CLINICAL STUDY PROTOCOL

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)

Study Number:	IgPro20_2001
Study Product:	IgPro20 (subcutaneous immunoglobulin, Hizentra®) IgPro10 (intravenous immunoglobulin, Privigen®)
Development Phase:	Phase 2
Sponsor:	CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg Germany
Protocol Version:	Amendment 4
EudraCT Number:	2018-003149-41
IND Number:	Not applicable
Protocol Date:	22 February 2021
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation), ethical principles that have their origin in the Declaration of Helsinki, and all applicable national and local regulations.

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

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

REVISION HISTORY

Date	Version	Summary of Changes
06 December 2018	Original	Not applicable
16 July 2019	Amendment 1	• Addition of text regarding identified risk of TEE in treatment population, including new exclusion criteria, monitoring and study stopping rules • Expansion of hemolysis testing as a safety assessment during IgPro20 treatment • Clarification of timing for study endpoint measures • Addition of exclusion criterion to address use of contraception by potential male subjects • Addition of exclusion criteria to address subjects with potential risks of TEE • Addition of DNA and RNA as biomarkers and additional collection of whole blood to obtain DNA and RNA • Addition of TEEs as an Adverse Event of Special Interest • Minor corrections and clarifications
07 November 2019	Amendment 2	• Modification of exclusion criterion 8 • Modification of Primary and Secondary Endpoints to include summaries of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) • Addition of rules for stopping infusion of IgPro20 or IgPro10 and discontinuation of treatment • Addition of text and assessments to monitor renal safety • Addition and classification of hemolysis and potential acute renal injury as AESIs • Addition of guidance regarding the maximum infusion rate for subjects with renal dysfunction • Addition of maximum doses of IgPro20 and IgPro10, based on body weight • Removal of CCI [redacted] (CCI [redacted]) assessment at Baseline • Clarification of the method of scoring for CCI [redacted] • Addition of interim analysis • Minor corrections and clarifications

Date	Version	Summary of Changes
21 October 2020	Amendment 3	• Revision of exclusion criterion 17 • Define adjustments that are effective during the COVID-19 pandemic and provided detailed guidance and procedures that allow investigators the flexibility to complete critical protocol safety and efficacy assessments while limiting subject exposure to COVID-19 at study sites • Minor corrections and clarifications
22 February 2021	Amendment 4	• Added guidance in Section 5.2.3 regarding dispensing investigational product to subjects during a state of emergency or public health crisis • Added an option for remote visits during a state of emergency or public health crisis in Section 8.6.10 • Revised contingencies in Appendix #4 that are effective during a state of emergency or a public health crisis

Clinical Study Protocol Synopsis

Title	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)
Study Number	IgPro20_2001
Sponsor	CSL Behring (CSLB)
Phase	Phase 2
Study Product	IgPro20 (Hizentra) IgPro10 (Privigen)
Indication	Systemic Sclerosis (SSc)
Study Summary and Overview	This is a prospective, multicenter, randomized, open-label, crossover study to investigate the safety, tolerability, relative bioavailability and pharmacokinetics (PK) of weekly subcutaneous (SC) administration of IgPro20 and intravenous (IV) administration of Ig Pro10 every 4 weeks (over 2 to 5 consecutive days) in subjects with diffuse cutaneous SSc (dcSSc) over 16 week treatment periods.
Primary Objectives	The primary objective of the study is to evaluate the safety of IgPro20 in adults with dcSSc.
Primary Endpoints	The primary endpoint is the safety of IgPro20 based on adverse events (AEs) and the change in other clinical tests measured by treatment, treatment sequence, combination of treatment, at the end of each treatment period (Period 1, Week 16; Period 2, Week 32; combination of treatment, Week 32): • Number and percentage of subjects with AEs, treatment-emergent AEs, serious AEs, and AEs of special interest (total, severity, causality, and outcome) • Number and percentage of subjects with AEs categorized as infusion site reactions (ISRs) (total, severity, causality and outcome) • 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)

Secondary Objectives	The secondary objectives of the study are to evaluate: • Relative bioavailability of IgPro20 • PK of IgPro20 • PK of IgPro10 • Safety of IgPro10

Secondary Endpoints	The secondary endpoints to be determined at the end of each treatment period (Period 1, Week 16; Period 2, Week 32; combination of treatment, Week 32) are:
	• IgPro20 relative bioavailability (%F)
	• IgPro20 PK parameters (area under the curve $[AUC]_{0\text{-tau}}$, $AUC_{0\text{-last}}$, maximum [peak] plasma drug concentration $[C_{max}]$, minimum plasma drug concentration $[C_{trough}]$)
	• IgPro10 PK parameters ($AUC_{0\text{-tau}}$, $AUC_{0\text{-last}}$, C_{max}, C_{trough})
	• The safety of IgPro10 based on:
	  ○ AEs
	  ○ Change in other clinical tests

Study Design	Multicenter, randomized, open-label, crossover, phase 2 study
Number of Subjects	Approximately 26 eligible subjects will be enrolled and randomized to expect 20 evaluable subjects (10 subjects per treatment sequence) to complete the study.
Study Duration	Up to 40 weeks for each subject, including a Screening Period of up to 4 weeks, a Treatment Period of 32 weeks (16 weeks each for Treatment Period 1 and Treatment Period 2) and a follow-up telephone call at 4 weeks after end of treatment The overall duration of this study (eg, first subject's Screening Visit to last subject's End of Study [EOS] telephone call) will be approximately 24 months.
Study Population and Main Criteria for Eligibility	**Key inclusion criteria** To be enrolled into the study, subjects must meet all of the following inclusion criteria: • Age ≥ 18 years (male or female) at time of providing written informed consent • Documented diagnosis of systemic sclerosis (scleroderma) according to American College of Rheumatology and European League Against Rheumatism criteria 2013 (diffuse cutaneous form of SSc) • CCI [redacted] • Disease duration ≤ 5 years defined as the time from the first non-Raynaud's phenomenon manifestation

Key exclusion criteria

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

- Primary rheumatic autoimmune disease other than dcSSc, including but not limited to rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disorder, polymyositis, dermatomyositis, as determined by the investigator. Note: subjects with fibromyalgia, secondary Sjogren's syndrome, and scleroderma-associated myopathy at screening are not excluded
- CCI
- History of skin condition or clinical signs and symptoms of a chronic skin disease other than SSc or skin manifestation of an allergic disease or other dermatological conditions precluding SC infusion at the potential SC infusion sites (eg, dermatitis, eczema, psoriasis)
- Subject has clinical signs and symptoms of skin irritation (eg, pruritus, burning, erythema) or hypo- / hyperpigmentation (eg, scars, tattoos) at the potential SC infusion sites
- Significant pulmonary arterial hypertension as documented by mean pulmonary arterial pressure > 30 mmHg on right heart catheterization requiring SC or intravenous (IV) prostacyclin or use of dual oral therapies
- CCI
- SSc renal crisis within 2 years before screening
- Evidence of chronic kidney disease with an estimated glomerular filtration rate < 45 mL/min/1.73m^2 (as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation) or if subject is receiving dialysis. Subjects with current confirmed diagnosis of diabetes mellitus requiring medication with an estimated glomerular filtration rate < 90 ml/min/1.73m^2
- History of documented thrombotic episode eg, pulmonary embolism, deep vein thrombosis, myocardial infarction, thromboembolic stroke at any time (note: history of superficial thrombophlebitis is not exclusionary)
- Known documented thrombophilic abnormalities including current blood hyperviscosity (within 4 weeks before screening), protein S or protein C deficiency, anti-thrombin-3 deficiency, plasminogen deficiency, antiphospholipid syndrome, Factor V Leiden mutation, dysfibrinogenemia, or prothrombin G20210A mutation

	• Recent surgery requiring general anesthesia within the last 4 weeks before Screening • Greater than 3 specified current risk factors for thromboembolic events (TEEs [for documented and currently ongoing conditions]): atrial fibrillation, coronary disease, diabetes mellitus, dyslipidemia, hypertension, obesity (body mass index ≥ 30 kg/m^2), recent significant trauma and immobility (wheelchair-bound or bedridden) • Cardiac insufficiency (New York Heart Association Class III or IV), cardiomyopathy, significant persistent arrhythmia, unstable or advanced ischemic heart disease, or uncontrolled hypertension
Study Product Dose, Dosing Regimen and Administration	IgPro20 (Hizentra®, 20% normal human immunoglobulin) will be administered twice weekly during Treatment Period 1 (Sequence A) and Treatment Period 2 (Sequence B) by SC infusion at a total dose of 0.5g/kg/week for 16 weeks. IgPro10 (Privigen®, 10% normal human immunoglobulin) will be administered over 2 to 5 consecutive days every 4 weeks during Treatment Period 1 (Sequence B) and Treatment Period 2 (Sequence A) via IV infusion at a total dose of 2 g/kg/4 weeks for 16 weeks.
Comparator Product, Dose, Dosing Regimen and Administration	Not applicable.
Efficacy Assessments	CCI [redacted]
Safety Assessments	Safety and tolerability as assessed by AEs, physical examination, vital signs, ECGs, pregnancy tests, PFTs, clinical laboratory tests, hemolysis, TEE, and renal function safety assessments, and patient diary completion and review.
Pharmacokinetics	The PK parameters $AUC_{0\text{-}tau}$, $AUC_{0\text{-}last}$, C_{max}, and C_{trough} will be assessed in order to determine the relative bioavailability of IgPro20.
Other Assessments	CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]

Statistical Analyses	The sample size is mainly based on feasibility, not driven by power calculations for statistical hypothesis testing. With the target sample size of 20 subjects (10 patients per 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% confidence interval with half width ≤ 0.0261 using Wilson score method; if the rate is 0.5, the half width of the 95% confidence interval will be ≤ 0.0414.

Schedule of Assessments: Sequence A, Treatment Period 1 (IgPro20)

Visit[A,B]	Screening	Week 1		Week 3		Week 5		Week 7		Week 9		Week 11		Week 13		Weeks 2, 4, 6, 8, 10, 12		Week 14		Week 15	UNS[C]
Time relative to infusion	**≤ 28 days before randomization**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**		
Informed consent	X																				
Inclusion / exclusion criteria	X	X																			
Assess and record demographics	X																				
Assess and record medical history	X																				
Randomization[D]		X																			
Physical examination[E]	X	X		X		X		X		X		X		X							
Height	X																				
CCI		X																			
CCI		X																			
CCI		X																			
ECG	X	X																			
PFTs (CCI)[F]	X	X																			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight	X	X		X		X		X		X		X		X							
Hematology[G]	X																				
Serum chemistry[G]	X																				
Virology[G]	X																				
Serum pregnancy	X																				
Hemolysis safety[H] assessments	X																				
TEE safety assessments[I]	X	X		X		X		X		X		X		X							
Renal function assessments[J]	X																				
Biomarkers [K]	X					X															

Visit[A,B]	Screening	Week 1		Week 3		Week 5		Week 7		Week 9		Week 11		Week 13		Weeks 2, 4, 6, 8, 10, 12		Week 14		Week 15	UNS[C]
Time relative to infusion	**≤ 28 days before randomization**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**		
Autoantibody	X																				
Serum IgA	X																				
ABO rhesus	X																				
PK sample [L]		X				X				X				X				X	X	X	
Urinalysis	X																				
Urine pregnancy		X				X				X				X							
CCI	X	X																			
CCI		X																			
CCI		X																			
CCI		X																			
CCI		X																			
CCI		X																			
CCI		X																			
Review Patient diary / dispense new Patient diary[M]		X		X		X		X		X		X		X							
IP assignment		X		X		X		X		X		X		X							
IgPro20 SC infusion[N, O]		X		X		X		X		X		X		X		X		X			
Complete infusion form[P]			X		X		X		X		X		X		X		X		X		
Assess and record AEs[Q]	X	X		X		X		X		X		X		X		X		X			X
Record concomitant therapy[Q]	X	X		X		X		X		X		X		X		X		X			X

A = during or after infusion; AE = adverse event; CCI = CCI; CCI = CCI; ECG = electrocardiogram; CCI = CCI; IgA = immunoglobulin A; IgG = immunoglobulin G; IP = investigational product; CCI = CCI; CCI = CCI; P = before infusion; PFT = pulmonary function test; CCI = CCI; PK = pharmacokinetics; SC = subcutaneous; CCI = CCI; CCI = CCI; TEE = thromboembolic event; CCI = CCI; UNS = unscheduled.

Notes to the schedule of assessments:

A: Sequence A, Treatment Period 1 (IgPro20): Weeks 2, 4, 6, 8, 10, 12, 14, and 15 are home visits. Infusions and additional procedures, as applicable, are to be completed at home by a nurse at these visits.

B: A visit window of ± 2 days relative to Randomization is applicable to all treatment visits.

C: At unscheduled visits, any procedure may be performed at the discretion of the investigator.

D: All assessments should be done before randomization with the exception of the infusion and completion of the infusion form. Vital signs should be assessed before and after infusion.

E: A full physical exam will be conducted at Screening and Week 1. An abbreviated physical exam will be performed at all other applicable visits.

F: At the Week 1 Visit, only CCI is to be assessed.

G: See Table 1 for specific laboratory tests.

H: Hemolysis safety assessments; refer to Section 8.1.1.2 for detailed description.

I: TEE safety assessments; refer to Section 8.1.1.3 for detailed description.

J: Renal function assessments (blood chemistry parameters and urine sample). Refer to Section 8.1.1.4.

K: Serum for retention and analysis of biomarkers and whole blood for RNA and DNA to be collected. Blood for DNA collected only at Screening. Blood for autoantibodies not collected Week 5.

L: Refer to Pharmacokinetic Schedule of Assessments: Sequence A for full PK sample collection schedules.

M: At the Week 1 Visit, the patient diary will only be dispensed, not reviewed.

N: The first IgPro20 infusion of the week at Weeks 1, 3, 5, 7, 9, 11 and 13 will be administered at the study site. The second infusion may be administered at home by a nurse. Additional procedures to be completed at these visits: Vital sign assessment as per Table 2, Infusion form completion, Patient diary completion, and AE and concomitant medication documentation.

O: IgPro20 infusion at UNS visit only if applicable per dosing schedule. IgPro20 assignment at UNS visit only if weight change requires dose volume adjustment; changes of > 10% of body weight from baseline / reference visit will require a dose adjustment.

P: Patient diary is to be completed (at the study site or home at any time between infusion and next study visit. IgPro20 infusion form to be completed by study personnel or nurse only, immediately after infusion.

Q: Adverse events and concomitant therapy will not be recorded at site or home visits if PK sample collection is the only scheduled activity.

Schedule of Assessments: Sequence A, Treatment Period 2 (IgPro10)

Visit[A]	Week 17		Week 19	Week 21		Week 23	Week 25		Week 27	Week 29		Week 30	Week 31	UNS[B]	EOT (Week 32) / Early Termination	EOS (Week 36[C]) (via Telephone)
Time relative to infusion	**P**	**A**		**P**	**A**		**P**	**A**		**P**	**A**					
Physical examination[D]	X		X	X		X	X		X	X			X		X	
CCI	X														X	
CCI	X														X	
CCI	X														X	
ECG	X														X	
PFTs (CCI)	X														X	
Vital signs[E]	X	X		X	X		X	X		X	X				X	
Body weight[F]	X			X			X			X			X			
Hematology[G]	X														X	
Serum chemistry[G]	X														X	
Virology[G]															X	
Serum pregnancy															X	
PK sample[H]	X			X			X			X	X	X	X		X	
Hemolysis safety assessment[I]	X		X			X			X				X			
TEE safety assessment[J]	X		X	X		X	X		X	X					X	
Renal function assessments[K]	X		X			X			X				X			
Biomarkers [L]	X														X	
Autoantibody	X														X	
Urinalysis	X														X	
Urine pregnancy	X			X			X			X						
CCI	X														X	
CCI	X														X	
CCI	X														X	
CCI	X														X	
CCI	X														X	
CCI	X														X	
CCI	X														X	
Review Patient diary	X															

Visit[A]	Week 17		Week 19	Week 21		Week 23	Week 25		Week 27	Week 29		Week 30	Week 31	UNS[B]	EOT (Week 32) / Early Termination	EOS (Week 36[C]) (via Telephone)
Patient Treatment Preference Questionnaire[M]															X	
IP assignment	X			X			X			X						
IgPro10 IV infusion[N]	X			X			X			X						
Complete infusion form		X			X			X			X					
Assess and record AEs[O]	X		X	X		X	X		X	X			X	X	X	X
Record concomitant therapy[O]	X		X	X		X	X		X	X			X	X	X	X

A = during or after infusion; AE = adverse event; CCI = CCI; CCI = CCI; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; CCI = CCI; IgG = immunoglobulin G; IP = investigational product; IV = intravenous; CCI = CCI; CCI = CCI; P = before infusion; PFT = pulmonary function test; CCI = CCI; PK = pharmacokinetics; CCI = CCI; CCI = CCI; TEE = thromboembolic event; CCI = CCI; UNS = unscheduled.

Notes to the schedule of assessments:

A: A visit window of ± 2 days relative to Randomization is applicable to all treatment visits.
B: At unscheduled visits, any procedure may be performed at the discretion of the investigator.
C: The safety follow-up EOS Visit is to be conducted via telephone.
D: A full physical exam will be conducted at Week 17 and EOT / Early Termination. An abbreviated physical exam will be performed at all other applicable visits.
E: Vital signs to be assessed before, during, and after each IgPro10 infusion.
F: Body weight to be assessed prior to each IgPro10 infusion.
G: See Table 1 for specific laboratory tests. EOT virology samples are for retention.
H: Refer to Pharmacokinetic Schedule of Assessments: Sequence A for full PK sample collection schedules.
I: Blood and urine samples for hemolysis testing will be collected at Week 17 and within 7 to 14 days after each IgPro10 dose.
J: TEE safety assessments; refer to Section 8.1.1.3 for detailed description.
K: Renal function assessments (blood chemistry parameters and urine sample). Refer to Section 8.1.1.4.
L: Serum for retention and analysis of biomarkers and whole blood for RNA and DNA to be collected.
M: To be completed only by patients who completed both treatment periods.
N: IgPro10 will be administered at the study site over 2 to 5 consecutive days. IgPro10 assignment at UNS visits only if weight change requires dose volume adjustment; changes of > 10% of body weight from baseline / reference visit will require a dose adjustment. IgPro10 infusion at UNS visit only if applicable per dosing schedule.
O: Adverse events and concomitant therapy will not be recorded at site or home visits if PK sample collection is the only scheduled activity.

Schedule of Assessments: Sequence B, Treatment Period 1 (IgPro10)

Visit[A]	Screening	Week 1		Week 3	Week 5		Week 7	Week 9		Week 11	Week 13		Week 15	Weeks 14, 16	UNS[B]
Time relative to infusion	**≤ 28 days before randomization**	**P**	**A**		**P**	**A**		**P**	**A**		**P**	**A**			
Informed consent	X														
Inclusion / exclusion criteria	X	X													
Assess and record demographics	X														
Assess and record medical history	X														
Randomization[C]		X													
Physical examination[D]	X	X		X	X		X	X		X	X		X		
Height	X														
CCI		X													
CCI		X													
CCI		X													
ECG	X	X													
PFTs (CCI)[E]	X	X													
Vital signs[F]	X	X	X		X	X		X	X		X	X			
Body weight[G]	X	X			X			X			X		X		
Hematology[H]	X														
Serum chemistry[H]	X														
Virology[H]	X														
Serum pregnancy	X														
Hemolysis safety assessment[I]	X			X			X			X			X		
TEE safety assessment[J]	X	X		X	X		X	X		X	X		X		
Renal function assessments[K]	X			X			X			X			X		
Biomarkers[L]	X				X										
Autoantibody	X														
Serum IgA	X														
ABO rhesus	X														
PK sample[M]		X			X			X			X	X	X	X	
Urinalysis	X														
Urine pregnancy		X			X			X			X				

Visit[A]	Screening	Week 1		Week 3	Week 5		Week 7	Week 9		Week 11	Week 13		Week 15	Weeks 14, 16	UNS[B]
Time relative to infusion	**≤ 28 days before randomization**	**P**	**A**		**P**	**A**		**P**	**A**		**P**	**A**			
CCI	X	X													
CCI		X													
CCI		X													
CCI		X													
CCI		X													
CCI		X													
CCI		X													
IP assignment		X			X			X			X				
IgPro10 IV infusion[N]		X			X			X			X				
Complete infusion form			X			X			X			X			
Assess and record AEs[O]	X	X		X	X		X	X		X	X		X		X
Record concomitant therapy[O]	X	X		X	X		X	X		X	X		X		X

A = during or after infusion; AE = adverse event; CCI = CCI; CCI = CCI; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; CCI = CCI; IgA = immunoglobulin A; IgG = immunoglobulin G; IP = investigational product; IV = intravenous; CCI = CCI; CCI = CCI; P = before infusion; PFT = pulmonary function test; CCI = CCI; PK = pharmacokinetics; CCI = CCI; CCI = CCI; TEE = thromboembolic event; CCI = CCI; UNS = unscheduled.

Notes to the schedule of assessments:

A: A visit window of ± 2 days relative to Randomization is applicable to all treatment visits.
B: At unscheduled visits, any procedure may be performed at the discretion of the investigator.
C: All assessments should be done before randomization with the exception of infusion and completion of the infusion form.
D: A full physical exam will be conducted at Screening and Week 1. An abbreviated physical exam will be performed at all other applicable visits.
E: At the Week 1 Visit, only CCI is to be assessed.
F: Vital signs to be assessed before, during, and after each IgPro10 infusion
G: Body weight to be assessed before each IgPro10 infusion.
H: See Table 1 for specific laboratory tests.
I: Blood and urine samples for hemolysis testing will be collected at Screening and within 7 to 14 days after each IgPro10 dose.
J: TEE safety assessments; refer to Section 8.1.1.3 for detailed description.
K: Renal function assessments (blood chemistry parameters and urine sample). Refer to Section 8.1.1.4.

L: Serum for retention and analysis of biomarkers and whole blood for RNA and DNA to be collected. Blood for DNA collected only at Screening. Blood for autoantibodies not collected Week 5.
M: Refer to Pharmacokinetic Schedule of Assessments: Sequence B for full PK sample collection schedules.
N: IgPro10 will be administered at the study site over 2 to 5 consecutive days. IgPro10 assignment at UNS visit only if weight change requires dose volume adjustment; changes of > 10% of body weight from baseline / reference visit will require a dose adjustment. IgPro10 infusion at UNS visit only if applicable per dosing schedule.
O: Adverse events and concomitant therapy will not be recorded at site or home visits if PK sample collection is the only scheduled activity.

Schedule of Assessments: Sequence B, Treatment Period 2 (IgPro20)

Visit[A,B]	Week 17		Week 19		Week 21		Week 23		Week 25		Week 27		Week 29		Weeks 18, 20, 22, 24, 26, 28		Week 30		Week 31	UNS[C]	EOT (Week 32) / Early Termination	EOS (Week 36[D]) (via Telephone)
Time relative to infusion	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**				
Physical examination[E]	X		X		X		X		X		X		X								X	
CCI [redacted]	X																				X	
CCI [redacted]	X																				X	
CCI [redacted]	X																				X	
ECG	X																				X	
PFTs (CCI [redacted])	X																				X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Body weight	X		X		X		X		X		X		X									
Hematology[F]	X																				X	
Serum chemistry[F]	X																				X	
Virology[F]																					X	
Serum pregnancy																					X	
Hemolysis safety assessment[G]	X																				X	
TEE safety assessment[H]	X		X		X		X		X		X		X								X	
Renal function assessments[I]	X																				X	
PK sample[J]	X				X				X				X				X	X	X			
Biomarkers[K]	X																				X	
Autoantibody	X																				X	
Urinalysis	X																				X	
Urine pregnancy	X				X				X				X									
CCI [redacted]	X																				X	
CCI [redacted]	X																				X	
CCI [redacted]	X																				X	
CCI [redacted]	X																				X	
CCI [redacted]	X																				X	
CCI [redacted]	X																				X	
CCI [redacted]	X																				X	

Visit[A,B]	Week 17		Week 19		Week 21		Week 23		Week 25		Week 27		Week 29		Weeks 18, 20, 22, 24, 26, 28		Week 30		Week 31	UNS[C]	EOT (Week 32) / Early Termination	EOS (Week 36[D]) (via Telephone)
Time relative to infusion	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**	**P**	**A**				
Patient Treatment Preference Questionnaire[L]																					X	
Review patient diary / dispense new patient diary[M]	X		X		X		X		X		X		X								X	
IP assignment	X		X		X		X		X		X		X									
IgPro20 SC infusion[N,O]	X		X		X		X		X		X		X		X		X					
Complete infusion form[P]		X		X		X		X		X		X		X		X	X					
Assess and record AEs[Q]	X		X		X		X		X		X		X		X		X			X	X	X
Record concomitant therapy[Q]	X		X		X		X		X		X		X		X		X			X	X	X

A = during or after infusion; AE = adverse event; CCI = CCI; CCI = CCI; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; CCI = CCI; IgG = immunoglobulin G; IP = Investigational Product; CCI = CCI; CCI = CCI; P = before infusion; PFT = pulmonary function test; CCI = CCI; PK = pharmacokinetics; SC = Subcutaneous; CCI = CCI; CCI = CCI; TEE = thromboembolic event; CCI = CCI; UNS = unscheduled.

Notes to the schedule of assessments:

A: Sequence B, Treatment Period 2 (IgPro20) Weeks 18, 20, 22, 24, 26, 28, 30, and 31 are home visits. Infusions and additional procedures, as applicable, to be completed at home by a nurse at these visits.

B: A visit window of ± 2 days relative to Randomization is applicable to all treatment visits.

C: At unscheduled visits, any procedure may be performed at the discretion of the investigator.

D: The safety follow-up EOS Visit is to be conducted via telephone.

E: A full physical exam will be conducted at Week 17 and EOT / Early Termination. An abbreviated physical exam will be performed at all other applicable visits.

F: See Table 1 for specific laboratory tests. EOT virology samples are for retention.

G: Hemolysis safety assessments; refer to Section 8.1.1.2 for detailed description.

H: TEE safety assessments; refer to Section 8.1.1.3 for detailed description.

I: Renal function assessments (blood chemistry parameters and urine sample). Refer to Section 8.1.1.4.

J: Refer to Pharmacokinetic Schedule of Assessments: Sequence B for full PK sample collection schedules.

K: Serum for retention and analysis of biomarkers and whole blood for RNA to be collected.

L: To be completed only by patients who completed both treatment periods.

M: At the Week 1 Visit, the patient diary will only be dispensed, not reviewed.
N: The first IgPro20 infusion of the week at Weeks 17, 19, 21, 23, 25, 29, and 31 will be administered at the study site. The second infusion may be administered at home by a nurse. Additional procedures to be completed at these visits: Vital sign assessment as per Table 2, Infusion form completion, Patient diary completion, and AE and concomitant medication documentation.
O: IgPro20 infusion at UNS visit only if applicable per dosing schedule. IgPro20 assignment at UNS visits only if weight change requires dose volume adjustment; changes of > 10% of body weight from baseline / reference visit will require a dose adjustment.
P: Patient diary is to be completed (at the study site or home) at any time between infusion and next study visit. IgPro20 infusion form to be completed by study personnel or nurse only, immediately after infusion.
Q: Adverse events and concomitant therapy will not be recorded at site or home visits if PK sample collection is the only scheduled activity.

Pharmacokinetic Schedule of Assessments: Sequence A

Treatment Period 1

Week	1	5	9	13	14						15
PK Timepoint[D]	Baseline (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion of Week 14)[A]	24 h (1 d) ± 4 h (after 1st infusion, Week 14)	48 h (2 d) ± 6 h (after 1st infusion, Week 14)	72 h (3 d) ± 6 h (after the 1st infusion, Week 14)	96 h (4 d) ± 6 h (after 1st infusion, Week 14)	168 h (7 d) ± 10 h (after 1st infusion, Week 14)	240 h (10 d) ± 10 h (after 1st infusion, Week 14)
PK sample collection	AH1[B]	AH2[B]	AH3[B]	AH4[B]	AH5[C]	AH6[C]	AH7[C]	AH8[C]	AH9[C]	AH10[C, D]	AH11[C]

AH = Treatment Period 1 IgPro20; d = days; min = minutes; PK = Pharmacokinetic.

Treatment Period 2

Week	17	21	25	29				30		31	32
PK Timepoint[D]	(1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Immediately after the end of 1st infusion, Week 29 (1 to 60 min)[A]	1 to 60 min after 2nd infusion, Week 29	168 h (7d) ± 6 h (after 1st infusion, Week 29)	264 h (11d) ± 10 h (after 1st infusion, Week 29)	336 h (14d) ± 10 h (after 1st infusion, Week 29)	504 h (21 d) ± 24 h (after 1st infusion, Week 29)	672 h (28d) ± 24 h (after 1st infusion, Week 29)
PK sample collection	AP12[B]	AP13[B]	AP14[B]	AP15[B]	AP16[B]	AP17[B]	AP18[C,D]	AP19[C]	AP20[C,D]	AP21[C,D]	AP22[B,D]

AP = Treatment Period 2 IgPro10; d = days; min = minutes; PK = pharmacokinetic.

A: Serves as the reference collection for the subsequent follow-up collections.
B: Sample collected at a site visit.
C: Sample collected at a home visit.
D: Sample should be collected at the hour of timepoint (± window) indicated, even if not aligned with indicated week.

Pharmacokinetic Schedule of Assessments: Sequence B

Treatment Period 1

Week	1	5	9	13				14		15	16
PK Timepoint[E]	Baseline (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Immediately after the end of 1st infusion, Week 13 (1 to 60 min)[A]	1 to 60 min after 2nd infusion, Week 13	168 h ± 6 h (7d) (after 1st infusion, Week 13)	264 h (11 d) ± 10 h (after 1st infusion, Week 13)	336 h (14 d) ± 10 h (after the 1st infusion, Week 13)	504 h (21 d) ± 24 h (after the 1st infusion, Week 13)	672 h (28 d) ± 24 h (after 1st infusion, Week 13)
PK sample collection	BP1[B]	BP2[B]	BP3[B]	BP4[B]	BP5[B]	BP6[B]	BP7[C,E]	BP8[C]	BP9[C,E]	BP10[B,E]	BP11[D,E]

BP = Treatment Period 1 IgPro10; d = days; min = minutes; PK = Pharmacokinetic.

Treatment Period 2

Week	17	21	25	29	30						31
PK Timepoint[E]	1 to 60 min before 1st infusion	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion)	Trough (1 to 60 min before 1st infusion, Week 30)[A]	24 h (1 d) ± 4 h (after 1st infusion, Week 30)	48 h (2 d) ± 6 h (after 1st infusion, Week 30)	72 h (3 d) ± 6 h (after 1st infusion, Week 30)	96 h (4 d) ± 6 h (after 1st infusion, Week 30)	168 h (7 d) ± 10 h (after 1st infusion, Week 30)	240 h (10 d) ± 10 h (after 1st infusion, Week 30)
PK sample collection	BH12[B,D]	BH13[B]	BH14[B]	BH15[B]	BH16[C]	BH17[C]	BH18[C]	BH19[C]	BH20[C]	BH21[C,E]	BH22[C]

BH = Treatment Period 2 IgPro20; d = days; min = minutes; PK = Pharmacokinetic.

A: Serves as the reference collection for the subsequent follow-up collections.
B: Sample collected at a site visit.
C: Sample collected at a home visit.
D: BP11 and BH12 can be taken at the same time point, if appropriate with dosing schedule and visit window.
E: Sample should be collected at the hour of timepoint (± window) indicated, even if not aligned with indicated week.

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List of Abbreviations

Abbreviation	Term
ACR	American College of Rheumatology
AE	Adverse event
AESI	Adverse event of special interest
AMS	Aseptic meningitis syndrome
AUC	Area under the curve
β-hCG	Beta-human chorionic gonadotropin
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
C_{max}	Maximum plasma drug concentration
COVID-19	Coronavirus disease 2019
CCI	CCI
CSLB	CSL Behring
C_{trough}	Minimum plasma drug concentration
dcSSc	Diffuse cutaneous systemic sclerosis
CCI	CCI
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full analysis set
CCI	CCI
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
CCI	CCI
CCI	CCI
HIV	Human immunodeficiency virus

Abbreviation	Term
HRCT	High-resolution computed tomography
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ISR	Infusion site reaction
ITP	Immune thrombocytopenic purpura
IV	Intravenous
IVIG	Intravenous immunoglobulin
lcSSc	Limited cutaneous systemic sclerosis
CCI	CCI
CCI	CCI
PE	Pulmonary embolism
PFT	Pulmonary function test(s)
CCI	CCI
PID	Primary immunodeficiency
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
CCI	CCI
SMQ	Standardized MedDRA queries
SSc	Systemic sclerosis
CCI	CCI
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic events

Abbreviation	Term
CCI	CCI
US	United States of America
CCI	CCI

Glossary	
Baseline	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.
Reference visit	Reference visit for Treatment Period 1 is defined as the baseline of the study. Reference visit for Treatment Period 2 is defined as the most recent assessment before the first infusion in Treatment Period 2, after completion of planned treatment in Treatment Period 1.
Session	Each weekly dose of IgPro20 will be divided into two separate infusions and administered in two sessions: Session 1 and Session 2. Each treatment of IgPro10 will be administered over 2 to 5 consecutive days every 4 weeks.
Sequence	The study will consist of 2 sequences, Sequence A or Sequence B. Each subject will be randomized to 1 of the 2 treatment sequences.
Sequence A	IgPro20 0.5g/kg/week subcutaneous (SC) infusion in Treatment Period 1 + IgPro10 2g/kg/4 weeks intravenous (IV) infusion in Treatment Period 2
Sequence B	IgPro10 2g/kg/4 weeks IV infusion in Treatment Period 1 + IgPro20 0.5g/kg/week subcutaneous (SC) infusion in Treatment Period 2
Treatment	Treatment will be either IgPro20 0.5g/kg/week or IgPro10 2g/kg/4 weeks.

Treatment period	Each sequence will consist of two 16-week periods of treatment, a period of IgPro20 treatment and a period of IgPro10 treatment.

1 Introduction

1.1 Background

Systemic sclerosis (SSc) is a rare and progressive autoimmune connective tissue disorder with a prevalence rate of approximately 50-300 cases per million worldwide [Chifflot et al, 2008]. SSc is one of the most life-threatening rheumatic autoimmune diseases [Ioannidis et al, 2005; Elhai et al, 2012]; cumulative survival for patients with this disease has been estimated at 74.9% at 5 years and 62.5% at 10 years from diagnosis [Rubio-Rivas et al, 2014]. Pulmonary involvement represents the main cause of death in these patients [Rubio-Rivas et al, 2014; Tyndall et al, 2010; Lefevre et al, 2013]. The clinical manifestations of SSc are extremely heterogeneous and the prognosis is generally poor, with the majority of patients having skin thickening and variable involvement of internal organs [van den Hoogen et al, 2013; Denton, 2016; Denton and Khanna, 2017]. The disease is characterized by progressive vascular damage (Raynaud's phenomenon, digital ulcers, hypertensive renal failure, cardiomyopathy, and pulmonary hypertension) and organ fibrosis (skin thickening, pulmonary fibrosis, gastrointestinal dysmotility, and myocardial fibrosis). The most widely accepted clinical criterion is to separate patients with SSc based on the distribution of skin thickening into limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) [LeRoy et al, 1988; Leroy and Medsger, 2001]. Patients with lcSSc in general have skin thickening limited to areas distal to the elbows and knees, face, and neck while dcSSc is characterized by skin thickening over the entire extremity. Patients with dcSSc, accounting for 20% to 40% of all of cases of SSc, generally experience early rapid progression of skin thickening and are at high risk for early, widespread, and severe internal organ involvement [Ferreli et al, 2017]. Therefore, dcSSc is associated with numerous detrimental effects on health-related quality of life and often results in disability and substantial morbidity and mortality [Ferreli et al, 2017; Khanna et al, 2011a].

While treatment recommendations were recently published for SSc, the mainstays of current treatment of SSc are organ-based and primarily aimed at improving symptoms and managing complications [Young and Khanna, 2015; Kowal-Bielecka et al, 2017]. There are no approved disease-modifying treatment modalities for the disease. Available systemic therapeutic options, primarily immunosuppressants, are used off label (except in Japan where cyclophosphamide and azathioprine are approved for refractory SSc based on evidence in the public domain) and are generally only partially effective and associated with unwanted immunosuppressive side effects including severe infection [Kowal-Bielecka et al, 2017; Khanna et al, 2016b]. Therefore, there is a high unmet medical need for new therapeutic options for the SSc patient population.

Immunoglobulin G (IgG) therapy has been part of the treatment armamentarium for autoimmune disorders for many years [Enk et al, 2016; Kerr et al, 2014; Sewell et al, 2014; Baleva and Nikolov et al, 2011]. IgPro20 (Hizentra®, 20% SC human immunoglobulin) and IgPro10 (Privigen®, 10% IV human immunoglobulin) have been approved for the treatment of autoimmune diseases (IgPro20 – chronic inflammatory demyelinating polyneuropathy [CIDP]; IgPro10 – CIDP and chronic immune thrombocytopenic purpura [ITP]). Although a relatively small number of publications are available on intravenous immunoglobulin (IVIG) use in patients with SSc, including lcSSc and dcSSc, IVIG may have a beneficial effect on multiple clinical manifestations in SSc patients [Baleva and Nikolov, 2011; Cantarini et al, 2015; Poelman et al, 2015; Raja et al, 2016; Sanges et al, 2017], CCI [redacted]

Based on experience in other indications, it is known that the adverse event (AE) profiles of IVIG and SCIG are different and mostly specific to the route of administration. SCIGs are characterized by a lower rate than IVIGs of systemic AEs such as flushing, fever, nausea, and vomiting during or shortly after infusion, lower rates of hemolysis, fewer thromboembolic events (TEEs), lower rates of aseptic meningitis, and a minimal "wearing off" effect at the end of the dosing interval in the treatment [Perez et al, 2017]. The most common AEs associated with SCIG products are local infusion site reactions (ISRs); eg, erythema, edema, local itch, heat, or pain. However, ISRs are predominantly mild and quickly resolve without special treatment and usually decrease in frequency over time [Cherin et al, 2016; Ballow et al, 2017; Perez et al, 2017]. Overall lower rates of systemic AEs, flexible dosing regimens, improved quality of life, and cost savings are all important advantages of SCIG administration for treatment of any condition currently treated with IVIG [Berger et al, 2010; Jolles et al, 2011; Shapiro, 2013; Perez et al, 2017].

Nevertheless, the safety of SCIG products in SSc requires special attention as this disease pathology is characterized by small vessel vasculopathy and excessive collagen deposition in the skin and internal organs. The change in skin and SC tissues leads to fibrosis and sometimes ulceration [Denton, 2016], and this vasculopathy and other alterations in connective tissues may impact the safety profile and pharmacokinetics (PK) (eg, absorption) of immunoglobulin through SC administration to patients with SSc. Therefore, before efficacy and safety of any other SCIG product is assessed in a large-scale clinical study, a separate investigation of safety, as well as a PK assessment of IgPro20 in dcSSc patients is

warranted. In order to assess the relative bioavailability of IgPro20, the PK of IgPro10 will also be evaluated in the same patient in the proposed study population.

1.2 Information on Study Products

1.2.1 Overview

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 immunodeficiency (PID) syndromes and other indications.

IgPro10 is a ready-to-use 10% liquid formulation of IgG with > 98% IgG purity for intravenous (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 PID in patients ≥ 3 years of age, for CIDP in adults, and for chronic ITP 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.

The mechanism of action of IgG therapy in autoimmune conditions and, specifically, in SSc, is complex and not fully understood [Baleva and Nikolov, 2011; Cantarini et al, 2015; Berger and Steen, 2017]. Published reports suggest that the potential mechanisms of action of therapeutic IgG includes neutralizing toxins and super-antigens, neutralizing and / or increasing the catabolism of autoantibodies, blocking Fc receptors, inhibiting inflammatory mediators (eg, cytokines and chemokines), and reducing immune complexes [Baleva and Nikolov, 2011; Galeotti et al, 2017; Schwab and Nimmerjahn, 2013]. However, detailed studies in autoimmune neuropathies suggest that the most important mechanisms in vivo are anti-idiotypic neutralization of pathogenic autoantibodies, increased catabolism of autoantibodies, and inhibition of complement deposition and activation [Berger, 2013]. To the extent that autoantibodies contribute to the pathophysiology of SSc, it may thus be expected that IgG therapy may ameliorate their effects by these mechanisms. The anti-fibrotic effects of IgG may also be mediated through the suppression of profibrotic cytokines, down-regulation of fibroblast transforming growth factor-beta, inhibition of complement activation, and through the presence of anti-fibrotic antibodies within IgG preparations [Cantarini et al, 2015].

A detailed description of the chemistry, pharmacology, efficacy, and safety of IgPro20 and IgPro10 is provided in the respective Investigator's Brochures.

1.2.2 Nonclinical Evaluation

Human IgGs are naturally occurring proteins with a well-established safety and tolerability record. The testing of human immunoglobulin preparations in animal models is of limited value because immunoglobulins are immunologically active and can cross-react between species. IgPro20 contains the same purified IgG drug substance as IgPro10, the marketing approval of which was based on a broad nonclinical assessment. Therefore, the nonclinical studies with IgPro20 focused on its SC use (local tolerance after single and multiple doses, PK) and safety regarding hypotensive effects. None of these studies identified any relevant safety findings that might translate into a safety concern in clinical studies of IgPro20. The safety of the excipient L-proline was assessed in a nonclinical study with IgPro20 as well as in a number of studies during the development of IgPro10, from which it was concluded that the use of L-proline as an excipient at the specified concentrations raises no safety concerns.

1.2.3 Clinical Experience

IgPro20 has been developed for clinical use in immunoglobulin replacement therapy. Three pivotal phase 3 studies and 4 extension and follow-up studies in a total of 231 subjects with PID were completed, and 2 studies are ongoing (70 total subjects planned). A phase 4 postmarketing study in PID and secondary immunodeficiency was also completed (this study enrolled 25 subjects; all subjects with PID).

IgPro20 has also been developed for the treatment of CIDP as maintenance therapy to prevent relapse of neuromuscular disability and impairment. Two CIDP studies were completed: 1 pivotal phase 3 study with a total of 172 subjects (115 IgPro20 and 57 placebo subjects); and 1 extension study with a total of 82 subjects; all extension study subjects also participated in the pivotal study).

In addition, 1 phase 1 study in 28 healthy subjects was conducted, which investigated the local tolerability and safety of IgPro20, IgPro16, and Vivaglobin.

Marketing approval of IgPro10 was based on 2 pivotal, prospective, open-label, single-arm, multicenter, phase 3 studies; 1 study performed in the EU in subjects with chronic ITP (Study ZLB03_003CR) and another study performed in the US and the EU in subjects with PID (Study ZLB03_002CR).

Moreover, Study ZLB05_006CR was an extension study to Study ZLB03_002CR in subjects with PID, and Study IgPro10_4001 was performed in the EU in subjects with ITP.

CSLB has also completed 2 phase 3 studies with IgPro10 in the neurological indication CIDP (Study IgPro10_3001 in the EU, and Study IgPro20_3003 in the EU, the US and other regions), and has 1 ongoing phase 3/4 study with IgPro10 in pediatric CIDP (Study IgPro10_4002 in the US).

1.3 Study Overview

This prospective, multicenter, randomized, open-label, crossover study will investigate the safety, tolerability, and PK of IgPro20 at the weekly SC dose of 0.5g/kg body weight in subjects with dcSSc. The study also aims to evaluate the relative bioavailability of IgPro20, and characterize PK of IgPro20 and IgPro10, respectively, in subjects with dcSSc. Additionally, the safety of IgPro10 will be assessed. See Section 3.1 for specific details about this study.

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

1.4.1.1 IgPro20 Risks

Although the safety profile of IgPro20 has not been evaluated in patients with SSc, IgPro20 has, in general, been demonstrated to be a safe product based on safety data obtained from previous clinical studies sponsored by CSLB in various indications. IgPro20 safety data have been accumulated with weekly doses up to 0.4 mg/kg. In a recently completed global CIDP program (IgPro20_3003; a 24-week pivotal study [172 subjects] and a 48-week extension study [82 subjects]), 0.4 and 0.2 g/kg weekly doses were evaluated. In both CIDP studies, the systemic AE rate was low and local reactions were mild to moderate and decreased in frequency over time. Neither infusion rate nor volume had an effect on systemic AEs or local reaction rates.

The most commonly reported adverse reactions have included local ISRs (see below), headache, diarrhea, fatigue, back pain, nausea, pain in extremities, cough, rash, pruritis, vomiting, abdominal pain, migraine, pain, and nasopharyngitis. The majority of adverse reactions in all completed clinical studies were mild to moderate.

IgPro20 is also associated with important identified risks, including local reactions, ulceration-like ISRs, anaphylactic reactions, aseptic meningitis syndrome (AMS), and TEE. Other unknown IgPro20-associated risks maybe linked with home based SC (self-) administration, such as exacerbation of existing hyperprolinemia, hemolysis, or transmission of infectious agents.

The most common AEs associated with SCIG products are local ISRs; eg, erythema, edema, local itch, heat, or pain. Depending on the method and timing of evaluation, these AEs occur very commonly in patients administered SCIG. However, ISRs are predominantly mild, quickly resolve without special treatment, and usually decrease in frequency over time [Cherin et al, 2016; Ballow et al, 2017; Perez et al, 2017]. For this population of SSc patients with skin conditions, ISRs will be monitored and evaluated during this study.

Further details on identified potential risks of IgPro20 are available in the Investigator's Brochure.

1.4.1.2 IgPro10 Risks

IgPro10 has been demonstrated to have a favorable safety profile based on safety data obtained from previous clinical studies sponsored by CSLB in various indications, including PID, secondary immunodeficiency, chronic ITP and CIDP, and postmarketing experience collected over the past 11 years.

The important identified risks with the use of IVIG products are AMS, hemolysis, hypersensitivity and anaphylactic reactions, TEEs, and acute renal failure. Important potential risks include transfusion-related acute lung injury and potential for transmission of infectious agents.

Thrombosis may occur following treatment with immunoglobulin products. Thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism, and deep vein thromboses are assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in patients at high risk. Enrollment of subjects with high risk factors for thrombosis or histories of TEEs will be limited in this study. To prevent potentially severe hypersensitivity and anaphylactic reactions, the study will also exclude subjects with a history of anaphylactic or severe systemic reaction to the administration of human immune globulin or immunoglobulin A (IgA)-deficiency with known anti-IgA antibodies. Acute renal dysfunction / failure may occur with the use of IVIG products, particularly in those products containing sucrose (IgPro10 does not contain sucrose). The study will ensure that patients are not volume depleted and their renal function is adequately monitored. Additionally, enrollment will exclude subjects with severe and moderate-to-severe chronic renal disease (see Section 4.1.2 [exclusion criterion 8] and Section 8.1.1.4).

Further details on identified potential risks of IgPro10 are available in the Investigator's Brochure.

1.4.1.3 Crono S-PID-100 Infusion Pump Risks

IgPro20 will be administered using the Crono S-PID-100 Infusion Pump. There are no specific risks associated with Crono S-PID-100 Infusion Pump use. Technical malfunctioning or leakage from connections between syringe, tubing and / or needle, or the infusion site itself (eg, due to inadequate placement of the butterfly needle) may occur.

1.4.2 Potential Benefits

1.4.2.1 IgPro20 Benefits

To date, there are no published data on the use of SCIG products in any form of SSc. Although a relatively small number of publications are available on IVIG use in patients with SSc, including lcSSc and dcSSc, IVIG may have a beneficial effect on multiple clinical manifestations in SSc patients [Baleva and Nikolov, 2011; Cantarini et al, 2015]. CCI [redacted]

In addition, the kinetics and dosing regimen of SCIG are different from that of IVIG; therefore, it is possible that SCIG will have fewer systemic reactions and wear-off effect [Perez et al, 2017]. Furthermore, SCIG administration and home therapy regimens in clinical practice have been found to be generally well tolerated and associated with improvement in quality of life and treatment satisfaction due to increased independence and scheduling flexibility as compared with IVIG administration. The dose of SCIG can be divided into smaller portions and self-administered after adequate training 1 to 2 times a week or more frequently depending on individual dose and tolerability in other indications [Jones et al, 2012; Sidhu et al, 2014; Sriaroon and Ballow, 2015].

1.4.2.2 IgPro10 Benefits

A potential benefit of IgPro10 is the improvement in skin score and stabilization of organ function as measured by the outcome assessments. As indicated earlier, based on current literature, an improvement from pretreatment baseline in skin score / thickening and other clinical outcome measures by 2g/kg/month IVIG in patients with SSc has been observed [Baleva and Nikolov, 2011; Cantarini et al, 2015]. IVIG preparations in general have a well-known safety and efficacy profile in autoimmune diseases in dermatology, neurology, and

chronic ITP [Enk et al, 2016; Baleva and Nikolov, 2011; Cantarini et al, 2015; Eibl, 2003; Wittstock and Zettl, 2006].

1.4.3 Benefit-risk Conclusion

Overall, based on the associated benefit-risk for this study, it is acceptable for subjects who continue on their current background therapy (see Section 7.2) to be enrolled into this phase 2 study to evaluate the safety and PK of IgPro20 and IgPro10 in patients with dcSSc.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoints

2.1.1 Primary Objective

The primary objective of the study is to evaluate the safety of IgPro20 in adults with dcSSc.

2.1.2 Primary Endpoints

The primary endpoint of the study is the safety of IgPro20 based on:

Safety Endpoints	Summary Measure
AEs, including any AEs, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs)	AEs measured by treatment, treatment sequence, combination of treatment, and treatment period (Period 1, Week 16; Period 2, Week 32; combination of treatment, Week 32): • Number and percentage of subjects with AEs, TEAEs, SAEs, and AESIs (total, severity, causality, and outcome) • Number and percentage of subjects with AEs categorized as ISRs (total, severity, causality and outcome) • Rate of ISRs per subject and per infusion • Onset and duration of ISRs
Change in other clinical tests	Changes from baseline as measured by treatment, treatment sequence, combination of treatment and treatment period: • Vital signs • Body weight • Clinical laboratory tests • Electrocardiogram (ECG) • Pulmonary function tests (PFTs)

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of the study are to evaluate:

- Relative bioavailability of IgPro20
- PK of IgPro20
- PK of IgPro10
- Safety of IgPro10

2.2.2 Secondary Endpoints

Secondary Objective	Endpoint	Summary Measure(s) (To be determined at the end of each treatment period [Period 1, Week 16; Period 2, Week 32; combination of treatment, Week 32])
1	IgPro20 relative bioavailability (%F)	Geometric mean ratio of area under the serum IgG concentration time curves within a dosing duration (dose-normalized area under the curve to the end of the dosing period [$AUC_{0\text{-}tau}$]) following administration of the first dose of IgPro20 or IgPro10 in the last week of dosing for Sequence A and / or Sequence B
2	IgPro20 PK parameters ($AUC_{0\text{-}tau}$, area under the curve to the last dosing period [$AUC_{0\text{-}last}$], maximum [peak] plasma drug concentration [C_{max}], minimum plasma drug concentration [C_{trough}])	Geometric mean of PK parameters and corresponding 95% confidence interval (CI) by treatment in each sequence
3	IgPro10 PK parameters ($AUC_{0\text{-}tau}$, $AUC_{0\text{-}last}$, C_{max}, C_{trough})	Geometric mean of PK parameters and corresponding 95% CI by treatment in each sequence
4	The safety of IgPro10 based on AEs, including any AEs, TEAEs, SAEs, and AESIs	AEs measured by treatment, treatment sequence, combination of treatment and treatment period: • Number and percentage of subjects with AEs, TEAEs, SAEs, and AESIs (total, severity, causality and outcome) • Number and percentage of subjects with categorized as ISRs (total, severity, causality and outcome)

Secondary Objective	Endpoint	Summary Measure(s) (To be determined at the end of each treatment period [Period 1, Week 16; Period 2, Week 32; combination of treatment, Week 32])
	The safety of IgPro10 based on the change in other clinical tests	Changes from baseline as measured by treatment, treatment sequence, combination of treatment and treatment period • Vital signs • Body weight • Clinical laboratory tests • ECG • PFTs

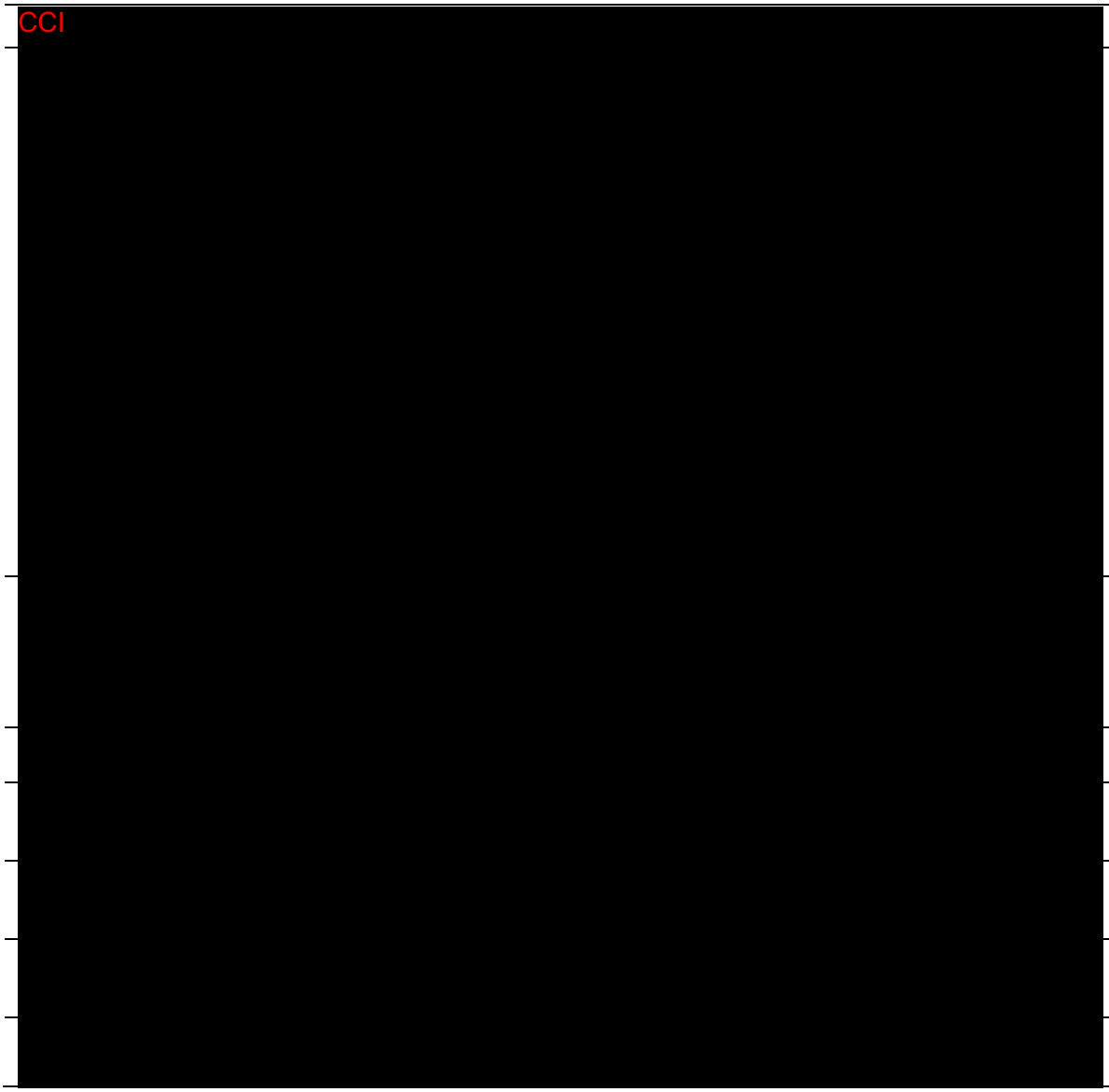
2.3 CCI

2.3.1 CCI

CCI

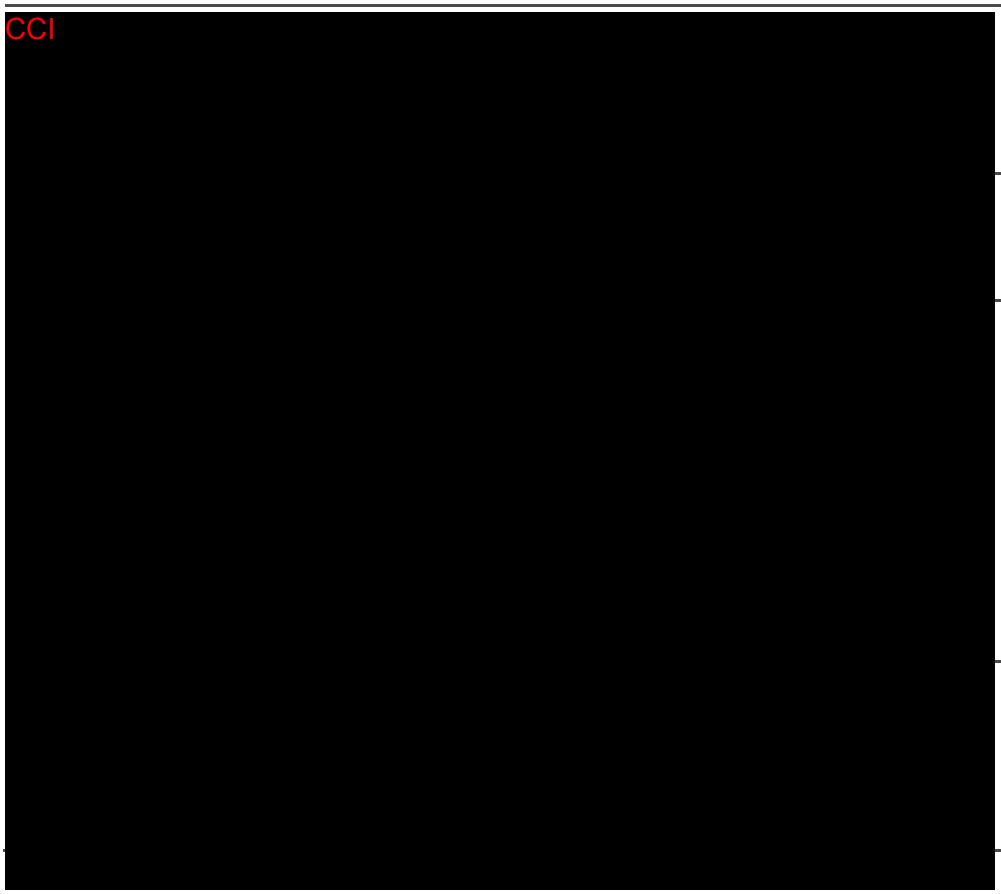
2.3.2 CCI

CCI



2.4 CCI

CCI



3 Study Overview

3.1 Study Design and Rationale

This is a prospective, multicenter, randomized, open-label, crossover study to investigate the safety and PK of IgPro20 and IgPro10 in subjects with 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 subjects with dcSSc.

The study design is illustrated in Figure 1. Subjects 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. During a screening period, investigators will evaluate the eligibility of potential subjects utilizing the 2013 European League Against Rheumatism / American College of Rheumatology (EULAR / ACR) criteria [van den Hoogen et al, 2013] for SSc and diffuse features [LeRoy and Medsger, 2001; LeRoy et al, 1988] to accurately confirm their classification as dcSSc. All eligible subjects will be randomized (1:1) to Sequence A (IgPro20-IgPro10 treatment sequence) or Sequence B (IgPro10-IgPro20 treatment sequence). Each subject will complete Treatment Period 1 and Treatment Period 2

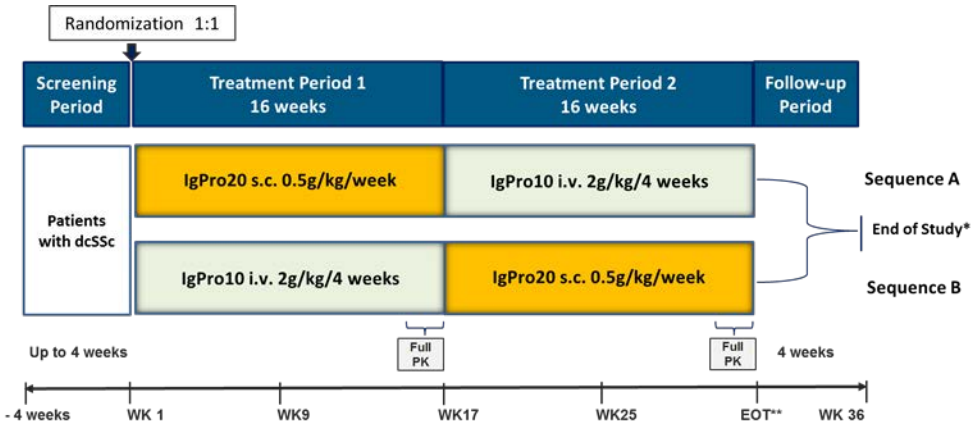
(16 weeks each), with up to 40 weeks (including Screening) of study duration for an individual subject.

In this crossover study, subjects in Sequence A will receive a total dose of 0.5 g/kg IgPro20 over 2 sessions per week every week in Treatment Period 1, and a total dose of 2 g/kg IgPro10 over 2 to 5 sessions on consecutive days every 4 weeks in Treatment Period 2. Subjects in Sequence B will receive a total dose of 2 g/kg IgPro10 over 2 to 5 sessions on consecutive days every 4 weeks in Treatment Period 1 and a total dose of 0.5 g/kg IgPro20 over 2 sessions per week every week in Treatment Period 2.

The weekly 0.5 g/kg body weight dose of IgPro20 is equivalent to an every 4 week dose of IgPro10 (2 g/kg body weight) if using a 1:1 conversion. This is the highest possible IgPro20 SC dose due to volume limitation and safety (ISR) concerns in subjects with SSc. Stable background therapy will be allowed in the study (see Section 7.2).

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

Figure 1 IgPro20_2001 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

dcSSc = Diffuse cutaneous systemic sclerosis; EOT = End of Treatment; i.v. = intravenous; PK = pharmacokinetics; s.c. = subcutaneous; WK = Week

3.2 Dose and Dosing Regimen

The total dose / volume of all IPs will be calculated based on body weight. Body weight will be measured at every site visit prior to IP infusion and changes of > 10% of body weight from baseline / reference visit will require a dose adjustment. Once a dose adjustment as a result of body weight change occurs at a certain visit, body weight at that visit would become the

reference assessment for future body weight change calculations in that treatment period. See Section 5.1.3 for additional dosing information.

3.2.1 IgPro20

Subjects will receive IgPro20 infusions at a total weekly dose of 0.5g/kg split between 2 infusion sessions (eg, Day 1 and Day 3 or Day 4 for each week) every week. The total dose / volume of IP will be calculated based on body weight (see Section 3.2).

3.2.2 IgPro10

Subjects will receive IgPro10 at a total dose of 2 g/kg split over 2, 3, 4, or 5 consecutive days, depending on total dose and individual tolerability, every 4 weeks. The total dose / volume of all IP will be calculated based on body weight. Changes of > 10% of body weight and the corresponding adjustment will follow the same way as IgPro20 in Section 3.2.

3.3 Scientific Rationale

3.3.1 Study Design Rationale

The proposed crossover design with 2 sequences will provide a reliable estimate of IgPro20 relative bioavailability because IgPro20 and IgPro10 treatment differences are measured within a subject rather than between subjects with SSc; both inter- and intra-individual variability will be characterized. This study design will also help to investigate the potential difference in the relative bioavailability of IgPro20 (SCIG) when given before or after IgPro10 (IVIG) in SSc subjects. During both Treatment Period 1 and Treatment Period 2 in each sequence, several PK samples to measure IgG trough concentrations will be collected to assess the steady state of IgPro20 or IgPro10 and carry-over effects on Treatment Period 2 from Treatment Period 1. In addition, PK samples will be frequently collected over the last dose period to fully characterize the PK of IgPro20 and IgPro10, respectively, for each treatment period in this patient population. Specific PK assessments are described in Section 8.1.2.

The 16 weeks of treatment for both IgPro20 and IgPro10 will allow for the assessment of safety and preliminary efficacy signals as well as assessment of IgPro20 and IgPro10 PK profiles at the steady state. The duration of PK assessments is based on IgG trough

concentrations measured in the pivotal phase 3 study in patients with CIDP (IgPro20_3003 study), indicating that IgPro20 and IgPro10 would reach steady state within approximately 8 weeks. Importantly, several trough concentrations will be determined for IgPro20 and IgPro10 in this study to confirm that steady state is reached before the full PK profile of IgPro20 or IgPro10 is assessed in subjects with SSc.

Not having a washout period between treatments will not impact the full PK characterization, since the full PK profile of IgPro10 in the respective treatment period of each sequence will be obtained at the end of the treatment period, when it is assumed that steady state will be reached. The relative bioavailability of IgPro20 will be evaluated based on the dose-normalized $AUC_{0\text{-}tau}$ of IgPro20 and IgPro10 without the need of a washout interval. Moreover, no washout period between the 2 treatments will shorten the study duration and potentially be less burdensome for SSc subjects.

3.3.2 Dose Rationale

There are no published data on any SCIG products in the treatment of SSc. The majority of IVIG studies used 2 g/kg/4 weeks and provided promising clinical benefits in SSc. The conversion of IVIG to SCIG (1:1 ratio) is based on the methodology used in other autoimmune indications (eg, CIDP). IgPro20 0.5 g/kg/week is proposed for this first study in SSc subjects. In addition, an IgPro20 dose higher than 0.5g/kg/week is limited due to SC volume and safety concerns where subjects with pathological changes in skin and SC tissues may impact ISRs in SSc.

3.4 Planned Study Duration

After up to 4 weeks of screening, the duration of the study for an individual subject who completes the study is expected to be approximately 36 weeks.

The overall study duration (ie, first subject's Screening Visit to last subject's End of Study [EOS] telephone call) will be approximately 24 months.

3.5 Planned Number of Subjects

Approximately 26 eligible subjects will be enrolled and randomized to achieve 20 evaluable subjects (10 subjects per treatment sequence) completing the study.

3.6 Definition of End of the Clinical Study

The end of the clinical study (ie, completion of the study at all participating study sites) is defined as the date of the last visit of the last subject and consists of a telephone call to assess safety.

3.7 Stopping Criteria

No specific study stopping rules will be implemented.

A subject may withdraw from the study at any time point for any reason at their own request or at the discretion of the investigator or CSLB. Specific stopping criteria for a subject to discontinue study treatment are described in detail in Section 4.3.1. If IP is discontinued, regardless of the reason, the End of Treatment (EOT) / Early Termination evaluations will be performed as completely as possible.

4 Selection and Withdrawal of Subjects

4.1 Eligibility Criteria

The study population will be selected based on the inclusion and exclusion criteria described in the sections below. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the investigator's study team before subjects are enrolled in the study and reconfirmed at Week 1 before administration of IP.

4.1.1 Inclusion Criteria

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

1. Age ≥ 18 years (male or female) at time of providing written informed consent
2. Documented diagnosis of SSc (scleroderma) according to ACR and EULAR criteria 2013 (dcSSc)
3. CCI ≥ 15 and ≤ 45 at screening
4. Disease duration ≤ 5 years defined as the time from the first non-Raynaud's phenomenon manifestation
5. Capable of providing written informed consent and willing and able to adhere to all protocol requirements

4.1.2 Exclusion Criteria

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

1. Primary rheumatic autoimmune disease other than dcSSc, including but not limited to rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disorder, polymyositis, dermatomyositis, as determined by the investigator. Note: subjects with fibromyalgia, secondary Sjogren's syndrome, and scleroderma-associated myopathy at screening are not excluded
2. CCI [redacted]
3. History of skin condition or clinical signs and symptoms of a chronic skin disease other than SSc or skin manifestation of an allergic disease or other dermatological conditions precluding SC infusion at potential SC infusion sites (eg, dermatitis, eczema, psoriasis)
4. Subject has clinical signs and symptoms of skin irritation (eg, pruritus, burning, erythema) or hypo / hyperpigmentation (eg, scars, tattoos) at the potential SC infusion sites
5. Significant pulmonary arterial hypertension as documented by mean pulmonary arterial pressure > 30 mmHg on right heart catheterization requiring SC or IV prostacyclin or use of dual oral therapies
6. CCI [redacted]
7. SSc renal crisis within 2 years before screening
8. Evidence of chronic kidney disease with an estimated glomerular filtration rate (eGFR) of < 45 mL/min/1.73 m^2 (as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation) [Levey et al, 2009; Stevens et al, 2010] or if subject is receiving dialysis. Subjects with current confirmed diagnosis of diabetes mellitus requiring medication with an eGFR < 90 mL/min/1.73m^2
9. History of documented thrombotic episode eg, pulmonary embolism, deep vein thrombosis, myocardial infarction, thromboembolic stroke at any time (note: history of superficial thrombophlebitis is not exclusionary)
10. Known documented thrombophilic abnormalities including current blood hyperviscosity (within 4 weeks before screening), protein S or protein C deficiency, anti-thrombin-3 deficiency, plasminogen deficiency, antiphospholipid syndrome, Factor V Leiden mutation, dysfibrinogenemia, or prothrombin G20210A mutation

11. Recent surgery requiring general anesthesia within the last 4 weeks before Screening
12. Greater than 3 specified current risk factors for TEEs (documented and currently ongoing conditions): atrial fibrillation, coronary disease, diabetes mellitus, dyslipidemia, hypertension, obesity (body mass index ≥ 30 kg/m^2), recent significant trauma and immobility (wheelchair-bound or bedridden)
13. Cardiac insufficiency (New York Heart Association Class III or IV), cardiomyopathy, significant persistent arrhythmia, unstable or advanced ischemic heart disease or uncontrolled hypertension
14. Ongoing active serious infection (including, but not limited to, pneumonia, bacteremia / septicemia, osteomyelitis / septic arthritis, bacterial meningitis, visceral abscess) at screening or hospitalization and / or treatment with IV antibiotics for a serious infection within 2 months before screening
15. A positive result at screening of any of the following viral markers: human immunodeficiency virus -1 / -2 (HIV-1 / 2), hepatitis C virus, and hepatitis B virus
16. Malignancy in the past 2 years, except for non-melanoma skin cancer, cervical carcinoma in situ, or other in situ cancer if it has been excised and treated within the past year
17. Known medical conditions whose symptoms and effects could alter protein catabolism and or IgG utilization (eg, protein-losing enteropathies, nephrotic syndrome) and proteinuria (defined as albumin-to-creatinine ratio, ACR > 30mg/g)

Note: Transient and clinically insignificant proteinuria as based on investigator's judgment should be discussed with the Medical Monitor and is not exclusionary.

18. Known hyperprolinemia type I or II
19. Known IgA deficiency or serum IgA level < 5% lower limit of normal
20. History of clinically significant or uncontrolled illness that, in the opinion of the investigator, would prevent participation in the study
21. Psychiatric, addictive, or other disorders that compromise the ability to give informed consent for participating in this study. This includes subjects with a recent history of abusing alcohol or illicit drugs
22. Clinically significant abnormal 12-lead ECG that, in the opinion of the investigator, would prevent participation in the study
23. Clinically significant abnormal laboratory testing at screening that, in the opinion of the investigator, would prevent participation in the study

24. Currently receiving or having received therapy not permitted during the study or during predefined windows before screening: for a list of prohibited medications, see Section 7.3
25. Known allergic or other severe reactions to immunoglobulins or other blood products, including a history of hemolysis after IVIG infusion
26. Known or suspected antibodies to the IP, or to excipients of the IP
27. A female who is pregnant, breastfeeding, or is a woman of childbearing potential who does not agree to use acceptable methods of contraception; a male who does not agree to use acceptable methods of contraception
28. Participated in another study with an investigational agent within 3 months
29. Involved in the planning and / or conduct of the study (applies to CSLB staff and dependents, staff at the study site, site examiner, or third-party vendors)
30. Individuals who have institutionalized as a result of an official or court order
31. Any issues or conditions that would render the subject unsuitable for participation in the study

4.2 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (ie, screen failure) may be rescreened once after Medical Monitor review and approval.

4.3 Discontinuation of Treatment and / or Subject Withdrawal

4.3.1 Discontinuation of Study Treatment

Subjects may discontinue treatment with the IP at any time at their own request, or at the discretion of the investigator or CSLB for safety, behavioral, or administrative reasons (eg, due to an AE, protocol deviation, loss to follow-up, subject noncompliance, study termination).

Infusions will be stopped and treatment with IP will be discontinued if the subject:

- Develops anaphylaxis.

- Develops any severe or Grade 3 infusion-related reactions such as, but not limited to, TEEs (see Section 8.1.1.3), acute lung injury / pulmonary edema, acute renal injury (see Section 8.1.1.4), or Grade 3 or higher hemolysis (see Section 8.1.1.2).

Subjects will discontinue treatment with IP at the discretion of the Investigator when the reaction(s) is / are not rapidly responsive to symptomatic medication and / or brief interruption of infusion, or if symptoms recur following initial improvement or upon re-initiating infusion.

Subjects who discontinue treatment with IgPro20 or IgPro10 will be withdrawn from the study. Refer to Section 4.3.2 for details on handling subject withdrawals.

4.3.2 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or at the discretion of the investigator or CSLB for safety, behavioral, or administrative reasons. The reasons for withdrawal must be determined by the investigator and recorded in the subject's medical records and on the electronic case report form (eCRF). If the subject is withdrawn for more than 1 reason, each should be documented in the source document and the most clinically relevant reason should be entered on the eCRF. Reasons for discontinuation include but are not limited to:

- Disease exacerbation that requires prohibited medication
- An AE
- Protocol deviation
- Loss to follow-up
- Subject noncompliance
- Study withdrawal
- Death
- Withdrawal by subject
- Other (must be specified)

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

4.3.3 Procedures for Handling Withdrawals

If a subject is withdrawn from the study, attempts will be made to complete and document the EOT / Early Termination assessments listed in the Schedule of Assessments (Sequence A or Sequence B). If the subject is withdrawn from the study after receiving IgPro20 or IgPro10, every effort will be made to ensure that the relevant safety assessments are completed.

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

4.3.4 Subjects Lost to Follow-up

If a subject repeatedly fails to return for scheduled visits, the site must attempt to contact the subject and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and / or should continue in the study. All attempts to contact the subject should be documented in the subject's source documents medical record. A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. All efforts should be made to contact the subject, including the sending of a certified letter. Subjects lost to follow-up will be considered to have withdrawn from the study.

5 Study Interventions

5.1 Investigational Products

5.1.1 Description of IgPro20

Substance name	IgPro20
Active substance	Normal human immunoglobulin
Trade name	Hizentra®
Storage	IgPro20 will be supplied to the study sites by CSLB. IgPro20 must be stored under temperature-monitored conditions in a secure storage area as specified in the Site IP Manual.
Dosage form	Sterile solution for SC infusion containing 0.2 g per mL (20%) of IgPro20.

5.1.2 Description of IgPro10

Substance name	IgPro10
Active substance	Normal human immunoglobulin
Trade name	Privigen®
Storage	IgPro10 will be supplied to the study sites by CSLB. IgPro10 must be stored under temperature-monitored conditions in a secure storage area as specified in the Site IP Manual.
Dosage form	Sterile solution for IV infusion containing 0.1 g per mL (10%) of IgPro10.

IgPro20 and IgPro10 will be manufactured by CSLB in accordance with ICH Good Manufacturing Practice (GMP) guidelines and local regulatory requirements.

Information on the preparation and administration of IgPro20 and IgPro10 is provided in the Site IP Manual.

5.1.3 Dosing and Administration of Investigational Products

The investigator (or delegate) will administer or dispense IgPro20 or IgPro10 only to subjects included in this study following the procedures set out in this study protocol.

IgPro20 Administration

Subjects will receive SC IgPro20 infusions at 2 sessions at a total dose of 0.5 g/kg every week. The total dose / volume of IgPro20 will be calculated based on body weight. Body weight will be measured at every site visit before infusion and possible adjustment to dose / volume may occur as described in Section 3.2. Subjects weighing ≥ 100 kg will receive a fixed dose of 50 g, every week. A dosing regimen of 2 times a week (eg, Day 1 and Day 3 or Day 4 each week) will be followed.

The SC infusions should be performed at appropriate infusion sites with sufficient normal skin areas or CCI ≤ 2 and any other skin conditions precluding SC infusion (eg, on the abdomen, thighs, and / or lateral hip). Infusion sites in the normal skin or CCI ≤ 2 in abdominal area are recommended in this study, with at least 2 inches (~5 cm) between infusion sites. Other anatomic locations approved for SC infusions should be used with extreme caution and only if recommended by the study investigator. The number of infusion sites depends on the total volume to be administered and tolerability, not to exceed 4 infusion sites simultaneously. Any changes in volume or rate of infusion should be discussed with the

Principal Investigator. The maximum rate and the maximum volume per infusion site should not be exceeded, and any increase rate or volume should be done gradually, as tolerated. The maximum rate and the maximum volume per infusion site is recommended:

Volume	1st 2 infusion sessions : ≤ 20 mL/site; all subsequent infusions: ≤ 50 mL/site as tolerated
Rate	1st 2 infusion sessions : ≤ 20 mL/h/site; all subsequent infusions: ≤ 50 mL/h/site as tolerated

Note: Attempts to reach the maximum values for both the volume and flow rate per infusion site during the same infusion should be performed gradually with caution and strictly as tolerated.

Detailed information in reference to IgPro20 administration (eg, infusion start time / day, infusion stop time / day, number of infusion sites, infusion rate, total administered IgPro20 dose, site of administration, and whether infusion was omitted, interrupted or stopped and reason) will be documented on the IgPro20 infusion form completed by site personnel or home health nurse qualified to administer IgPro20. Refer to the Site IP Manual for further information.

IgPro10 Administration

Subjects will receive IV IgPro10 infusions split over 2, 3, 4 or 5 consecutive days, depending on total dose and individual tolerability, at a total dose of 2 g/kg every 4 weeks. The total dose / volume of all IPs will be calculated based on body weight. Body weight will be collected before each infusion and possible adjustment to dose / volume may occur as described in Section 3.2. Subjects weighing ≥ 100 kg will receive a fixed dose of 200 g, every 4 weeks.

Recommended Rate of Infusion:

First infusion session	Rate of 0.3 mL/kg/h (30 mg/kg/h; 0.005 mL/kg/min; 0.5 mg/kg/min); If well tolerated within 30 min: increase to 0.6 mL/kg/h (60 mg/kg/h; 0.01 mL/kg/min; 1.0 mg/kg/min) for another 30 min; If well tolerated within an additional 30 min: increase to 1.2 mL/kg/h (120 mg/kg/h; 0.02 mL/kg/min; 2.0 mg/kg/min).
Second infusion session	Rate of 0.3 mL/kg/h (30 mg/kg/h; 0.5 mg/kg/min; 0.005 mL/kg/min); If well tolerated within 30 min: increase to 0.6 mL/kg/h (60 mg/kg/h; 0.01 mL/kg/min; 1.0 mg/kg/min) for another 30 min; If well tolerated within an additional 30 min can increase to 1.2 mL/kg/h; If well tolerated within an additional 30 min can increase to 2.4 mL/kg/h.
Subsequent infusions	Initial rate of 0.3 mL/kg/h (30 mg/kg/h; 0.005 mL/kg/min; 0.5 mg/kg/min), incremental increases of infusion rate can exceed 1.2 mL/kg/h as tolerated (up to the maximum recommended infusion rate of 4.8 mL/kg/h [480 mg/kg/h; 0.08 mL/kg/min; 8 mg/kg/min]).

Recommended Rate of Infusion in Subjects with Renal Dysfunction:

First infusion	Rate of 0.3 mL/kg/h (30 mg/kg/h; 0.005 mL/kg/min; 0.5 mg/kg/min); If well tolerated within 30 min: increase to 0.6 mL/kg/h (60 mg/kg/h; 0.01 mL/kg/min; 1.0 mg/kg/min); If well tolerated within an additional 30 min: increase to 1.2 mL/kg/h (120 mg/kg/h; 0.02 mL/kg/min; 2.0 mg/kg/min).
Subsequent infusions	Rate of 0.3 mL/kg/h (30 mg/kg/h; 0.005 mL/kg/min; 0.5 mg/kg/min); If well tolerated within 30 min: increase to 0.6 mL/kg/h (60 mg/kg/h; 0.01 mL/kg/min; 1.0 mg/kg/min) for another 30 min; If well tolerated within an additional 30 min increase to 1.2 mL/kg/h (120 mg/kg/h; 0.02 mL/kg/min; 2 mg/kg/min); If well tolerated within an additional 30 min increase to 2 mL/kg/h (200 mg/kg/h; .033 mL/kg/min; 3.3 mg/kg/min) *(An infusion rate 2 mL/kg/h is the maximum for subjects with eGFR < 90 mL/min/1.73m^2 at Screening and for subjects with elevated serum creatinine level as detailed in the renal safety management algorithm in Section 8.1.1.4; lower infusion rates may be administered at the discretion of the investigator).*

Increases in infusion rate should be performed cautiously, as the risk of AEs in IVIG infusions generally tends to correlate with the infusion rate. Subjects with renal insufficiency should always be infused at the lowest practicable rate.

Detailed information in reference to IgPro10 administration (eg, amount of IgPro10 received, any dose adjustments, infusion rate, whether infusion was omitted, interrupted or stopped and reason, and infusion start / stop time / date) will be documented on the IgPro10 infusion form.

5.1.3.1 Treatment Compliance

All doses of IgPro20 will be administered by qualified personnel at the study site or at home by a home health nurse. All doses of IgPro10 will be administered by qualified personnel at the study site. Details of all infusions will be recorded. The number of unused, partially used, and empty vials will be recorded and kept until the drug accountability documentation has

been checked by the monitor. Treatment compliance will be monitored by counting the used vials, the results of which will be recorded. Treatment compliance for IgPro20 and IgPro10 will be measured as a percentage (= 100 * [used vials divided by planned vials]) overall and summarized using descriptive statistics. A percentage between 80% and 120% is regarded as compliant to treatment.

5.1.3.2 Overdose

Overdose is defined as the accidental or intentional infusion of any dose of a product that is considered excessive of the dose specified in the protocol. The effects of any potential overdose with IgPro20 or IgPro10 have not been studied. IgPro20 and IgPro10 are normal human proteins with broad range of normal concentrations in serum. The risk of overdosing with IgPro20 or IgPro10 is considered to be negligible. See Section 9.6.5 for overdose reporting requirements.

5.1.4 Medical Devices

The Crono Infusion Pump Model S-PID 100 is an ambulatory syringe infusion pump (Cane S.R.L., Turin, Italy) that is being provided for use in this study for the purposes of administration of IgPro20. See the Crono S-PID 100 User Guide for further details of the device including proper use and training.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

5.2 Packaging, Labeling, Supply and Storage

5.2.1 Packaging and Labeling

IgPro20 and IgPro10 will be packaged and labeled according to current ICH GMP and GCP guidelines, and national legal requirements.

Specific details regarding packaging of IgPro20 and IgPro10 are provided in the Site IP Manual. IgPro20 and IgPro10 will be labeled as required per country requirements.

5.2.2 Supply and Storage

IgPro20 and IgPro10 will be supplied to the study sites by CSLB or delegate.

IgPro20 and IgPro10 must be stored under temperature-controlled and monitored conditions at the predefined temperature range, and protected from light, in a secure storage area as specified in the Site IP Manual.

5.2.3 Dispensing Investigational Product to Subjects During Emergencies

If required to as a response to a state of emergency or public health crisis, IP may be dispensed from the study site to the subject and will be delivered in accordance with all applicable local regulations.

5.3 Accountability and Destruction

IgPro20 and IgPro10 must be used only as directed in this clinical study protocol.

The investigator or study site personnel delegated by the investigator will confirm receipt of all shipments of IP in the interactive response technology (IRT) system.

All supplies of IgPro20 and IgPro10 must be accounted for throughout the study.

Records for the delivery of IgPro20 and IgPro10 to the study site, the inventory at the study site, the use by each subject, and the destruction or return of IgPro20 and IgPro10 to CSLB / designee must be maintained by the investigator (or delegate) using the appropriate form or IRT system.

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

Further details regarding accountability and destruction of IgPro20 and IgPro10 are provided in the Site IP Manual.

5.4 Access to Investigational Product After the End of Study

Subjects will not be provided with IP by CSLB after completion or discontinuation from the study.

6 Allocation to Treatment

6.1 Subject Assignment

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

6.2 Randomization Procedures

Eligible subjects will be randomized in a 1:1 ratio by means of IRT to either one of the following sequences: IgPro20 followed by IgPro10 (Sequence A) or IgPro10 followed by IgPro20 (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.

6.3 Blinding Procedures

Not applicable.

7 Contraindications, Permitted Therapies and Prohibited Therapies

7.1 Contraindications and Precautions to Further Dosing

Hypersensitivity and anaphylactic reactions: True hypersensitivity reactions are rare. They can occur in the very rare cases of IgA deficiency with anti-IgA antibodies.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with an anaphylactic reaction, even in subjects who have tolerated previous treatment with human immunoglobulin.

In case of an adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the reaction. In case of shock, standard medical treatment for shock should be implemented.

Thrombotic events: Thrombotic events can occur in treatment with IgPro20 and IgPro10. Subjects should be informed about the first symptoms of thrombotic events, including shortness of breath, pain and swelling of a limb, focal neurological deficits, and chest pain and should be advised to contact their physician immediately upon onset of symptoms. Subjects should be sufficiently hydrated before the use of IgPro20 and IgPro10 and TEE safety assessments will be performed at every site study visit as described in Section 8.1.1.3.

Aseptic meningitis syndrome: AMS can occur with IgPro20 and IgPro10. The syndrome usually begins within several hours to 2 days following treatment. AMS is characterized by the following signs and symptoms: severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Subjects exhibiting signs and symptoms of AMS should

receive a thorough neurological examination, including cerebral spinal fluid studies, to rule out other causes of meningitis. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

Hemolysis: Cases of clinically significant hemolysis are rare but can appear during treatment with IgPro10. If a subject has a confirmed hemolysis of Grade 3, no further IgG should be infused and the subject should be removed from the study.

Transfusion-related acute lung injury: Noncardiogenic pulmonary edema may very rarely occur following treatment with IVIG products. Transfusion-related acute lung injury is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. Transfusion-related acute lung injury may be managed using oxygen therapy with adequate ventilatory support.

Premedication: Premedication according to local standards may precede the IVIG application.

Hydration: In all subjects, hydration status should be assessed before initiation of the IVIG infusion.

Vaccination: Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella for a period of at least 6 weeks and up to 3 months. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore, subjects receiving measles vaccines should have their antibody status checked before treatment.

7.2 Permitted Therapies

Prednisone or equivalent to ≤ 7.5 mg/day, mycophenolate (≤ 3g/day), methotrexate (≤ 25 mg/week), azathioprine (≤ 3 mg/kg/day), hydroxychloroquine (≤ 400 mg/day; stable dose 1 month before screening) are permitted during the study. There can be no change in these permitted concomitant therapies during the study; however, temporary adjustment to permitted stable treatment during the study (eg. immunosuppressant dose interruption during infection or acute treatment with prednisone for systemic reaction / allergy) will be allowed.

7.3 Prohibited Therapies

Excluded Previous and Concomitant Therapy

The following medications / therapy are prohibited:

- Within 1 month or 5 times the half-life, whichever is longer:
  - Tocilizumab
  - Tumor necrosis factor-α inhibitors
  - Abatacept
  - Any other non-topical immunosuppressive or immunomodulatory medications
- Within 3 months or 5 times the half-life, whichever is longer:
  - Plasma exchange, blood, or IgG
  - Cyclophosphamide
- Within 6 months before screening:
  - Rituximab

7.4 Reproductive Restrictions

To be eligible for study participation, female subjects should be either:

- Post-menopausal (24 consecutive months of spontaneous amenorrhea and age ≥ 51)
- Surgically sterile (having undergone one of the following surgical procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 3 months post-sterilization
- Females with a negative serum pregnancy test at screening and negative urine pregnancy test on Week 1 before dosing

Female subjects of childbearing potential or male subjects must use a medically reliable form of contraception for the study duration and for 30 days after the last infusion of IP.
Acceptable methods of contraception are:

- Abstinence, where abstinence is the preferred and usual lifestyle of the subject, including refraining from heterosexual intercourse during the entire period of risk associated with the IP

- Hormonal methods associated with inhibition of ovulation. Acceptable hormonal methods include: oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen / progestin vaginal ring, or contraceptive medication implant
- At least 2 barrier methods. For example, female or male condoms with spermicidal foam or spermicidal jelly, or diaphragm with spermicidal foam or spermicidal jelly. The female condom and male condom should not be used together
- Use of intrauterine device (placed more than 3 months before providing informed consent)
- Bilateral tubal occlusion of female subjects (3 months before providing informed consent)
- Vasectomy of male subjects (3 months before providing informed consent)

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are **NOT** acceptable definitions of contraception.

8 Study Procedures and Visit Schedule

8.1 Clinical Procedures

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

All assessments and procedures are to be performed by an investigator or a qualified designee who has been trained on the study protocol.

8.1.1 Demographics, Baseline, and Safety Assessments

Demographic information such as age, sex, ethnicity / race will be collected as allowed by local law.

Medical history will include specific questions on SSc (date of diagnosis, date of first Raynaud's phenomena, date of the first non-Raynaud and its description). The history of co-morbid autoimmune disorders will be collected. Medical history will also include tobacco use. Additionally, specific cardiopulmonary, renal, and TEE risk history will be obtained.

The clinical procedures to be conducted during this study-related to the evaluation of safety are provided in Table 1. Clinical laboratory assessments are to be performed at time points as detailed in the Schedule of Assessments. The time windows for each type of assessment are detailed in Table 2.

Table 1 Baseline and Safety Assessments

Assessment	Description		
Physical examination	Full: an evaluation of the following body systems: general appearance, hydration status, skin, eyes / ears / nose / throat, spine / neck / thyroid, musculoskeletal, cardiovascular, pulmonary, abdomen, and neurological	Abbreviated: a review of the following body systems: hydration status, skin, cardiovascular, respiratory, and abdomen	
ECG	Heart Rate QT Interval QRS Duration Interpretation (investigator's overall interpretation)	PR Interval QTcB Interval QTcF Interval	
Vital signs	BP (Systolic and Diastolic) in mmHg Respiratory rate (breaths / minute) Pulse rate (beats per minute) Body temperature (Celsius)		
Pregnancy test	Urine or serum test for β-hCG, as indicated for women of childbearing potential Document contraception method		
Hematology laboratory tests	Hb DAT ESR Leukocytes with differential counts (neutrophil, basophils, eosinophils, lymphocytes, monocytes)	Hct Platelets Erythrocytes (RBC Count) with all indices IgA Spherocytes d-dimers[a]	Reticulocytes RBC: MCV; MCH; MCHC; RDW ABO blood group including Rh factor

Assessment	Description		
Serum chemistry laboratory tests	Bicarbonate	Potassium	Sodium
	Urate (Uric Acid)	Phosphate	Chloride
	Glucose	Albumin	Calcium
	LDH	ALP	BUN
	ALT	Bilirubin (total, direct and indirect)	CRP
	AST		CK
	eGFR	GGT	Aldolase
	Haptoglobin	Creatinine	Protein (total)
Urine clinical laboratory tests	Total urinalysis including microscopic examination of the urine sediment.		
Virology clinical laboratory tests	Blood samples are to be tested for the presence of antibodies to human immunodeficiency virus, hepatitis B, and hepatitis C.		
Hemolysis safety assessment	Hematology, serum chemistry, urine for hemolysis testing, physical examination; see Section 8.1.1.2 for details		
TEE safety assessments	TEE risk assessment; see Section 8.1.1.3 for details		
Renal function assessments	Serum chemistry (creatinine, BUN, eGFR) and urine testing (albumin / creatinine ratio); see Section 8.1.1.4 for details		
PFTs	Spirometry including CCI, CCI		
Patient diary	Review or dispense new diary		
AEs	Evaluation of all AEs (eg, causality / relatedness, severity, outcome, seriousness) Evaluation of AEs categorized as ISRs		

ABO = Histo-blood group ABO system transferase; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BP = blood pressure; BUN = blood urea nitrogen; CK = creatine kinase; CRP = C-reactive protein; DAT = direct antiglobin test; CCI = CCI; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; CCI = CCI; GGT = gamma-glutamyl transferase; Hb = hemoglobin; Hct = hematocrit; IgA = immunoglobulin A; ISR = infusion site reaction; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PFT = pulmonary function test; RBC = red blood cell; RDW = red blood cell distribution width; Rh = rhesus; TEE = thromboembolic event

[a] Will be performed only if TEE risk is high or TEE suspected

8.1.1.1 Physical Examination

A full physical exam will be conducted at Screening, Weeks 1 and 17, and EOT / Early Termination by a qualified individual, licensed in their respective state or region (eg, physician, physician's assistant, or nurse practitioner).

Full physical examination will include an evaluation of the following body systems: general appearance, hydration status, skin, eyes / ears / nose /throat, spine / neck / thyroid, musculoskeletal, cardiovascular, pulmonary, abdomen, and neurological. Abbreviated physical examination, performed at time points as detailed in the Schedule of Assessments, will be composed of a review of the following body systems: hydration status, skin, cardiovascular, respiratory, and abdomen.

Any unfavorable findings considered by the investigator to be clinically significant at screening will be documented in the medical history of the subject. Unfavorable changes occurring thereafter will be documented as an AE.

8.1.1.2 Hemolysis Safety Assessment

Clinical hemolysis will be assessed at time points as detailed in the Schedule of Assessments. The time windows for each assessment are detailed in Table 2.

Criterion A

- Drop in hemoglobin of > 1 g/dL within a 28-day interval since the time of last administration of IgPro10 without clinical evidence of blood loss from gastrointestinal bleeding, menorrhagia, hemoptysis, major hematoma, or injury and not explained by repeated phlebotomy.

Criterion B

Presence of minor criteria documented within 28 days of last exposure to IgPro10, consisting of:

- Direct antiglobulin test (DAT) positive
- Haptoglobin < lower limit of normal
- Lactate dehydrogenase > upper limit of normal
- Total or indirect (unconjugated) bilirubin > upper limit of normal or jaundiced
- Hemoglobinuria or red / dark urine
- Hemoglobinemia
- Spherocytosis
- Hepatosplenomegaly

Subjects fulfilling criterion A and at least 2 of the minor criteria of criterion B, where 1 of the minor criteria must be DAT positive, will be considered to have hemolysis.

If an AE of hemolysis is reported it should be graded by the investigator using this scale:

- Grade 1 – Laboratory evidence of hemolysis only (eg, direct antiglobulin test, schistocytes, decreased haptoglobin
- Grade 2 – Clinical evidence of hemolysis and ≥ 2 g/dL decrease in hemoglobin
- Grade 3 – Transfusion or medical intervention indicated (eg, steroids)
- Grade 4 – Life-threatening consequences; urgent intervention indicated
- Grade 5 – Death

Subjects with hemolysis Grade 3 and above will be assessed by an investigator or medically qualified designee whether it is in the best interest of the subject to continue the study and safe to continue the investigational treatment.

8.1.1.3 Thromboembolic Events Safety Assessment

To reduce the risk of potential TEEs, this study excludes specific patient groups (Section 4.1.2 includes 4 exclusion criteria pertaining to TEE risk). Nevertheless, TEE risk will be monitored continuously during the study.

The Treating Physician will assess the subject for the suspicion of a TEE at every study visit using Wells' Deep Vein Thrombosis (DVT) Criteria or Wells' Pulmonary Embolism (PE) Criteria. If there is no suspicion of DVT or PE, the Wells' Criteria will not be assessed and a score of "0" will be entered in the eCRF.

If there is suspicion of DVT or PE (score of ≥ 1), the Wells' DVT Criteria [Modi et al, 2016] or Wells' PE Criteria [Doherty, 2017] numerical score will be assessed and entered in the eCRF.

Positive D-dimer testing in any subject regardless of Wells' Criteria score requires ultrasound imaging to rule out DVT.

In order to diagnose PE, additional imaging, eg, computerized tomographic pulmonary angiography or ventilation / perfusion scan, or other modalities will be done per the site's standard of care.

When a diagnosis of DVT or PE is confirmed, IP treatment should be discontinued; however, the subject may continue in the study for other study assessments.

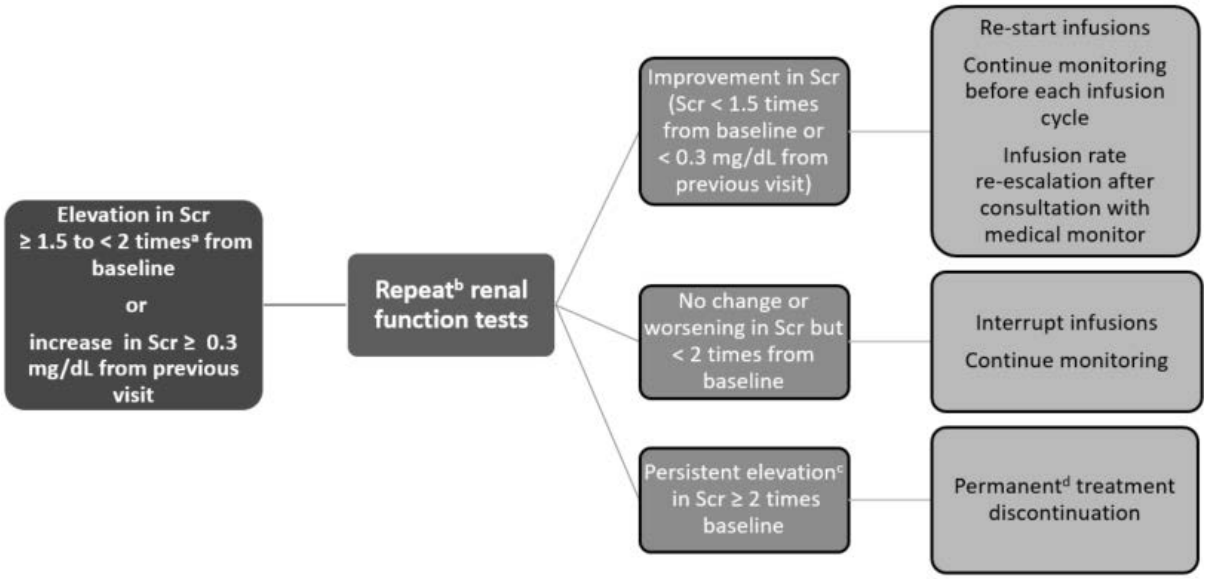
All TEEs, including but not limited to DVT and PE, will be classified as AESIs (see Sections 9.1.3 and 9.6.4). Follow-up monitoring and treatment (eg, anticoagulation) will be performed according to the site's standard of care using established guidelines (eg, American Society of Hematology, 2018).

8.1.1.4 Renal Function Assessments

All subjects will have their renal function assessed as measured by physical examination (including weight) and clinical laboratory tests (including serum creatinine, BUN in blood and ACR in urine) as detailed in the Schedule of Assessments.

The recommendations for management of elevation in renal function parameters, including subject stopping rules are presented in Figure 2. Acute renal injury events will be reported to CSLB as AESIs (see Section 9.1.3).

Figure 2 Management of Elevation in Renal Function Parameters



Scr = serum creatinine

[a] Stages align with creatinine level changes for acute renal injury [Kidney Disease: Improving Global Outcomes, 2012].

[b] As soon as possible from when abnormal Scr results are reported (within 2 weeks).

[c] Two consecutive visits / assessments.

[d] Permanent treatment discontinuation reasons include scleroderma renal crisis and persistent and clinically significant increases in systolic or diastolic blood pressure as judged by the investigator.

8.1.1.5 12-lead Electrocardiogram

A 12-lead ECG will be performed at times specified in the Schedule of Assessments. When ECG and PK results are collected on the same day, the ECG must be monitored before the PK results are collected. All ECGs will be performed using central ECG provider's equipment. An instruction manual will be provided. The investigator's assessment of ECG tracing as normal or abnormal must be recorded and if abnormal his / her determination of whether abnormality is clinically significant or not will be documented.

Any abnormal findings considered by the investigator to be clinically significant at screening will be documented in the medical history of the subject. Unfavorable changes occurring thereafter will be documented as an AE.

8.1.1.6 Vital Signs

Vital signs will be measured at times specified in the Schedule of Assessments and will include sitting blood pressure (systolic and diastolic), pulse rate, sitting respiratory rate, oral or tympanic temperature. Measurements will be taken by a trained individual. The time windows for each assessment are detailed in Table 2.

Any abnormal findings considered by the investigator to be clinically significant at screening will be documented in the medical history of the subject. Unfavorable changes occurring thereafter will be documented as an AE.

8.1.1.7 Pregnancy Tests

Serum or urine beta-human chorionic gonadotropin (β-hCG) pregnancy tests will be conducted at the study sites as indicated in the Schedule of Assessments.

Entry into the study and continued participation is contingent on negative pregnancy test results. Additional pregnancy tests may be performed at the investigator's discretion.

8.1.1.8 Pulmonary Function Tests

Pulmonary function tests will be performed at times specified in the Schedule of Assessments. Subjects will undergo a complete spirometry test, lung volume, and CCI measurements. PFT measurements will be performed according to American Thoracic Society / European Respiratory Society consensus and standardization. The measurements will be reported as absolute values and as percentages of predicted. The predicted normal values will be calculated according to sex, age, height, and race using the appropriate reference ratio. CCI values will be adjusted to anemia (hemoglobin levels). Experienced,

trained and certified healthcare professionals will be performing PFTs. Manuals from the central laboratory will be provided to sites.

8.1.1.9 Clinical Laboratory Tests

Clinical laboratory tests will be obtained from the subject as outlined in the Schedule of Assessments. Clinical laboratory test results from the central and / or local laboratory that are outside the normal reference range and are deemed clinically significant by the investigator are to be recorded as AEs (Section 9.6.1) or SAEs (Section 9.6.2). Refer to Table 1 for specific serum biochemistry, hematology, urinalysis, and virology parameters for testing. Safety parameters should be repeated if the specimen is hemolyzed.

Refer to the Laboratory Manual for details about the collection, storage, handling, and transportation of biological specimens.

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must recorded as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range. Verification of sample collection and a notation for out of range laboratory results (yes / no) to be assessed for clinical significance will be documented.

8.1.1.10 Patient Diary

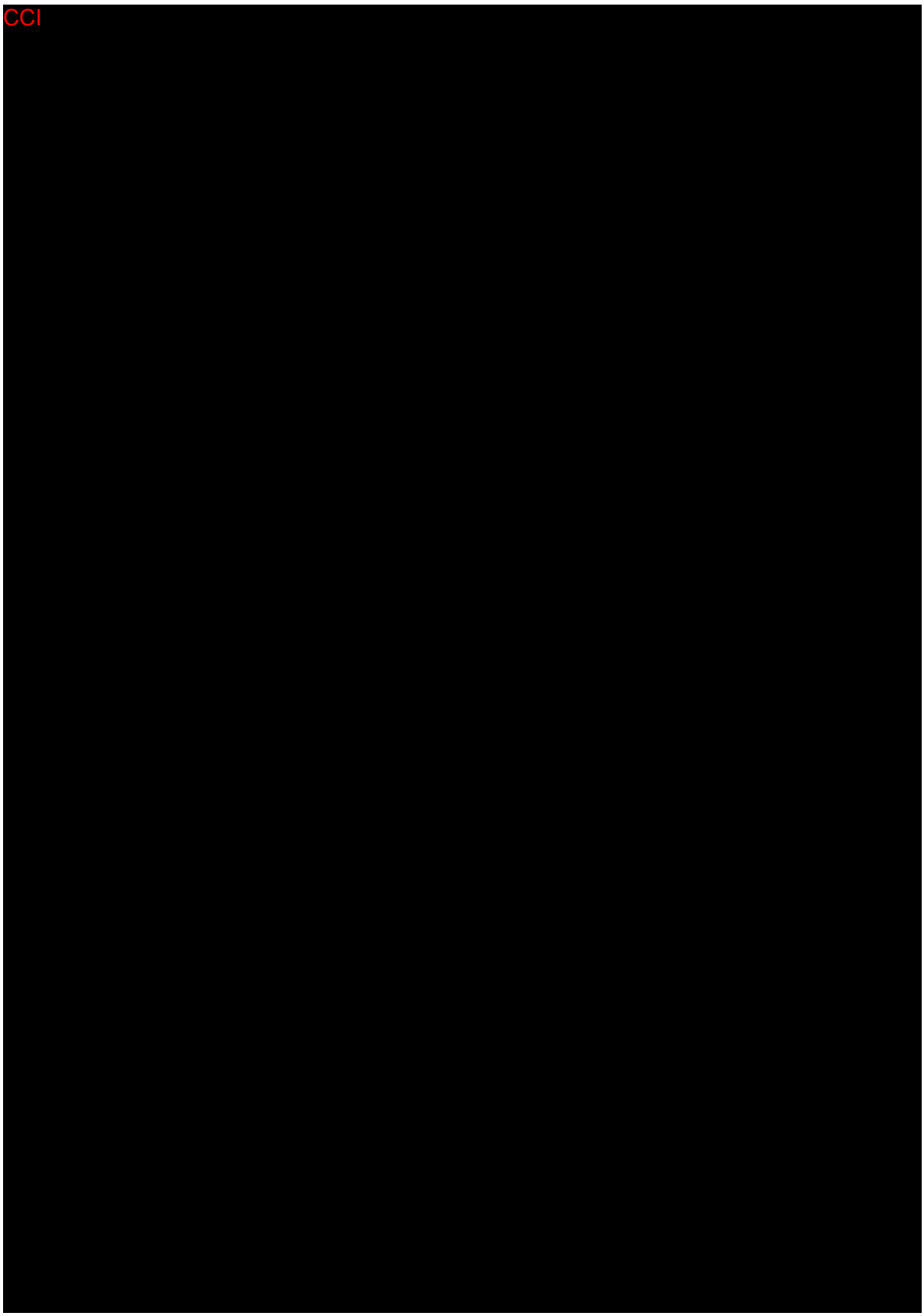
Subjects will receive a patient diary at each site visit during the IgPro20 sequence and will be instructed to record any side effects that occur between site visits, including start and stop dates. Subjects will return the diary at the next site visit and receive a new diary. Investigators will review the diaries and determine if any of the side effects qualify as AEs.

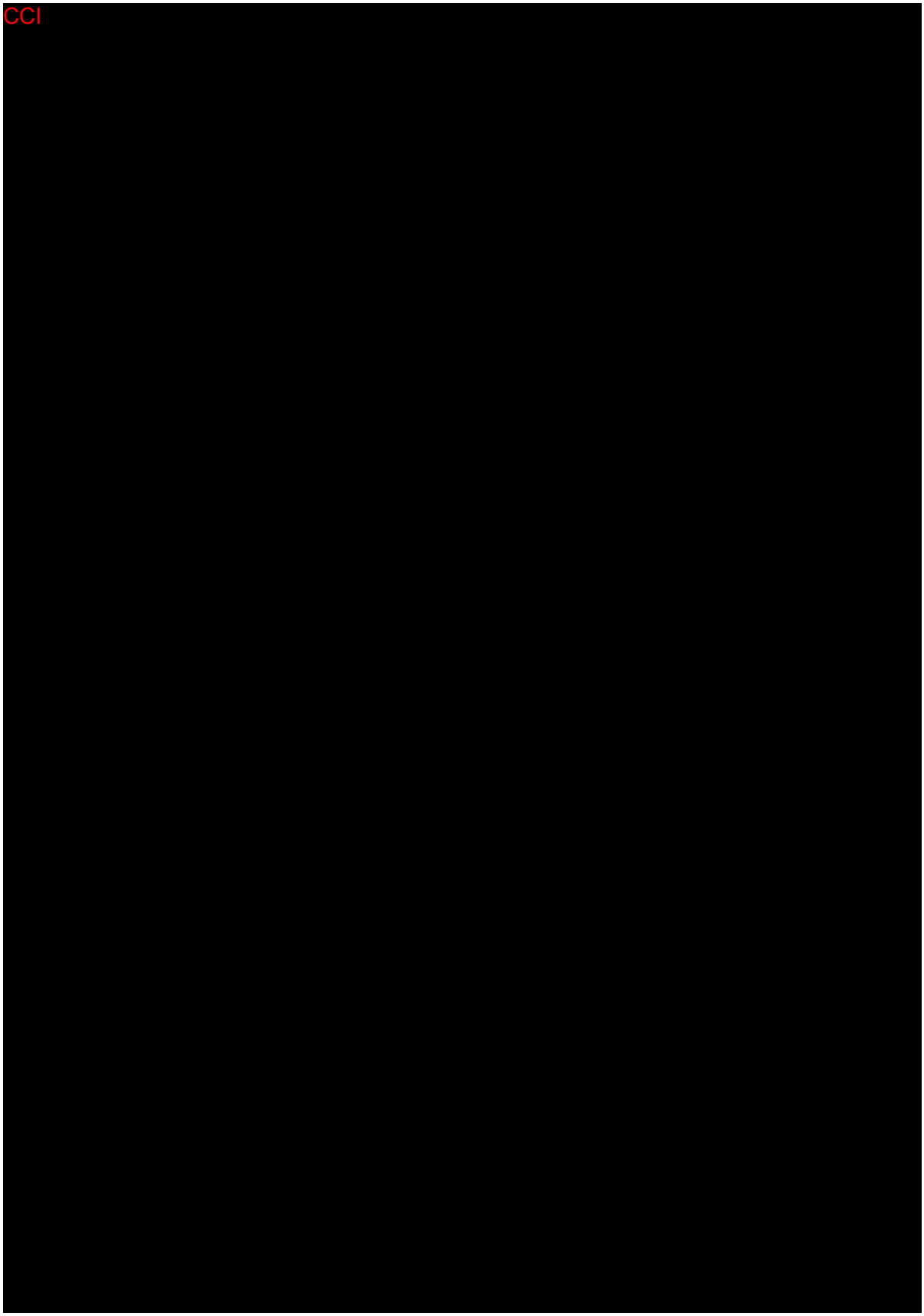
8.1.2 Pharmacokinetic Assessments

The PK assessments are to be performed at time points as detailed in the Pharmacokinetic Schedule of Assessments. The PK parameters $AUC_{0\text{-}tau}$, $AUC_{0\text{-}last}$, C_{max}, and C_{trough} will be assessed in order to determine the relative bioavailability of IgPro20.

8.1.3 Efficacy Assessments

Efficacy assessments are to be performed at time points as detailed in the Schedule of Assessments. The time windows for each type of assessment are detailed in Table 2.


CCI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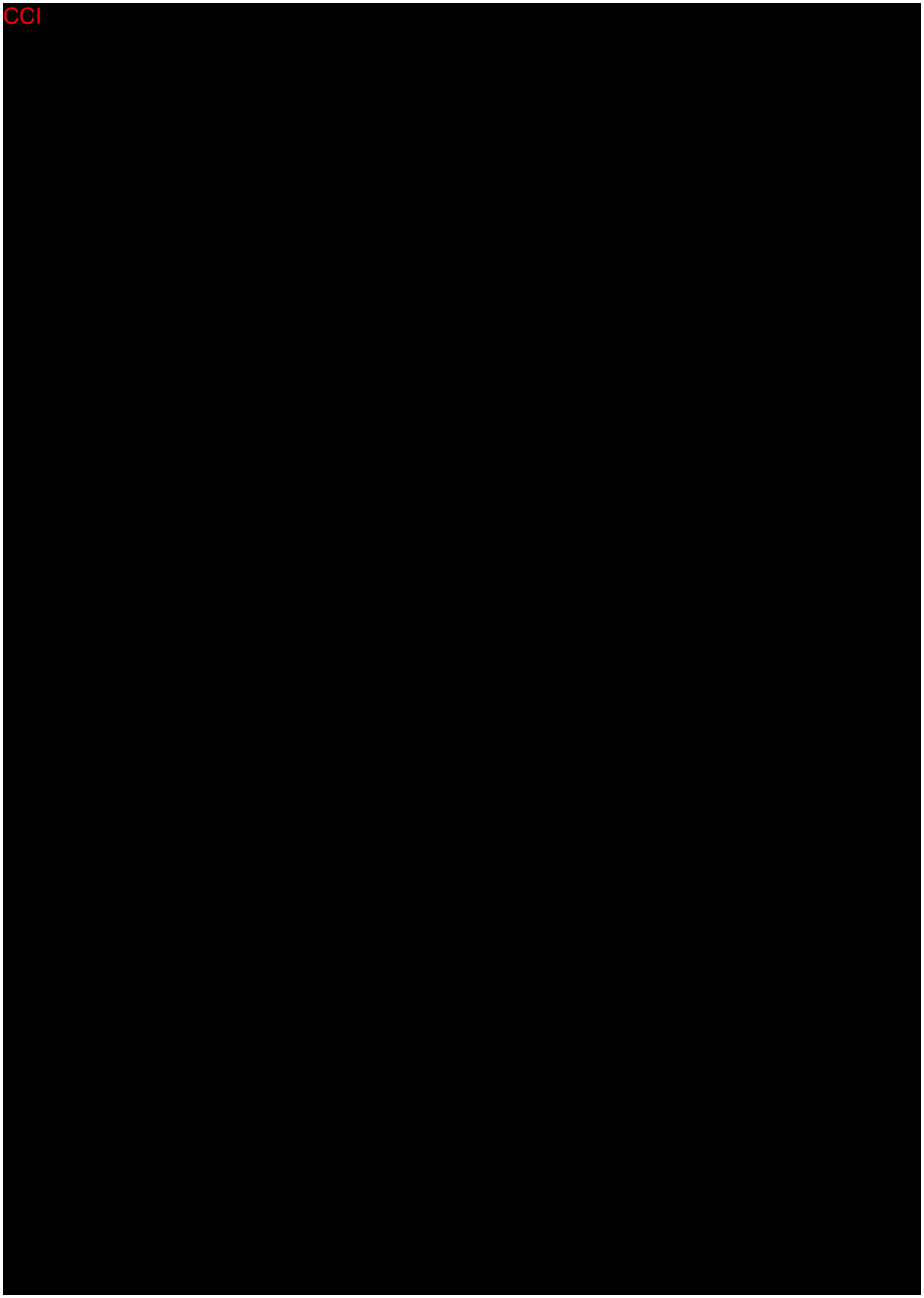
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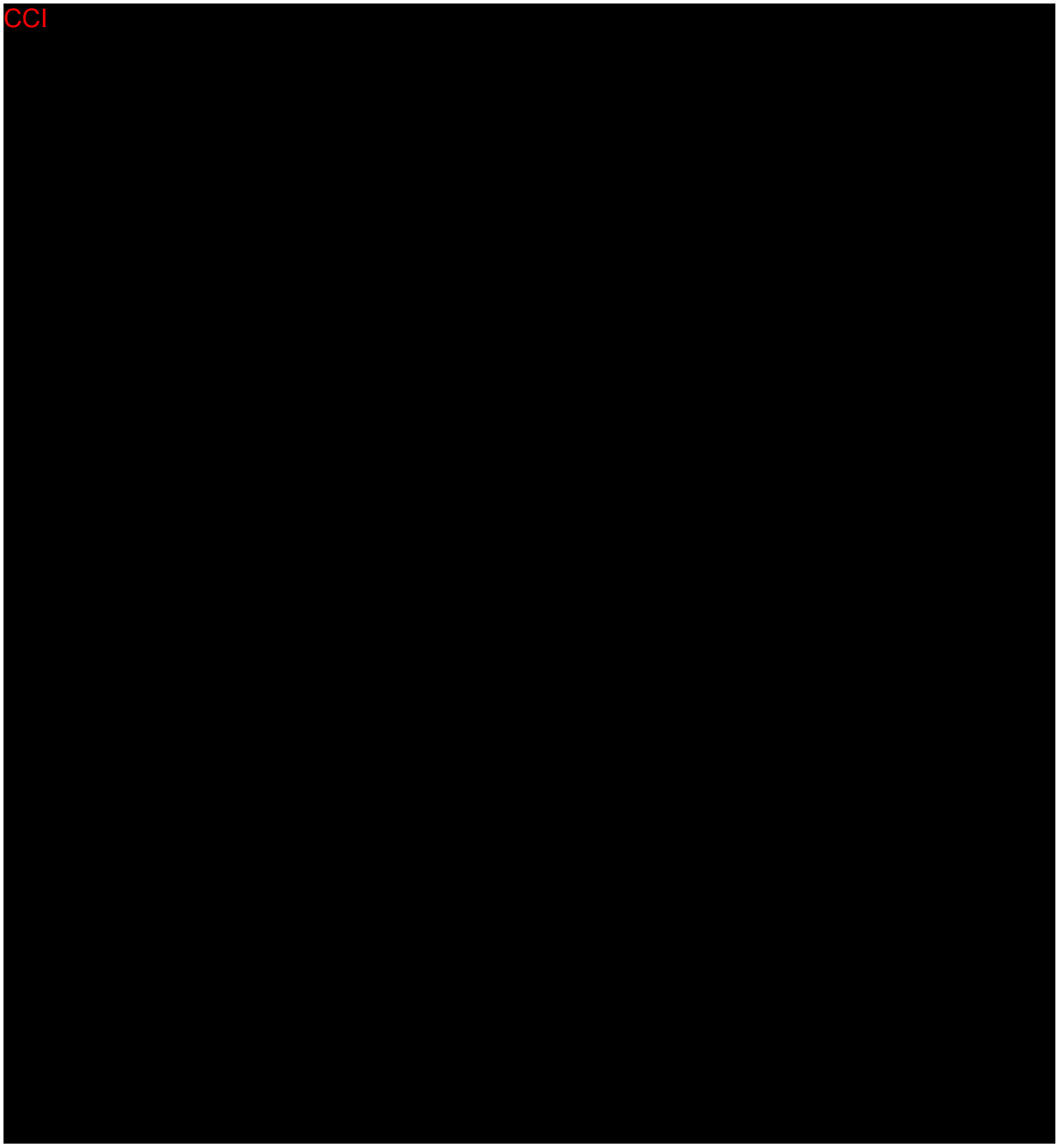

8.1.4 Pharmacodynamic Assessments

Not applicable.

8.1.5 Other Assessments

8.1.5.1 CCI

CCI

CCI

CCI

CCI

8.1.5.2 CCI

CCI

8.1.5.3 CCI

CCI

8.2 CCI

CCI

8.3 Blood Samples

During the study, a maximum total of approximately 218 mL of blood will be taken from each subject for mandatory and scheduled laboratory safety assessments, PK evaluations, and viral testing. Detailed information on the volume of blood to be sampled for each assessment will be available in the ICF and Laboratory Manual.

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

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

8.4 Retention of Samples

Retention samples of serum and plasma for virology will be obtained during the study, as specified in the Schedule of Assessments. Virology retention samples will be stored at the central laboratory. In case of any evidence of a possible treatment-emergent virus infection within 1 year after study completion, the retention sample will be analyzed in the central laboratory.

CCI

8.5 Concomitant Therapies

All drugs and / or procedures currently being administered to a subject at the time of signing informed consent, and which continue to be taken in addition to IgPro20 or IgPro10 during the study, are regarded as concomitant therapies and must be documented as such in the eCRF. Refer to Section 7.3 for details about prohibited therapies during the study.

8.6 Visit Schedule

Table 2 Visit / Procedure Time Window (relative to scheduled visit / procedure)

Visit / Procedure	Time Window (Relative to Visit / Procedure)
Screening	Up to 28 days before randomization
Week 1 through Week 32	± 2 days
EOS Phone call (Week 36)	~28 days after EOT
Sequence A, Treatment Period 1 Blood collection for PK Weeks 1, 5, 9, 13, 14, and 15	Refer to the Pharmacokinetic Schedule of Assessments: Sequence A for individual sampling time windows.
Sequence A, Treatment Period 2 Blood collection for PK Weeks 17, 21, 25, 29, 30, 31 and EOT / Early Termination	Refer to the Pharmacokinetic Schedule of Assessments: Sequence A for individual sampling time windows.
Sequence B, Treatment Period 1 Blood collection for PK Weeks 1, 5, 9, 13, 14, 15, and 16	Refer to the Pharmacokinetic Schedule of Assessments: Sequence B for individual sampling time windows.
Sequence B, Treatment Period 2 Blood collection for PK Weeks 17, 21, 25, 29, 30, 31, and EOT / Early Termination	Refer to the Pharmacokinetic Schedule of Assessments: Sequence B for individual sampling time windows.
Hemolysis testing	Refer to the Schedule of Assessments.
Renal function assessments	Refer to the Schedule of Assessments.
Pregnancy testing	Before infusion
Physical examination	Before infusion
Vital signs	Before PK blood sample Before PFTs Relative to IgPro20 infusion: • Within 30 min before infusion • Within 30 min after infusion Relative to IgPro10 Infusion:

	• Within 30 min before infusion • Within 15 minutes after initiation of infusion • Every hour during infusion • Within 15 min before increasing rate of infusion • Within 30 min after infusion
Urine and blood collection for clinical safety	Before infusion
Infusion form	After infusion of IgPro20 and IgPro10
Review Patient diary	Before IgPro20 infusion
CCI , CCI)	Before CCI , CCI , CCI
CCI	After last infusion
CCI	Before infusion
ECG[a]	Before PFTs and infusion
PFTs[a]	After vital signs and ECG and before infusion

ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; CCI = CCI ; CCI = CCI ; min = minutes; CCI = CCI ; PFT = pulmonary function test; CCI = CCI ; PK = pharmacokinetic; CCI = CCI

[a] Recommended order.

8.6.1 Screening

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

Screening Assessments (Sequence A and Sequence B)

The following procedures will be conducted and documented at the Screening Visit:

- Obtain written informed consent
- Review inclusion and exclusion criteria
- Assess and record demographics
- Assess and record medical history
- Perform full physical examination
- Measure height

- Conduct ECG
- Perform PFTs (CCI)
- Measure vital signs
- Measure body weight
- Collection of urine sample to assess the following:
  - Urinalysis
  - Renal function
  - Hemolysis
- Collection of blood samples to assess the following:
  - Hematology
  - Serum chemistry
  - Serum pregnancy test, if applicable
  - Renal function
  - Virology markers of HIV-1 / -2, Hepatitis B, and Hepatitis C
  - Hemolysis
  - Biomarkers
  - Autoantibodies
  - Serum IgA
  - ABO rhesus
- TEE safety assessment
- Conduct CCI
- Assess and record AEs
- Record prior and concomitant therapies

8.6.2 Week 1 (Site Visit; Sequence A and Sequence B)

Before Randomization

- Confirmation of inclusion and exclusion criteria

- Perform full physical examination
- TEE safety assessment
- Perform CCI [redacted]
- Perform CCI [redacted]
- Perform CCI [redacted]
- Conduct ECG
- Perform PFT (CCI [redacted])
- Measure vital signs
- Measure body weight
- Collection of blood sample for PK assessment (see Pharmacokinetic Schedule of Assessments: Sequence A or Pharmacokinetic Schedule of Assessments: Sequence B)
- Collection of urine sample for Pregnancy test, if applicable
- Conduct CCI [redacted]
- Conduct CCI [redacted]
- Conduct CCI [redacted]
- Conduct CCI [redacted]
- CCI [redacted] score to be derived programmatically
- Conduct CCI [redacted]
- Conduct CCI [redacted]
- Assess and record AEs
- Record concomitant therapies

8.6.3 Sequence A / Treatment Period 1 (IgPro20)

The following procedures are to be performed at each visit:

8.6.3.1 Week 1 (Site Visit)

After Randomization

- Dispense IgPro20 patient diary

- IP assignment
- Infusion of IgPro20

After Infusion

- Measure vital signs
- Completion of infusion form

8.6.3.2 Weeks 3, 7, and 11 (Site Visits)

Before Infusion

- Abbreviated physical exam
- TEE safety assessment
- Measure vital signs
- Measure body weight
- Review of IgPro20 patient diary / dispense new IgPro20 patient diary
- Assess and record AEs
- Record concomitant therapies
- IP assignment
- Infusion of IgPro20 (Session 1)

After Infusion

- Measure vital signs
- Completion of infusion form

8.6.3.3 Weeks 5, 9, and 13 (Site Visits)

Before Infusion

- Abbreviated physical exam
- TEE safety assessment
- Measure vital signs

- Measure body weight
- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence A) and biomarkers (biomarkers are only assessed at Week 5)
- Collection of urine sample for pregnancy test, if applicable
- Review of IgPro20 patient diary / dispense new IgPro20 patient diary
- Assess and record AEs
- Record concomitant therapies
- IP assignment
- Infusion of IgPro20 (Session 1)

After Infusion

- Measure vital signs
- Completion of infusion form

8.6.3.4 Weeks 1, 3, 5, 7, 9, 11, and 13 (Home Visits)

- Assess and record AEs
- Record concomitant therapies
- Measure vital signs before and after each session
- Infusion of IgPro20 (Session 2)
- Completion of infusion form

8.6.3.5 Weeks 2, 4, 6, 8, 10, and 12 (Home Visits)

- Assess and record AEs
- Record concomitant therapies
- Measure vital signs before and after each session
- Infusion of IgPro20 (Sessions 1 and 2)
- Completion of infusion form

8.6.3.6 Week 14 (Home Visit)

- Measure vital signs before and after each session
- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence A)
- Assess and record AEs
- Record concomitant therapies
- Infusion of IgPro20 (Sessions 1 and 2)
- Completion of infusion form

8.6.3.7 Week 15 (Home Visit)

- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence A)

8.6.4 Sequence A / Treatment Period 2 (IgPro10)

The following procedures are to be performed at each visit:

8.6.4.1 Week 17 (Site Visit)

Before Infusion

- Perform full physical examination
- TEE safety assessment
- Perform CCI [redacted]
- Perform CCI [redacted]
- Perform CCI [redacted]
- Conduct ECG
- Perform PFTs (CCI [redacted])
- Measure vital signs
- Measure body weight
- Collection of blood samples to assess the following:
  - Hematology

  - Serum chemistry
  - Renal function
  - Biomarkers
  - Autoantibody
  - Hemolysis
  - PK (see Pharmacokinetic Schedule of Assessments: Sequence A)
- Collection of urine sample to assess the following:
  - Urinalysis
  - Renal function
  - Urine Pregnancy test, if applicable
  - Hemolysis
- Conduct CCI
- Conduct CCI
- Conduct CCI
- Conduct CCI
- Conduct CCI
- Conduct CCI
- CCI score to be derived programmatically
- Review of IgPro20 patient diary
- Assess and record AEs
- Record concomitant therapies
- IP assignment
- Infusion of IgPro10 over 2 to 5 consecutive days

During Infusion

- Measure vital signs

After Infusion

- Measure vital signs
- Completion of infusion form

8.6.4.2 Weeks 19, 23, and 27 (Site Visits)

- Abbreviated physical exam
- TEE safety assessments
- Collection of blood sample to assess the following:
  - Renal function
  - Hemolysis
- Collection of urine sample to assess the following:
  - Renal function
  - Hemolysis
- Assess and record AEs
- Record concomitant therapies

8.6.4.3 Weeks 21, 25, and 29 (Site Visits)

Before Infusion

- Abbreviated physical exam
- TEE safety assessment
- Measure vital signs
- Measure body weight
- Collection of urine sample for pregnancy test, if applicable
- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence A)
- Assess and record AEs
- Record concomitant therapies
- IP assignment

- Infusion of IgPro10 over 2 to 5 consecutive days

During Infusion

- Measure vital signs

After Infusion

- Collection of blood sample for PK (Week 29 only; see Pharmacokinetic Schedule of Assessments: Sequence A)
- Measure vital signs
- Completion of infusion form

8.6.4.4 Week 30 (Home Visit)

- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence A)

8.6.4.5 Week 31 (Site Visit)

- Abbreviated physical exam
- Measure body weight
- Collection of urine samples to assess the following:
  - Renal function
  - Hemolysis
- Collection of blood samples to assess the following:
  - Renal function
  - Hemolysis
  - PK (see Pharmacokinetic Schedule of Assessments: Sequence A)
- Assess and record AEs
- Record concomitant therapies

8.6.5 Sequence B / Treatment Period 1 (IgPro10)

The following procedures are to be performed at each visit:

8.6.5.1 Week 1 (Site Visit)

After Randomization

- IP assignment
- Infusion of IgPro10 over 2 to 5 consecutive days

During Infusion

- Measure vital signs

After Infusion

- Measure vital signs
- Completion of infusion form

8.6.5.2 Weeks 3, 7, and 11 (Site Visits)

- Abbreviated physical exam
- TEE safety assessment
- Collection of urine sample to assess the following:
  - Renal function
  - Hemolysis
- Collection of blood sample to assess the following:
  - Renal function
  - Hemolysis
- Assess and record AEs
- Record concomitant therapies

8.6.5.3 Week 5, Week 9, and Week 13 (Site Visits)

Before Infusion

- Abbreviated physical exam
- TEE safety assessment
- Measure vital signs

- Measure body weight
- Urine pregnancy test, if applicable
- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence B) and biomarkers (biomarkers are only assessed at Week 5)
- IP assignment
- Infusion of IgPro10 over 2 to 5 consecutive days
- Assess and record AEs
- Record concomitant therapies

During Infusion

- Measure vital signs

After Infusion

- Collection of blood samples for PK (Week 13 only; see Pharmacokinetic Schedule of Assessments: Sequence B)
- Measure vital signs
- Completion of infusion form

8.6.5.4 Week 15 (Site Visit)

- Abbreviated physical exam
- Measure body weight
- TEE safety assessment
- Collection of urine sample to assess the following:
  - Renal function
  - Hemolysis
- Collection of blood sample to assess the following:
  - Renal function
  - Hemolysis
  - PK (see Pharmacokinetic Schedule of Assessments: Sequence B)

- Assess and record AEs
- Record concomitant therapies

8.6.5.5 Weeks 14 and 16 (Home Visit)

- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence B)

8.6.6 Sequence B / Treatment Period 2 (IgPro20)

The following procedures are to be performed at each visit:

8.6.6.1 Week 17 (Site Visit)

Before Infusion

- Perform full physical examination
- TEE safety assessment
- Perform CCI [redacted]
- Perform CCI [redacted]
- Perform and CCI [redacted]
- Conduct ECG
- Perform PFTs (CCI [redacted])
- Measure vital signs
- Measure body weight
- Collection of blood samples for safety to assess the following:
  - Hematology
  - Serum chemistry
  - Renal function
  - Hemolysis
  - Biomarkers
  - Autoantibody
  - PK (see Pharmacokinetic Schedule of Assessments: Sequence B)

- Collection of urine sample to assess the following:
  - Urinalysis
  - Renal function
  - Urine Pregnancy test, if applicable
  - Hemolysis
- Conduct CCI
- Conduct CCI
- Conduct CCI
- Conduct CCI
- Conduct CCI
- Conduct CCI
- CCI score to be derived programmatically
- Dispense new IgPro20 patient diary
- Assess and record AEs
- Record concomitant therapies
- IP assignment
- Infusion of IgPro20

After Infusion

- Completion of infusion form
- Measure vital signs

8.6.6.2 Weeks 19, 23, 27 (Site Visits)

Before Infusion

- Abbreviated physical exam
- TEE safety assessment
- Measure vital signs

- Measure body weight
- Review of IgPro20 patient diary / dispense new IgPro20 patient diary
- Assess and record AEs
- Record concomitant therapies
- IP assignment
- Infusion of IgPro20 (Session 1)

After Infusion

- Measure vital signs
- Completion of infusion form

8.6.6.3 Weeks 21, 25, and 29 (Site Visits)

Before Infusion

- Abbreviated physical exam
- TEE safety assessment
- Measure vital signs
- Measure body weight
- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence B)
- Collection of urine sample for pregnancy test, if applicable
- Review of IgPro20 patient diary / dispense new IgPro20 patient diary
- Assess and record AEs
- Record concomitant therapies
- IP assignment
- Infusion of IgPro20 (Session 1)

After Infusion

- Measure vital signs

- Completion of infusion form

8.6.6.4 Weeks 17, 19, 21, 23, 25, 27, and 29 (Home Visits)

- Assess and record AEs
- Record concomitant therapies
- Measure vital signs before and after each session
- Infusion of IgPro20 (Session 2)
- Completion of infusion form

8.6.6.5 Weeks 18, 20, 22, 24, 26, and 28 (Home Visits)

- Assess and record AEs
- Record concomitant therapies
- Measure vital signs before and after each session
- Infusion of IgPro20 (Sessions 1 and 2)
- Completion of infusion form

8.6.6.6 Week 30 (Home Visit)

- Assess and record AEs
- Record concomitant therapies
- Measure vital signs before and after each session
- Infusion of IgPro20 (Sessions 1 and 2)
- Completion of infusion form
- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence B)

8.6.6.7 Week 31 (Home Visit)

- Collection of blood sample for PK (see Pharmacokinetic Schedule of Assessments: Sequence B)

8.6.7 End of Treatment (Week 32; Sequence A and Sequence B) / Early Termination (Site Visit)

The following procedures are to be performed at the EOT / Early Termination Visit:

- Perform full physical examination
- Perform CCI [redacted]
- Perform CCI [redacted]
- Perform CCI [redacted]
- Conduct ECG
- Perform PFTs (CCI [redacted])
- Measure vital signs
- TEE safety assessment
- Collection of blood samples to assess the following:
  - Hematology
  - Serum chemistry
  - Virology markers of HIV-1 / -2, Hepatitis B, and Hepatitis C
  - Serum pregnancy test, if applicable
  - Renal function, if applicable
  - Hemolysis, if applicable
  - Biomarkers (optional, only for subjects that provided baseline sample)
  - Autoantibody
  - PK, if applicable
- Collection of urine sample to assess the following:
  - Urinalysis
  - Renal function, if applicable
  - Hemolysis
- Conduct CCI [redacted]
- Conduct CCI [redacted]

- Conduct CCI
- Conduct CCI
- Conduct CCI
- Conduct CCI
- CCI score to be derived programmatically
- Conduct CCI (only subjects that completed both treatments)
- Assess and record AEs
- Record concomitant therapies
- Review of IgPro20 patient diary, if applicable

8.6.8 End of Study (Week 36; Sequence A and Sequence B; Telephone Call)

The safety follow-up EOS Visit (Week 36) is to be conducted via telephone:

- Assess and record AEs
- Record concomitant therapies

8.6.9 Unscheduled Visits (Sequence A and Sequence B)

The following procedures are to be performed at any unscheduled visit:

- Assess and record AEs
- Record concomitant therapies
- Any other assessments or procedures may be performed at the discretion of the investigator

8.6.10 Remote Visits During Emergencies

In the event of a state of emergency or public health threat resulting in restrictions that prevent a subject from returning to the study site for required study assessments or procedures, these may be conducted remotely with CSLB approval. Options that may be

implemented in the event of local restrictions at the discretion of CSLB are provided in Appendix 4.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

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

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

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition other than SSc.
- Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- A clinical event occurring after consent but before IgPro20 or IgPro10 administration.
- Intercurrent illnesses with an onset after administration of IgPro20 or IgPro10.

Adverse events do not include:

- Events identified at screening that meet exclusion criteria
- Medical or surgical procedures (the condition that leads to the procedure is the AE)
- Situations where an untoward medical occurrence has not taken place. For example:
  - Planned hospitalizations (except for receiving IP infusions) due to pre-existing conditions, which have not worsened.
  - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).

- Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy).
- Overdose of IgPro20 or IgPro10.
- Any concomitant therapy that does not result in any adverse signs or symptoms.

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

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

Any clinically significant findings in vital signs, ECG, spirometry, or any other assessment, including information in the patient diary that is considered by the investigator to be clinically significant should be reported as an AE.

9.1.2 Serious Adverse Event

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

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.
- **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization** – CSLB considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or

for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.

- **Results in persistent or significant disability or incapacity**.
- **Is a congenital anomaly or birth defect**.
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

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

9.1.3 Adverse Event of Special Interest

An AESI is an AE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor is appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the sponsor to other parties (eg, IDMC, regulators) might also be warranted.

The safety risk management plan of IgPro20 specifies the 'Important Identified Risks' and 'Important Potential Risks' for IgPro20. This involves systemic reactions reported to occur with IgPro20.

In this study, hemolysis, TEEs, and acute renal injury will be treated as AESIs.

All hemolysis events under the standardized MedDRA queries (SMQ) "hemolytic disorders, broad" will be considered AESI.

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.

9.1.4 Medical Device Incident

A medical device incident is any malfunction or deterioration in the characteristics and / or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject / user / other person or to a serious deterioration in his / her state of health.

Note, not all medical device incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been because of fortunate circumstances or to the intervention of health care personnel.

Examples of medical device incidents include:

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study intervention is interrupted or compromised by a medical device failure.

The reporting requirements for medical device incidents are detailed in Section 9.6.3.

9.2 Intensity of Adverse Events

The intensity of each AE is to be assessed by the investigator as follows:

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

9.3 Causality of Adverse Events

The causal relationship of an AE to IgPro20 or IgPro10 **must always be assessed** by the investigator. All AEs will be classified as either **related** or **not related** to IgPro20 or IgPro10.

If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to IgPro20 or IgPro10.

The degree of certainty with which an AE is attributed to IgPro20 or IgPro10 or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of IgPro20 or IgPro10.
- Clinically and / or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor).
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with IgPro20 or IgPro10, drug withdrawal or reproduced on rechallenge).

9.4 Observation Period for Adverse Events

The observation period for the reporting of AEs (and SAEs) for an individual subject will start at the time of giving written informed consent for participation in the current study and finish 4 weeks after the last visit.

If the investigator becomes aware of an SAE or that has started after the observation period has finished, and there is at least a possible causal relationship to IgPro20 or IgPro10, the event must be reported to CSLB (see Section 9.6.2).

Medical device incidents or malfunctions that result in an AE are to be reported during all periods of the study in which the medical device is used. If the investigator becomes aware of any incident that has started after a subject has been discharged from the study, and such incident is considered at least possibly related to a medical device provided for the study, the event must be reported to CSLB (see Section 9.6.3).

9.5 Follow-up of Adverse Events

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

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs.

9.6 Adverse Event Reporting

9.6.1 Adverse Events

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

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

9.6.2 Serious Adverse Events

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

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

All SAEs that occur during the course of the study, whether or not causally related to IgPro20 or IgPro10, must be reported and entered into the eCRF immediately (within 24 hours of the event) to CSLB.

Adverse events occurring in the period between the times the subject gave written informed consent and the first exposure to IgPro20 or IgPro10 that meet 1 or more of the seriousness criteria will be entered into the eCRF in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the EOS Visit that is considered to be causally related to IgPro20 or IgPro10 must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSLB.**

The minimum reporting requirements for reporting of SAEs include:

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

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

In addition, the investigator must:

- Report all SAEs to the relevant Institutional Review Board (IRB) / Independent Ethics Committee (IEC) within the timeframe specified by the IRB / IEC.
- Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for any SAE is entered in the eCRF.

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

9.6.3 Medical Device Incidents

The investigator must promptly report all incidents occurring with any medical device provided for use in the study in order for CSLB to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies

Any event that meets the definition of a medical device incident must be documented in the appropriate page of the eCRF **immediately (within 24 hours of the investigator becoming aware of the event)**. Medical device incidents that meet the definition of an AE or SAE must also be reported as described in Section 9.6.1 (AEs) and Section 9.6.2 (SAEs).

9.6.4 Adverse Events of Special Interest Incidents

Adverse events of special interest, whether or not causally related to IgPro20 or IgPro10, must be reported and entered into the eCRF **immediately (within 24 hours of the event) to**

CSLB.
Any AESIs that occurs after the EOS Visit that is considered to be causally related to IgPro20 or IgPro10 must be reported **immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSLB**.

9.6.5 Overdose

Any overdose that occurs in association with an adverse sign or symptom must be entered into the eCRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 9.6.2).

Details (ie, volume, location of infusions, infusion rate) of administration of IgPro20 or IgPro10 (defined in Section 5.1.3.2) must be recorded in the study treatment administration eCRF. Details of overdose of any concomitant therapy must be recorded in the Concomitant Medication eCRF.

9.6.6 Pregnancy and Breastfeeding

A female subject who becomes pregnant while participating in the study, or up to and including 30 days after the last dose of IgPro20 or IgPro10, must notify the investigator immediately.

If a female subject becomes pregnant, she must discontinue treatment with IgPro20 or IgPro10, but may continue other study procedures at the discretion of the investigator. If the female subject is in the active treatment period of the study, her participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in Section 4.3).

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

Whenever possible, a pregnancy in a subject exposed to IgPro20 or IgPro10 should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to CSLB using a Pregnancy Reporting / Outcome Form.

9.7 IRB / IEC Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and IP-related unexpected SAEs is stipulated by each IRB / IEC. It is the investigator's responsibility to

comply with the requirements for IRB / IEC notification. CSLB will provide investigators with all details of all SAEs reported to regulatory authorities.

10 Statistics

10.1 Sample Size Estimation

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 patients per 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.

10.2 Description of Study Analysis Sets

10.2.1 Full Analysis Set

The Full Analysis Set (FAS) will comprise all subjects who provide informed consent / assent and who are enrolled in the study after Screening. Screening failures will not be included in the FAS. However, the number of screening failures will be summarized in the disposition tables and all screening failures will be listed.

10.2.1.1 Safety Analysis Set

The Safety Analysis Set (SAF) will comprise all subjects who receive at least 1 infusion of IgPro20 or IgPro10.

10.2.1.2 Pharmacokinetic Analysis Set

The PK Analysis Set will be primarily used for the PK parameter ($AUC_{0\text{-}tau}$, $AUC_{0\text{-}last}$, C_{max}, and C_{trough}) estimation and analysis. The PK Analysis Set will comprise all subjects in the safety population who receive at least 1 infusion of IgPro20 or IgPro10 and for whom at least 1 concentration value is reported.

Reasons for exclusion from the PK Analysis Set (eg, potentially confounding concomitant medication or major protocol deviations) will be assessed case-by-base before database lock.

10.3 Statistical Analyses and Methods

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan, which will be finalized before database lock.

For continuous endpoints, descriptive statistics including number of subjects (n), mean, SD, median, first quantile, third quantile, minimum, and maximum, will be provided. For categorical variables, frequency distributions with counts and corresponding percentages of subjects in each category, will be calculated.

10.3.1 Subject Disposition and Characteristics

10.3.1.1 Subject Disposition

Summary tables by treatment sequence, treatment period, and total population will present:

- The number of subjects enrolled into the study (ie, signed the ICF) (FAS set).
- The number of subjects treated (SAF set).
- The number of subjects who completed study treatment.
- The number of subjects who prematurely discontinued IP.
- The number of subjects who were withdrawn from the study.

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

10.3.1.2 Subject Characteristics

Subject characteristics will be presented in summary tables. Continuous data will be summarized in descriptive statistics by treatment sequence. Categorical data will be summarized in frequency distributions by treatment sequence. Age will be described as both a continuous and a discrete variable. Supportive data will be listed by subject.

10.3.2 Analyses of Primary Endpoints

10.3.2.1 Safety of IgPro20

Safety data collected while subjects are treated with IgPro20 will be summarized by treatment sequence. All AEs will be coded by the Medical Dictionary for Regulatory Activities in System Organ Class and Preferred Term. Treatment-emergent adverse events, defined as AEs reported at or after the start of the first infusion in the study, will be summarized in number and percentages by treatment sequence. Summaries of TEAEs by

severity, causal relationship, seriousness, and leading to interruption and / or withdrawal will be provided.

Infusion site reactions will also be summarized separately following the analyses for all TEAEs. Additional summary statistics including 95% CIs will be presented for rate of ISRs per subject and per infusion. Descriptive statistics of time to onset and duration of ISRs will be presented. Detailed information about ISRs related to infusion sites will be provided.

10.3.2.2 Other Clinical Tests

Observed values and changes from baseline / reference visit to assessment time point in clinical laboratory parameters, vital signs will be presented in descriptive statistics by treatment, treatment sequence, and combination of treatment and treatment period. ECG, PFTs, use of concomitant medications, and clinical significant changes in physical examinations will be listed.

10.3.3 Analyses of Secondary Endpoints

10.3.3.1 Relative Bioavailability of IgPro20

Relative bioavailability of IgPro20 will be assessed using Mixed Model Repeated Measures on Log-transformed Dose-normalized $AUC_{0\text{-}tau}$. The model will include treatment, treatment period, and treatment-by-period interaction as fixed effects, and subject as a random effect 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 $AUC_{0\text{-}tau}$. In addition, the relative bioavailability of IgPro20 will be summarized in descriptive statistics by sequence.

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

10.3.3.2 Pharmacokinetic Parameters

The PK parameters ($AUC_{0\text{-}tau}$, $AUC_{0\text{-}last}$, C_{max}, and C_{trough}) will be derived from serum IgG levels using a non-compartmental analysis approach. PK parameters will be summarized descriptively by sequence and treatment period with geometric means and corresponding 95% CI.

Additional information on the analyses of PK parameters will be provided in the Statistical Analysis Plan.

10.3.3.3 Safety of IgPro10

Safety data of IgPro10 will be summarized in the same manner as IgPro20 as described in Section 10.3.2.1. In addition, hemolysis will be analyzed descriptively.

10.4 CCI

CCI

10.4.1 Extent of Exposure

Summary statistics will be provided to describe treatment administration data on infusion level and on subject level by treatment. The characteristics of treatment administration to be summarized include but are not limited to, treatment duration, planned and actual volumes, infusion rates, and infusion duration. The data will be listed by subject with additional information on the lot number, start and end date, time of infusion, and dose adjustment if applicable.

10.4.2 Interim Analyses

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.

11 Quality Assurance

The study may be subject to an audit by CSLB, an authorized representative(s) of CSLB and / or inspections by an authorized regulatory authority (eg, US Food and Drug Administration). Regulatory authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSLB will notify the investigator of any upcoming audit / inspection.

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

12 Regulatory and Ethics Considerations

12.1 Regulatory Considerations

CSLB or its agents will submit the appropriate documents to the local regulatory agencies and will await approval before study start.

This study will be conducted under a registered clinical trial application in the EU, and under Therapeutic Goods Administration Clinical Trial Notification and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this study protocol are designed to ensure that CSLB and the investigator abide by the principles of the current ICH GCP guideline on the conduct,

evaluation and documentation of this study, as described in ICH Topic E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

12.2 Institutional Review Board / Independent Ethics Committee

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

12.3 Subject Information and Informed Consent

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

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

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

12.4 Subject Confidentiality

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

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

Subject medical records pertaining to the study may be inspected / audited at any time by CSLB employees or their duly authorized representatives, a regulatory authority or the

IRB / IEC. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections / audits.

12.5 Indemnity and Compensation

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

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

13 Administrative Considerations

13.1 Clinical Trial Research Agreement

This study will be conducted under a Clinical Trial Agreement between CSLB ("Sponsor") and the institution(s) representing the investigational study site(s) ("Authority"). Financial support to the investigational site(s) will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and CSLB, and will form the contractual basis under which the clinical study will be conducted. Clinical Trial Agreements may be executed by electronic signature (current provider DocuSign) in compliance with 21 CFR Part 11 and simple or advanced electronic signature according to EU Regulation No 910/2014 – eIDAS.

13.2 Clinical Study Registration and Results Disclosure

CSLB will provide the relevant study protocol information in public database(s) before or at commencement of the study. CSLB may also provide study information for inclusion in national registries according to local regulatory requirements.

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

13.3 Implementation of the Protocol / Protocol Amendment(s)

With the exception of medical emergencies, no changes or deviations in the conduct of the signed protocol will be permitted without documented approval of the CSLB Medical Monitor or designee and the IRB / IEC. In the event of a medical emergency, the investigator

at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the CSLB Medical Monitor and the IRB / IEC.

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

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

13.4 Protocol Deviations

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

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

13.5 Documentation and Record Keeping

13.5.1 Data Collection

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, or physical examinations, administration of IgPro20, IgPro10, or concomitant therapy, any AEs experienced, and other notes as appropriate. These records (electronic or paper) constitute source data.

Electronic CRF entries will be considered source data if the eCRF is the site of the original recordings (ie, there is no other written or electronic record of the data). In this study, the eCRF will not be used as the source document.

An eCRF will be provided by CSLB (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the

study. All entries on the eCRF must be backed up by source data unless the eCRF is considered source data. All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

An eCOA solution will be used by the subjects and / or sites.

The eCOA solution is provided as a means to capture electronic source data in a controlled and consistent way, and to provide access for investigators to these source data. The system also allows the subject's health status to be remotely monitored during the study. The data residing in the eCOA system provider's database are considered the source, and are under the control of the investigator at all times.

The investigator (or delegate) will have access to all eCOA data entered at site via a secure, role-based web portal provided by an external eCOA system provider. The eCOA system provider will transfer a copy of the source data across to CSLB's clinical data warehouse at a predefined frequency via a secure data channel for systematic review by the CSLB clinical team.

The eCOA vendor engaged for this study is responsible for providing a solution that conforms to all pertinent regulations. The solution is not in any way intended as a substitute for normal medical care of the subject. The vendor provides the service of hosting of the eCOA data on behalf of the study investigators, until such a time as the investigator is in receipt of a certified archive copy of all data relating to subjects at that site and has confirmed it is readable.

13.5.2 Data Quality Assurance

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

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

13.5.3 Record Retention

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

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

The study may be audited or inspected by qualified delegates from CSLB or a competent regulatory authority.

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

13.6 Study and Site Closure

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

13.7 Clinical Study Report

A clinical study report will be written after the completion of the study. CSLB or its agent will write the report in consultation with the investigator or, if applicable, a nominated coordinating investigator (or delegate). It is required by CSLB that the coordinating investigator will sign the clinical study report.

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

13.8 Use of Data and Publications

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

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15 Appendices

Appendix 1 Signatures

Signature on Behalf of Sponsor

Study Title: 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)

Protocol Number: IgPro20_2001

I have read the Clinical Study Protocol titled "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)" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

(Printed name)

PPD

(Title)

PPD

Date (DD MMM YYYY)

Signature of Principal Investigator

Study Title: 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)

Protocol Number: IgPro20_2001 Site Number:

I have read the Clinical Study Protocol entitled "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)."

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

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

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

_____ _____

(Signature) Date (DD MMM YYYY)

_____

Printed name

(Title)

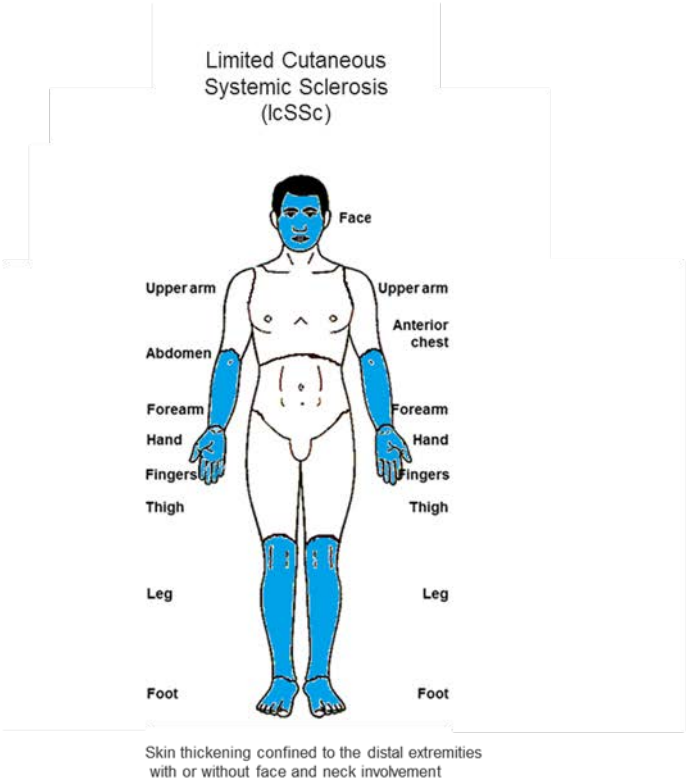
Appendix 2 The American College of Rheumatology / European League Against Rheumatism Criteria for the Classification of Systemic Sclerosis (SSc)

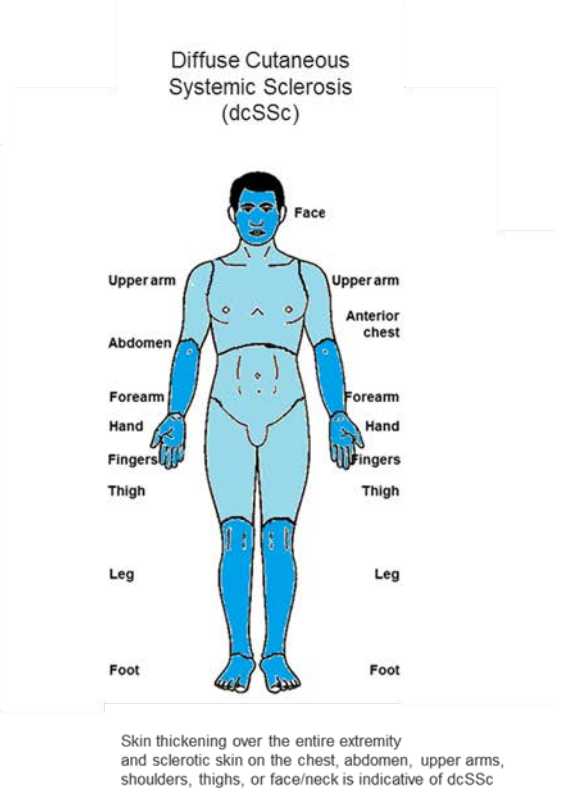
Item	**Sub-item(s)**	**Weight / Score†**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (*sufficient criteria*)	-	9
Skin thickening of the fingers (*only count the highest score*)	Puffy fingers Sclerodactyly of fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesion (*only count the highest score*)	Digital up ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nail fold capillaries	-	2
Pulmonary arterial hypertension and / or interstitial lung disease *(Maximum score is 2)*	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) *(maximum score is 3)*		3

Reference:

van den Hoogen, 2013

Appendix 3 Diffuse Cutaneous Systemic Sclerosis (dcSSc) Versus Limited Cutaneous Systemic Sclerosis (lcSSc)





References

LeRoy and Medsger, 2001

LeRoy et al, 1988

Appendix 4 Contingency Procedures

In the event of a state of emergency or public health threat resulting in restrictions that prevent a subject from returning to the study site for protocol-specified study assessments or procedures, some assessments / procedures may be omitted or completed remotely (as indicated) with CSL Behring approval. The following options may be implemented "on-demand" in the event of local restrictions and at the discretion of CSL Behring.

If the investigator implements changes to the protocol for subject safety and to limit subjects' exposure to COVID-19 other than those specified in these contingencies, those changes should be documented as deviations resulting from the COVID-19 pandemic. Documented deviations must be reported to the Institutional Review Board (IRB) / Independent Ethic Committee (IEC) and appropriate regulatory authorities.

The purpose of these contingencies is to make coronavirus disease 2019 (COVID-19) pandemic related adjustments to the most current protocol. These contingencies are effective during the COVID-19 pandemic and provide detailed guidance and procedures to investigators, allowing them the flexibility to complete critical safety and efficacy protocol assessments while limiting subjects' exposure to COVID-19 at a study center / site.

The following apply to subjects who are treated with IgPro20 and IgPro10 during the COVID-19 pandemic:

1. **Eligibility Confirmation on** CCI [redacted]

   Documented CCI [redacted] (CCI [redacted]) results obtained up to 1 year before Screening can be used by investigators for eligibility confirmation with prior approval by the Medical Monitor.

   Reason:

   - CCI [redacted] testing at pulmonary centers other than the study center / site may be restricted due to management of COVID-19 patients
   - To limit a subject's potential exposure to COVID-19 at the study center / site

2. Body Temperature Measurement / Methodology (Safety Assessment - Vital Signs)

In addition to the listed oral and tympanic measurements of body temperature in Section 8.1.1.6, other standard methodologies in use at the study center / site are allowed.

Reason: Allows study centers / sites to follow their standard procedures of body temperature collection during the COVID-19 pandemic.

3. For Subjects in the Treatment Period Receiving IgPro20

Scheduled visits can be conducted as a telephone or video conference (remote visit) or as a home visit, if approved in advance by the investigator and the Medical Monitor, except for Screening, Baseline Week 17 and End of Study Visit. Telephone or video conferencing and home visits are intended only to be conducted if a study subject is unable to visit the study center / site due to the COVID-19 pandemic. Safety assessments, including laboratory tests, should not be missed. If safety assessments are unable to be performed at the study center / site, blood and urine samples for safety assessments should be collected, if possible, by a home health nurse as a part of a home visit.

The following should be performed by designated study site personnel when conducting a study visit or portion of a study visit by telephone or video conferencing:

- Investigational product (IP) assignment (IP may be shipped to the subject's home following a CSL defined procedure)
- Confirm compliance with and record the results of home pregnancy testing in women of childbearing potential at protocol-defined time points (study center / site staff to liaise with home health nurse to verify that a pregnancy test was performed and record the result)
- Record concomitant therapies
- Assess and record adverse events
- Review the subject diary
- Thromboembolic Events (TEE) safety assessment

  Note: If the risk for TEE has increased or there is any suspicion that a TEE has

occurred, the subject should have a full TEE evaluation as per study site's standard of care as soon as possible.

The following assessments should be performed by the home health nurse while conducting a study visit or portion of a study visit as a home visit:

- Vital signs, including body weight at protocol-defined time points
- IgPro20 SC infusion
- Complete the infusion form including assessment and recording of potential adverse events
- Pharmacokinetic sample collection at protocol-defined time points as needed
- Safety laboratory sample collection (including pregnancy testing) as needed
- Assess changes in health and / or concomitant therapies
- Collect and dispense a new subject diary

The following assessments are not required when conducting remote visits:

- Physical examination

In case the IP has been dispensed from the study center / site to the subject's home, subject personal and medical data will be protected; a special courier service and a process that ensures confidentiality will be utilized.

Reason: The purpose of this change is to indicate the type of visits required for collecting critical safety and efficacy data.

If the investigator implements changes to the protocol for subject safety and to limit subjects' exposure to COVID-19 other than those specified in these contingencies, those changes should be documented as deviations resulting from the COVID-19 pandemic. Documented deviations must be reported to the IRB / IEC and appropriate regulatory authorities.

4. For Subjects in the Treatment Period Receiving IgPro10

For subjects in the IgPro10 treatment period, procedures should be followed per protocol. Actual visits may occur prior to or after a defined visit window if necessary, if approved by the Medical Monitor in advance. Intravenous infusions must be

conducted at the study center / site. Safety assessments, including hemolysis safety, renal function, and TEE risk assessments, should not be missed. If safety assessments are unable to be performed at the study site, blood and urine samples for hemolysis, renal function, and other safety assessments should be collected by a home health nurse as a part of a home visit.

Remote Visits (Sequence A: Weeks 19, 23, 27, 31; Sequence B: Weeks 3, 7, 11, 15)

Site visits at which no infusions are to be given can be conducted remotely via telephone or video conferencing if approved in advance by the Medical Monitor. Remote telephone or video conferencing study visits are preferred. These remote visits are intended only to be conducted when a study subject is unable to attend the study site due to the COVID-19 associated restrictions.

The following critical assessments should be performed by study site personnel when conducting a remote study visit or portion of a remote study visit via telephone or video conferencing:

- Record concomitant therapies
- Assess and record adverse events
- TEE safety assessment

Note: If the risk for TEE has increased or there is any suspicion that a TEE has occurred, the subject should have a full TEE evaluation as per study site's standard of care as soon as possible.

- Assess for clinical signs of hemolysis (eg, ask the subject about any changes in urine color or skin color, problems associated with physical exercise, chills, abdominal pain, or dizziness)
- Blood and urine samples for hemolysis and renal function safety assessments should be collected by a home health nurse as a part of a remote visit

Note: Study site personnel should liaise with home nursing service to ensure appropriate tests are performed according to the protocol.

As stated above, for subjects receiving IgPro10, home infusions are not allowed. If a subject who is scheduled for an IgPro10 infusion is unable or unwilling to attend a scheduled on-site study infusion visit, that subject should be discontinued from the study after discussion with and approval of the Medical Monitor.

Reason: The purpose of these changes is to limit subject exposure to COVID-19 at the study center / site yet maintain a safe level of treatment and monitoring of subjects receiving IgPro10.

5. Critical Visits

For subjects in either the IgPro20 or IgPro10 treatment periods, Screening, Baseline, Week 17, and the End of Treatment (EOT) Visits should be conducted on-site and all procedures performed as outlined in protocol. These critical visits may occur at the study center / site within the protocol defined visit window and if further adjustment to accommodate a subject is needed, an approval by Medical Monitor should be requested in advance. If the EOT Visit cannot be performed within the protocol-defined day the EOT Visit in its entirety should be performed as soon as possible after that date.

Reason: This change ensures the critical visits and EOT Visit are conducted, at the study center / site, even if delayed.

If the investigator deviates from the protocol for subject safety and to limit subjects' exposure to COVID-19 other than those specified in these contingencies, such deviations should be documented as resulting from the COVID-19 pandemic and must be reported to the IRB / IEC and appropriate regulatory authorities.

If an investigator or the Medical Monitor determines that the safety of a subject cannot be assured using the monitoring approaches described within these contingencies, the subject should be discontinued from the study.

Signature Page

IgPro20_2001 - Protocol Amendment - 4 - 22Feb2021

Signed By	Date (GMT)
PPD	24-Feb-2021 20:17:57
Approved-Clinical Safety Physician Approval	
PPD	24-Feb-2021 20:33:55
Approved-PPD Approval	
PPD	25-Feb-2021 08:44:49
Approved-PPD Approval	
PPD	25-Feb-2021 09:36:55
Approved-Clinical Safety Physician Approval	

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