date of completion of / or withdrawal from the Treatment and Observation Period, and date of study completion or withdrawal from the study;
- Screening failures with the reason;
- Subjects who discontinued from study treatment with the reason for discontinuation and subjects who discontinued from the study with the reason for discontinuation;
- Subject assignment to analysis sets and reasons for exclusion.

9.2 Protocol Deviations

A protocol deviation occurs when an investigator site, or study subject, does not adhere to protocol-specified requirements. Deviations will be assessed by CSL Behring as they are reported and then evaluated periodically during study conduct, based on the protocol deviation plan for this study developed by CSL Behring.

Deviations will be categorized as either major or minor. Major protocol deviations for subjects in the Safety Analysis Set will be summarized for number and percentage of subjects with each protocol deviation, though all major and minor deviations will be listed. The summary will be given by treatment group and overall.

The final decision regarding protocol deviations and assignment of subjects to analysis population will be made during the blinded data review meeting.

A by-subject listings will be provided based on the Safety Analysis Set covering the following information:

- All protocol deviations (including inclusion and exclusion criteria violations).

9.3 Demographic and Baseline Characteristics

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

The following summaries will be provided for the Safety Analysis Set by treatment group and overall:

- Demographic characteristics (eg, age, race, ethnicity, sex, smoking history, baseline height, and baseline body weight, and body mass index (BMI)). In addition to summarization as a continuous variable, age will also be categorized and summarized by ≥ 40 to ≤ 64 years, ≥ 65 to ≤ 74 years, ≥ 75 to ≤ 84 years and ≥ 85 years;
- Disease characteristics including the duration since IPF diagnosis and previous treatment with nintedanib or pirfenidone, baseline FXIIa-mediated kallikrein activity, baseline absolute and percent predicted in FVC;
- Medical history (coded using MedDRA – the MedDRA version will be populated in the outputs) will be presented by SOC and preferred term.

Corresponding by-subject listings will be provided. The by-subject listing for disease characteristics will include but is not limited to the year of diagnosis as well as the duration of IPF. The medical history by-subject listing will also provide an indicator of whether the condition was active at the time of entry into the screening period.

Nonpharmacological procedures will only be presented in a by-subject listing.

9.4 Prior/Concomitant Medications

Prior/concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) B3. The version will be populated in the outputs.

The reported medication will be classified as ‘Prior only’, ‘Prior and concomitant’ or ‘Concomitant only’. These 3 categories are mutually exclusive:

- 'Prior only': if the subject has not taken any IP; or if the medication end date (/time) is before IP start date (/time). If the medication end date is partially missing, the medication will only be assigned to 'Prior only' if the partial date gives clear evidence that the medication stopped before IP start date (eg, a partial medication stop date of – – Mar 2022 is clearly before an IP start date of 03 Apr 2022).
- 'Concomitant only': if the medication start date (/time) is on or after IP start date (/time). If the medication start date is partially missing, the medication will only be assigned to 'Concomitant only' if the partial date gives clear evidence that the medication started on or after IP start date.
- 'Prior and concomitant': all medications which are not assigned as 'Prior only' nor 'Concomitant only'.

Concomitant medications (ie, medication classified as 'Prior only', 'Concomitant only' or 'Prior and concomitant') will be summarized showing the number and percentage of subjects taking concomitant medications by ATC classification level 4 and preferred term. If the ATC level 4 coding is not available for a preferred term, the next available lower level ATC code will be used. Tables will be provided for the Safety Analysis Set by treatment group and overall.

The following by-subject listing will be provided:

- Prior and concomitant medication.

9.5 Study Population - Derived Variables

Derivation of Body Mass Index (BMI)

BMI data will be used from eCRF as collected. In case of missing BMI, BMI will be calculated using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (m)}]^2,$$

using the height measured at Screening and the weight measured at Day 1 (if available). If weight at Day 1 is not available, the assessment at Screening will be used (if available). If neither is available, then BMI is missing.

10 Efficacy Analyses

There are no primary or secondary efficacy endpoints in this study. The analysis of FVC as exploratory efficacy endpoint is described in Section 13.2.1.

10.1 Treatment Compliance

The calculation of overall compliance is based on receiving the IV loading dose and all 3 SC injections of IP. An infusion or injection of at least 80% of the planned volume will satisfy the criteria of receiving a compliant infusion or injection at each of the 4 visits. The following summaries will be provided by treatment group for the Safety Analysis Set:

- The number of subjects receiving all 4 doses of IP;
- The number of subjects receiving at least 80% of the planned infusion/injection volume at each visit.

A by-subject listing will be provided including:

- By infusion/injection: the randomized and actual treatment administered, planned and actual volume of IP, individual and categorized compliance;
- Overall (across all IP doses): cumulative planned and cumulative actual volume of IP, individual and categorized compliance, number of doses of IP.

Calculation of compliance and extent of exposure (as described in Section 11.1) will be based on drug accountability data collected by eCRF.

11 Safety Analyses

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

11.1 Extent of Exposure

Exposure to the IP will be descriptively summarized by treatment group:

- Number of subjects receiving loading dose;
- Summary statistics for loading dose received;
- Summary statistics for Total dose received (mg) per visit and overall;
- Summary statistics for Total volume received (ml) per visit and overall.

The listing of individual subject data will include all variables presented in the summary tables.

11.2 Adverse Events

AEs will be coded using the MedDRA dictionary (the MedDRA version will be populated in the tables output). AEs will start to be collected upon the subject's signing of the informed consent form (ICF). TEAEs, defined as AEs starting on or after the date (and time if available) of the first administration of IP (IV loading dose) through the end of the Treatment and Observation Period, will be summarized. The summary will be given by treatment group and overall. All AEs regardless of whether they were treatment-emergent or not will be listed.

Where AE start dates and/or times are missing or partially missing, AEs will be assumed to be treatment-emergent, except if the partial start dates and/or times or the AE end date and/or time indicate that the AE started before the first administration of IP (Table 2).

Table 2 TEAE Assignment in Case of Missing AE Start Date Elements

Missing elements of AE start	Rule	
Regardless of any missing information for AE start: AE end date / time < IP start date / time		non TEAE
Otherwise (ie, if AE end date / time ≥ IP start date / time)		
- all		TEAE
- day and month	AE start year ≥ IP start year	TEAE
	AE start year < IP start year	non TEAE
- day	AE start month / year ≥ IP start month / year	TEAE
	AE start month / year < IP start month / year	non TEAE
- time	AE start date ≥ IP start date	TEAE
	AE start date < IP start date	non TEAE

If AE start dates or end dates are missing or partially missing for an AE, no duration will be calculated. A missing category will be shown in summary tables by severity in case the severity is missing (the same is applicable for relationship to study treatment). No imputations for missing AE information will be done.

The AESIs defined for this study are:

- Bleeding events - Standardised MedDRA Query "Haemorrhages (SMQ)" (narrow)
- Thromboembolic events (TEE) - Standardized MedDRA Query "Embolic and thrombotic events (SMQ)" (narrow) consisting of:

  - Embolic and thrombotic events, arterial (SMQ);
  - Embolic and thrombotic events, venous (SMQ);
  - Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ).

- Severe Hypersensitivity including anaphylaxis - Standardised MedDRA Query "Hypersensitivity (SMQ)" (broad), "Anaphylactic reaction (SMQ)" (broad), and "Anaphylactic/anaphylactoid shock conditions (SMQ)" (broad). Here, broad scope includes narrow and broad search.

An overview summary of TEAEs, including number and percentages of subjects as well as the number of events will be provided including the following:

- Any TEAE;
- TEAEs related to study treatment;
- TEAEs in each severity category;
- TEAEs leading to discontinuation of study treatment (obtained from AE eCRF);
- TEAEs leading to study withdrawal (obtained from "End of Treatment" or "Conclusion of Subject Participation" eCRF);
- TEAEs leading to dose adjustments or dose interruptions;
- Treatment-emergent AESIs;
- Treatment-emergent AESIs related to study treatment;
- Serious TEAEs;
- Serious TEAEs related to study treatment;
- Fatal TEAEs.

COVID-19 associated TEAEs will be included in AE overview table as (as described in Section 7.1):

- Any TEAE (related/not related);
- Serious TEAE (related/not related);
- Fatal TEAE (related/not related);

- TEAE leading to discontinuation of study treatment (obtained from AE eCRF) (related/not related);
- TEAE leading to dose adjustments or dose interruptions (related/not related);
- TEAE leading to study withdrawal (related/not related);
- TEAE by maximum severity (mild, moderate, severe, missing).

The following frequency tables will be generated for TEAEs, including number and percentages of subjects and the number of events:

- TEAEs by SOC and preferred term;
- TEAEs by preferred term;
- TEAEs by SOC, preferred term, and maximum severity (without number of events);
- Related TEAEs by SOC and preferred term;
- Related TEAEs by preferred term;
- Treatment-emergent AESIs by preferred term;
- Serious TEAEs by SOC and preferred term;
- Related serious TEAEs by SOC and preferred term;
- TEAEs with result in drug discontinuation;
- TEAEs related to COVID-19 infection.

AEs will be presented in summaries by decreasing overall frequency (overall frequency as the number of subjects with that AE beginning with the SOC, followed by preferred term). If 2 AEs have the same overall frequency, the AEs will be ordered alphabetically.

The following by-subject listings will be provided:

- All AEs;
- SAEs;
- AEs leading to study withdrawal or permanent discontinuation of study treatment;
- AESIs by type of AESI;
- Subjects receiving COVID-19 vaccine;
- AEs occurring within 7 days after COVID-19 vaccine administration.

11.3 Clinical Laboratory Evaluations

The following hematology and serum biochemistry central laboratory tests will be summarized by visit and by treatment group. The summaries will be provided for the analysis population (Safety Analysis Set) as described in Section 11. Data for urinalysis will only be listed.

Hematology: Hematocrit, hemoglobin, platelet count, reticulocytes, erythrocytes (red blood cell count [RBC]) count, RBC indices of mean corpuscular hemoglobin concentration (MCHC); mean corpuscular hemoglobin (MCH); mean corpuscular volume (MCV); red cell (erythrocyte) distribution width (RDW), leukocyte (white blood cell count [WBC]) counts, differential (absolute and percentage) of neutrophils; neutrophil band forms, lymphocytes, monocytes, eosinophils, and basophils.

Serum Biochemistry: Sodium, potassium, chloride, bicarbonate, calcium, blood urea nitrogen (BUN), urea, creatinine, glucose, protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma-glutamyl-transferase (GGT), bilirubin (total), bilirubin (direct), magnesium, phosphate, high sensitivity-C reactive protein (hs-CRP), cholesterol, high-density Lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, urate (uric acid), creatine kinase / creatine phosphokinase (CK / CPK), activated partial thromboplastin time (aPTT), prothrombin time (PT) / international normalized ratio (PT / INR), pF1+2, fibrinogen (Clauss assay), D-dimer.

Urinalysis: Specific gravity, pH, occult blood, leukocyte esterase, nitrite, erythrocytes, ketones, bilirubin, protein, urobilinogen, glucose.

Standard safety laboratory data from central lab will be presented in international system of units (SI units) and in the order presented as above given. Measured laboratory values will be summarized descriptively by scheduled visit. Changes from baseline for laboratory parameter will be derived and presented in the same way as measured laboratory values.

A laboratory value that is outside the reference range is either high abnormal (value above the upper limit of the normal [ULN] reference range) or low abnormal (value below the lower limit of the normal [LLN] reference range). An abnormal laboratory value is not necessarily of potential clinical interest. For each of the hematology and serum biochemistry lab tests, shift tables will be constructed to compare the individual subject baseline value with respect to the normal range to their Day 92 (or last observed value prior to Day 92 in case of dropouts or missing assessment at Day 92) value with respect to the normal range.

The denominator in percentage calculation at a scheduled visit will be based on the number of subjects with a non missing value at that particular visit. The definition of the baseline assessment is given in Section 8.2.3.

A by-subject listing of all laboratory values including flag for values out of normal range will be provided. By-subject listing will include in general all visits (scheduled and unscheduled).

Immunogenicity:

The number and percentage of subjects with a positive immunogenicity test (presence of binding antibodies to CSL312) at any time and separate for Day 36 and Day 92 during treatment will be summarized by treatment group for the analysis population (Safety Analysis Set) as described in Section 11.

A by-subject listing for immunogenicity will be provided.

11.4 Other Safety Measures

11.4.1 Vital Signs

The vital signs will be summarized by visit and by treatment group. The summaries will be provided for the analysis population (Safety Analysis Set) as described in Section 11.

The following summaries will be provided for systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, weight, and BMI:

- Values of vital signs by scheduled visit,
- Change from baseline by scheduled visit.

The position of vital sign measurement and the location of body temperature measurement will be not included in the summaries, ie the summaries will be not provided by position or location.

A by-subject listing of all vital sign data (scheduled and unscheduled visits) will also be presented. The by-subject listing will include a flag for values of potential clinical importance.

11.4.2 Electrocardiogram (ECG)

The ECG parameter (PR interval, QRS duration, QT interval, QTcB, QTcF, and heart rate) and their changes from baseline will be summarized by visit and by treatment group. The

summaries will be provided for the analysis population (Safety Analysis Set) as described in Section 11.

A by-subject listing of all ECG data (scheduled and unscheduled visits) will also be presented. The by-subject listing will include a flag for values of potential clinical importance.

11.4.3 Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO)

DLCO and its changes from baseline will be summarized by visit and by treatment group. The summary will be provided for the analysis population (Safety Analysis Set) as described in Section 11.

A by-subject listing for DLCO data (scheduled and unscheduled visits) will also be presented.

11.4.4 Physical Examination

Abnormalities of physical examination reported at screening will be recorded as medical history. Abnormalities of physical examination reported at other visit will be recorded as an AE.

12 Pharmacokinetic Analyses

All noncompartmental analyses are to be performed using CSL312 plasma concentrations according to CSL SOP PK-GDL-01 and will be performed by ICON, under the direction of CSL Behring Clinical Pharmacology and Pharmacometrics, by using WinNonLin® version 8.0 or later.

The merge of PK concentration data and CRF data to generate SDTM domain PC with nominal blood sampling times, actual blood sampling time relative to dosing, actual dosing, and CSL312 plasma concentrations will be performed after DBL by Parexel. Parexel will produce the SDTM PC domain needed by ICON for PK parameter derivation.

ICON, under the direction of CSL Behring Clinical Pharmacology and Pharmacometrics, will derive the individual PK parameters and will provide them to Parexel. From this, Parexel will produce the SDTM domain PP and will generate the analysis dataset. Any CSL312 plasma concentrations which have been excluded from the derivation of the PK parameters will be flagged by ICON in SDTM PC domain and provided to Parexel.

All analyses in this section will be based on the PK Analysis Set.

12.1 Drug Concentration Measures

Handling of PK concentration data and imputation of below limit of quantification (BLQ) values for non compartmental analyses will be performed according to PK-GDL-01. The imputation rules below will be used for summary statistics of CSL312 plasma concentrations. The summaries will be given by nominal (planned) time point.

- The sampling time of pre dose samples relative to start of the dose will be treated as zero;
- Concentration values that are BLQ in pre dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;
- Post dose BLQ concentrations flanked by quantifiable concentrations will be set to missing;
- If 2 or more BLQ concentrations occur in succession, the profile will be considered to have terminated at the quantifiable concentration prior to the 2 consecutive BLQs. All subsequent values will be treated as missing;
- Post dose BLQ concentrations after the last quantifiable point will be set to missing for summary statistics of plasma concentrations;
- The mean/median value at a time point where 1 or more samples have BLQ values will be reported (in tabular or graphical fashion) even if the mean/median value is BLQ of the assay;
- Zero mean or median values will be included in summary tables.

The lower limit of quantification for CSL312 in plasma is 100.0 ng/mL. Concentrations that are below BLQ should be reported as "< LLOQ" in by-subject listings.

Summary statistics for CSL312 plasma concentration-time data will be presented as follows: number of observations (n), mean, SD, %CV (CV% = 100* standard deviation / mean), median, geometric mean, geometric %CV, minimum, and maximum.

$$\text{Geometric CV\%} = 100 * \sqrt{\exp(SD^2) - 1}.$$

In addition, summary statistics will also include the percentage of BLQ values relative to the total number of observations:

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

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

Individual CSL312 plasma concentration-time profiles (on linear and log-linear scale) will be plotted using actual sampling time.

Plots for mean (± SD) CSL312 plasma concentration-time profiles (on linear and log-linear scale) will be plotted using nominal (planned) time.

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

12.2 Deriving and Summarizing Pharmacokinetic Parameters

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

The PK parameter derivation including imputation of the values BLQ and missing data will be conducted in accordance to PK-GDL-01 which gives guidance on how to derive PK parameters in the presence of missing data. The PK parameters will be calculated by standard non-compartmental analysis using actual sampling times and actual doses.

The following PK parameters will be summarized after SC administration of CSL312 at each SC dosing interval:

Variable	**Statistical Parameters:**
C_{trough} after first, second and third SC dose; C_{max} after last SC dose; $AUC_{0\text{-}tau}$ after last SC dosing interval	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
T_{max} after last SC dose	n, minimum, median, and maximum

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

Variable	Statistical Parameters:
C_{max} C_{trough}	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
T_{max}	n, minimum, median, and maximum

All PK parameters will be reported to at least 3 significant digits, but to no more significant digits than the precision of the original data.

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

13 Pharmacodynamic and Biomarkers Analyses

Unless otherwise specified, analyses in this section will be based on the PD Analysis Set.

13.1 Pharmacodynamic Analyses

The absolute 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 Day 92 (Week 14). The change from baseline will be compared between CSL312 and placebo using a mixed-model repeated measure (MMRM) analysis, with treatment group and visit as fixed effects, and baseline as a covariate. Interactions with visit will be included for treatment group and baseline. The analysis will be implemented by using SAS PROC MIXED. 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. Mean difference in least square means (LSMeans) between treatment groups and its 95% confidence interval will be provided at each time point, assuming that the data is normally distributed. If the data are not normally distributed by visual inspection of residual plots (QQ plots), an appropriate data transformation, log transformation, may be done.

FXIIa-mediated kallikrein activity will be summarized by nominal time point with the following descriptive statistics: n, mean, SD, %CV, minimum, Q1, median, Q3, maximum, geometric mean, geometric %CV, and percent below the limit of quantification (% BLQ).

Individual observed FXIIa-mediated kallikrein activity-time profiles will be plotted using actual sampling times. Mean (± SD) observed FXIIa-mediated kallikrein activity-time profiles will be plotted by using nominal (planned) time points.

The absolute change from baseline, percent change from baseline, and percent of baseline of FXIIa-mediated kallikrein activity over time will be summarized using descriptive statistics as done for the observed values of FXIIa-mediated kallikrein activity. The absolute change from baseline and percent of baseline of FXIIa-mediated kallikrein activity will also be presented graphically by treatment group as done for the observed FXIIa-mediated kallikrein activity.

Other observed PD parameter of FXII concentration will be summarized by nominal time point by descriptive statistics (n, mean, SD, %CV, minimum, Q1, median, Q3, maximum, geometric mean, geometric %CV). The absolute and percent change from baseline for those PD parameters will also be summarized by nominal time point by descriptive statistics. For all PD parameters, including aPTT, the absolute changes from baseline will be analyzed by the MMRM as described for FXIIa-mediated kallikrein activity.

Individual observed PD parameter time profiles will be plotted using actual sampling times. Mean (± SD) observed PD parameter time profiles will be plotted by using nominal (planned) time points.

A by-subject listing of PD parameters including observed values, absolute and percent change from baseline will be provided.

13.2 Biomarker Analyses

For biomarkers the observed values, the absolute and percent change from baseline will be summarized by nominal time point by descriptive statistics (n, mean, SD, %CV, minimum, Q1, median, Q3, maximum, geometric mean, geometric %CV). The MMRM as described for FXIIa-mediated kallikrein activity is also applicable for all biomarkers and aPTT (absolute change from baseline for each).

Individual observed biomarker time profiles will be plotted using actual sampling times. Mean (± SD) observed biomarker time profiles will be plotted by using nominal (planned) time points.

Biomarker: C-C motif chemokine ligand 18 (CCL-18), plasminogen activator inhibitor 1 (PAI-1), surfactant protein A (SP-A), surfactant protein D (SP-D), YKL-40, released N

terminal pro-peptide of type III collagen (PROC3), C terminal of released C5 domain of type VI collagen (PROC6), neo-epitope of MMP-9 mediated degradation of type III collagen (C3M), neo-epitope of MMP-2 mediated degradation of type VI collagen (C6M).

A by-subject listing of biomarkers including observed values, absolute and percent change from baseline will be provided.

Additional exploratory biomarker analyses, if deemed necessary, will be reported in a separate report.

13.2.1 Pulmonary Function Data Analyses

The Safety Analysis Set will be used for this analysis.

The absolute change from baseline in FVC and percent predicted FVC over time will be analyzed using the same MMRM as for FXIIa-mediated kallikrein activity, 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 in LSMeans between treatment groups and its 95% confidence interval will be provided at each time point, assuming that the data is normally distributed. If the data are not normally distributed by visual inspection of residual plots or statistical testing, an appropriate data transformation may be done. There is no imputation of missing FVC data planned.

For FVC and percent predicted FVC the observed values and absolute change from baseline will be summarized by nominal time point by descriptive statistics (n, mean, SD, minimum, Q1, median, Q3, maximum). The descriptive summary for both parameter will be provided for Safety Analysis Set and PD Analysis Set.

Mean (± SD) time profiles for observed values and absolute change from baseline for FVC and percent predicted FVC will be plotted by using nominal (planned) time points.

The number and proportion of subjects with ≥ 5% or ≥ 10% absolute (absolute change from baseline) or relative (percent change from baseline) decline in FVC percent predicted at Day 92 will be presented.

The absolute change from baseline in FVC at Day 92 versus the absolute change from baseline in FXIIa-mediated kallikrein activity at Day 92 will be graphically displayed by a scatter plot. The Pearson correlation coefficient and Spearman correlation coefficient by treatment group will displayed. Those scatter plots of absolute change in FVC at Day 92 versus the absolute change at Day 92 will be repeated for all PD parameter (FXII

concentration and aPTT) and biomarkers (CCL-18, PAI-1, SP-A, SP-D, YKL-40, PROC3, PROC6, C3M, C6M).

A second series of those scatter plots will be provided by using the percent change from baseline in FVC at Day 92 versus the percent change from baseline in PD parameter (FXIIa-mediated kallikrein activity, FXII concentration, aPTT) and biomarkers (CCL-18, PAI-1, SP-A, SP-D, YKL-40, PROC3, PROC6, C3M, C6M) at Day 92.

A third series of those scatter plots will be provided by using the absolute change in FVC percent predicted at Day 92 versus the absolute change from baseline in PD parameter (FXIIa-mediated kallikrein activity, FXII concentration, aPTT) and biomarkers (CCL-18, PAI-1, SP-A, SP-D, YKL-40, PROC3, PROC6, C3M, C6M) at Day 92.

A by-subject listing of FVC and percent predicted FVC including observed values, absolute and percent change from baseline will be provided.

14 References

(1) PK-GDL-01, Guideline on the Conduct of Noncompartmental Pharmacokinetic Analyses, CSL Behring.

15 Appendices

15.1 Pharmacokinetic Parameters

Term	Definition [unit]	Calculation method
$AUC_{0\text{-}tau}$	AUC during a dosing interval (tau) [mass * time * volume^{-1}]	Partial AUC from dosing time to dosing time plus Tau, using the linear up/log down rule
C_{max}	Maximum observed in plasma [mass * volume^{-1}]	
C_{trough}	Observed concentration at the end of a dosing interval, immediately before the next dose administration [mass * volume^{-1}]	
T_{max}	Time to reach maximum (peak) drug concentration in plasma [time]	

Signature Page

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Signed By	Date (GMT)
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