

Statistical Analysis Plan

A Multicenter, Randomized, Open-label, Crossover, Phase 2 Study to Evaluate the Safety and Pharmacokinetics of IgPro20 (subcutaneous immunoglobulin, Hizentra®) and IgPro10 (intravenous immunoglobulin, Privigen®) in Adults with Systemic Sclerosis (SSc)

Investigational Medicinal Products: IgPro20, IgPro10

Protocol Number: IgPro20_2001

Version: 2.0

Version Date: 09 NOV 2021

Sponsor:

CSL Behring LLC

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1 Modification History

Ver- sion	Effective Date	Author of Modification	Reason for Change
1.0	17 Dec 2019	PPD	N/A – New document.
2.0	09 Nov 2021	PPD	<ul style="list-style-type: none"> • Minor editorial changes • Signature page adapted to new electronic signature process • Major PD -> Key PD • Section 3: Document versions updated • Glossary: Infusion terminology clarified. • Section 4.6/ 5: Interim Analysis: Changed timing and purpose (change from CSP), specification added • Section 6: SAF-IgPro10 and SAF-IgPro20 added • Section 6: PP-IgPro10 and PP-IgPro20 added, PK analysis set removed • Section 7.4 (COVID-19 Impact) added • Section 8.1.2: Imputation rules for Concomitant Medication changed • Section 8.2.3: Duration of AE and Time to Onset from last infusion is expressed in minutes • Section 8.2.3: Duration since SSc history event added • Section 8.2.9 and 10.1: CCI response added • Section 8.2.13: 'Other aids' can now be assigned to an activity • Section 8.2.13: Screenshots for CCI CCI added • Section 8.3.2: Categorization of Concomitant Medications takes now start and end times into account • Section 8.4.2: Deleted "two consecutive visits" for vital signs and CCI • Section 9: Clarification of handling of re-screened subjects • Section 9.1: List of parameters re-arranged • Section 9.3: Auto-antibodies at baseline added • Section 9.3/9.4: Summaries for background therapy/ immunosuppressants at baseline added

Ver- sion	Effective Date	Author of Modification	Reason for Change
			<ul style="list-style-type: none"> • Section 9.4: Changed categories of Prior/ Concomitant Medications • Section 9.4: Summary added for concomitant medications used to treat COVID-19 associated adverse events • Section 10.1: Clarify that bootstrap method will be used to derive confidence intervals. • Section 11.1: Addition of parameters for IgPro10 • Section 11.1: Separated "Duration" into "Duration of infusion" and "Duration of Treatment" to avoid confusion • Section 11.2: Replaced "Treatment-emergent AESIs by Category, PT and grade" by "... maximum grade (without number of events)" • Section 11.2: "Injection site reaction" added to the list of HLTs to find "Infusion site reactions" • Section 11.2: Clarification of calculations for ISR • Section 11.2: Listing of TEAEs leading to permanent discontinuation of IP added • Section 11.2: Due to expected low number of events: no summary of SAE and TEAEs leading to permanent discontinuation of IP by treatment sequence • Section 12: PK analysis will be done on SAF; sensitivity analysis added for bioavailability • Section 12.2, Table 9: Reference interval for Tmax/Cmax ends at AH10/BH21 • Section 12.3: "baseline-corrected AUC " is used for bioavailability. Bioavailability will be additionally assessed by Treatment Sequence. • Section 12.3: Subject as a random effect will be dropped from the MMRM

2 List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADaM	Analysis data model
AE	Adverse event
AMS	Aseptic meningitis syndrome
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUC _{0-last}	AUC from time point zero to the last quantifiable time point
AUC _{0-tau}	AUC from time point zero to tau
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
CM	Concomitant medication
C _{max}	Maximum concentration
CCI	CCI
C _{trough}	Trough concentration
DRM	Data review meeting
dcSSc	Diffuse cutaneous systemic sclerosis
CCI	CCI
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EOS	End of study
EULAR	European League Against Rheumatism
FAS	Full analysis set
CCI	CCI
CCI	CCI
HIV	Human immunodeficiency index
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IP	Investigational product
IRT	Interactive response technology

Abbreviation	Definition
ISR	Infusion site reaction
ITP	Immune thrombocytopenic purpura
IV	Intravenous
lcSSc	Limited cutaneous systemic sclerosis
LLN	Lower limit of normal
CCI	CCI
MedDRA	Medical Dictionary for Regulatory Activities
CCI	CCI
PFT	Pulmonary function test
CCI	CCI
PID	Primary immunodeficiency
PK	Pharmacokinetics
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
CCI	CCI
SMQ	Standardized MedDRA queries
SOC	System Organ Class
SSc	Systemic sclerosis
CCI	CCI
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
CCI	CCI
ULN	Upper limit of normal
CCI	CCI

Glossary of Terms

Term	Definition
Baseline Value	The most recent assessment before the first infusion in Treatment Period 1.
End of Study (EOS)	The follow-up telephone call occurs 4 weeks after completing study treatment or early termination follow-up visit, whichever occurs later.
End of Treatment (EOT)	End of treatment is either end of Week 32 for completed subjects or at early termination visit.
Infusion	<p>IgPro10 An infusion comprises all IP exposure on one day of infusion. In the IgPro10 Treatment Periods, there are 2 to 5 consecutive days of infusions and so 2 to 5 Infusions planned per 4-week period.</p> <p>IgPro20 An infusion comprises all IP exposure on one day (one session). In the IgPro20 Treatment Periods, there are 2 sessions and so 2 infusions planned per week.</p>
Infusion Cycle (IgPro10 only)	One Infusion Cycle consists of 2, 3, 4 or 5 consecutive days of infusions with a planned total dose of 2 g/kg IgPro10 every 4 weeks. There are 4 planned Infusion Cycles of IgPro10 per IgPro10 Treatment Period in each Treatment Sequence.
Weekly Infusions (IgPro20 only)	A Weekly Infusion consists of 2 sessions (2 Infusions) with a planned total dose of 0.5 g/kg IgPro20 per week. There are 14 Weekly Infusions of IgPro20 per IgPro20 Treatment Period per each Treatment Sequence.
Infusion Session (IgPro20 only)	One Infusion Session consists of 1 infusion day. There are 2 Infusion Sessions within each weekly infusion with a planned total dose of 0.5 g/kg IgPro20 per week.
Protocol Deviation	<p>All instances when either subjects who have been entered in the study and / or the study sites deviate from the IEC / IRB-approved study protocol.</p> <p>A key protocol deviation is any protocol deviation that could have a significant effect on the subject's safety, rights, or welfare and / or on the integrity of the study data.</p>
Reference Visit	Reference visit for Treatment Period 1 is Week 1. Reference visit for Treatment Period 2 is Week 17.
Treatment Sequence	The study will consist of 2 Treatment Sequences, Treatment Sequence A or Treatment Sequence B. Each subject will be randomized to 1 of the 2 Treatment Sequences.

Term	Definition
Treatment Sequence A	IgPro20 0.5 g/kg/week subcutaneous (SC) infusion in Treatment Period 1 + IgPro10 2 g/kg/4 weeks intravenous (IV) infusion in Treatment Period 2.
Treatment Sequence B	IgPro10 2 g/kg/4 weeks IV infusion in Treatment Period 1 + IgPro20 0.5 g/kg/week SC infusion in Treatment Period 2.
Treatment	Treatment will be either IgPro20 0.5 g/kg/week or IgPro10 2 g/kg/4 weeks.

3 Purpose

This statistical analysis plan (SAP) provides a detailed and complete description of the planned statistical analyses for the final analysis of the study IgPro20_2001 to support the Clinical Study Report. Mock tables, listings, and figures shells are provided in separate supporting documents.

This SAP complies with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials. It is based upon the following study documents:

- Case Report Form (CRF), version 10 (27 Jul 2021)
- Clinical Study Protocol, Amendment 4 (22 Feb 2021)
- Data Transfer Specification Respiratory, version 3.0 (09 May 2019)
- Data Transfer Specification eCOA, version 1.0 (05 Jun 2019)
- Data Transfer Specification ICON lab services, version 7.0 (06 May 2020)
- Data Transfer Specification ECG, version 2.0 (01 Apr 2019)
- Data Transfer Specification PK, version 1.0 (02 Sep 2020)

All decisions regarding the final analysis of the study results, as defined in this SAP document, have been made prior to Database Lock of the study data.

The PK/PD and biomarker analysis will be described and reported outside the scope of this SAP (within a separate document/report).

4 Study Design

4.1 Study Design

This is a prospective, multicenter, randomized, open-label, crossover study to investigate the safety and PK of IgPro20 and IgPro10 in patients with diffuse cutaneous systemic sclerosis (dcSSc). The PK portion of the study aims to evaluate the relative bioavailability of IgPro20, and characterize the PK of IgPro20 and IgPro10, respectively, in patients with dcSSc.

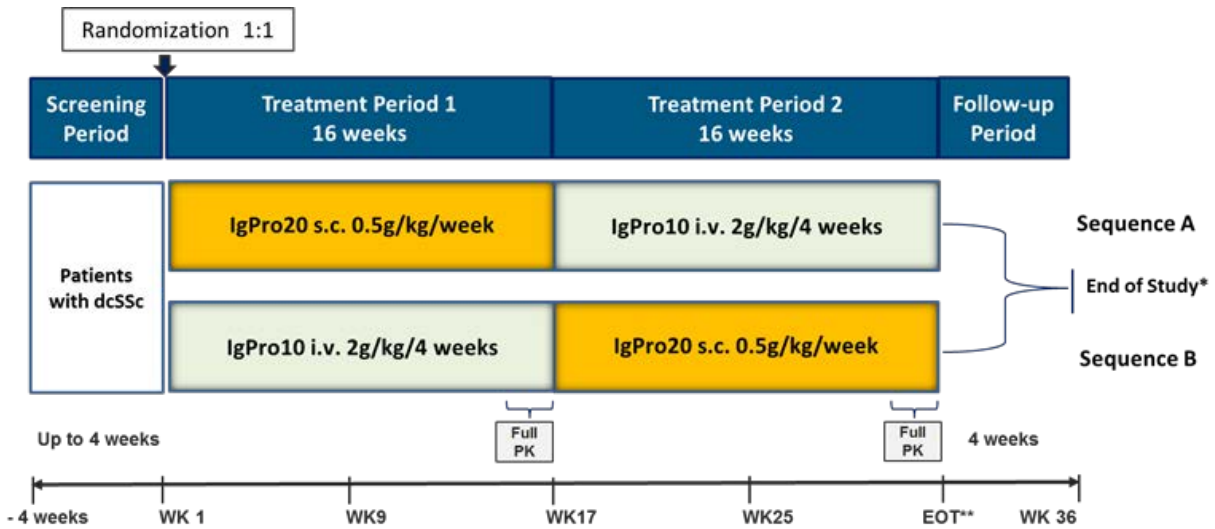
The study design is illustrated in [Figure 1](#). Patients with a diagnosis of dcSSc with disease duration ≤ 5 years and skin thickness scores of ≥ 15 to ≤ 45 as measured by **CCI** will be eligible to enroll in the study. All eligible subjects will be randomized (1:1) to Treatment Sequence A (IgPro20-IgPro10 Treatment Sequence) or Treatment Sequence B (IgPro10-IgPro20 Treatment Sequence). Each subject will complete Treatment Period 1 and Treatment Period 2 (16 weeks each), with up to 40 weeks (including Screening) of study duration for an individual subject.

In this crossover study, subjects in Treatment Sequence A will receive a total dose of 0.5 g/kg IgPro20 over 2 infusions per week every week in Treatment Period 1, and a total dose of 2 g/kg IgPro10 over 2 to 5 consecutive days every 4 weeks in Treatment Period 2. Subjects in Treatment Sequence B will receive a total dose of 2 g/kg IgPro10 over 2 to 5 consecutive days every 4 weeks in Treatment Period 1 and a total dose of 0.5 g/kg IgPro20 over 2 infusions per week every week in Treatment Period 2. Subjects weighing ≥ 100 kg will receive a fixed dose of 50 g IgPro20 every week, or 200 g IgPro10 every 4 weeks, respectively.

The dose of IgPro20 at 0.5 g/kg body weight weekly is equivalent to 2 g/kg body weight every 4 week dosing of IgPro10 if using 1:1 conversion and is the highest possible SC IgPro20 dose due to infusion volume limitation and potential safety concerns in subjects with SSs. As defined in the protocol, certain concomitant medications, below defined maximum doses, will be allowed for the treatment of dcSSc.

All subjects who complete the study or discontinue early will have a follow-up visit approximately 4 weeks after the last dose is administered.

Figure 1: Study Design



* Follow-up visit at the end of study approximately 4 weeks after the last dose administration

**EOT: The treatment period 2 stops at the end of Week 32

4.2 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety of IgPro20 in adults with dcSSc	<ul style="list-style-type: none"> Number and percentage of subjects treatment-emergent AEs (TEAEs), serious AEs (SAEs), and AEs of special interest (AESIs) (total, by severity, by causal relationship) Number and percentage of subjects with AEs categorized as infusion site reactions (ISRs) (total, by severity, by causal relationship) Rate of ISRs per subject and per Infusion Onset and duration of ISRs Changes from baseline in vital signs and body weight, clinical laboratory tests, electrocardiogram (ECG), and pulmonary function tests (PFTs)

Objectives	Endpoints
Secondary	
<p>To evaluate:</p> <ul style="list-style-type: none"> • Relative bioavailability of IgPro20 • PK of IgPro20 • PK of IgPro10 • Safety of IgPro10 	<ul style="list-style-type: none"> • IgPro20 relative bioavailability (%F) • IgPro20 PK parameters (area under the curve [AUC]_{0-tau}, AUC_{0-last}, maximum [peak] plasma drug concentration [C_{max}], trough plasma drug concentration [C_{trough}]) • IgPro10 PK parameters (AUC_{0-tau}, AUC_{0-last}, C_{max}, C_{trough}) • The safety of IgPro10 based on: <ul style="list-style-type: none"> ○ Number and percentage of subjects with TEAEs, SAEs, AESIs, and ISR (total, by severity, by causal relationship) ○ Changes from baseline in vital signs and body weight, clinical laboratory tests, ECG, and PFTs
<p>CCI</p> <ul style="list-style-type: none"> • CCI • • • • • • 	<ul style="list-style-type: none"> • CCI • • • • • •

4.3 Study Treatments

IgPro20 is a ready-to-use 20% liquid formulation of human IgG with > 98% IgG purity for SC administration, and is manufactured by CSL Behring (CSLB). IgPro20 is approved in the

United States of America (US), the European Union (EU), and other countries under the brand name Hizentra[®] for SC application in primary immune deficiency syndromes and other indications.

IgPro10 is a ready-to-use 10% liquid formulation of IgG with > 98% IgG purity for IV administration, and is manufactured by CSLB. The protein moiety of IgPro10 is approved in the US under the brand name Privigen[®] for the treatment of primary immunodeficiency (PID) in patients ≥ 3 years of age, for CIDP in adults, and for chronic immune thrombocytopenic purpura for patients ≥ 15 years of age. In addition, Privigen is approved for the treatment of CIDP in the adult and pediatric populations in the EU, Switzerland, Canada, and other countries.

4.4 Randomization Procedures and Blinding

Eligible subjects will be randomized in a 1:1 ratio by means of Interactive Response Technology (IRT) to one of the following Treatment Sequences:

- IgPro20 0.5 g/kg/week for 16 weeks followed by IgPro10 2 g/kg/ 4 weeks for 16 weeks (Treatment Sequence A)
- IgPro10 2 g/kg/ 4 weeks for 16 weeks followed by IgPro20 0.5 g/kg/week for 16 weeks (Treatment Sequence B).

The randomization list will be generated by the IRT external service provider according to the approved randomization specifications. The IRT external service provider will keep the randomization code on file.

This is an open-label study, blinding procedures are not applicable.

4.5 Determination of the Sample Size

The sample size for this study is not determined as based on hypothesis testing considerations. The sample size is mainly based on feasibility, not driven by power calculations for statistical hypothesis testing. However, based on the 9 IgPro20 studies completed by CSLB (8 studies on PID and 1 study in CIDP), the rate of ISRs per IgPro20 infusion is expected to be approximately 0.1, with 0.5 likely to be the maximum. With the target sample size of 20 subjects (10 subjects per Treatment Sequence) and each subject receiving 28 IgPro20 SC infusions, there are a total of 560 planned IgPro20 infusions overall

for the entire study. If the rate of ISRs per infusion is 0.1, the study will have 80% chance to have a 95% CI with half width ≤ 0.0261 using Wilson score method; if the rate is 0.5, the half width of the 95% CI will be ≤ 0.0414 .

4.6 Interim Analyses Other Than Sample Size Re-estimation

An interim analysis is planned after 10 subjects have completed at least 8 weeks of IgPro20 treatment in either Treatment Period for the purposes of safety review and bioavailability.

The tables produced for the interim analysis will be a subset of the tables for the final analysis. No changes to the tables for the special purpose of the interim analysis will be done. Tables to be produced are marked in a separate document.

4.7 Interim Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

5 Changes in the Conduct of Planned Analyses

The primary endpoint (CSP 2.1.2) requests to summarize AEs, TEAEs, AESIs, and SAEs in total and by severity and causality. In deviation to this, the summary of AEs will be restricted to TEAEs only.

In section CSP 2.2.2 “Secondary Endpoints” C_{trough} is defined as “minimum plasma drug concentration”. This is corrected to “trough plasma drug concentration”.

In section CSP 10.3.2.1 “Safety of IgPro20” 95% confidence intervals (CI) are requested for the rate of ISR per subject and per infusion. The CIs for the rate of ISR per infusion will not be calculated as the infusions are not statistically independent.

The Full Analysis Set (section CSP 10.2.1) is renamed to ITT Analysis Set, and the description was reworded for clarity. The definition of the set is not changed.

Section 10.4.2 of the CSP (Interim Analysis) states:

"An interim analysis is planned after all subjects randomized to Sequence A have finished IgPro20 treatment (Treatment Period 1). This interim analysis is planned for safety review and reporting."

The timing and purpose of the Interim Analysis has changed (see Section 4.6 of this SAP).

CSP section 10.3.3.1 requires "... subject as a random effect ..." in the model to assess relative bioavailability. This effect will not be applied.

6 Study Analysis Sets

6.1 Screened Analysis Set (SCR)

The SCR will comprise all subjects who provide informed consent/assent and who underwent study screening procedures.

6.2 Intent to Treat (ITT) Analysis Set

The ITT analysis set will include all subjects who are randomized, regardless of whether they received treatment.

6.3 Safety Analysis Set (SAF)

The SAF will comprise all subjects who receive at least 1 partial infusion of IgPro20 or IgPro10.

6.4 Safety Analysis Set IgPro10 (SAF-IgPro10)

The SAF-IgPro10 will comprise all subjects who receive at least 1 partial infusion of IgPro10.

6.5 Safety Analysis Set IgPro20 (SAF-IgPro20)

The SAF-IgPro20 will comprise all subjects who receive at least 1 partial infusion of IgPro20.

6.6 Per Protocol Analysis Set IgPro10 (PP-IgPro10)

The PP-IgPro10 will comprise all subjects for whom the dose-normalized baseline-corrected $AUC_{0-\tau}$ can be derived for the IgPro10 treatment period. Reasons for exclusion from the PP-IgPro10 (eg, potentially confounding concomitant medication or key protocol deviations) will be assessed case-by-base before database lock in the Data Review Meeting (DRM).

6.7 Per Protocol Analysis Set IgPro20 (PP-IgPro20)

The PP-IgPro20 will comprise all subjects for whom the dose-normalized baseline-corrected AUC_{0-tau} can be derived for the IgPro20 treatment period. Reasons for exclusion from the PP-IgPro20 (eg, potentially confounding concomitant medication or key protocol deviations) will be assessed case-by-base before database lock in the DRM.

7 General Considerations

Analysis datasets will be created according to CDISC standards, and data will be displayed according to reporting standards in this SAP.

SAS version 9.3 or higher will be used to perform all data analyses and to generate tables, figures, and listings.

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, Q1, Q3, minimum and maximum. Other descriptive statistics (eg, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Additional statistical parameters will be defined together with analyses for which they are needed. Summaries of continuous variables that have some values recorded using approximate values (eg, < or >) will use the numeric part of the value in calculations. Listings will present the data in its original format.

All listings will include subject number, Treatment Sequence, Treatment Period, and basic demographics (age and sex).

Summary statistics of central tendency will be reported to one more decimal place than the collected data. Summary statistics of variability will be reported to one more decimal place than the commensurate measure of central tendency. For example, the mean and median for age will be reported to one decimal place because it is collected in full years. The standard deviation of age will then be reported to 2 decimal places.

Formatting for dates and times will be:

- Dates only – ddmmmyyyy (e.g., 03MAR2019)
- Times only – hh:mm or hh:mm:ss (as appropriate)
- Dates and times – ddmmmyyyy hh:mm or ddmmmyyyy hh:mm:ss (as appropriate)

Unless otherwise stated, all listings will be sorted by Treatment Sequence, Treatment Period, subject number, and then by visit date. If any of these variables do not apply to a listing, then that listing will use only those that do in the order given here.

Generally, only pre-specified planned times will be used in the summaries, statistical analyses, and calculations of any derived parameters; unscheduled readings will be included in the listings.

Actual, rather than planned, sampling times will be used in the derivation of PK parameters and in the individual concentration-time plots and listing of PK concentration data. Planned times will be used in the descriptive summaries and in mean plots. Concentration-time data will be listed according to actual sampling times relative to dosing time.

Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.

Deviations from the analyses in this SAP will be identified in the CSR.

7.1 Multicenter Studies

Data from all participating sites will be pooled prior to analysis. However, a summary of subject disposition by country will be produced.

7.2 Treatment Descriptors

Displays will be grouped by treatment (IgPro20, IgPro10), Treatment Sequence (Treatment Sequence A, Treatment Sequence B), Treatment Period (Treatment Period 1, Treatment Period 2) if applicable, and / or combinations. All outputs (tables, listings, and figures) will contain all elements to uniquely identify the level of aggregation.

A total column is added for selected displays as indicated in the display mock-ups.

7.3 Multiple Comparisons and Multiplicity

There is no statistical hypothesis testing for this study thus there is no adjustment for multiple comparisons or multiplicity.

7.4 COVID-19 Impact

During the course of this study, the global COVID-19 pandemic occurred, impacting the study in a variety of ways. This section describes how the 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 be assessed at the DRM whether it is considered associated with 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 adverse events will then be identified based on whether the MedDRA code for the AE is included in the broad COVID-19 standard MedDRA query (SMQ).

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

Demographic and Baseline Characteristics

As only 3 subjects have been enrolled prior to the COVID-19 pandemic onset, demographic and baseline characteristics will not be summarized by COVID-19 period, ie before and after pandemic onset. COVID-19 pandemic onset will be considered to be 04-Mar-2020, the date of the first positive SARS-CoV-2 test in Poland (only Polish sites in the study by that date).

Subjects with enrollment date after the pandemic onset will be flagged in the listings of demographic and baseline characteristics.

Concomitant Medications

For concomitant medications which are linked to specific adverse events, the eCRF collects information to identify the specific adverse event. As described in the Adverse Events section, relevant adverse events will be identified by broad COVID-19 SMQ.

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

Adverse Events

Adverse events associated with COVID-19, which can include a clinically significant laboratory finding like a positive test result for COVID-19, will be reported by investigators. COVID-19 associated adverse events are identified via MedDRA coding. Relevant adverse events will be identified for reporting by the broad COVID-19 standard MedDRA query (SMQ). All COVID-19 associated adverse events will be included in standard AE tables.

An overview summary table of COVID-19 associated treatment-emergent adverse events (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)
- Any serious TEAE (related/not related)
- TEAE resulting in death (related/not related)
- TEAE leading to permanent discontinuation of IP (related/not related)
- TEAE leading to interruption of IP (related/not related)
- TEAE leading to withdrawal from study (related/not related)
- TEAE by severity (mild, moderate, severe, missing)

A listing showing all COVID-19 associated adverse events will be provided.

A descriptive table will be generated for all COVID-19 associated TEAEs by PT, including number of subjects, percentages of subjects, and the number of events.

COVID-19 Vaccinations

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. Standardised Drug Grouping (SDG) from WHO Drug Dictionary will be utilized to identify COVID-19 vaccines using the narrow SDG 'Vaccines for COVID-19'.

For subjects receiving COVID-19 vaccination during the study all treatment-emergent adverse events occurring within 7 days of COVID-10 vaccination will be summarized by System Organ Class and preferred term.

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, number of subjects with missed visits or alternate visit modality, by visit, will be summarized. Data will be listed.

Missing assessment to be evaluated:

- Clinical laboratory tests
- ECG
- Pulmonary function tests
- Vital signs
- Body weight
- CCI components
 - CCI
 - CCI
 - CCI
 - CCI
 - CCI
- TEE Safety assessment
- Hemolysis assessment

Alternate visit modality:

- Visits without "Visit Status" form are considered performed as planned.
- Missing visits without "Visit Status" form are considered not missing due to COVID-19.
- Unscheduled visits cannot have alternate visit modality.

- In protocol, there are ‘Site Visits’, ‘Home Visits’, ‘Telephone Call’, and mixed ‘Site/ Home Visits’. Only site visits and some home visits are captured in eCRF using a visit form. Most home visits and the telephone call at EOS do not have a visit form, and consequently cannot have an alternate visit modality.

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. Pandemic related protocol deviations are identified within CTMS using the term ‘Epidemic/Pandemic’ in column ‘Caused by Business Continuity Issue?’.

All COVID-19 related protocol deviations will appear in the listing of protocol deviations and will be flagged.

Missed Doses

Missed doses due to COVID-19 are identified using the Protocol Deviation tracker.

Overview of COVID-19 Impact

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

- Subjects with Any COVID-19 Impact
- Protocol Deviations (key and non-key)
- Missed Doses
- Missing Assessment
- Missing Visit
- Alternate Visit Modality
- Study Treatment Discontinuation (by period)
- Study Discontinuation
- Any AEs/TEAEs
- Any Serious AEs/TEAEs
- Received COVID-19 Vaccine
- Concomitant Medications Received for Treatment of COVID-19

8 Data Handling Conventions

8.1 Missing Data

8.1.1 Imputation of Non-Date Missing Data

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

Subjects with the designation of treatment relationship for AEs and SAEs missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”. There will be no other imputation for missing data other than as described in Section 8.1.2 for partial dates and times.

In the event that the study is terminated, all available data will be listed and a review carried out by the study team to assess which statistical analyses are to be performed.

8.1.2 Imputation of Partial Dates

Imputed dates will not be used to derive study day, duration, or elapsed time variables if not stated otherwise. Dates will be displayed in listings as recorded in the CRF.

Partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the data set that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D = 'Day': indicates that the day portion of the date is imputed

M = 'Month': indicates that the month and day portions of the date are imputed

Y = 'Year': indicates that the entire date (year, month, and day) is imputed

Adverse Events

Imputations in the adverse events dataset are used for slotting events to the appropriate study periods and for sorting in data listings. If an AE start or end date is missing, then the duration of the AE will be set to missing.

In general, an incomplete AE start date will be imputed such that the event starts as early as possible after the first IP infusion, irrespective of actual treatment.

Date	Missing Element	Rule
Start Date	day, month, and year	Do not impute completely missing AE start dates. The AE will be deemed treatment-emergent if the AE end date does not indicate that the AE ended prior to study treatment start date.
	day, month only	<ul style="list-style-type: none"> • If the study treatment start date is not missing: <ul style="list-style-type: none"> • If the year of AE start date is the same as the year of study treatment start date • If the AE end date indicates the AE ended prior to study treatment start date then set AE month and day to January 1 • Otherwise set month and day of AE start date to study treatment start date • If the study treatment start date is missing then set month and day of AE start date to January 1.
	day only	<ul style="list-style-type: none"> • If the study treatment start date is not missing: <ul style="list-style-type: none"> • If the month and year of AE start date is the same as the month and year of study treatment start date • If the AE end date indicates the AE ended prior to study treatment start date then set day of AE start date to the 1st of the month • Otherwise set day of AE start date to study treatment start date • If the study treatment start date is missing then set day of AE start date to 1st day of the month of AE start date.
End Date	any date element	No imputation for completely or partially missing AE end dates; the AE duration will be set to missing.

Medical History

End dates of Medical History are used to differentiate between past and current medical condition. If a partial end date is possibly after first IP intake the MH will be considered concomitant.

Date	Missing Element	Rule
Start Date	any date element	No imputation for completely or partially missing start dates
End Date	day, month, and year	Do not impute completely missing MH end dates. The MH will be deemed “concomitant”.
	day, month only	Set the end date to December 31.
	day only	Set the end date to the end of the month.

Concomitant Medication

Start and end dates will be imputed for use to derive the reference variables for concomitant medication start and end relative to treatment; any imputed dates will be included in analysis datasets with an identifier as imputed. The reference variables will be used to differentiate before, during and after treatment for the concomitant medication.

In general, an incomplete CM start date will be imputed such that the medication starts as early as possible after the first IP infusion, irrespective of actual treatment.

Date	Missing Element	Rule
Start Date	day, month, and year	Do not impute completely missing concomitant medication start dates; all values that depend on this date will be set to missing
	day, month only	<ul style="list-style-type: none"> If the study treatment start date is not missing: <ul style="list-style-type: none"> If the year of CM start date is the same as the year of study treatment start date <ul style="list-style-type: none"> If the CM end date indicates the CM ended prior to study treatment start date then set CM month and day to January 1 Otherwise set month and day of CM start date to study treatment start date If the study treatment start date is missing then set month and day of CM start date to January 1.
	day only	<ul style="list-style-type: none"> If the study treatment start date is not missing: <ul style="list-style-type: none"> If the month and year of CM start date is the same as the month and year of study treatment start date <ul style="list-style-type: none"> If the CM end date indicates the CM ended prior to study treatment start date then set day of CM start date to the 1st of the month Otherwise set day of CM start date to study treatment start date If the study treatment start date is missing then set day of CM start date to 1st day of the month of CM start date.

Date	Missing Element	Rule
	time	If the (imputed) start date of the medication is equal to the date of the study treatment start date, then set start time of medication to time of first study treatment start. Otherwise set to 00:00.
End Date	day, month, and year	Do not impute completely missing concomitant medication start dates; all values that depend on this date will be set to missing
	day, month only	If partial end date contains year only, set end date to the earliest of December 31 and the last visit in the study.
	day only	If the partial end date contains month and year, set the end date to the earliest of the last day of the end month reported and the last visit in the study.
	time	If the (imputed) end date is not missing then set to 23:59

8.2 Derived Variables

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

8.2.1 Reference Dates

Reference date for Treatment Period 1 is first infusion date of Week 1 Visit. Reference date for Treatment Period 2 is the first infusion date of Week 17 Visit.

8.2.2 Study Day

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

8.2.3 Time to Event Variables and Durations

The following durations are calculated:

- Time to onset of AE from start of last infusion prior to onset of AE (minutes)

$$\text{Time to onset of AE from start of last infusion time} = \frac{(\text{start date/time of AE} - \text{start date/time of most recent infusion})}{60}$$

If the start time of an AE is missing, the time to onset of AE from last infusion will be missing.

- Time to onset of AE from start of corresponding Treatment Period (days)

$$\text{Time to onset of AE from start of corresponding Treatment Period} = \text{start date of AE} - \text{start date of first infusion of Treatment Period} + 1$$

- Duration of AE (minutes)

$$\text{Duration of AE} = (\text{end date/time of AE} - \text{start date/time of AE})$$

If the start time or the end time of the AE is missing, the duration of the AE will be missing.

- Duration of Exposure (days)

$$\text{Duration of Exposure (Overall)} = \text{start date of first IP infusion} - \text{end date of last IP infusion} + 1$$

$$\text{Duration of Exposure (IgPro10)} = \text{start date of first infusion of IgPro10} - \text{end date of last infusion of IgPro10} + 1$$

$$\text{Duration of Exposure (IgPro20)} = \text{start date of first infusion of IgPro20} - \text{end date of last infusion of IgPro20} + 1$$

- Duration since *SSc history event* (months)

$$\text{Duration} = (\text{start date of first IP infusion} - \text{imputed date of } SSc \text{ history event}) / 30.4375$$

where *SSc history event* is Date of Diagnosis of SSc, Date of first Raynaud's phenomenon, and Date of first non-Raynaud's phenomenon.

If only the year of the event date is reported, the event date will be imputed by July, 1st of that year. If only year and month of the event date is reported, the event date will be imputed by the 15th of that month.

When reporting durations in months, the number of days will be divided by 30.4375; to report in weeks the number of days will be divided by 7; to report in years the number of days will be divided by 365.25.

8.2.4 Baseline Definition

Baseline is defined as the most recent, non-missing value prior to the start date and time of the first study treatment infusion. Results from unscheduled visits will be taken into account.

If date is given for an assessment only and the time is missing, and the date of the assessment is the same as the date of the first study treatment infusion then this assessment is NOT considered baseline.

8.2.5 Change from Baseline or Reference Visit

Change from baseline will only be calculated for measures that have post-baseline records. Change from baseline is calculated as:

- Change from baseline = visit value – baseline value.

Percentage change from baseline is calculated as:

- Percentage change from baseline = $100 * \text{change from baseline} / \text{baseline value}$

If either the baseline or visit value is missing, the change from baseline and percentage change from baseline is set to missing as well.

The change from reference visit will be calculated following the same rules.

8.2.6 Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during data set creation to re-assign assessments to other visits or time points based on such windows).

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

8.2.7 Actual Treatment

The subjects' actual treatment will be derived from exposure data delivered by IRT. If a subject receives study treatment that is the same as the assigned treatment, then actual treatment is the assigned treatment. If a subject receives study treatment that is different from the assigned treatment for the entire time of a Treatment Period, then actual treatment is the different treatment (the treatment actually received).

8.2.8 Body Mass Index (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 Week 1. If weight at Week 1 is not available, the assessment at Screening will be used. If neither is available, then BMI is missing.

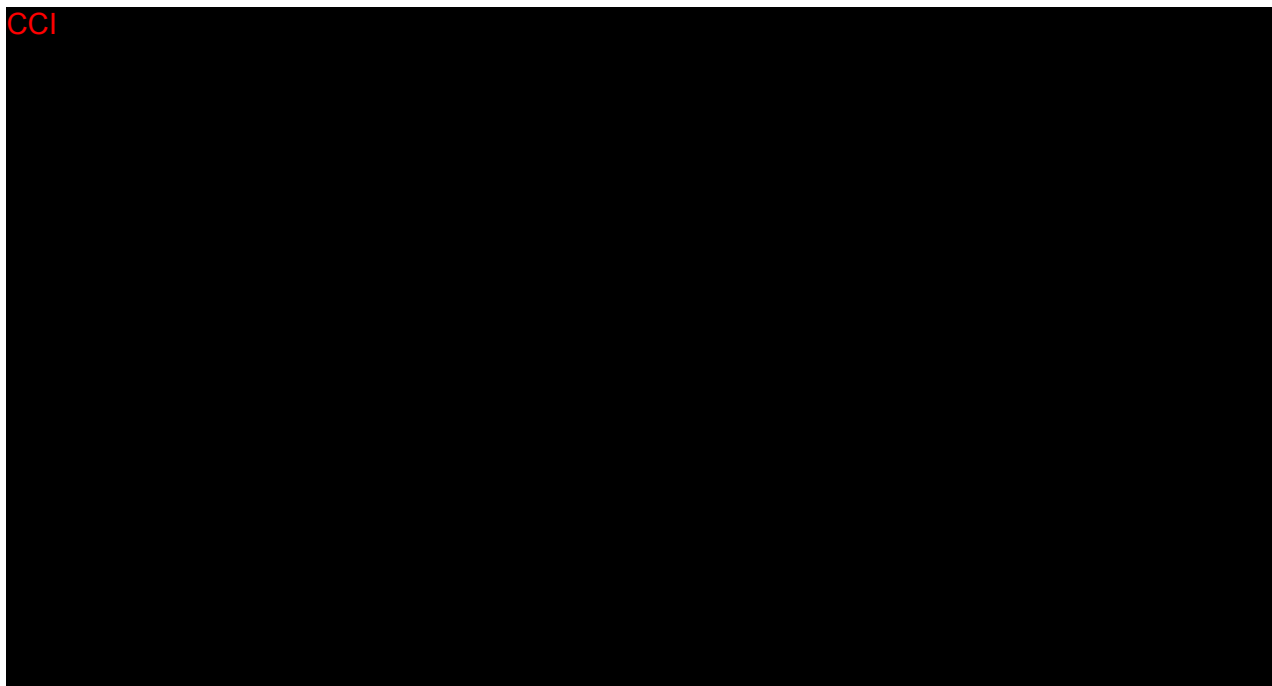
8.2.9

CCI

CCI

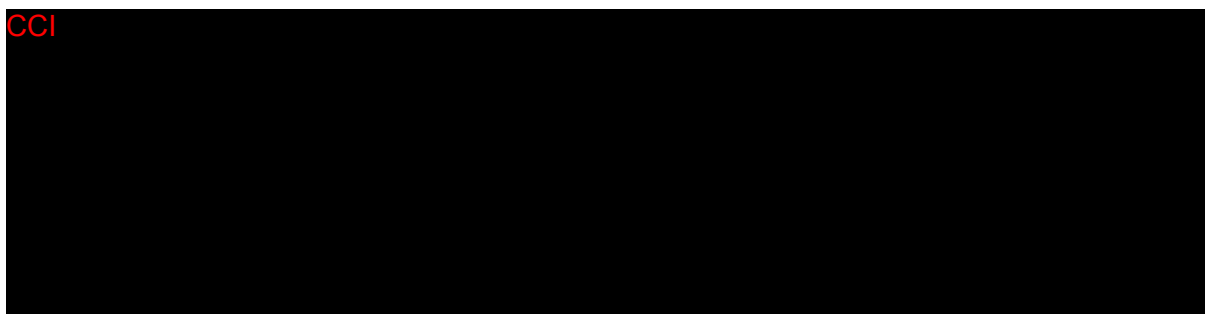


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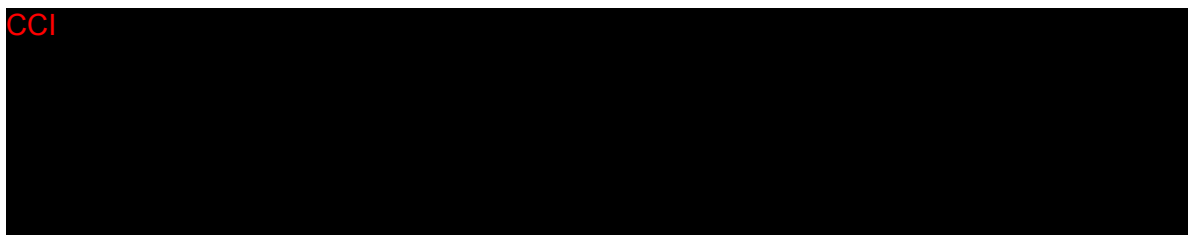
8.2.10 CCI

CCI



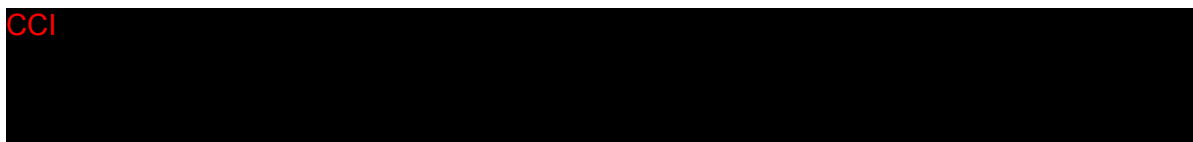
8.2.11 CCI

CCI



8.2.12 CCI


CCI



CCI



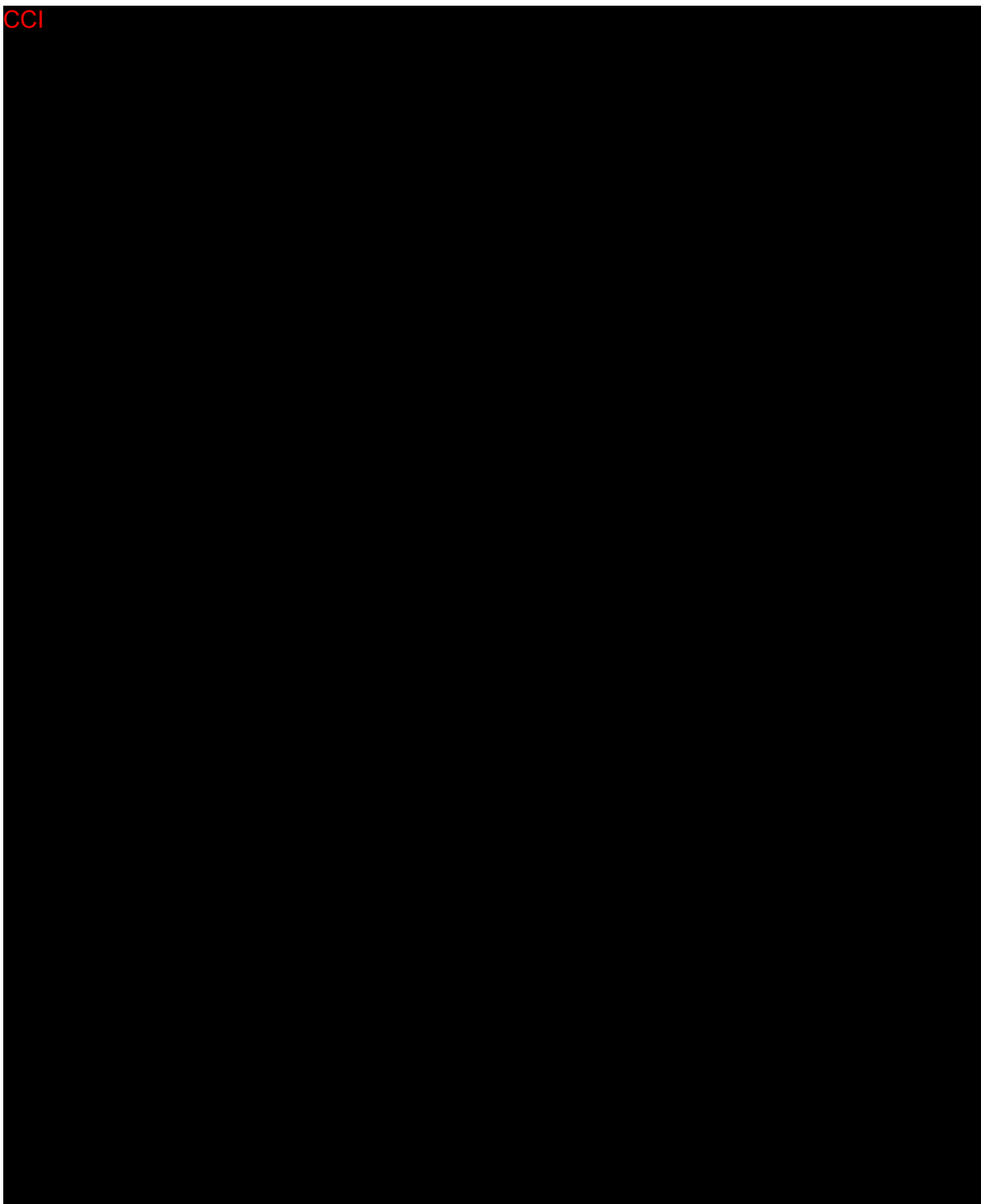
8.2.13 CCI



CCI



Figure 2: **CCI**



CCI



CCI



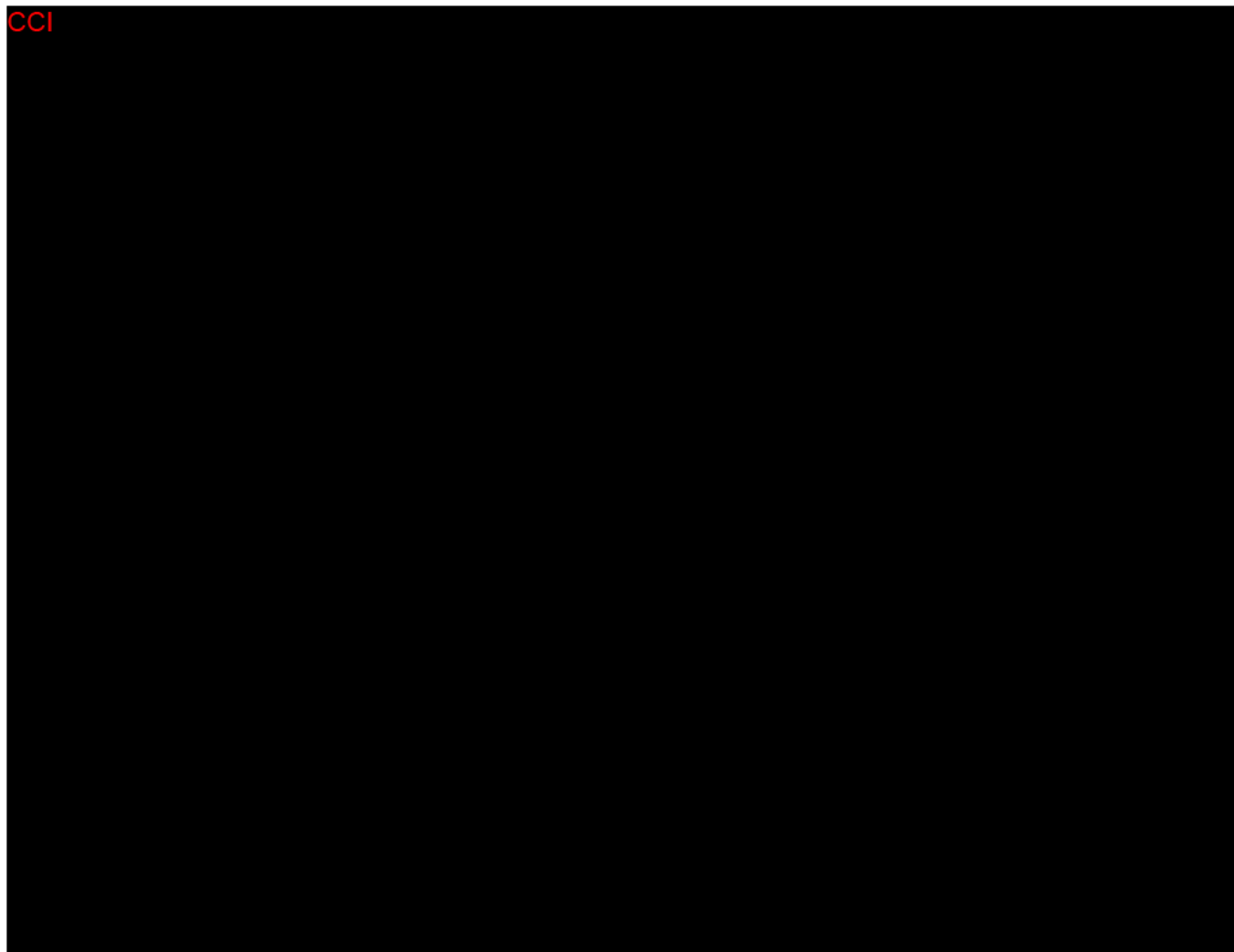
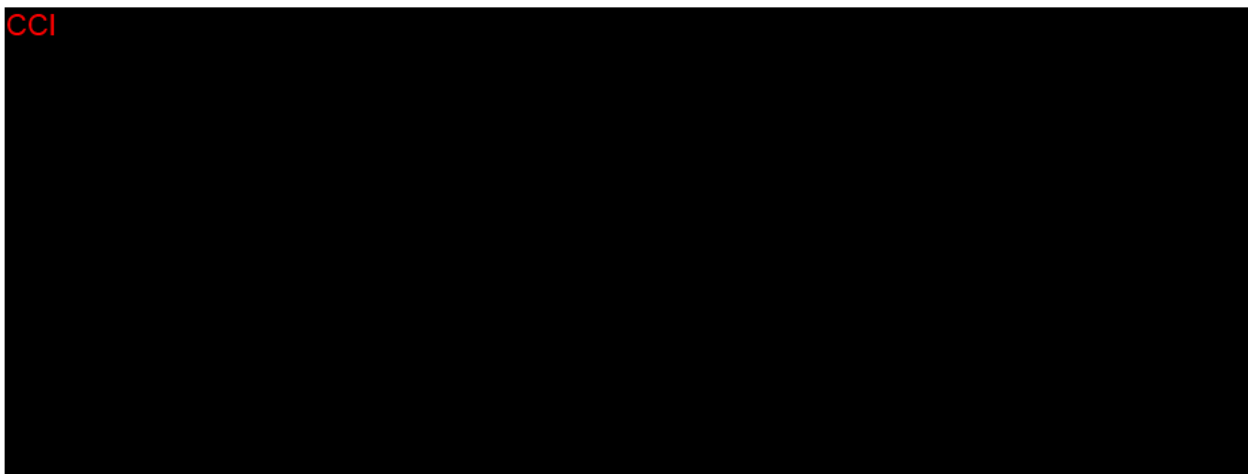


Figure 3: CCI



CCI



CCI



8.2.14 CCI


CCI



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8.2.15 CCI



CCI



CCI



Figure 4: CCI

CCI



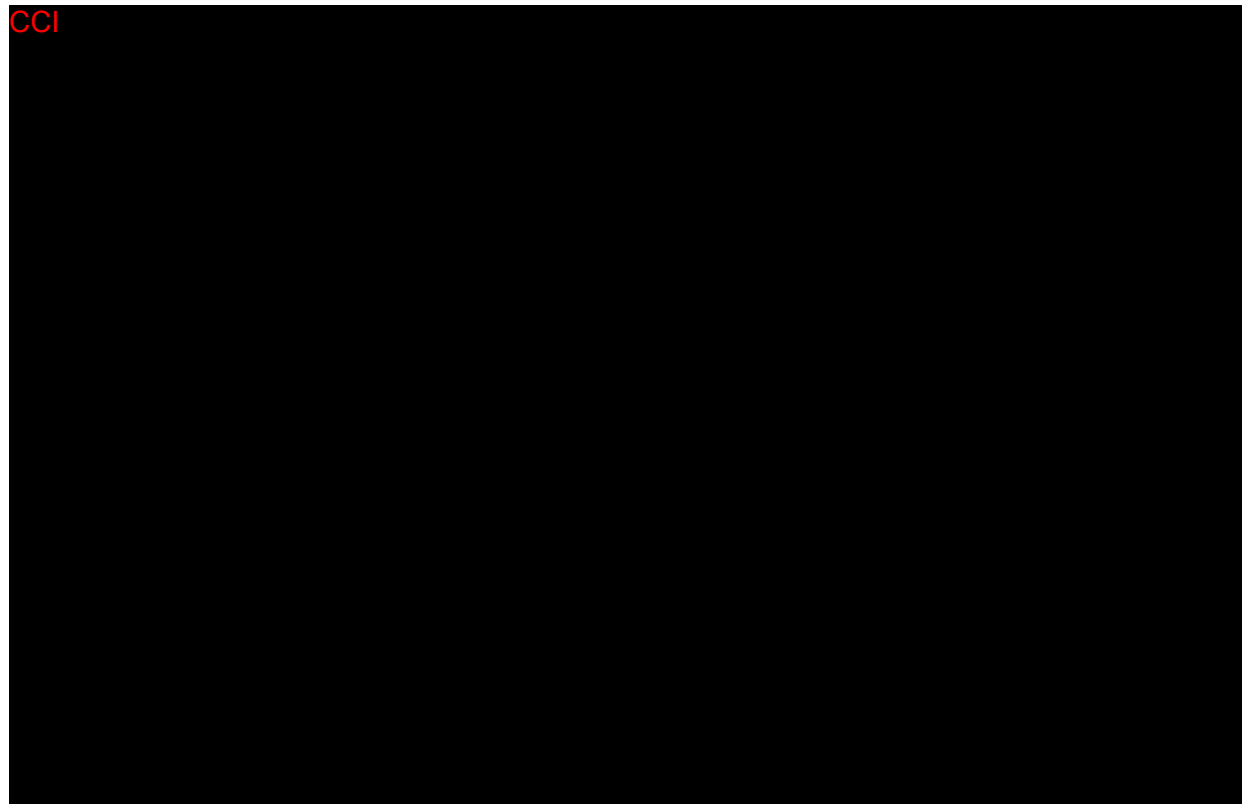
CCI



CCI



CCI



8.2.16 CCI

CCI

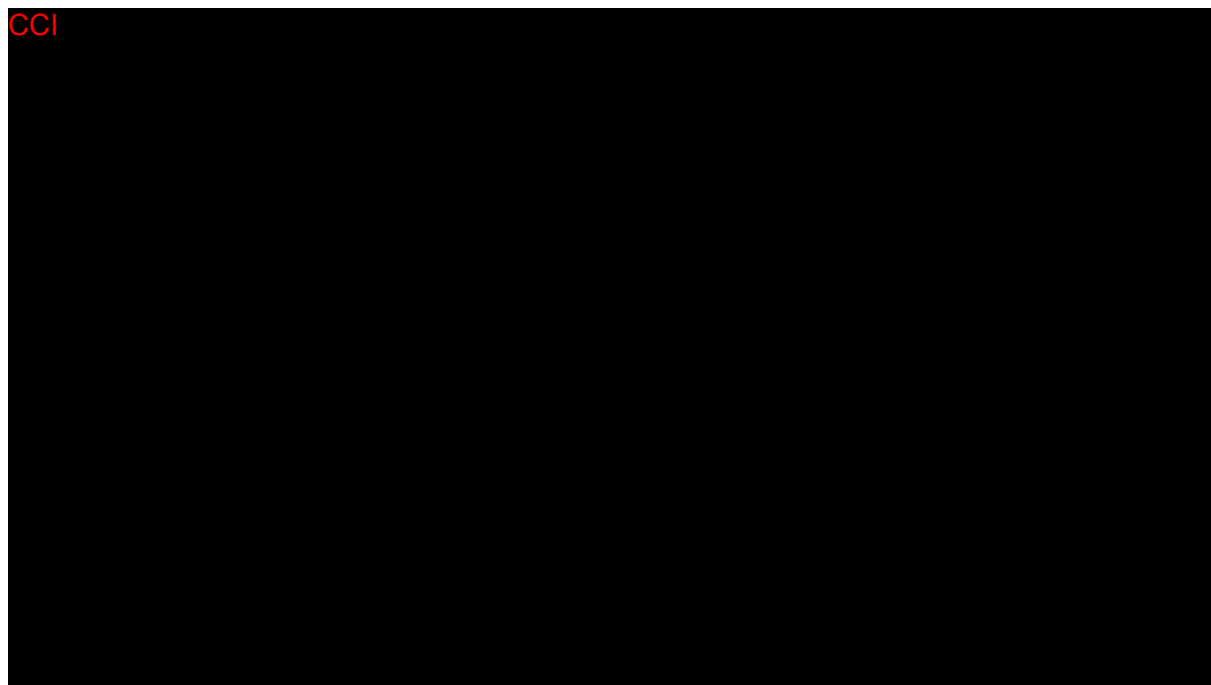
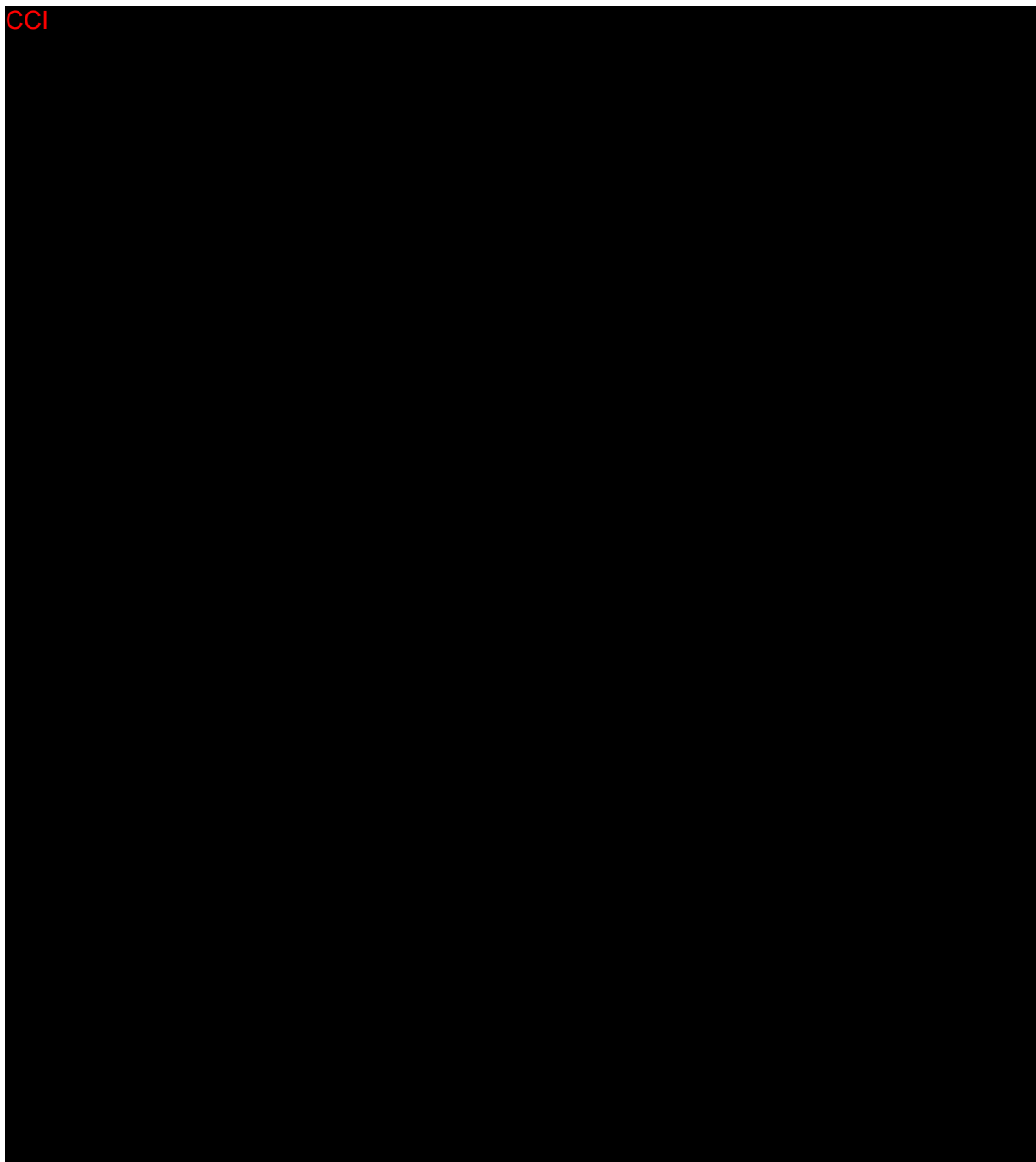


Figure 5: CCI [Redacted]



8.2.17 CCI [Redacted]

CCI [Redacted]

CCI [Redacted]

8.2.18 CCI [Redacted]

CCI [Redacted]

8.2.19 CCI [Redacted]

CCI [Redacted]

8.2.20 CCI [Redacted]

CCI [Redacted]

8.2.21 CCI [Redacted]

CCI [Redacted]

Figure 6: CCI

CCI



8.3 Study Periods Relative to Treatment

Definitions of the endpoint assessment and definition of start and end of study periods are presented in [Table 1](#) and [Table 2](#).

Table 1: Timing of Endpoint and Reference Assessments

	Definition	Start of Assessment Period	End of Assessment Period
By Treatment	1 IgPro20 Treatment Sequence A/ Treatment Period 1 and Treatment Sequence B/ Treatment Period 2	Week 1 Week 17	Week 17 ¹ Week 32
	2 IgPro10 Treatment Sequence A/ Treatment Period 2 and Treatment Sequence B/ Treatment Period 1	Week 17 Week 1	Week 32 Week 17 ²
By Treatment Sequence	1 Treatment Sequence A	Week 1	Week 32
	2 Treatment Sequence B	Week 1	Week 32
By Treatment and Treatment Period	1 IgPro20 in Treatment Period 1 Treatment Sequence A	Week 1	Week 17 ¹
	2 IgPro10 in Treatment Period 1 Treatment Sequence B	Week 1	Week 17 ²
	3 IgPro10 in Treatment Period 2 Treatment Sequence A	Week 17	Week 32
	4 IgPro20 in Treatment Period 2 Treatment Sequence B	Week 17	Week 32
Overall	1 Both Treatment Sequences, all Treatment Periods Treatment Sequence A/ Treatment Period 1, Treatment Sequence B/ Treatment Period 1, Treatment Sequence A/ Treatment Period 2, Treatment Sequence B/ Treatment Period 2	Week 1 Week 17	Week 17 Week 32

¹ Before first infusion of IgPro10.² Before first infusion of IgPro20.

Table 2: Treatment Periods

Treatment Sequence/ Treatment Period	Treatment	Start of Treatment Period	End of Treatment Period
Treatment Sequence A/ Treatment Period 1	IgPro20	Start date and time of the first IgPro20 Infusion	Start date and time of the first IgPro10 Infusion or EOS, if there is no IgPro10 Infusion
Treatment Sequence A/ Treatment Period 2	IgPro10	Start date and time of the first IgPro10 Infusion	EOS
Treatment Sequence B/ Treatment Period 1	IgPro10	Start date and time of the first IgPro10 Infusion	Start date and time of the first IgPro20 Infusion or EOS, if there is no IgPro20 Infusion
Treatment Sequence B/ Treatment Period 2	IgPro20	Start date and time of the first IgPro20 Infusion	EOS

8.3.1 Study Periods for Adverse Events

AEs with onset date/ time at or after start of first infusion of study treatment are TEAEs. If the time of onset of an AE is missing: AEs with onset date at or after start of first infusion of study treatment are TEAEs. Assessment whether an AE is considered treatment-emergent, will take place after imputation of partially missing dates (see [Section 8.1.2](#)).

The TEAE analysis will be done for the study periods and groups shown in [Section 11](#). An AE will be counted for the analysis of a study period if the onset of the event falls within the study period. For the definition of start and end of the study periods see [Table 2](#).

8.3.2 Study Periods for Concomitant Medications

Concomitant Medication start and end dates will be assigned to study periods as described below.

- Start relative to treatment
 - Assign to 'BEFORE' if the concomitant medication start date/time is prior to study treatment start date/time; if subject has not taken any study treatment; or the concomitant medication start date/time is missing and the concomitant medication end date/time is before the study treatment start date/time.
 - Assign to 'DURING PERIOD 1' if the concomitant medication start date/time falls into Treatment Period 1 ([Table 2](#)); or the concomitant medication start date/time is missing.
 - Assign to 'DURING PERIOD 2' if the concomitant medication start date/time falls into Treatment Period 2 ([Table 2](#)).
 - Assign to 'AFTER' if the concomitant medication start date/time is after the date/time of the end of the last treatment period.
- End relative to treatment
 - Assign to 'BEFORE' if the concomitant medication end date/time is prior to study treatment start date/time or if the subject has not taken any study treatment.
 - Assign to 'DURING PERIOD 1' if the concomitant medication end date/time falls into Treatment Period 1 ([Table 2](#)).
 - Assign to 'DURING PERIOD 2' if the concomitant medication end date/time falls into Treatment Period 2 ([Table 2](#)).
 - Assign to 'AFTER' if the concomitant medication end date/time is after the date/time of the end of the last treatment period; or the concomitant medication end date/time is missing.

If a start or end date/time is partially missing, the imputation takes place before the classification of the medication in the categories above.

8.3.3 Study Periods for Medical History

Prior medical conditions are those which end before the start of first infusion of IP. All other Medical History entries are Concomitant medical conditions, including those with missing end date. Assessment whether a Medical History is considered prior or concomitant, will take place after imputation of partially missing end dates (see [Section 8.1.2](#)).

8.4 Values of Potential Clinical Importance

8.4.1 Laboratory Parameters

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.

Table 3: Potential Clinically Important Values: Laboratory Panels

Test Name or Test combinations (Test code in lab data transfer)	Outlier Criteria (in conventional units delivered by lab)
Chemistry Panel	
Bilirubin, total (TBILIARC)	>1.5 x ULN
Alkaline phosphatase (ALPARCH)	>2.5 x ULN
SGOT, AST (ASTARCH)	>3 x ULN
SGPT, ALT (ALTARCH)	>3 x ULN
Drug Induced Liver Injury (DILI) Screening	AST or ALT >3 x ULN and Total Bilirubin >2 x ULN*
Urea nitrogen (BUNARCH)	>2.5 x ULN*
Creatinine, serum (CREATARCH)	>1.5 x baseline assessment* or change >0.3mg/dL since last visit
Glucose, blood (non-fasting) (GLURNARCH)	<55mg/dL or >160mg/dL*
Calcium (CAARCH)	<7mg/dL or >11.5mg/dL
Total protein, plasma or serum (TPARCH)	<5g/dL* or >9g/dL*

Test Name or Test combinations (Test code in lab data transfer)	Outlier Criteria (in conventional units delivered by lab)
Albumin (ALBARCH)	<3g/dL
Sodium (NAARCH)	<130mmol/L or >150mmol/L*
Potassium, serum/plasma (KARCH)	<3mmol/L or >5.5mmol/L
Uric acid, serum (UAARCH)	>10mg/dL Males* , >8mg/dL Females*
Gamma Glutamyl Transpeptidase (GGTARCH)	>2.5 x ULN
Phosphorus, inorganic (PHOSARCH)	<2.5mg/dL or >5mg/dL*
Lactate dehydrogenase (LDHARCH)	>3 x ULN*
Hematology and Differential Panel	
Hemoglobin (HGB)	<10g/dL
Platelet count (PLT)	<75 x 10 ⁹ /L or >500 x 10 ⁹ /L*
White Blood Cell Count (WBC)	<3 x 10 ⁹ /L or >16 x 10 ⁹ /L*
Neutrophils, absolute (ABSNEUT) Neutrophils, differential (NEUT)	<1.5 x 10 ⁹ /L <40%*
Lymphocytes, absolute (ABSLYMPH) Lymphocytes, differential (LYMPH)	<0.8 x 10 ⁹ /L <10% or > 50%
Urine Panel	
Protein (UPROTNARCH)	>20mg/dL

*flag level based on CSLB medical monitor recommendation; all other levels are established as based on CTCAE v5.0 moderate grade.

8.4.2 Vital Signs and Spirometry

To identify vital signs values of potential clinical importance, CSLB medical monitor recommendation will be used.

Table 4: Potential Clinically Important Values: Vital Signs and Spirometry

Test Name	Outlier Criteria
Vital Signs and Spirometry	
Systolic BP (mmHg)	<ul style="list-style-type: none"> • <100 or ≥ 140 • ≥ 140 AND increase >10 from reference visit
Diastolic BP (mmHg)	<ul style="list-style-type: none"> • <50 or ≥ 90 • ≥ 90 AND increase >10 from reference visit
Pulse (beats/ minute)	<ul style="list-style-type: none"> • <50 or ≥ 120 • ≥ 120 AND increase >15 from reference visit
Weight (kg)	<ul style="list-style-type: none"> • $\geq 10\%$ change (increase and decrease) from baseline assessment
Body Temperature ($^{\circ}\text{C}$)	<ul style="list-style-type: none"> • >39 or <35 (oral, tympanic, axilla or forehead)
CCI (%)	<ul style="list-style-type: none"> • Decrease >10 percentage points from reference visit

8.4.3 ECG

Table 5: Potential Clinically Important Values: ECG

Test Name	Outlier Criteria
ECG	
ECG interpretation	Abnormal clinically significant (CS) at any study visit post baseline
Heart Rate (beats per minute)	$\leq 50^*$ or $\geq 100^*$
PR Interval (msec)	$\geq 200^*$
QRS Interval (msec)	$\geq 120^*$

Test Name	Outlier Criteria
QT, QTcB, QTcF (msec)	$\geq 480^*$ and $\leq 500^*$ $> 500^*$
QT, QTcB, QTcF, increase from baseline (msec)	$\geq 30^*$ and $< 60^*$ $\geq 60^*$

*flag level based on CSLB medical monitor recommendation; all other levels are established as based on CTCAE v5.0 moderate grade.

9 Study Population

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

Individuals who do not meet the criteria for participation in this study (ie, screen failures) may be re-screened. In case of re-screening, the assessments from the re-screening visit will be summarized only, not the assessments from the original, failed screening attempt. Reasons for re-screening will be listed.

9.1 Disposition of Subjects

Summary tables by Treatment Sequence, Treatment Period, and total population will present for all subjects screened:

- The number of subjects screened.
- The number of screen failures incl. reasons for screen failure.
- The number of subjects per analysis set.
- The number and percentage of subjects completed each treatment period.
- The number and percentage of subjects treated in each treatment period.
- The number and percentage of subjects who completed each treatment period and the study.
- The number and percentage of subjects who prematurely discontinued by treatment period.

Percentages will be based on the number of subjects randomized.

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

Reasons for screened failures will be listed by subject.

9.2 Protocol Deviations

A summary of all key protocol deviations, including inclusion and exclusion deviations, will be provided by Treatment Sequence.

A listing of all protocol deviations will be provided.

Protocol deviations will be identified and classified into key/ non-key by CSLB. The final decision will be made in the DRM.

9.3 Demographic and Baseline Characteristics

The following summaries will be provided by Treatment Sequence and total:

- Demographic characteristics: sex (female, male, unknown), age (years provided by IRT), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), baseline height (cm), baseline body weight (kg), baseline BMI (kg/m²);
- In addition to summarization as a continuous variable, age will also be categorized and summarized (18-64 years, > 64 years).
- Demographic characteristics for the PP-IgPro10 and PP-IgPro20 analysis sets.
- Disease characteristics.
 - time since Systemic Sclerosis Initial diagnosis until randomization (months)
 - time since first Raynaud's phenomenon until randomization (months)
 - time since first non-Raynaud's phenomenon clinical manifestation until randomization (months)
 - ABO Blood Group and Rh Factor
 - Antiglobulin Test, Direct at Screening
 - Number of background therapy/immunosuppressants at Baseline (definition see [Section 9.4](#))

- Auto-antibodies at Baseline, categorized as follows:
 - Antinuclear Antibodies:
 - Negative (< 1:40), Positive (>= 1:40)
 - Centromere IgG Antibody (AU/mL):
 - Negative (<= 29), Equivocal/Positive (>= 30)
 - Fibrillarin (U3 RNP) Antibody:
 - Negative, Positive (all categories of positive combined)
 - PM/Scl-100 IgG Antibody:
 - Negative, Positive (all categories of positive and borderline combined)
 - RNA Polymerase III IgG Antibody (U):
 - Negative (<= 19), Positive (>= 20)
 - Ribonucleoprotein-70 IgG Antibody (AU/mL):
 - Negative (<= 29), Equivocal/Positive (>= 30)
 - Scl-70 IgG Antibody (AU/mL):
 - Negative (<= 29), Equivocal/Positive (>= 30)
- Past medical conditions present at screening.
- Current medical conditions present at screening.
- Smoking history

The following listings will be provided:

- Demographic characteristics.
- Disease characteristics.
- Past and current medical conditions.

9.4 Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug Dictionary Enhanced (WHO-DDE) 2018 Mar B3 or more recent version, summarized and listed. The summary of concomitant medications will show the number and percentage (in proportion to subjects in Safety Analysis Set) of subjects taking prior and concomitant medications.

In the summary of concomitant medications, each subject is counted once within each unique term. For example, if a subject takes Amoxicillin on two separate occasions, the subject is counted only once under the ingredient “amoxicillin”.

Concomitant medication start and end dates are used select data to include in summaries as follows:

- Summary of Prior Medications: This summary will contain medications with end dates relative to treatment assigned to 'BEFORE'.
- Summary of Concomitant Medications: This summary will contain medications with start dates relative to treatment assigned to ('BEFORE', 'DURING PERIOD 1', 'DURING PERIOD 2') and end dates relative to treatment assigned to ('DURING PERIOD 1', 'DURING PERIOD 2', 'AFTER').
- Summary of Concomitant Medications with onset in IgPro10 Treatment Period: This summary will contain medications with start dates relative to treatment assigned to
 - Treatment Sequence A: 'DURING PERIOD 2',
 - Treatment Sequence B: 'DURING PERIOD 1'.
- Summary of Concomitant Medications with onset in IgPro20 Treatment Period: This summary will contain medications with start dates relative to treatment assigned to
 - Treatment Sequence A: 'DURING PERIOD 1',
 - Treatment Sequence B: 'DURING PERIOD 2'.
- Summaries of background therapy and immunosupprants intake at baseline: This summary will contain medications with
 - start dates relative to treatment assigned to 'BEFORE' AND
 - end dates relative to treatment assigned to ('DURING PERIOD 1', 'DURING PERIOD 2', 'AFTER') AND
 - indication for the medication is 'Study Indication (Systemic Sclerosis)' AND
 - ATC 2 code is L01 (ANTINEOPLASTIC AGENTS), L04 (IMMUNOSUPPRESSANTS) or H02 (CORTICOSTEROIDS FOR SYSTEMIC USE).
- Summary for concomitant medications used to treat COVID-19 associated adverse events

10 Efficacy

All efficacy analyses will be based on the ITT analysis set.

Summaries will be presented for the following combinations of Treatment Sequence and Treatment Period (respective Treatment Sequences [A/B] and Treatment Periods [1/2] are given in parentheses):

By Sequence

- Treatment Sequence A (A/1 and A/2)
- Treatment Sequence B (B/1 and B/2)
- Total

By Treatment

- IgPro20 (A/1 and B/2)
- IgPro10 (A/2 and B/1)

By Period – IgPro10

- Period 1 (B1)
- Period 2 (A2)

By Period – IgPro20

- Period 1 (A1)
- Period 2 (B2)

10.1 CCI

CCI



Table 6: CCI [Redacted]

CCI	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

CCI	

10.2 Treatment Compliance

Treatment compliance for IgPro20 and IgPro10 will be measured as a percentage overall and summarized using descriptive statistics. A percentage between 80% and 120% is regarded as compliant to treatment.

Compliance (%) =

$100 * \text{total administered volume (mL) per subject} / \text{total planned volume (mL) per subject}$

11 Safety Analyses

All safety analyses will be based on the SAF analysis set.

11.1 Extent of Exposure

Exposure to the investigational product will be descriptively summarized by treatment.

For both **IgPro20** Treatment Periods and IgPro20 combined:

- Number of Weekly Infusions
- Planned and administered volume by Weekly Infusion and subject
- Administered total dose by subject
- Maximum infusion rate per infusion site by Infusion and subject
- Maximum volume per infusion site by Infusion and subject
- Duration of infusion by Infusion and Weekly Infusion
- Number of infusion sites per Infusion
- Duration of treatment

There are several levels of aggregation for study drug exposure.

Level 1: Infusion. Observation in database extract.

Level 2: Weekly Infusion. One Weekly Infusion consists of 2 Infusion.

Level 3: Subject. All Weekly Infusions of the IgPro20 Treatment Period for a subject.

Table 7: Derivation of Exposure Variables IgPro20

Variable	Infusion	Weekly Infusion	Subject
Total planned volume (mL)	n/a	derived	sum
Total administered volume (mL)	entered	sum	sum
Total number of infusion sites	entered	n/a	n/a
Maximal number of infusion sites used in parallel	entered	n/a	n/a
Actual total dose (g)	n/a	derived	derived
Maximum infusion rate per infusion site (mL/h)	entered	max	max
Maximum volume per infusion site (mL)	derived	max	max
Duration of Infusion	derived	sum	n/a
Duration of Treatment	n/a	n/a	derived

derived= see derivation rule below

sum= sum of values of the lower level of the same variable

max= maximum of the values of the lower level of the same variable

Total Planned Volume (mL)

Level: Weekly Infusion

The total planned volume is entered twice per week, once for each infusion. The value of the total planned volume will be taken from the entry of the first infusion of each week.

Actual Total Dose (g)

Level: Subject

$$\text{Actual Total Dose (g)} = \text{Total Administered Volume (mL)} * 0.2 \text{ g/mL}$$

Level: Weekly Infusion

$$\text{Actual Dose (g)} = \text{Administered Volume in respective week (mL)} * 0.2 \text{ g/mL}$$

Maximum volume per infusion site (mL)

Level: Infusion

Maximum volume per infusion site (mL) =
Total administered volume (mL) / maximal number of infusion sites used in parallel

Duration of Infusion

Level: Infusion

duration (min) = end time (min) – start time (min)
if duration < 0 (i.e., end is on the next day) then duration = duration + 24 * 60

Duration of treatment

Level: Subject

duration (days) =
last day with IgPro20 treatment – first day of IgPro20 treatment + 1

For both **IgPro10** Treatment Periods and IgPro10 combined:

- Number of Infusion Cycles
- Planned and administered volume by Infusion Cycle and subject
- Administered total dose by Infusion Cycle and subject
- Duration of infusion by Infusion and Infusion Cycle
- Duration of treatment
- Maximum infusion rate by subject (mL/h, mL/kg/h, mg/kg/min)

There are several levels of aggregation for study drug exposure.

Level 1: Infusion. Observation in database extract.

Level 2: Infusion Cycle. One Infusion Cycle consists of 2-5 Infusions.

Level 3: Subject. All Infusion Cycles of the IgPro10 Treatment Period for a subject.

Table 8: Derivation of Exposure Variables IgPro10

Variable	Infusion	Infusion Cycle	Subject
Total planned volume (mL)	n/a	derived	sum
Total administered volume (mL)	entered	sum	sum
Initial infusion rate (mL/h)	entered	n/a	n/a
Initial infusion rate (mL/kg/h, mg/kg/min)	derived	n/a	n/a
Maximum infusion rate (mL/h, mL/kg/h, mg/kg/min)	derived	max	max
Actual total dose (g)	n/a	derived	derived
Duration of infusion	derived	sum	n/a
Duration of treatment	n/a	n/a	derived

derived= see derivation rule below

sum= sum of values of the lower level of the same variable

max= maximum of the values of the lower level of the same variable

Total Planned Volume (mL)

Level: Infusion Cycle

The total planned volume is entered once for each infusion. The value of the total planned volume will be taken from the entry of the first infusion of each Infusion Cycle.

Initial Infusion Rate (mL/kg/h)

Level: Infusion

$$\text{Initial Infusion Rate (mL/kg/h)} = \text{Initial Infusion Rate (mL/h)} / \text{reference weight (kg)}$$

Reference body weight is the baseline body weight. After a change of planned volume for the week, the most recent body weight before the change of planned volume is the reference weight.

Initial Infusion Rate (mg/kg/min)

Level: Infusion

$$\text{Initial Infusion Rate (mg/kg/min)} = 100 \text{ mg/mL} * \text{Initial Infusion Rate (mL/h)} / \text{reference body weight (kg)} / 60$$

Maximum Infusion Rate (all units)

Level: Infusion

The maximum infusion rate is the maximum of the initial infusion rate and all infusion rates after a change of infusion rate.

Actual Total Dose (g)

Level: Infusion Cycle, Subject

$$\text{Actual Total Dose (g)} = \text{Total Administered Volume (mL)} * 0.1 \text{ g/mL}$$

Duration of Infusion

Level: Infusion

$$\text{duration (min)} = \text{end time (min)} - \text{start time (min)}$$

if duration < 0 (i.e., end is on the next day) then duration = duration + 24 * 60

Duration of treatment

Level: Subject

$$\text{duration (days)} = \text{last day with IgPro10 treatment} - \text{first day of IgPro10 treatment} + 1$$

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

11.2 Adverse Events

All AEs will be coded by the Medical Dictionary for Regulatory Activities. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

Summaries will be presented for the following combinations of Treatment Sequence and Treatment Period (respective Treatment Sequences [A/B] and Treatment Periods [1/2] are given in parentheses):

- IgPro20 (A/1 and B/2)
- IgPro10 (A/2 and B/1)
- IgPro20/ Treatment Period 1 (A/1)
- IgPro20/ Treatment Period 2 (B/2)
- IgPro10/ Treatment Period 1 (B/1)
- IgPro10/ Treatment Period 2 (A/2)
- Total (A/1, A/2, B/1, and B/2)

Infusion site reactions (ISR) comprise all AEs reported within the MedDRA HLTs “Administration site reactions NEC” or “Infusion site reactions”.

Summaries of AEs created to assess the COVID-19 impact are described in Section 7.4.

Refer to Section 11.3 for the definition of Adverse Events of Special Interest (AESIs).

- An overview summary of TEAEs, including number of subjects, percentages of subjects, and the number of events by Treatment Sequence, treatment, and Treatment Period including the following:
 - Any TEAE
 - Any serious TEAE
 - TEAEs leading to interruption of IP
 - TEAEs leading to permanent discontinuation of IP
 - TEAEs leading to withdrawal from study
 - Temporally associated TEAEs
 - Treatment-emergent AESIs (Hemolysis, TEE, Acute Renal Injury)
 - Any serious treatment-emergent AESIs
 - Treatment-emergent AESIs leading to permanent discontinuation of IP
 - Treatment-emergent AESIs leading to withdrawal from study

- Related treatment-emergent AESIs
 - Treatment-emergent AESIs by Grade
 - Treatment-emergent AESIs Grade 3 and above
 - TEAEs by causality (related to IP)
 - TEAEs by severity (mild, moderate, severe)
 - TEAEs by outcome (“recovered or resolved” vs. all other outcomes combined)
 - Any ISR
 - ISRs leading to interruption of IP
 - ISRs leading to permanent discontinuation of IP
 - ISRs leading to withdrawal from study
 - ISRs by causality (related to IP)
 - ISRs by severity (mild, moderate, severe)
 - ISRs by outcome (“recovered or resolved” vs. all other outcomes combined)
- The following descriptive tables will be generated for TEAEs, including number of subjects, percentages of subjects, and the number of events:
 - TEAEs by SOC and PT
 - TEAEs by PT
 - TEAEs by SOC, PT, and maximum severity (without number of events)
 - Causally related TEAEs by SOC and PT
 - Causally related TEAEs by SOC, PT, and maximum severity (without number of events)
 - Temporally associated TEAEs by SOC, PT and maximum severity (without number of events)
 - Temporally associated TEAEs and/or causally related TEAEs by SOC, PT and maximum severity (without number of events)
 - Serious TEAEs by SOC and PT
 - Serious, causally related TEAEs by SOC and PT
 - TEAEs leading to permanent discontinuation of IP by SOC and PT
 - Treatment-emergent AESIs by Category, SOC and PT
 - Treatment-emergent AESIs by Category and PT
 - Treatment-emergent AESIs by Category, PT and maximum grade (without number of events)
 - Treatment-emergent AESIs Grade 3 and above by Category and PT
 - Serious treatment-emergent AESIs by Category and PT

-
- Related treatment-emergent AESIs by Category and PT
 - All AE summaries presented by SOC and preferred term will include a virtual SOC “Infusion Site Reactions”, i.e., all AEs reported within the MedDRA High level terms “Administration site reactions NEC”, “Infusion site reactions” or “Injection site reactions”. AEs will be presented in the virtual SOC and the regular SOC.
 - All AE summaries presented by SOC and preferred term will include a virtual SOC “Thromboembolic Events” comprising all AEs reported within the MedDRA SMQs in [Section 11.3](#). AEs will be presented in the virtual SOC and the regular SOC.

Additional summary statistics for ISR will be presented for IgPro20 Treatment Periods only (see [Table 2](#)):

- Number and percent of subjects with ISR, incl. 95% Wilson score CI
- Number and percent of subjects with ISR per week, incl. 95% Wilson score CI
An ISR will be counted for the week of the most recent infusion before the onset of the ISR.
- ISR rate per Infusion
- ISR rate per Infusion per week
- Duration of ISR
- Time to onset of ISR since start of corresponding Treatment Period
- Time to onset of ISR since start of last infusion prior to onset of AE

$$\text{ISR rate per infusion} = \frac{\text{total number of ISRs across all subjects while on IgPro20}}{\text{total number of IgPro20 Infusions across all subjects}}$$

Temporally associated TEAEs are defined as AEs with an onset between the start of the infusion and up to 72 h after the end of infusion. In case time of onset of AE is missing, the AE is considered temporally related, if the onset of the AE is between the day of the start of infusion and the day of the end of infusion + 3 days (inclusive).

The following listings will be provided:

- All Adverse Events
- Serious TEAEs
- Deaths
- Treatment-emergent AESIs

- Treatment-emergent AESIs Grade 3 or Higher
- ISRs
- TEAEs leading to permanent discontinuation of IP

11.3 Adverse Events of Special Interest (AESIs)

In this study, hemolysis, TEEs, and acute renal injury will be treated as AESIs. The classification of AEs into AESI categories will be done using standardized MedDRA queries (SMQ).

In addition to the comprehensive search by SMQs, the site enters their assessment in the eCRF on whether the AE is of special interest. These entries are listed but not summarized.

All **hemolysis** events under the SMQ “hemolytic disorders, broad” will be considered AESIs.

The following 3 narrow SMQs will be utilized for **TEE** evaluation:

- Embolic and thrombotic events, arterial
- Embolic and thrombotic events, venous
- Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous

All **acute renal injury** events under SMQ “acute renal failure, narrow” will be considered AESIs.

Descriptive tables for AESI will be generated similarly to TEAEs as described in [11.2](#).

11.4 Clinical Laboratory Evaluations

The laboratory tests in Section 8.1.1 of the protocol will be summarized as described in this section.

Laboratory data will be presented in units provided by the central laboratory.

Lab values will be summarized descriptively by visit using only values from scheduled visits.

Separate summary tables for hematology, biochemistry, and virology laboratory tests will be produced. Changes from reference visit and shift tables are produced for hematology and biochemistry only. For a list of laboratory tests see Clinical Study Protocol, Table 1.

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

The following summaries will be provided by groups defined in [Section 11](#):

- All laboratory values by visit
- Laboratory value changes from reference visit
- Laboratory value shifts from reference visit with respect to the normal range
- Summaries of potential clinically important values will be provided according to the categories in [Section 8.4.1](#).

Listings to be produced are:

- All Laboratory values, including changes from Baseline and Reference visit, values outside normal range will be flagged

11.5 Vital Signs

Observed values and changes from baseline/reference visit to assessment time point in vital signs and body weight will be presented in descriptive statistics by treatment, Treatment Sequence, and combination of treatment and Treatment Period.

Summaries of potential clinically important values will be provided according to the categories in [Section 8.4.2](#).

11.6 Spirometry

Observed values and changes from baseline/reference visit to assessment time point in **CCI** will be presented in descriptive statistics by treatment, Treatment Sequence, and combination of treatment and Treatment Period. All other PFT results delivered by the vendor will be listed only.

Summaries of potential clinically important values will be provided according to the categories in [Section 8.4.2](#).

11.7 ECG

Observed values and changes from baseline/reference visit to assessment time point in ECG will be presented in descriptive statistics by treatment, Treatment Sequence, and combination of treatment and Treatment Period.

Summaries of potential clinically important values will be provided according to the categories in [Section 8.4.3](#).

11.8 Wells' Criteria Score

Data for Wells' criteria Score for deep vein thrombosis (DVT) and pulmonary embolism (PE) will be analyzed descriptively, separately.

12 Pharmacokinetic Analyses

Serum samples for IgG trough level determination will be collected at several study visits.

Additional blood samples for rich PK sampling of IgG levels will be collected at the end of each Treatment Period to calculate PK parameters.

The merge of PK concentration data and eCRF data to generate a dataset with actual blood sampling times, actual sampling time relative to the start of the dose infusion, actual infusion durations, actual dose and PK concentrations, along with derivation of PK parameters will be performed after database lock by CSLB or their designate.

All analyses in this section will be based on the SAF analysis set. As sensitivity analysis, the analyses for population relative bioavailability and individual relative bioavailability will be repeated on the PP-IgPro10 and PP-IgPro20 analysis set.

12.1 Drug Concentration Measures

IgG concentrations from PK sampling will be listed for individual subjects and summarized by nominal (planned) time points. Individual concentration-time profiles and mean (\pm standard deviation) profiles following the first infusion of the last infusion cycle in each Treatment Period and Treatment Sequence will be plotted using actual time points for individual plots and nominal (planned) time points for mean profiles.

The handling and imputation of BLQ values for PK parameter derivation is described in PK-GDL-01, Guideline on the Conduct of Non-compartmental Pharmacokinetic Analyses, CSL Behring. The imputation rules below will be used for summary statistics IgG serum concentrations. The summaries will be given by sampling time point (planned time points) and treatment group.

- The sampling time of pre-dose samples relative to dosing will be set to zero.
- Any BLQ in the listing of individual concentrations will be presented as BLQ.
- Set any pre-dose BLQ to zero for summaries.

- Set any BLQ occurring in the profile or at the end of the profile to missing and exclude missing values from the calculation of the means.
- Calculate mean concentrations at any individual time point if at least 50% of the individual values are available (i.e. are quantifiable and not missing) at this time point otherwise report as “not calculated (NC)”.

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

12.2 Deriving and Summarizing Pharmacokinetic Parameters

Non-compartmental PK analysis will be performed by CSLB or its designate for PK parameter estimations using Phoenix WinNonlin, Version 6.3 or higher. Only concentrations - time profiles following the first infusion of the last infusion cycle in each Treatment Period and Treatment Sequence will be used to calculate the PK parameters. The following PK parameters will be derived using actual sampling collection times:

AUC _{0-tau}	Area Under the concentration-time Curve from time point zero to tau, calculated using a combined linear and logarithmic trapezoidal rule (linear up-log down).
AUC _{0-last}	<p>Area under the concentration time curve from time point zero to the last quantifiable time point, calculated by the linear up/log down rule [mass x time x volume⁻¹]. Interpolation is linear in the constant and ascending parts of the concentration-time profiles, while the interpolation is logarithmic in the descending parts as follows:</p> $\text{if } C_{i+1} \geq C_i \quad \text{AUC}_{i,i+1} = \frac{(t_{i+1} - t_i) \cdot (C_i + C_{i+1})}{2}$ $\text{and if } C_{i+1} < C_i \quad \text{AUC}_{i,i+1} = \frac{(t_{i+1} - t_i) \cdot (C_{i+1} - C_i)}{\ln(C_{i+1}) - \ln(C_i)}$ <p>where AUC_{i, i+1} is the area in the time span (t_{i+1} – t_i) and C_i is the concentration at time t_i. The total area AUC_{0-last} is obtained as the sum of AUC_{S_i, i+1} from all the time intervals:</p> $\text{AUC}_{0-last} = \sum_{x=1}^n \text{AUC}_{(i, i+1)}$ <p>x : sampling number n: last sampling number</p>
C _{trough}	Trough concentration in serum, collected prior to the next infusion during a treatment regimen.
C _{max}	Maximum observed concentration in serum.
t _{max}	Time to reach C _{max}

The plasma PK parameters will be listed and summarized by Treatment Period in each Treatment Sequence with mean (\pm SD) and geometric mean (geometric % CV and 95% CI) for all PK parameters except t_{\max} based on the PK set. C_{trough} will be summarized by each time point by treatment in each Treatment Sequence. t_{\max} will be listed only.

Table 9: Reference time points for the calculation of PK parameters

Treatment	Parameter	Start *	End *
IgPro20	tau	168 h	
	AUC _{0-tau}	AH5 BH16	AH10 BH21
	C _{max} t _{max}	AH5 BH16	Last quantifiable time point at or before AH10/BH21
	AUC _{0-last}	AH5 BH16	Last quantifiable time point at or before AH11/BH22
IgPro10	tau	672 h	
	AUC _{0-tau}	AP15 BP4	AP22 BP11
	AUC _{0-last} C _{max} t _{max}	AP15 BP4	Last quantifiable time point at or before AP22/BP11

* AH5/BH16= 1 to 60 min before 1st infusion
 AH10/BH21= 168 h (7 days) \pm 10 h after 1st infusion
 AH11/BH22= 240 h (10 days) \pm 10 h after 1st infusion
 AP15/BP4= 1 to 60 min before 1st infusion
 AP22/BP11= 672 h (28 days) \pm 24 h after 1st infusion

12.3 Relative Bioavailability of IgPro20

Baseline-corrected AUC_{0-tau}

For the analysis of relative bioavailability, the baseline-corrected AUC_{0-tau} will be calculated. For patients randomized into Sequence A, baseline value is defined by AH1 (1 to 60 min before 1st infusion of Week 1). For patients randomized to Sequence B, baseline value is defined by BP1 (1 to 60 min before 1st infusion of Week 1). The baseline-corrected IgG concentration values will be derived by CSLB or its designate for PK parameter estimations

according to the rules in CSL Guideline for Conducting Non-Compartmental Pharmacokinetic Analyses (PK-GDL-01). Baseline-corrected concentrations for listings and summaries will be calculated by Parexel.

Baseline-corrected values for plasma concentrations are the change from baseline calculated as described in [Section 8.2.4](#). Following baseline correction, any non-positive values occurring post-dose and before the first positive value will be set to zero, whilst any nonpositive values occurring between two positive values or at the end of the profile will be set to missing. If two or more non-positive values occurred in succession, the profile will be deemed to have terminated at the final positive value and subsequent values will be treated as missing.

Dose-normalized baseline-corrected AUC_{0-tau}

dose-normalized baseline-corrected AUC_{0-tau} = baseline-corrected AUC_{0-tau} / Total Dose (g)

where Total Dose is calculated as follows:

Treatment Sequence A / Treatment Period 1 (IgPro20):

$$\text{Total Dose (g)} = \text{Total Administered Volume in Week 14 (mL)} * 0.2 \text{ g/mL}$$

Treatment Sequence A / Treatment Period 2 (IgPro10):

$$\text{Total Dose (g)} = \text{Total Administered Volume in Week 29 (mL)} * 0.1 \text{ g/mL}$$

Treatment Sequence B / Treatment Period 1 (IgPro10):

$$\text{Total Dose (g)} = \text{Total Administered Volume in Week 13 (mL)} * 0.1 \text{ g/mL}$$

Treatment Sequence B / Treatment Period 2 (IgPro20):

$$\text{Total Dose (g)} = \text{Total Administered Volume in Week 30 (mL)} * 0.2 \text{ g/mL}$$

Population bioavailability

Population bioavailability of IgPro20 will be assessed using Mixed Model Repeated Measures (MMRM) on log-transformed dose-normalized baseline-corrected AUC_{0-tau}. The model will include treatment, Treatment Period, and treatment-by-Treatment-Period interaction as fixed effects with an unstructured covariance matrix. Geometric Mean Ratio and corresponding 90% CI derived from the statistical model will be used to assess the relative bioavailability of IgPro20 based on dose-normalized baseline-corrected AUC_{0-tau}.

Additionally, population bioavailability will be assessed for each Treatment Sequence separately. The MMRM will be reduced to include only the treatment effect and subject as a random effect. All other aspects of the model will be as described above.

Individual relative bioavailability

In addition, the individual relative bioavailability of IgPro20 will be summarized in descriptive statistics by Treatment Sequence and overall.

The individual relative bioavailability %F per subject will be calculated as

$$\%F = \frac{\text{dose-normalized baseline-corrected AUC}_{0-168h} (\text{IgPro20 Treatment Period})}{\text{dose-normalized baseline-corrected AUC}_{0-672h} (\text{IgPro10 Treatment Period})}$$

Subjects with either IgPro20 or IgPro10 dose-normalized baseline-corrected $\text{AUC}_{0-\tau}$ unavailable will be excluded from the assessment of relative bioavailability.

13 References

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Man A, Correa JK, Ziemek J, Simms RW, Felson DT, Lafyatis R. Development and validation of a patient-reported outcome instrument for skin involvement in patients with systemic sclerosis. *Ann Rheum Dis.* 2017a;76:1374–80.

IMACS Form 04a: Instructions for the Health Assessment Questionnaire

14 Appendices

Not applicable

Signature Page

IgPro20_2001 - Statistical Analysis Plan - v2.0 - 09Nov2021

Signed By	Date (GMT)
PPD [REDACTED]	17-Nov-2021 20:33:50
Approved-Internal Approval	
PPD [REDACTED]	17-Nov-2021 21:37:38
Approved-Clinical Development Physician Approval	
PPD [REDACTED]	18-Nov-2021 07:25:18
Approved-PPD [REDACTED] Approval	
PPD [REDACTED]	18-Nov-2021 14:52:50
Approved-Subject Matter Expert Approval	

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