CLINICAL STUDY PROTOCOL

Study Title:	Double-blind, Randomized, Placebo-controlled Phase 3 study Evaluating Efficacy and Safety of IgPro20 (subcutaneous immunoglobulin, HIZENTRA®) in post-COVID-19 Postural Orthostatic Tachycardia Syndrome (POTS)
Study Number:	IgPro20_3010
Version:	Original
Study Product:	IgPro20 (subcutaneous immunoglobulin, HIZENTRA®)
Brief Title:	Double-blind, Randomized, Placebo-controlled Study Evaluating Efficacy and Safety of IgPro20 in post-COVID-19 POTS
Study Phase:	Phase 3
Sponsor Name and Legal Registered Address:	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America

Regulatory Agency Identifier Number(s):

Pending

EudraCT and / or EU Clinical Trial number:	2023-508744-22-00
IND:	29874
WHO:	NA
ClinicalTrials.gov:	NA
Protocol Version Date:	11 April 2024

SPONSOR SIGNATORY

PPD

PPD

Date
(DD Month YYYY)

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

A list of the 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 the Sponsor and provided to the study sites as needed.

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
CIDP	Chronic inflammatory demyelinating polyneuropathy
COMPASS-31	Composite Autonomic Symptom Score 31
COVID-19	Coronavirus disease 2019
CSP	Clinical Study Protocol
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
ECG	Electrocardiogram
EOS	End of Study
EQ-5D-5L	EuroQol-5 dimension-5 levels
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
HR	Heart rate
HRT	Hormone replacement therapy
HRQoL	Health-related Quality of Life
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Infusion site reaction
ITT	Intention-to-treat
IVIG	Intravenous immunoglobulin

Abbreviation	Term
MI	Multiple imputation
OHQ	Orthostatic Hypotension Questionnaire
OI	Orthostatic intolerance
PCR	Polymerase chain reaction
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PID	Primary immunodeficiency
PK	Pharmacokinetics
POTS	Postural Orthostatic Tachycardia Syndrome
PP	Per-protocol
PRO	Patient-reported outcomes
PROMIS	Patient-reported Outcomes Measurement Information System
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SD	Standard deviation
SF-12	Short Form – 12 Item
TEAE	Treatment-emergent adverse event
TS	total score
ULN	Upper limit of normal
US	United States
WPAI:SHP	Work Productivity & Activity Impairment: Specific Health Problems

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1. PROTOCOL SUMMARY

1.1. Synopsis

Study Title

Double-blind, Randomized, Placebo-controlled Phase 3 Study Evaluating Efficacy and Safety of IgPro20 (subcutaneous immunoglobulin, HIZENTRA®) in post-COVID-19 Postural Orthostatic Tachycardia Syndrome (POTS)

Development Phase: 3	

Objective(s)

The primary objective of this study is to evaluate the efficacy of IgPro20 in comparison with placebo in adult subjects with post-COVID POTS.

Overall Design

This is a prospective, phase 3, multicenter, double-blind, randomized placebo-controlled study to investigate the efficacy, safety, and pharmacokinetics (PK) of repeat doses of IgPro20 in subjects with post SARS-CoV-2 infection 2019 postural orthostatic tachycardia syndrome (post-Coronavirus Disease 2019 [COVID-19] POTS, hereafter referred to as post-COVID POTS).

Eligible subjects will be randomized in a 2:1 ratio to receive subcutaneous (SC) infusions of IgPro20 at doses of [redacted] g/kg/week or placebo for 24 weeks followed by an Open-label Treatment Period of 28 weeks as depicted in Section 1.2.

Study Course for Individual Subject

The study will consist of a Screening Period of up to 4 weeks, a Double-blind Treatment Period (placebo-controlled) of 24 weeks, an Open-label Treatment Period of 28 weeks, and a 4-week Safety Follow-up Period after the last investigational medicinal product (IMP) administration.

During the Double-blind Treatment Period, at least the first infusion for Week 1 and Week 2 are mandatory on site; training and supervised IMP SC infusions will be conducted at these site visits on Week 1 and Week 2. Optional visits can occur at Weeks 3 and 4 for infusion training only. The next mandatory visit is Week 5.

Following the Double-blind Treatment Period, subjects will receive open-label treatment for 28 weeks and enter a 4-week Safety Follow-up Period after the last IMP administration. The first infusion of Week 25 should also occur on site under supervision as some subjects will be switched from placebo to active treatment.

Study Duration for Individual Subject

The estimated overall study duration for an individual subject will be approximately 60 weeks (15 months), based on the durations of the following study periods:

- Screening Period: 4 weeks
- Double-blind Treatment Period: 24 weeks
- Open-label Treatment Period: 28 weeks
- Safety Follow-up Period: 4 weeks

Number of Subjects

Approximately 177 adult subjects with a confirmed diagnosis of post-COVID POTS will be enrolled into the study.

Note: Subjects are considered "enrolled" in the study when they, or their legally acceptable representative, have agreed to participate in a clinical study after completing the informed consent process and screening. Potential subjects who are screened to determine their eligibility but fail screening or do not meet all eligibility criteria, are not considered enrolled.

Diagnosis and Main Enrollment Criteria

Inclusion Criteria

1. Provide written informed consent and be willing and, in the opinion of the investigator, able to adhere to all protocol requirements
2. Males and females aged ≥18 at the time of providing written informed consent
3. Diagnosis of post-COVID POTS, defined by both:
    - Preceding COVID-19 infection, based on confirmed historical documentation of the following:
        - Documented history of SARS-CoV-2 infection (documented by antigen or polymerase chain reaction [PCR] test)

          OR
        - Documented clinical diagnosis of SARS-CoV-2 infection, based on the following criteria:
            1. One of the following documented physician-reported criteria:
                - COVID-19 specific treatment (eg, Nirmatrelvir + Ritonavir / Paxlovid, Remdesivir / Veklury, Molnupiravir / Lagevrio)

                  OR
                - Documentation of one of the following ICD-10 codes: U07.1 (COVID-19, virus identified), U07.2** (COVID-19, virus not identified), U09.9** (post-COVID-19 condition, unspecified)

                AND
            2. Documented patient-reported signs or symptoms*

               AND
            3. Documented patient-reported positive self-administered SARS-CoV-2 antigen test

    *Acceptable signs or symptoms:

    - Acute onset of fever AND cough (influenza-like illness)

      OR

- Any 3 or more of the following signs or symptoms: Fever, cough, general weakness / fatigue, headache, myalgia, sore throat, coryza, dyspnoea, nausea, diarrhea, anorexia

**Subjects with documentation of the ICD-10 codes U07.2 and U09.9 need to be discussed with the Sponsor's Internal Medical Monitor to confirm eligibility based on entirety of documented evidence for preceding SARS-CoV-2 infection

AND

- Onset of POTS symptoms developing within 4 months after COVID-19 infection, as defined per consensus criteria [Vernino et al, 2021]
  - A sustained HR increase of ≥ 30 bpm [≥ 40 bpm for subjects aged 18 to 19 years] within 10 minutes of head-up tilt or standing test, in the absence of orthostatic hypotension (ie, sustained 20 mmHg decrease in SBP)

    AND
  - The presence of post-COVID POTS with persisting symptoms (eg, brain fog, fatigue, palpitations) for at least 3 months

4. Composite Autonomic Symptom Score 31 (COMPASS-31) score of at least 40 at the Screening visit
5. Positive confirmatory standardized standing test (ie, HR increase of ≥ 30 bpm [≥ 40 bpm for subjects aged 18 to 19 years] within 10 minutes in the absence of orthostatic hypotension) at the Screening visit

Exclusion Criteria

1. Treatment with IgG or plasmapheresis within 12 weeks before Screening
2. Symptoms and / or diagnosis of or receiving treatment for POTS before COVID-19 infection
3. Prior diagnosis of or receiving current treatment at Screening for the following conditions (unless onset was related to the inciting POTS-associated COVID-19 infection):
   - Neurologic conditions such as peripheral neuropathy, myalgic encephalomyelitis encephalitis / chronic fatigue syndrome, stroke, spinal cord injury or any known lesions in the central nervous system by imaging or neurological exam
   - Autoimmune conditions such as Sjögren's syndrome, autoimmune autonomic neuropathy, multiple sclerosis, Crohn's disease, celiac disease, lupus erythematosus, rheumatoid arthritis, myasthenia gravis
   - Pre-existing psychiatric disorders such as generalized anxiety disorder (formally diagnosed), anorexia nervosa, disorders causing hyperventilation
   - Endocrine disorders such as hyperthyroidism, pheochromocytoma
   - Cardiac disorders causing sinus tachycardia such as inappropriate sinus tachycardia, or arrythmias

- Other disorders / conditions causing sinus tachycardia such as Ehlers Danlos syndrome, mast cell activation syndrome, fever, pain, infection, moderate to severe anemia, hypovolemia or severe deconditioning caused by prolonged bed rest

4. Presence of active infections such as:
   - Human immunodeficiency virus infection (or history of)
   - Hepatitis B: subjects who are hepatitis B core antibody-positive and who are hepatitis B surface antibody-negative will need to have a negative hepatitis B virus PCR result before enrollment. Hepatitis B surface antigen-positive or hepatitis B virus PCR-positive subjects will be excluded
   - Hepatitis C: subjects who are hepatitis C virus antibody-positive will need to have a negative hepatitis C virus PCR result before enrollment. Hepatitis C PCR-positive subjects will be excluded
   - Any uncontrolled systemic infection
   - Active SARS-CoV-2 infection

Investigational Product(s), Dosage, and Mode of Administration

IgPro20 is a 20% ready-to-use liquid formulation of polyvalent human IgG for SC administration produced by CSL Behring. The IgG portion represents all IgG subclasses present in human plasma. IgG function (fragment crystallizable region and antigen binding fragment mediated activity) is retained. The sterile 20% IgG solution is stabilized with 250 mmol/L L-proline at pH 4.8. IgPro20 also contains 8 to 30 mg/L polysorbate 80 (P80). It has a low sodium content (< 10 mmol/L), with an osmolality of approximately 380 mOsmol/kg, and does not contain any preservatives.

In this study, IgPro20 will be administered at CCI g/kg/week at a flow rate of up to 50 mL/h/site.

The placebo comparator contains 2% human albumin solution in 250 mmol/L L-proline and 20 mg/L polysorbate 80. Placebo will be volume-matched for weekly administration.

Criteria for Evaluation

Primary Endpoint

- Proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test (ie, no longer experiencing HR increase of ≥ 30 bpm), in the absence of 20 mmHg decrease of SBP [orthostatic hypotension]) at the end of the Double-blind Treatment Period.

Key Secondary Endpoints

- Change from baseline in orthostatic intolerance (OI) score of COMPASS-31 at the end of Double-blind Treatment Period.
- Change from baseline in COMPASS-31 total score at the end of the Double-blind Treatment Period.
- Change from baseline in HR increase within 10 minutes of standing test at the end of the Double-blind Treatment Period.

PK Assessments

Blood samples for IgG level determination will be collected pre-dose at baseline and all applicable study visits. Additional blood samples for IgG levels will be collected in a subset of subjects (N = approximately 25) during the Open-label Treatment Period for serial PK sampling starting at Week 41.

Efficacy Assessments

Heart rate as measured by a standardized standing test, OI score of COMPASS-31, and total COMPASS-31 score.

Safety Assessments

Adverse events (AEs), physical examinations, vital signs, and clinical safety laboratory tests.

Quality of Life Assessments

COMPASS-31, Malmö Symptom Score, Work Productivity & Activity Impairment: Specific Health Problems (WPAI:SHP), Short Form – 12 item (SF-12), EuroQol-5 dimension-5 levels (EQ-5D-5L), Patient-reported Outcomes Measurement Information System (PROMIS) Short Formv2.0 – Cognitive Function 6a, Orthostatic Hypotension Questionnaire (OHQ).

Data Monitoring / Other Committees

An unblinded Independent Data Monitoring Committee (IDMC) will monitor the safe conduct of the study. An IDMC charter outlines the roles and responsibilities of the committee and guides its operations.

Statistical Methods

The study is designed to test the null (H_{01}) versus the alternative (H_{11}) hypothesis of the primary endpoint for the proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test (ie, no longer experiencing HR increase of ≥ 30 bpm, in the absence of orthostatic hypotension [ie, sustained 20 mmHg decrease of SBP]) at the end of the Double-blind Treatment Period.

All statistical tests will be 2-sided and will be performed at the 5% level of significance, unless otherwise stated.

In general, continuous variables will be summarized using descriptive statistics (number of observations [n], mean, standard deviation [SD], median, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages. For repeated observations of continuous variables, change from baseline will also be summarized. Summary statistics will be described separately for each treatment group.

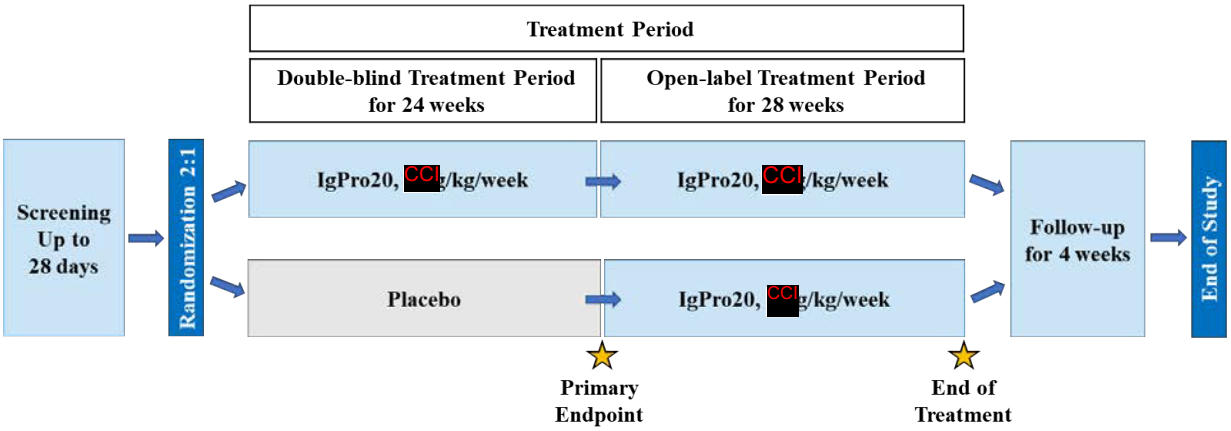
Baseline refers to the last measurement or the last calculated value before the first administration of IgPro20. For COMPASS-31, the assessment at the Screening visit will be used as baseline value (for total as well for all domains).

Missing dates / times in AE and concomitant therapies data will be handled as described in the Statistical Analysis Plan (SAP). There will be no imputation schemes applied to missing data unless otherwise specified in the SAP. Values that are below the limit of quantification in the PK data will be handled as described in the SAP.

Sample size assumptions are based on the 30% and 60% response for the placebo and IgPro20 group, respectively; under these assumptions, at least 126 subjects will be required to provide 90% power (2:1 randomization) to detect a 30% difference in proportion of responders using a Farrington-Manning test. An additional 18 subjects will be included to account for a futility analysis at 54 patients, and an additional 33 subjects will be randomized to ensure > 100 subjects treated with IgPro20 for >1 year will be achieved considering approximately 20% early drop out. Therefore, the final number of patients to be randomized is 177 (118:59).

1.2. Study Schema

Figure 1: Overall Study Schema



1.3. Schedule of Activities

1.3.1. Schedule of Activities for Screening

	Day -28 to Day -1
Assessments	
Informed consent / IRT registration	X
Medical / surgical history and demographics	X
Inclusion / exclusion criteria	X
Record COVID-19 vaccination status	X
General physical examination, including height	X
12-lead ECG	X
Body weight	X
Vital signs	X
SARS-CoV-2 test [a]	X
Serum hCG pregnancy test	X
Hematology and biochemistry, including TSH[b] and morning cortisol levels[b]	X
Virology blood sample (safety)	X
Urine sodium [b]	X
Adverse events	X
Concomitant therapies	X
Standing test [c]	X
COMPASS-31 [d]	X
PGI-S [d]	X

COMPASS-31 = Composite Autonomic Symptom Score 31; ECG = electrocardiogram; eCOA = electronic clinical outcomes assessment; IRT = interactive response technology; PGI-S = patient global impression of severity; PRO = patient-reported outcomes; PROMIS = Patient-reported Outcomes Measurement Information System; RT-PCR = reverse transcription polymerase chain reaction; SARS-COV-2 = Severe acute respiratory syndrome coronavirus 2; TSH = thyroid stimulating hormone.

[a] Test to be performed at the study site as per local regulations. Negative for SARS-CoV-2 infection as determined using a molecular diagnostic test (RT-PCR or equivalent, rapid antigen test; antibody testing is not allowed) that has been approved by regulatory authorities or allowed under an emergency use authorization before Screening.

[b] For subjects where these tests have not already been completed and assessed as normal after symptom onset.

[c] The standing test should be the last assessment performed.

[d] The PRO questionnaires are completed under supervision at the study site using the eCOA solution and may be administered after the following Screening assessments: informed consent / IRT registration, medical / surgical history and demographics, inclusion / exclusion criteria, COVID-19 vaccination status, general physical examination including height, body weight, vital signs, and SARS-CoV-2 test. The PRO questionnaires should be completed before any other study assessments, including the standing test and any blood collections.

1.3.2. Schedule of Activities for the Double-blind and Open-label Treatment Periods

Period	24-week Double-blind Treatment							Transition visit	28-week Open-label Treatment [b]								Follow-up EOS	UNS [b]
Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 EOT	17		
Day / Week	D1 W1[a]	D8 W2[a]	D29 W5[a]	D57 W9	D85 W13	D113 W17	D141 W21	D169 W25[a]	D197 W29	D225 W33	D253 W37	D281 W41	D309 W45	D337 W49	D365 W53	D393 W57		
Window		±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d		
Inclusion / exclusion criteria review	X																	
Randomization	X																	
Physical Examination	X							X								X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG								X							X			X
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 test [c]	X [d]																	
Urine Pregnancy Test	X [d]							X								X	X	X
Hematology	X			X		X		X		X		X			X	X	X	X
Biochemistry	X			X		X		X		X		X			X	X	X	X
PK trough [e]	X			X		X		X		X		X			X	X	X	X
Serial PK [f]												X						
Autoantibodies [e]	X	X	X					X							X			
Disease biomarkers [e]	X	X	X					X							X			
Future research (optional) [e]	X		X					X							X			
RNA transcriptomics (optional) [e]	X		X					X										

Period	24-week Double-blind Treatment							Transition visit	28-week Open-label Treatment [b]							Follow-up	UNS [b]
Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 EOT	17	
Day / Week	D1 W1[a]	D8 W2[a]	D29 W5[a]	D57 W9	D85 W13	D113 W17	D141 W21	D169 W25[a]	D197 W29	D225 W33	D253 W37	D281 W41	D309 W45	D337 W49	D365 W53	D393 W57	
Window		±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	
Virology blood retention sample [g]	X							X							X		
IMP assignment by IRT	X	X	X	X	X	X	X	X [i]	X	X	X	X	X	X			X
IMP weekly dose administration [a]	X	X	X	X	X	X	X	X [i]	X	X	X	X	X	X			X
Infusion training/supervised infusion	X	X															X
eDiary Training	X																
Review eDiary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
COMPASS-31 [h]	X [d]		X	X	X	X	X	X				X			X	X	
Malmö Symptom Score [h]	X [d]							X							X		
WPAI:SHP [h]	X [d]							X							X		
PGI-S and PGI-C for Orthostatic intolerance, general symptoms [h]	X [d]		X	X	X	X	X	X							X		
EQ-5D-5L [h]	X [d]							X							X	X	
SF-12 [h]	X [d]							X							X		
OHQ [h]	X [d]							X							X		
PROMIS Cognitive Function Short Form 6a [h]	X [d]							X							X		
Standing test [j]			X	X	X	X	X	X				X			X		
Safety follow-up [k]																X	X

Period	24-week Double-blind Treatment							Transition visit	28-week Open-label Treatment [b]							Follow-up EOS	UNS [b]
Visit	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 EOT	17	
Day / Week	D1 W1[a]	D8 W2[a]	D29 W5[a]	D57 W9	D85 W13	D113 W17	D141 W21	D169 W25[a]	D197 W29	D225 W33	D253 W37	D281 W41	D309 W45	D337 W49	D365 W53	D393 W57	
Window		±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	
Adverse events	→																
Concomitant therapies	→																

COMPASS-31 = Composite Autonomic Symptom Score 31; D = day; ECG = electrocardiogram; eDiary = electronic diary; eCOA = Electronic clinical outcomes assessment; EOS = end of study; EOT = end of treatment; EQ-5D-5L= EuroQoL 5-Dimension Questionnaire; IMP = investigational medicinal product; IRT = interactive response technology; OHQ = Orthostatic Hypotension Questionnaire; PGI-C = patient global impression of change; PGI-S = patient global impression of severity; PK = pharmacokinetic; PRO = patient-reported outcomes; PROMIS = Patient-reported Outcomes Measurement Information System; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction; SC = subcutaneous; SF-12 = short form – 12 item; UNS = unscheduled visit; W = week; WPAI:SHP = Work Productivity & Activity Impairment: Specific Health Problems.

[a] Week 1 and Week 2 are mandatory on site; training and supervised IMP SC infusions will be conducted at the site for at least the first infusion on Week 1 and Week 2. Optional visits can occur at Weeks 3 and 4 for infusion training only. The next mandatory visit is Week 5. From Week 5, the subject will change to home treatment (with the exception of the first infusion of Week 25 to monitor infusions as some subjects will switch from placebo to active treatment). Subjects will self-administer IgPro20 on CCI infusion day(s) (see Section 6.6). All SC infusions for the previous week must be performed before the following study visit. All SC infusions planned in the same week as a study visit should not be started until after the study visit occurs (with the exception of Weeks 1 and 2 for training purposes and the first infusion of Week 25, which should also occur on site under supervision as some subjects will be switched from placebo to active treatment).

[b] Some visits may be performed remotely or by home health nurse at the subject's home when available and allowed by local regulations after confirmation by the Sponsor. Further details on which visits can be performed remotely and details on remote processes can be found in the applicable study-specific manuals.

[c] Test to be performed at the study site as per local regulations. Negative for SARS-CoV-2 infection as determined using a molecular diagnostic test (RT-PCR or equivalent, rapid antigen test; antibody testing is not allowed) that has been approved by regulatory authorities or allowed under an emergency use authorization.

[d] Assessment must be performed before first dose administration. Assessment can be completed either at the Day 1 visit or one day before as preferred by the site and the subject.

[e] Blood samples for IgG level determination, disease biomarkers, autoantibodies, future research, and RNA transcriptomics are to be collected pre-dose at baseline and all applicable study visits.

[f] Blood samples for serial PK will be collected in a subset of subjects (N = approximately 25) (see Section 1.3.3).

[g] Virology blood sample for possible future assessment in case of evidence for a possible treatment-emergent virus. Infection assessment to occur only if required and after additional consent is obtained from the subject. To be collected before first dose of IMP on Day 1, first dose of Week 25 are administered, and after all study infusions have been completed at the EOT visit.
[h] The PRO questionnaires are completed under supervision at the study site using the eCOA solution and administered before any other study procedures. COMPASS-31 recall period will be for the past week.
[i] Assignment of IgPro20 only after all assessments are completed. The Week 25 visit is the only other site visit after the initial weeks where at least one infusion is to be performed on site.
[j] The standing test should be the last assessment performed at any visit, as applicable.
[k] In all early termination subjects a safety follow-up will be conducted 4 weeks after the last IMP dose via a telephone call. It will not be performed for subjects discontinuing IMP but remaining in the study for at least 1 subsequent visit 4 weeks after IMP discontinuation. For subjects completing all study visits per protocol, safety follow-up will be completed at the Week 57 Visit on-site. Please refer to Sections 7.1 and 7.2 for further details.

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1.3.3. Schedule of Activities: Pharmacokinetic Sampling in a Subset of Subjects at Week 41

Timepoint	Timepoint Window
Day 2: 24 hours after the start of Day 1 infusion	± 3 hours
Day 3: 48 hours after the start of Day 1 infusion	± 3 hours
Day 4: 72 hours after the start of Day 1 infusion	± 3 hours
Day 6: 120 hours after the start of Day 1 infusion	± 3 hours

2. INTRODUCTION

2.1. Background

Long coronavirus disease (COVID) (also referred to as "post-acute sequelae of coronavirus disease 2019 [COVID-19]") is a multisystemic condition often comprising severe symptoms including fatigue, cognitive dysfunction, post-exertional malaise, and palpitations, following an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [Davis et al, 2021; Davis et al, 2023; Huang et al, 2021]. The underlying etiology is likely multifactorial, however autonomic dysfunction may play a significant role especially when manifested as Postural Orthostatic Tachycardia Syndrome (POTS), which has been documented following infection with SARS-CoV-2, independent of the severity of the preceding COVID-19 infection [Larsen et al, 2022]. Long COVID symptoms following acute COVID-19 infection in previously healthy and active individuals are debilitating and have many features of POTS including fatigue, palpitations, brain fog, dizziness, gastrointestinal issues, and exercise intolerance [Blitshteyn and Whitelaw, 2021; Davis et al, 2021; Goldstein, 2021; Parker et al, 2021; Thieben et al, 2007]. The diagnosis of POTS in adults requires presence of excessive orthostatic tachycardia of at least 30 bpm within 10 minutes of standing in the absence of orthostatic hypotension, accompanied by symptoms of chronic orthostatic intolerance (OI) (eg, brain fog, dizziness, palpitations) for a duration of at least 3 months [Bryarly et al, 2019; Raj et al, 2020]. Bearing hallmarks of a serious condition, POTS can significantly impair functional status, mental health, and quality of life (QoL) causing many patients to become bedridden subsequently leading to economic and employment challenges [Anderson et al, 2014; Ormiston et al, 2022; Taub et al, 2021; Zadourian et al, 2018]. Similarly, post-COVID POTS has been described as an urgent public health concern in adults, with high morbidity and significant impact on QoL, as well as economic and employment challenges, with up to 60% of patients with residual autonomic symptoms post-COVID being unable to return to work 6 to 8 months after an acute COVID-19 infection [Blitshteyn and Whitelaw, 2021; Bourne et al, 2021; Raj et al, 2021a]. While the prevalence of POTS before the outbreak of the recent COVID-19 pandemic ranged between 0.2 and 1% in developed countries [Fedorowski, 2019; Zadourian et al, 2018] and between 0.1% and 1% in the United States (US) population specifically [Arnold et al, 2017; Zadourian et al, 2018], there has been a sharp rise in the incidence of POTS cases since the beginning of the pandemic due to the long-term effects of COVID-19 [Ormiston et al, 2022; Tafler et al, 2023]. Although clinical studies of COVID-19–related dysautonomia are limited to small case series and anecdotal reports, post-COVID POTS-like symptoms were reported in 34% of respondents in an international web-based survey of nearly 4000 COVID-19 survivors [Blitshteyn and Whitelaw, 2021; Davis et al, 2021; Eshak et al, 2020; Goodman et al, 2021; Johansson et al, 2021; Novak, 2020], and recent reports indicate that approximately 2% to 14% of COVID-19 survivors develop post-COVID POTS [Davis et al, 2021; Ormiston et al, 2022]. The mean age of individuals with post-COVID POTS is 36 years with women being more predominantly affected than men [Amekran et al, 2022; Blitshteyn and Whitelaw, 2021; Gall et al, 2022; Parker et al, 2021]. The natural history of post-COVID POTS is not fully understood with medium-term to long-term prognosis of affected individuals undefined [Kwan et al, 2022; Orminston et al, 2022], and a

similar absence of information on the course of disease for patients left completely untreated [Eshak et al, 2020; Goodman et al, 2021; Johansson et al, 2021; Novak, 2020].

The pathophysiology of autonomic dysfunction in long COVID remains unknown but has been suggested to be immune-mediated in nature based on the presence of non-specific immune markers reported in symptomatic patients [Blitshteyn and Whitelaw, 2021; Goodman et al, 2021]. Persistent complement activation has been seen in long COVID and may be driven by antigen–antibody complexes, involving autoantibodies and antibodies against herpesviruses, as well as cross-talk with a dysregulated coagulation system [Cervia-Hasler et al, 2024]. As post-COVID POTS has been described to be a syndrome associated with an inflammatory autoimmune dysregulation [Chadda et al, 2022] and elevated levels of functional autoantibodies to several G-protein coupled receptors have been seen in affected individuals [Jamal et al, 2023], treatment with high dose immunoglobulin G (IgG) is expected to exert immunomodulatory effects [Galeotti et al, 2017] which are thought to translate into improvement of clinical symptoms and vital signs in individuals with post-COVID POTS.

There are no approved treatments for individuals with post-COVID POTS to date, and the current management of post-COVID POTS is targeted towards symptom relief, rather than addressing the underlying pathophysiology [Mallick et al, 2023]. Improvement of symptoms under pharmacological treatment has been described, however, even under pharmacological treatment, symptoms persist in many patients [Abbate et al, 2023].

Hence, there is an immediate unmet medical need for the development of novel treatment options that adequately address this serious condition in the described patient population. Based on limited but encouraging data from the literature on the use of IgG in POTS [Kesterson et al, 2023; Parker et al, 2021; Pitarokoili et al, 2021; Rodriguez et al, 2021; Schofield and Chemali, 2019; Weinstock et al, 2018], as well as the presumed mechanism of action of IgG and observed immunomodulatory effect in other closely related autoimmune conditions such as chronic inflammatory demyelinating polyneuropathy (CIDP), IgPro20 represents a promising treatment option in post-COVID POTS.

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

2.2. Study Rationale

Inflammation and autoimmunity are presumed underlying mechanisms of post-COVID POTS, supported by the presence of elevated autoantibodies and incidence of autoimmune conditions [Chadda et al, 2022; Jamal et al, 2023]. Even though the exact immunomodulatory mechanisms underlying IgG activity remain complex, high dose intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG) may exert its beneficial effects in inflammatory and autoimmune diseases associated with autoantibodies by several potential mechanisms including neutralization of autoimmune antibodies, decreases in the deposition of complement, immunomodulation through activation of inhibitory FcγIIb receptor signaling, and acceleration of pathologic antibody clearance through neonatal Fc receptor saturation [Galeotti et al, 2017]. The proposed mode of action of high dose IgG may

therefore have beneficial impact on autonomic dysfunction in individuals with post-COVID POTS as a causative treatment.

Investigators have seen improvement in POTS symptoms using high dose, off-label IVIG (up to 2 g/kg monthly) or SCIG (up to 1.9 g/kg monthly) in uncontrolled single cases or case series [Kesterson et al, 2023; Rodriguez et al, 2021; Schofield and Chemali, 2019; Weinstock et al, 2018], including individuals with post-COVID POTS [Parker et al, 2021]. Furthermore, weekly dosing of up to CCI g/kg of IgPro20 has demonstrated a positive benefit-risk ratio as immunomodulatory therapy in CIDP an approved indication for HIZENTRA, and is the same dose proposed for post-COVID POTS.

For both immune replacement (eg, primary immunodeficiency [PID]) as well as immunomodulation (eg, CIDP), a comparable short and long-term efficacy of SCIG and IVIG is assumed [Chapel et al, 2000; Chen et al, 2019]. Safety profiles of both IVIG and SCIG in immune replacement and immunomodulation have been well characterized. In contrast to IVIG, which can be associated with systemic side effects, the safety profile of SCIG is mainly characterized by local infusion site reactions [Ballow et al, 2018; Cherin et al, 2016; Gardulf and Nicolay, 2006; Nicolay et al, 2006; Perez et al, 2017]. Additionally, SCIG can be administered at home and has been shown to improve QoL, treatment satisfaction and therapy convenience [Gardulf and Nicolay, 2006; Nicolay et al, 2006]. In the context of post-COVID POTS, which primarily affects a younger, previously active and healthy adult patient population [Blitshteyn and Whitelaw, 2021; Larsen et al, 2022; Parker et al, 2021], home administration of SCIG might represent a patient-centric treatment option.

The current lack of treatment for post-COVID-related POTS outside of symptomatic management warrants the initiation of a randomized double-blind study targeting the underlying autoimmune pathophysiology in post-COVID POTS by means of SCIG treatment. Therefore, a placebo-controlled study evaluating the effects of IgPro20 in 177 subjects with POTS following acute COVID-19 infection is proposed. Randomization will be continued if the dropout rate is over 10%.

2.3. Benefit / Risk Assessment

IgPro20 is a marketed product that has been demonstrated to be a generally safe and well tolerated product in PID and CIDP. Weekly dosing of up to CCI g/kg of IgPro20 has demonstrated a positive benefit-risk ratio as immunomodulatory therapy in CIDP, which is the same dose proposed for post-COVID POTS.

2.3.1. Benefit Assessment

As post-COVID POTS is a disease with an autoimmune phenotype, affected individuals may experience benefits from the anti-inflammatory and immunomodulatory effects that high doses of IgPro20 exert. These include, but may not be limited to, reduction in symptoms of OI and improvement of inadequate heart rate (HR) increase after changing into a supine position, positively impacting QoL.

2.3.2. Risk Assessment

2.3.2.1. Identified and Potential Risks Pertaining to IgPro20

Although the safety profile of IgPro20 has not been evaluated in subjects with post-COVID POTS, IgPro20 has a well-established safety profile, with the important safety concerns from the risk management plan listed in Table 1. No additional risks are expected in this study.

As noted, IgPro20 has been demonstrated to be safe based on safety data obtained from previous CSL-sponsored clinical studies in various indications with dosing up to [redacted] g/kg, and post-marketing experience collected over the past 13 years. The majority of adverse events (AEs) observed with IgPro20 administration in currently approved indications are nonserious infusion site reactions (ISRs). Adverse reactions such as local reactions, headache, fatigue, nausea, pain, pruritus, rash, vomiting, and pyrexia were observed during the clinical development program. In addition, in the post-marketing setting, reactions such as hypersensitivity, tremor, and burning sensation were reported, as well as rare events such as anaphylaxis, aseptic meningitis syndrome, and thrombotic events.

The risk that products manufactured from plasma could transmit an infectious agent has been reduced by screening plasma donors for prior exposure to pathogens and by testing the donations for the presence of certain markers of infections. In addition, different complementary virus elimination processes used during the manufacture of IgPro20 (incubation at pH 4, virus filtration, fractionation, and depth filtration) effectively reduce the potential for viral transmission. The manufacturing process was also investigated for its capacity to eliminate hamster-adapted scrapie agent 263K, a model for Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease. The results demonstrated substantial removal of the infectious agent by the manufacturing process in all model systems. To date, no viral infection related to the infusion of IgPro20 has been reported. However, the possibility of transmitting infective agents cannot be totally excluded.

Table 1: Summary of Safety Concerns Pertaining to IgPro20[a]

Important identified risks	• Local reactions including ulceration-like ISRs. • Anaphylactic reactions. • Aseptic meningitis syndrome. • Thromboembolic events.
Important potential risks	• Increased or unknown risks in the home-based SC (self-) administration. • Exacerbation of existing hyperprolinemia. • Hemolysis. • Transmission of infectious agents.

ISR = infusion site reaction; SC = subcutaneous.
[a] as described in Hizentra Risk Management Plan 4.6

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

With regard to the use in POTS (including post-COVID POTS), continuous post-marketing safety surveillance did not identify additional safety signals that are relevant to the use of SCIG in patients with this condition. The limited available literature data reports good tolerability of SCIG in POTS patients [Kesterson et al, 2023; Parker et al, 2021; Pitarokoili et al, 2021], while the use of IVIG is described as effective, but associated with systemic side effects, eg, aseptic meningitis [Rodriguez et al, 2021; Schofield and Chemali, 2019; Weinstock et al, 2018]. Subjects will be closely monitored during the study for adverse drug reactions that are potentially serious and other events. In addition, the study will be monitored by an independent data monitoring committee (IDMC).

2.3.2.2. Potential Risks Pertaining to Placebo

In this study, a 2% human albumin solution is used as placebo. The formulation will be developed by diluting the commercially available liquid albumin preparation manufactured under Good Manufacturing Practice conditions. The tolerability of SC application of human albumin was tested in a clinical trial with CIDP and was found to be similar to the experience with other plasma proteins (eg, IgG), as described above. No additional harm is expected from the use of albumin as placebo in the study subjects. The currently established safety profile of the investigational medicinal product (IMP) covers fully the safety profile of the commercial albumin solution that is used for developing the placebo.

There is a high permeability for albumin between the SC compartment and the vascular system. In view of the SC data available, the absence of immunogenicity after intramuscular administration, and the high abundance of albumin in the body (> 25 mg/mL in interstitial fluid) [Poulsen, 1974], local reactions and immunogenicity are considered highly improbable at the doses administered in this study.

2.3.2.3. Risks Pertaining to Crono S-PID-100 Infusion Pump

The IMP 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.

2.3.2.4. Potential Risks of Failure of IgPro20

The efficacy of IgPro20 in post-COVID POTS is currently unknown.

2.3.3. Benefit / Risk Conclusion

Considering IgPro20's established safety profile and the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with IgPro20 are justified by the anticipated benefits that may be afforded to subjects with post-COVID POTS. Thus, the associated benefit-risk of the study is acceptable for subjects enrolled in the study.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2: Objectives, Endpoints, and Estimands

Objectives	Endpoints and Estimands
Primary	
The primary objective of this study is to evaluate the efficacy of IgPro20 in comparison with placebo in adults with post-COVID POTS	**Endpoint**: Proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test (ie, no longer experiencing HR increase of ≥ 30 bpm, in the absence of 20 mmHg decrease of SBP [orthostatic hypotension]) at the end of the Double-blind Treatment Period. **Estimand**: The primary comparison of interest is to quantify the treatment effect of IgPro20 versus placebo. The treatment effect of interest is the difference in the proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test (no longer experiencing HR increase of ≥ 30 bpm in the absence of 20 mmHg decrease of SBP [orthostatic hypotension]) Intercurrent events: see Section 9.4.2.1.1 **Population**: Intent-To-Treat **Treatment**: IgPro20 vs. Placebo **Population Summary**: Point estimate and 95% CI for the difference in proportions.

Objectives	Endpoints and Estimands
Key Secondary	
To further evaluate the efficacy of IgPro20 in comparison with placebo in adults with post-COVID POTS	**1. Endpoint**: Change from baseline in orthostatic intolerance score of COMPASS-31 at the end of Double-blind Treatment Period. **Estimand**: The comparison of interest is to quantify the treatment effect of IgPro20 versus placebo. The treatment effect of interest is differences from baseline in orthostatic intolerance score of COMPASS-31 at the end of the Double-blind Treatment Period. Intercurrent events: see Section 9.4.2.1.1 **2. Endpoint**: Change from baseline in COMPASS-31 total score at the end of the Double-blind Treatment Period. **Estimand**: The comparison of interest is to quantify the treatment effect of IgPro20 versus placebo. The treatment effect of interest is differences from baseline in COMPASS-31 total score at the end of the Double-blind Treatment Period. Intercurrent events: see Section 9.4.2.1.1 **3. Endpoint**: Change from baseline in HR increase within 10 minutes of standing test at the end of the Double-blind Treatment Period. **Estimand**: The comparison of interest is to quantify the treatment effect of IgPro20 versus placebo. The treatment effect of interest is differences from baseline in HR increase within 10 minutes of standing test at the end of the Double-blind Treatment Period. Intercurrent events: see Section 9.4.2.1.1
Secondary	
To evaluate the safety of IgPro20 in comparison with placebo in subjects with post-COVID POTS	• Frequency counts and percentage of subjects with TEAEs, related TEAEs, serious TEAEs, and related serious TEAEs • Frequency counts and percentage of subjects with abnormal electrocardiograms at Screening, Week 25, and Week 53, as well as change from baseline at Week 25 and Week 53.

Objectives	Endpoints and Estimands
Exploratory	
To evaluate the pharmacokinetics of IgPro20 in subjects with post-COVID POTS	• Concentration of serum total IgG: C_{trough} at multiple time points during the study. • In serial PK subjects only; serial IgG PK collection Period: • Steady-state PK (at Week 41) o C_{max} o Tmax o Cmin o AUC0-7d o AUC0-last
To further evaluate the efficacy of IgPro20 in comparison with placebo in adults with post-COVID POTS	• Proportion of subjects experiencing orthostatic hypotension at the end of the Double-blind Treatment Period. • Change from baseline in Malmö Symptom score at the end of the Double-blind Treatment Period. • Change from baseline in Mental Component Score, and Physical Component Score at the end of the Double-blind Treatment Period. • Change from baseline in remaining domains of COMPASS-31 at the end of the Double-blind Treatment Period. • Proportion of subjects whose orthostatic intolerance score and total COMPASS-31 score improved beyond the clinical meaningful difference thresholds (MSDs to be determined) at the end of the Double-blind Treatment Period. • Change from baseline in mean T-score on the PROMIS Cognitive function short form 6a at the end of the Double-blind Treatment Period. • Change from baseline in health utility index and global health status (VAS) as measured by EQ-5D-5L at the end of the Double-blind Treatment Period. • Change from baseline in each of the component scores for WPAI:SH. • Change from baseline in the 2 domains of the OHQ score.

AUC_{0-l} = Area under the concentration-time curve from time point 0 to the last quantifiable time point; AUC_{07d} = Area under the concentration-time curve from time point 0 to day 7; AUC_{0-last} = Area under the concentration-time curve from time point 0 to the time of the last measurable concentration; CI = confidence interval; C_{max} = maximum concentration; C_{min} = minimum concentration; COMPASS-31 = Composite Autonomic Symptom Score 31; EQ5D-5L = EuroQol-5 dimension; HR = heart rate; PK = pharmacokinetic; OHQ = Orthostatic Hypotension Questionnaire; POTS = Postural Orthostatic Tachycardia Syndrome; SBP = systolic blood pressure; SF-12 = Short Form – 12item; TEAE = treatment-emergent adverse event; T_{max} = time to reach maximum concentration; VAS = visual analog scale; WPAI:SH = Work Productivity & Activity Impairment: Specific Health Problems

4. STUDY DESIGN

4.1. Overall Design

This is a prospective, phase 3, multicenter, double-blind, randomized placebo-controlled study to investigate the efficacy, safety, and pharmacokinetics (PK) of repeat doses of IgPro20 in adult subjects with post-COVID POTS.

Approximately 177 adult subjects with a confirmed diagnosis of post-COVID POTS as defined in Section 5.1 will be randomized into the study.

An interim futility analysis will be conducted when 54 subjects have completed 24 weeks of treatment. Enrollment will be temporarily paused after the 54th subject has completed 24 weeks of treatment until IDMC recommendation after futility analysis review has been received and reviewed by the Sponsor. The futility analysis is further described in the IDMC Statistical analysis Plan (SAP) and IDMC charter.

Eligible subjects will be randomized in a 2:1 ratio to receive SC infusions of IgPro20 at doses of CCI g/kg/week or matching placebo for 24 weeks followed by an Open-label Treatment Period of 28 weeks as depicted in Figure 1. The study duration for an individual subject will be up to 60 weeks.

4.2. Scientific Rationale for Study Design

The study will enroll adult subjects with post-COVID POTS whose QoL is severely impacted as measured by Composite Autonomic Symptom Score 31(COMPASS-31) (ie, with COMPASS-31 score ≥40 [Kedor et al, 2021]). The COMPASS-31 is a self-reported questionnaire measuring autonomic symptoms and is being commonly used in recent POTS trials. Patients with a history of POTS before confirmed COVID-19 diagnosis, as well as concomitant conditions, unless related to COVID-19, such as polyneuropathy, Ehlers Danlos, myalgic encephalitis / chronic fatigue syndrome, etc, will be excluded to avoid confounders. Subjects with use of any IgG product or plasmapheresis within 12 weeks before Screening will be excluded to avoid any carry-over effects from previous immunomodulatory treatment.

The study population was chosen because patients with post-COVID POTS can be severely impacted by their condition in their daily life, and there is no approved treatment available. IgG has been shown to provide clinical benefits in the treatment of patients with POTS [Kesterson et al, 2023; Pitarokoili et al, 2021; Rodriguez et al, 2021; Schofield and Chemali, 2019; Weinstock et al, 2018], including individuals with post-COVID POTS [Parker et al, 2021]. Hence, IgG represents a promising treatment option for post-COVID POTS patients.

As outlined in Section 2.3.2.1, even though IVIG has been described as effective in POTS treatment, it is associated with systemic side effects. In contrast, SCIG administration is mainly characterized by local ISRs [Ballow et al, 2018; Cherin et al, 2016; Gardulf and Nicolay, 2006; Nicolay et al, 2006; Perez et al, 2017]. For both immune replacement as well as immunomodulation, a comparable long-term efficacy of SCIG and IVIG is assumed [Chapel et al, 2000; Chen et al, 2019]. Additionally, SCIG can be administered at home and has been shown to improve QoL, treatment satisfaction, and therapy convenience

[Gardulf and Nicolay, 2006; Nicolay et al, 2006]. In the context of post-COVID POTS which primarily affects a younger, previously active and healthy patient population [Blitshteyn and Whitelaw, 2021; Larsen et al, 2022], home administration of SCIG might represent a patient-centric treatment option. Assuming comparable efficacy and considering the overall lower rate of systemic AEs, flexibility in dosing administration and improved QoL compared to IVIG, SCIG was chosen as the study drug. Additionally, IVIG may lead to a volume expansion due to the lower concentration, ie, greater volume, and direct administration to the blood stream. Given that volume expansion is one of the non-pharmacologic treatment options in post-COVID POTS, this may confound the results. SCIG has a higher concentration and is absorbed slowly through the lymph over multiple days [Rojavin et al, 2020; von Achenbach et al, 2022]. Therefore, only a limited extent of volume expansion is expected, allowing a more reliable characterization of the immunomodulatory effects.

Additional rationale on the selection of the dose is described in Section 4.3.

A double-blind design is being used to avoid potential bias during data collection and evaluation of clinical endpoints. A placebo-controlled design is being used to optimize treatment sensitivity, reduce bias, and maintain the rigor of the study to support this indication. To collect additional longer-term safety data, the Double-blind Treatment Period will be followed by an Open-label Treatment Period.

The primary endpoint is the proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standing test (ie, no longer experiencing HR increase of ≥30 bpm, in the absence of 20 mmHg decrease in systolic blood pressure (SBP) [orthostatic hypotension]) evaluated after 24 weeks of double-blind treatment. It has been chosen as an HR increase of at least 30 bpm when standing is embedded in diagnostic criteria for POTS, based on consensus definition defined by major international Societies [Vernino et al, 2021]. Efficacy will be further characterized by 3 key secondary endpoints: change from baseline in both the OI subscale and total score (TS) of COMPASS-31 and change from baseline in HR measured by a standing test on a continuous scale. The OI subscale was chosen as a separate key secondary endpoint as OI symptoms were found to be most prominent to differentiate between POTS and other dysautonomias [Cortez et al, 2021], covering the most burdensome and frequent symptoms reported by POTS patients [Dipaola et al, 2020]. Consequently, this design allows for a thorough evaluation of the objective HR change tied back to the POTS diagnostic criteria first proposed in 1993 [Schondorf and Low, 1993], as well as the subjective assessment of how patients feel and function. The total COMPASS-31 score was chosen to evaluate the impact of treatment on multiple symptoms associated with POTS.

Data regarding the expected effect size and placebo effect in post-COVID POTS are limited, as it represents a newly identified condition first described in 2020 [Miglis et al, 2020]. The natural history of post-COVID POTS is not fully understood with medium-term to long-term prognosis of affected individuals undefined [Kwan et al, 2022; Ormiston et al, 2022], and a similar absence of information on the course of disease for patients left completely untreated [Eshak et al, 2020; Goodman et al, 2021; Johansson et al, 2021; Novak, 2020]. Based on a natural history study following 45 POTS patients, approximately 30% of patients no longer experienced HR increase meeting POTS consensus criteria after at least 1 year of observation [Kang et al, 2019]. The present study is assuming a 30% placebo rate. In the absence of an

established minimally clinically important difference for the primary endpoint and in correspondence with experts, 30% treatment effect size are assumed. Additionally, these assumptions are taking into account that findings from POTS are being applied to post-COVID POTS, as data in post-COVID POTS are sparse, and further research needs to be performed to shed light on potential differences and similarities.

4.3. Dose Rationale

To date, there are very few studies in the literature that examine SCIG or IVIG in POTS, and only one of these has been conducted in post-COVID POTS specifically (where 3 subjects were administered IVIG but the dose was not disclosed) [Parker et al, 2021]. In the available literature, SCIG and IVIG have been dosed up to 1.9 g/kg/month (approximately 0.48 g/kg/week) and 2.0 g/kg/month (ie, 0.5 g/kg/week), respectively, in the POTS population. To date, no studies have evaluated safety and tolerability of doses greater than 2 g/kg/month of IVIG or SCIG for this or other autoimmune conditions.

IgPro20 is approved for the immunomodulatory treatment of CIDP at the proposed dose level of up to CCI g/kg/week. There is significant clinical experience and safety data, both from clinical studies as well as post-marketing, for IgPro20 at CCI g/kg/week, demonstrating a good tolerability of the CCI g/kg/week dosing regimen. As described in the HIZENTRA® US Prescribing Information, the most commonly reported AEs for IgPro20 include Local Infusion Site Reactions, Headache, and Diarrhea.

Weekly dosing of CCI g/kg has been used to treat CIDP subjects in the pivotal IgPro20 study with a safety profile that was comparable to a low dose, with the most frequent AEs being local ISRs. All local reactions (with either dose) were mild or moderate in intensity and the frequency decreased over time. The population considered for the post-COVID POTS study is relatively young with a mean age of 36 years [Amekran et al, 2022; Blitshteyn and Whitelaw, 2021; Gall et al, 2022; Parker et al, 2021]. The population is also expected to have few comorbidities. Therefore, the expectation is that this regimen will be well tolerated in this population.

Considering the unmet medical need in this condition with no approved treatments, the established safety profile, and published data indicating clinical benefit with the proposed high dose of CCI g/kg/week, the proposed study assesses the relative efficacy of CCI g/kg/week versus placebo to maximize the chance for response.

4.4. Start of Study Definition

The study start date is the date on which the clinical study will be open for recruitment of subjects. The first act of recruitment is the time point when the first site is activated and will be considered the study start date.

4.5. End of Study Definition

The end of the study is defined as the date of the last visit of the last subject in the study / last scheduled procedure shown in the Schedule of Activities (Section 1.3) for the last subject in the study.

A subject is considered to have completed the study if they completed all study periods including the last visit.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study closeout visit has been performed.

5. STUDY POPULATION

Subjects must meet all inclusion criteria and none of the exclusion criteria to be eligible for enrollment into this study. Prospective approval of protocol deviations from eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

1. Provide written informed consent and be willing and, in the opinion of the investigator, able to adhere to all protocol requirements.
2. Males and females aged ≥18 at the time of providing written informed consent.
3. Diagnosis of post-COVID POTS, defined by both:
    - Preceding COVID-19 infection, based on confirmed historical documentation of the following (Figure 2):
        - Documented history of SARS-CoV-2 infection (documented by antigen or polymerase chain reaction [PCR] test)

          OR
        - Documented clinical diagnosis of SARS-CoV-2 infection, based on the following criteria:
            1. One of the following documented physician-reported criteria:
                - COVID-19 specific treatment (eg, Nirmatrelvir + Ritonavir / Paxlovid, Remdesivir / Veklury, Molnupiravir / Lagevrio

                  OR
                - Documentation of one of the following ICD-10 codes: U07.1 (COVID-19, virus identified), U07.2** (COVID-19, virus not identified), U09.9** (post-COVID-19 condition, unspecified)

              AND
            2. Documented patient-reported signs or symptoms*

               AND
            3. Documented patient-reported positive self-administered SARS-CoV-2 antigen test

    *Acceptable signs or symptoms:

    - Acute onset of fever AND cough (influenza-like illness)

      OR

- Any 3 or more of the following signs or symptoms: Fever, cough, general weakness / fatigue, headache, myalgia, sore throat, coryza, dyspnoea, nausea, diarrhea, anorexia

  **Subjects with documentation of the ICD-10 codes U07.2 and U09.9 need to be discussed with the Sponsor's Internal Medical Monitor to confirm eligibility based on entirety of documented evidence for preceding SARS-CoV-2 infection

Figure 2 provides a decision tree for assessing a SARS-CoV-1 infection.

AND

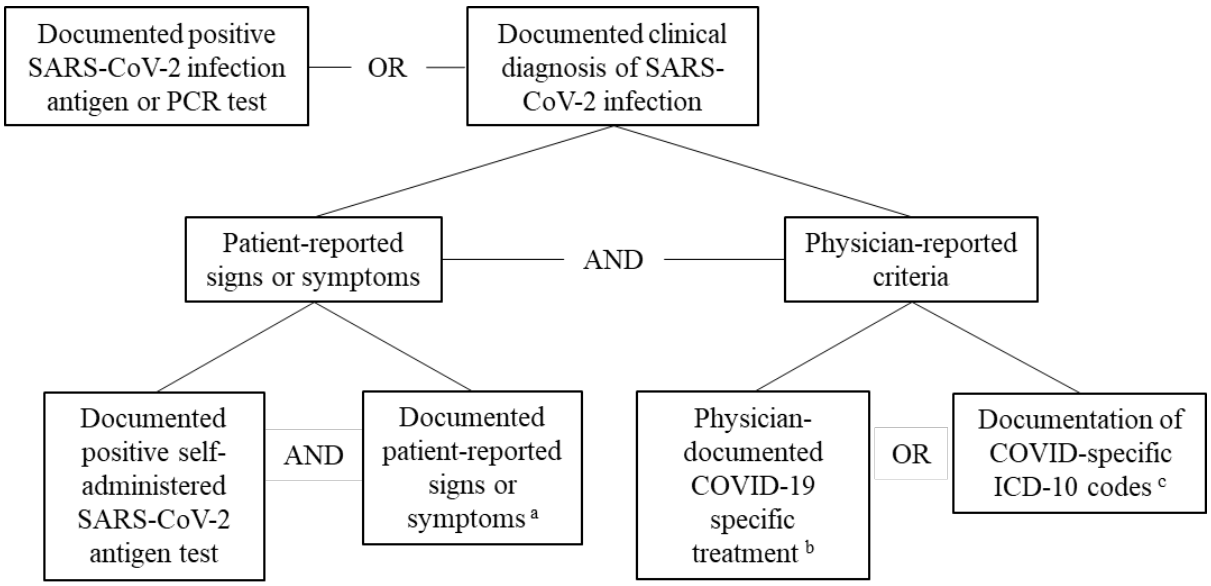
- Onset of POTS symptoms developing within 4 months after COVID-19 infection, as defined per consensus criteria [Vernino et al, 2021]
  - A sustained HR increase of ≥ 30 bpm [≥ 40 bpm for subjects aged 18 to 19 years] within 10 minutes of head-up tilt or standing test, in the absence of orthostatic hypotension (ie, sustained 20 mmHg decrease in SBP)

    AND

  - The presence of post-COVID POTS with persisting symptoms (eg, brain fog, fatigue, palpitations) for at least 3 months

4. COMPASS-31 score of at least 40 at the Screening visit
5. Positive confirmatory standardized standing test (ie, HR increase of ≥ 30 bpm [≥ 40 bpm for subjects aged 18 to 19 years] within 10 minutes in the absence of orthostatic hypotension) at the Screening visit
6. According to the investigator's judgment, the subject (or the subject's legally acceptable representative[s]) understands the nature, scope, and possible consequences of the study
7. Subject is capable of reading, understanding, and completing questions / assessments in an electronic clinical outcomes assessment (eCOA) solution
8. Subject is willing to complete 52 weeks of SC infusions

Figure 2: Acceptable Methods for Confirming a SARS-CoV-2 Infection



[a] Documented patient-reported signs or symptoms include either (1) acute onset of fever AND cough (influenza-like illness) or (2) any 3 or more of the following signs or symptoms: Fever, cough, general weakness / fatigue, headache, myalgia, sore throat, coryza, dyspnoea, nausea, diarrhea, anorexia. All reported signs and symptoms must be documented in the patient medical history.
[b] Examples of acceptable treatments include Nirmatrelvir + Ritonavir / Paxlovid, Remdesivir / Veklury, Molnupiravir / Lagevrio.
[c] Permissable ICD-10 codes are as follows: U07.1 (COVID-19, virus identified), U07.2* (COVID-19, virus not identified), U09.9* (post-COVID-19 condition, unspecified).
*If ICD-10 codes U07.2 and U09.9 are utilized, COVID-19 documentation to be reviewed by the Sponsor's Internal Medical Monitor before subject is enrolled in the study.

5.2. Exclusion Criteria

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

1. Treatment with IgG or plasmapheresis within 12 weeks before Screening
2. Symptoms and / or diagnosis of or receiving treatment for POTS before COVID-19 infection
3. Prior diagnosis of or receiving current treatment at Screening for the following conditions (unless onset was related to the inciting POTS-associated COVID-19 infection):
    - Neurologic conditions such as peripheral neuropathy, myalgic encephalomyelitis encephalitis / chronic fatigue syndrome, stroke, spinal cord injury or any known lesions in the central nervous system by imaging or neurological exam;

- Autoimmune conditions such as Sjögren's syndrome, autoimmune autonomic neuropathy, multiple sclerosis, Crohn's disease, celiac disease, lupus erythematosus, rheumatoid arthritis, myasthenia gravis;
- Pre-existing psychiatric disorders such as generalized anxiety disorder (formally diagnosed), anorexia nervosa, disorders causing hyperventilation;
- Endocrine disorders such as hyperthyroidism, pheochromocytoma;
- Cardiac disorders causing sinus tachycardia such as inappropriate sinus tachycardia, or arrythmias;
- Other disorders / conditions causing sinus tachycardia such as Ehlers Danlos syndrome, mast cell activation syndrome, fever, pain, infection, moderate to severe anemia, hypovolemia or severe deconditioning caused by prolonged bed rest.

4. Presence of active infections such as:
   - Human immunodeficiency virus infection (or history of).
   - Hepatitis B: subjects who are hepatitis B core antibody-positive and who are hepatitis B surface antibody-negative will need to have a negative hepatitis B virus PCR result before enrollment. Hepatitis B surface antigen-positive or hepatitis B virus PCR-positive subjects will be excluded.
   - Hepatitis C: subjects who are hepatitis C virus antibody-positive will need to have a negative hepatitis C virus PCR result before enrollment. Hepatitis C PCR-positive subjects will be excluded.
   - Any uncontrolled systemic infection.
   - Active SARS-CoV-2 infection.
5. Subjects with an implantable electronic defibrillator or pacemaker.
6. History of documented thromboembolic event within 26 weeks before Baseline.
7. Subjects receiving any prohibited treatments as described in Section 6.12, including new or changing exercise program.
8. History of known or acquired congenital coagulopathies or laboratory evidence of current hypercoagulable state at Screening.
9. Any ongoing malignancy unless in remission for > 1 year and clinically stable (except for basal cell carcinoma, carcinoma in situ, or localized cell carcinomas with surgical cure).
10. Known hyperprolinemia.
11. Protein-losing enteropathies or significant proteinuria, eg, nephrotic syndrome.
12. Known or suspected hypersensitivity or other severe reactions to the IMP, to any excipients of the IMP, or to other immunoglobulins, or severe reactions to blood products including albumin.

13. Concurrent participation in another clinical study.
14. Any condition that requires immediate initiation of IgG replacement or administration.
15. Has current signs or symptoms of severe, progressive, or uncontrolled active inflammatory, renal (estimated glomerular filtration rate < 60 mL/min/1.73 m^2), hepatic (aspartate aminotransferase [AST]/alanine aminotransferase [ALT] > 3 × upper limit of normal [ULN]), dermatologic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, psychiatric, or neurologic disease other than post-COVID POTS as judged by the investigator.
16. Any issue that would render the subject unsuitable for participation in the study or unable to comply with study procedures, eg, inability to self-administer IMP or by aid through a caregiver.
17. Pregnancy or breastfeeding, or intention to become pregnant or to father a child during the study.
18. Fertile male subject or female subject of childbearing potential either not using or not willing to use a medically reliable method of contraception (see Section 10.3.2), not sexually abstinent during the study or for 28 days after receipt of the last infusion of IgPro20, or not surgically sterile before study enrollment.
    - All female subjects are assumed to be of childbearing potential except:
      - Subjects aged > 60 years.
      - Subjects aged 45 to 60 years (inclusive) with amenorrhea for ≥ 1 year with documented evidence of follicle-stimulating hormone level > 30 IU/L. If the follicle-stimulating hormone value is not available before randomization, a urine pregnancy test is required.
      - Subjects who are surgically sterile for ≥ 3 months before providing informed consent.
    - All male subjects are assumed fertile except subjects who are surgically sterile for ≥ 3 months before providing informed consent.
19. Alcohol, drug, or medication abuse within 1 year of providing informed consent.
20. Any issue that, in the opinion of the investigator, would constitute a contraindication to perform standing test.
21. Involved in the planning and / or conduct of the study (applies to the Sponsor's staff, staff at the study site, and third-party vendors).

5.3. Lifestyle Considerations

Use of recreational drugs, either for recreational or potentially medical purposes, is not permitted. There are no other study-specific dietary or lifestyle restrictions for subjects who participate in the study.

Female subjects of childbearing potential must use a medically reliable form of contraception for the study duration. 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 IMP. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable definitions of abstinence.
- Hormonal methods associated with inhibition of ovulation. Acceptable hormonal methods include: oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen / progestin vaginal ring, or contraceptive medication implant.
- 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 > 12 weeks before providing informed consent).
- Bilateral tubal occlusion of female subjects (12 weeks before providing informed consent).
- Vasectomy of male partner of female subjects (12 weeks before providing informed consent).

5.4. Screen Failure

A screen failure is defined as a subject who consents to participate in the clinical study but does not meet eligibility criteria. If a subject is not eligible for the study (ie, screen failure), minimal information should be recorded in the electronic case report form (eCRF) (ie, demography, disease-specific medical history, screen failure details, eligibility criteria, and any serious adverse events [SAEs]) to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Subjects may be rescreened once after discussion with the Sponsor's Internal Medical Monitor.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

6.1. Investigational Products

In this protocol, IMP refers to both IgPro20 and placebo, unless specified otherwise.

Table 3: Pharmaceutical Properties and Formulation

Intervention Name	IgPro20	Placebo
Type	Biological / Vaccine	Biological / Vaccine
Use	Experimental	Placebo-Active Comparator
Dose Formulation	Solution for infusion	Solution for infusion
Unit Dose Strength	200 mg/mL IgG in 250 mmol/L L-proline and 8 -30 mg/L polysorbate 80	2% human albumin in 250 mmol/L L-proline and 20 mg/L polysorbate 80
Dose and Regimen (Refer to Section 6.6)	CCI g/kg/week	Volume-matched weekly administration
Route of Administration	Subcutaneous	Subcutaneous
Maximal infusion parameters	Flow rate: 50 mL/h/site Volume: 50 mL/site	
Anatomical Location	Abdomen, thigh, upper arm, or side of upper leg / hip	Abdomen, thigh, upper arm, or side of upper leg / hip
Sourcing	Provided centrally by the Sponsor or Sponsor's delegate	Provided centrally by the Sponsor or Sponsor's delegate
Storage	To be stored at the labeled conditions	To be stored at the labeled conditions
Packaging and Labeling	IgPro20 will be provided in 50mL vials. Each vial will be packaged and labeled according to current ICH GMP and GCP guidelines and national legal requirements	Placebo will be provided in 50mL vials. Each vial will be packaged and labeled according to current ICH GMP and GCP guidelines and national legal requirements

GCP = Good Clinical Practice; GMP = Good Manufacturing Practice; ICH = International Council for Harmonisation

Investigational medicinal product may be shipped from the study site to the subject's home in accordance with country-specific requirements.

To ensure proper subject data confidentiality, a suitable courier service will be selected by CSL or the study site with CSL approval.

6.2. Other Study Interventions

Not applicable.

6.3. Management of Investigational Product(s)

- The IMP will be packaged and labeled according to current ICH Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines, and applicable legal requirements. Specific details regarding packaging of the investigational product(s) are provided in the Site IMP Manual.
- The IMP will be shipped by the Sponsor or delegate according to ICH GxP requirements.
- The investigator or delegate will confirm receipt of all shipments of IMP in the Interactive Response Technology (IRT) system.
- Records for the delivery of IMP to the study site, the inventory at the study site, assignment to each subject, and the destruction or return of IMP to the Sponsor (or delegate) must be maintained by the investigator (or delegate) using the IRT system.
- All supplies of IMP must be accounted for throughout the study.
- The investigator (or delegate) must provide reasons for any discrepancies in drug accountability in the IRT system.

Further details regarding management of the IMP are provided in the Site IMP Manual.

6.4. Assignment of Subjects to Treatment Groups and Blinding

After providing written informed consent, the subject will be issued with a study-level unique subject identification 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 are not to be reassigned or reused for another subject in the study.

6.4.1. Randomization

Subjects will be randomized in a ratio of 2:1 to IgPro20 or matching placebo by means of the IRT. A centralized randomization schedule will be used.

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

6.4.2. Blinding

6.4.2.1. Blinding Method

Site staff, including the investigator(s), will be blinded to treatment allocation. Subjects and Sponsor staff (except for IRT and Clinical Trial Supplies personnel) or delegates participating in the conduct of the study will also be blinded to treatment allocation (double-blind).

The IMP will be packaged and labeled to ensure blinding is maintained. The study site personnel will ensure the contents remain blinded to the subject and the study site personnel who will be conducting assessments.

All samples analyzed by the central laboratory will remain blinded until database lock.

Study unblinding will take place after the study database has been locked except in the situations as outlined in Section 6.4.2.2, Section 6.4.2.3, and Section 6.4.2.4.

Adequate procedures are in place to ensure the integrity of the blinded data at the Sponsor. Study data will be provided to the IDMC as unblinded data, as requested. Details will be provided separately in the IDMC charter.

The bioanalyst and pharmacokineticist responsible for the sample analysis and PK evaluation will be unblinded. However, they will agree not to disclose the randomization schedule. The preliminary PK data available during the study will refer to mean data with descriptive statistics and individual data without revealing any individual randomization numbers, subject numbers, or other sensitive information with the potential to lead to unblinding (eg, dates or times).

6.4.2.2. Breaking the Blind for an Emergency

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

6.4.2.3. Planned Unblinding Procedures

Periodic unblinded safety reviews, as well as an interim analysis for futility after 54 subjects complete 24 weeks of treatment, are planned for this study for the purposes of safety monitoring activities review by the IDMC (see Section 10.1.8). With authorization from the Sponsor, randomization codes (only for subjects who are enrolled) will be provided to the external service provider performing analyses for the IDMC or the unblinded statistician, via the Clinical Data Warehouse.

At the end of the study, the Sponsor will authorize that the study be unblinded after database lock. The randomization codes will be accessed via the Sponsor's Clinical Data Warehouse.

6.4.2.4. Ad hoc Safety Unblinding

The Sponsor's Global Clinical Safety and Pharmacovigilance (GCSP) personnel may unblind the randomization code directly in the IRT ad hoc at any time during the study because of a safety concern. The purpose of the unblinded data review is to determine if there is a risk to subject safety that would require further action either for the management of an individual study subject or for the ongoing conduct of the study. The need to unblind on an ad hoc basis will be determined by the Sponsor's GCSP senior leadership.

6.5. Selection of Doses in the Study

Considering the unmet medical need in post-COVID POTS, the established safety profile, and published data indicating clinical benefit with the proposed high dose of IgPro20 CCI g/kg/week, the study assesses the relative efficacy of CCI g/kg/week versus placebo to maximize the chance for response.

6.6. Selection and Timing of Dose for Each Subject

All IMP in the study will be administered by SC infusions as weekly doses of CCI g/kg. Based on subject preference and tolerability, the total weekly infusion volume can be infused over CCI infusion days per week. Details on how to divide the total weekly infusion volume are provided in the IMP manual. The SC infusions should be performed in a similar way throughout the study, ie, the same number of infusions and the same number of days each week after Week 2; however, the number of SC infusions per week or number of infusion sites per infusion can be adjusted during the study in case of intolerability to the dosing volume. All SC infusions for the previous week must be performed before the following study visit. All SC infusions planned in the same week as a study visit should not be started until after the study visit occurs (with the exception of Weeks 1 and 2 for training purposes and the first infusion of Week 25, which should also occur on site under supervision as some subjects will be switched from placebo to active treatment). The total dose / volume of IMP will be calculated on the basis of the body weight and managed by the IRT system. For subjects with weight >CCI kg, the maximum dose will be CCI g / CCI mL IgPro20.

6.7. IMP Infusion Training

At least the first SC infusion for Week 1 and Week 2 must be administered during the study site visit to allow for training and confirmation of appropriate SC infusion technique. After Week 1 and Week 2, all weekly SC infusions will be self-administered by the subject or caregiver at home. Additional training at the site can be done at Weeks 3 and 4 if additional training is requested by the subject or, in the investigator's opinion, the subject needs additional training. Further details on training of the appropriate SC infusion technique are provided in the Site IMP Manual.

6.8. Dose Modification

Dosing modifications in either g/kg dose or dosing frequency are not permitted during the study. With regards to dosing volume, minimal impact on trough IgG levels is expected based on PK simulations with up to ± 5 kg body weight change for the same dose. To account for potential dose changes due to body weight changes, body weight will be measured regularly and changes in body weight > ± 5 kg will require a dose volume adjustment.

6.9. Investigational Product Compliance

At least the first SC infusion for Week 1 and Week 2 will be administered under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents. The dose of IMP and the subject's identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the IMP.

After Week 1 and Week 2, all weekly SC infusions will be self-administered at home after completing training (except for the Week 25 visit). Subjects will record details of their infusion in the electronic diary (eDiary) including whether the caregiver assisted in the SC infusion. In addition, subjects will bring all of their used / partially used vials of IMP to the study site at every study visit. Treatment compliance will be monitored based on review of the eDiary data and the number of returned vials, the results of which will be documented.

A record of the quantity of IMP dispensed to and administered by each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for IMP delays and / or dose reductions, will also be recorded.

6.10. Access to Investigational Product After the End of the Study

Subjects will not be provided with IgPro20 by the Sponsor after completion of or withdrawal from the study.

6.11. Overdose

- Overdose is defined as the accidental or intentional infusion or ingestion of any dose of a product that is considered excessive. The effects of any potential overdose with IgPro20 have not been studied.
- In the event of an overdose, the investigator should:
- Contact the Sponsor's Medical Monitor immediately.
- Evaluate the subject to determine, in consultation with the Sponsor's Medical Monitor, whether the IMP should be interrupted or discontinued, or whether the dose should be reduced, if applicable.
- Closely monitor the subject for any AE, SAE, or clinical laboratory abnormalities.
- Document the quantity of the excess dose of IMP and the duration of the overdose.

See Section 10.2.6.1 for reporting AEs associated with overdose.

6.12. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and / or herbal supplements) or other specific categories of interest that the subject is receiving at the time of enrollment or receives during the subject's study participation must be recorded along with the following:

- Indication.
- Dates of administration including start and end dates, if applicable.
- Dosage information including dose and frequency.

The Sponsor's Medical Monitor should be contacted if there are any questions regarding prior or concomitant therapy.

The following may be used concomitantly during the study:

- Nonpharmacological treatment if performed on stable regimen for at least 4 weeks before Screening and during the entire course of the study.
- Fludrocortisone, midodrine, beta blockers, calcium channel blockers, ivabradine, pyridostigmine, droxidopa, low dose naltrexone; on stable doses for at least 8 weeks before Screening and during entire course of the study.

The following are prohibited:

- Initiation of or changes to nonpharmaceutical treatment within 4 weeks before Screening and for the full course of study participation
  - IV fluids / albumin and parenteral nutrition within 4 weeks before study entry and during full course of study duration.
- New or changing exercise therapy within 4 weeks before study entry and during full course of study duration.
- Initiation of or changes to treatment with fludrocortisone, midodrine, beta blockers, calcium channel blockers, ivabradine, pyridostigmine, droxidopa, low dose naltrexone within 8 weeks before Screening and for the full course of study participation.
- Polyclonal IVIG or SCIG products, plasmapheresis within 12 weeks before Screening and during study.
- Average doses of prednisone equivalent ≥ 10 mg/day for ≥ 1 month before Baseline or during the full course of study participation.
- Pre-medication with corticosteroids prior to SCIG infusions.
- Systemic immunosuppressants within 12 weeks or 5 times the half-life before Screening, whichever is longer.
- Rituximab within 24 weeks before Screening.
- Live attenuated vaccines within 4 weeks of study entry and during full course of study duration.

7. SUBJECT WITHDRAWAL AND DISCONTINUATION OF INVESTIGATIONAL PRODUCT

7.1. Discontinuation of Investigational Product

Subjects may discontinue IMP at any time at their own request, or at the discretion of the investigator or the Sponsor for safety, behavioral, or administrative reasons.

Subjects who discontinue IMP will remain in the study to complete follow-up activities or allow data collection as detailed in the Schedule of Activities (Section 1.3).

If subjects discontinue IMP during the Double-blind Treatment Period, they are asked to complete the W25 treatment assessments at the study visit where IMP treatment is discontinued instead of the assessments scheduled for that particular visit. If subjects discontinue IMP during the Open-label Treatment Period, they are asked to complete the End of Treatment (EOT) assessments at the study visit where IMP treatment is discontinued instead of the assessments scheduled for that particular visit.

Subjects discontinuing IMP who decline further study procedures / visit participation will be withdrawn from the study (see Section 7.2).

7.1.1. Temporary Interruption

A temporary interruption in treatment is not permitted unless first discussed with the Sponsor's Medical Monitor.

7.1.2. Stopping Criteria for Investigational Product

The study may be stopped at any time per Sponsor's decision.

In addition, based on continuous safety monitoring or IDMC recommendation, the study can be either temporarily halted, modified via a protocol amendment, or stopped per Sponsor's decision, including as a result of the futility interim analysis (see Section 9.4.12).

If any of the following criteria are met, then all further administration of IMP and further enrollment of new subjects will be halted (ie, temporarily paused) until an assessment of the overall safety of continuing the study is completed:

- 1 subject develops an SAE that results in death and is considered by the investigator, IDMC and / or the Sponsor to be related to the administration of IgPro20;

  OR

- 1 subject develops any event that is deemed to pose an unacceptable risk to other subjects in the study, and these events are considered by the investigator, IDMC and / or CSL to be related to the administration of IgPro20.

If any study halting criteria are met and/or the study is halted per IDMC recommendation, the Sponsor's Global Safety Committees will conduct a safety assessment to establish if the study should be resumed or if the temporary halt should continue. The study can be resumed

on the recommendation of the Sponsor's Global Safety Committees, in agreement with the IDMC, if the safety assessment concludes that no further study modifications, protocol amendments, or risk mitigation measures are necessary, and it is safe to resume the study. Regulators (on a conditional basis) and the Independent Ethics Committee (IEC) / Institutional Review Board (IRB) will be notified of the temporary halt and subsequent resumption of the study. A substantial protocol amendment will be submitted to the Regulators and the IEC / IRB for approval if the safety assessment concludes that modifications to the protocol (including addition of new risk mitigation measures) are required to resume the study. Ad-hoc unblinding procedures may be initiated as per the Sponsor's standard operating procedures for further safety assessment, if needed. If the risk assessment concluded that continued dosing poses an unacceptable risk to subjects and no further risk mitigation steps can be applied, the Sponsor's Global Safety Committees will be involved in the recommendation to halt the study. Regulators and the IEC / IRB will be notified of a study stop.

7.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request or at the discretion of the investigator or CSL. The investigator should record in the eCRF and in the subject's medical records the reason for study withdrawal, if provided by the subject in the case of withdrawn consent, and date of subject withdrawal. Subjects will be asked to complete the End of Study (EOS) visit assessments.

In the case that subject IMP discontinuation and withdrawal from the study occur concurrently during the Double-blind Treatment Period, they are asked to complete the W25 treatment assessments as well as the EOS assessments at the study visit where IMP treatment is discontinued instead of the assessments scheduled for that particular visit. Assessments included in both W25 and EOS visits should not be performed twice.

If subject IMP discontinuation and withdrawal from the study occur concurrently during the Open-label Treatment Period, they are asked to complete the EOT assessments as well as the EOS assessments at the study visit where IMP treatment is discontinued instead of the assessments scheduled for that particular visit. Assessments included in both EOT and EOS visits should not be performed twice.

In either case, a safety follow-up telephone call 28 days after the last IMP dose will be conducted by the study site to document AE and concomitant therapies.

In accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) principles of GCP, the investigator always has the option to advise a subject to withdraw from treatment or 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.

If a subject withdraws from the study, the Sponsor may retain and continue to use any data collected before the subject's withdrawal of consent.

7.3. Lost to Follow-up

If a subject repeatedly fails to attend scheduled study visits (ie, site, telephone, or home), the site must make 3 attempts to contact the subject, counsel the subject on the importance of maintaining the assigned study visit schedule and ascertain whether the subject wishes to (and determine whether they should) continue in the study. All attempts to contact the subject should be documented in the subject's medical record.

A subject will be considered lost to follow-up if he or she repeatedly fails to attend scheduled visits and cannot be contacted by the study site after 3 attempts. When a subject is lost to follow-up, he or she will be considered to have withdrawn from the study.

7.4. Replacement Policy

Subjects withdrawn from the study will not be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures and their timing are summarized in the Schedule of Activities (Section 1.3). Protocol waivers or exemptions are not allowed.

The investigator should discuss any immediate safety concerns with the Sponsor's Medical Monitor immediately upon occurrence or when the investigator becomes aware of the safety concern to determine if the subject should continue or discontinue IMP.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a Screening log to record details of all subjects screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Procedures conducted as part of the subject's routine standard of care (eg, blood count) and obtained before signing of the informed consent form may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Section 1.3). Safety, laboratory, or analyte results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed approximately 200 mL.

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

Study visits and assessments may be performed in a remote / off-site setting utilizing the following methods (if approved by the Sponsor and allowed according to local regulations):

- Telemedicine visit, a virtual visit performed via videoconference or telephone by a delegated trained and qualified site personnel or a delegated mobile health provider who is trained and qualified to perform specific assessments or procedures.
- Dedicated mobile health provider.

An eDiary will be used in this study to collect home infusion compliance.

8.1. Screening Assessments

Screening / baseline assessments required to assess eligibility consist of obtaining informed consent, medical / surgical history, demographics, physical examination, including height, 12-lead electrocardiogram (ECG), body weight, vital signs, SARS-CoV-2 test (antigen / PCR test to rule out active COVID-19 infection [reverse transcription polymerase chain reaction [RT-PCR] or equivalent, rapid antigen test that has been approved by regulatory authorities or allowed under an emergency use authorization before Screening per site's local

regulations), clinical laboratory tests (including serum and urine hCG, hematology and biochemistry, urine sodium, and a virology blood sample), AEs, concomitant therapies, COMPASS-31, and a confirmatory standardized standing test.

The following assessments will also be performed at Screening but are not required to determine eligibility: COVID-19 vaccination status, patient global impression of severity (PGI-S), patient global impression of change (PGI-C), Malmö Symptom Score, Work Productivity & Activity Impairment: Specific Health Problems (WPAI:SHP), EuroQoL 5 Dimension Questionnaire (EQ-5D-5L), Short Form – 12 item (SF-12), Orthostatic Hypotension Questionnaire (OHQ), and Patient-reported Outcomes Measurement Information System (PROMIS) Cognitive Function Short Form 6a.

8.2. Efficacy Assessments

8.2.1. Standardized Standing Test

Efficacy will be assessed using a standardized standing test. The standardized standing test mimics daily activities of POTS in a standardized manner [Finucane et al, 2019], and is therefore considered to be an objective, interpretable, and meaningful measurement to both patients and health care professionals.

In general, subjects are asked to lie supine for 10 minutes to achieve stable baseline blood pressure (BP) values. At the end of the 10 minutes, baseline HR and BP will be assessed. After rest, subjects are asked to stand up as quickly as possible during inspiration (where possible) to minimize straining and arm movement. Heart rate and BP will be assessed at 1, 3, 5, 7 and 10 minutes after standing. Subjects are then asked to sit or lie down until they have recovered. A separate standardized standing test protocol will be provided to sites with more detail on how to perform this assessment.

The standardized standing test will be performed as the last assessment at the time points specified in the Schedule of Activities (Section 1.3).

8.2.2. Patient-reported Outcomes

All patient-reported outcome (PRO) assessments will be conducted electronically before any other study procedures.

8.2.2.1. COMPASS-31 Score

As key secondary endpoints, efficacy will be assessed by the change from baseline in both the OI score and total score of COMPASS-31 at the end of the Double-blind Treatment Period.

The COMPASS-31 is a self-reported questionnaire that measures autonomic symptoms related to 6 domains: OI, vasomotor, secretomotor, gastrointestinal (GI), bladder and pupillomotor. This questionnaire generates a weighted score from 0 to 100, with higher scores representing higher symptom burden. A COMPASS-31 score of ≥ 40 indicates that patients have severe autonomic dysfunction [Kedor, 2021]. For the purpose of this study, the recall period of 1 week will be used.

The OI subscale was chosen as key secondary endpoint as OI symptoms were found to be most prominent to differentiate between POTS and other dysautonomias [Cortez et al, 2021], covering the most burdensome and frequent symptoms reported by POTS patients [Dipaola et al, 2020].

COMPASS-31 will be performed at the time points specified in the Schedule of Activities (Section 1.3).

8.2.2.2. Malmö Symptom Score

As an exploratory measure, efficacy will be assessed by the change in Malmö Symptom score at the end of the Double-blind Treatment Period.

The Malmö Symptom score is a self-assessment of symptom burden using a visual analog scale graded from 0 (no symptoms) to 10 (very pronounced symptoms) based on 12 commonly reported symptoms: 5 cardiac symptoms (palpitations, dizziness, presyncope, dyspnea, chest pain) and 7 non-cardiac symptoms (GI, insomnia, concentration difficulties, headache, myalgia, nausea, fatigue) [Spahic, 2023].

The Malmö Symptom score assessment will be performed at the time points specified in the Schedule of Activities (Section 1.3).

8.2.2.3. Short Form – 12 Item (SF-12)

SF-12 is a 12-item survey that assesses self-reported health-related QoL. It measures the functional health and well-being based on the subject's assessment under 8 domains: physical activity, social activities, role activities, bodily pain, mental health, vitality, and general health perceptions [Ware, 1996].

The SF-12 will be performed at the time points specified in the Schedule of Activities (Section 1.3).

8.2.2.4. Orthostatic Hypotension Questionnaire (OHQ)

The OHQ [Kaufman, 2012] is a 10-item instrument developed to measure the presence and severity of symptoms and the impact of orthostatic symptoms on daily activities. It contains 2 domains: Orthostatic Hypotension Symptom Assessment (OHSA) (6 items) and Orthostatic Hypotension Daily Activity Scale (OHDAS) (4 items). Higher score indicates more severe symptoms. The instructions to the OHQ will be modified to exclude the note: "*You should rate only the symptoms that are due to your low blood pressure problem*" to make them more relevant to the study population.

8.2.2.5. EuroQoL 5-Dimension Questionnaire (EQ-5D-5L)

The EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The questionnaire, which is designed for self-completion by respondents, is applicable to a wide range of health conditions and treatments [EuroQol Group 1990].

The EQ-5D-5L consists of 2 parts:

- A descriptive profile comprising the following 5 dimensions: mobility, selfcare, usual activities, pain / discomfort, and anxiety / depression. Respondents rate each dimension based on 5 levels of severity (ie, no problems, slight problems, moderate problems, severe problems, and extreme problems).
- A vertical visual analog scale, on which the respondent rates their overall health from 'Best imaginable health state' to "Worst imaginable health state."

The EQ-5D-5L will be performed at the time points specified in the Schedule of Activities (Section 1.3).

8.2.2.6. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)

The efficacy of IgPro20 will be further evaluated by the change from baseline in the domain scores for WPAI:SHP Version 2.0. The subject will answer questions about the effect of his / her health on the ability to work or perform regular activities. The WPAI:SHP yields 4 types of scores: Absenteeism (work time missed); presenteeism (impairment at work / reduced on-the-job effectiveness); work productivity loss (overall work impairment / absenteeism plus presenteeism) and activity impairment. The with higher scores indicating greater impairment and less productivity.

The WPAI:SHP will be performed at the time points specified in the Schedule of Activities (Section 1.3).

8.2.2.7. Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C)

The PGI-S assesses the severity of OI and general symptoms, and the PGI-C assesses the change in severity of OI symptoms and overall disease impact.

8.2.2.8. PROMIS Cognitive Functioning Short Form 6a

POTS is known to impact patients' cognitive functioning. Patients often report difficulties with concentration, memory problems, and slowed information processing [Nadeem, 2023]. The level of cognitive impairment will be evaluated using the PROMIS Short Form v2.0 Cognitive Function – 6a instrument that consists of 6 items about concentration, memory, processing speed, and overall sharpness of mind.

8.3. Safety Assessments

Safety assessments will be performed at the time points specified in the Schedule of Activities (Section 1.3).

Table 4: Safety Assessments

Physical Examination, including Height and Weight	As per the site's standard procedure.
Vital Signs	• Blood Pressure (Systolic and Diastolic) • Body Temperature • Respiratory Rate • Pulse rate
12-lead ECG	Interpretation (investigator's overall interpretation)
Pregnancy Testing	• Serum or urine test for β-hCG, as indicated, for women of childbearing potential. • If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.
Hematology	• Platelets • Hematocrit • Hemoglobin • Erythrocytes (Red Blood Cell Count) • Leukocytes (White blood cell Count) • Reticulocytes • Red blood cell indices: Mean Corpuscular Hemoglobin Concentration, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Erythrocyte Distribution Width • Differential: Neutrophils, Neutrophil Band Forms, Lymphocytes, Monocytes, Eosinophils, Basophils • D-dimer[a] • Fibrinogen[a] • Prothrombin time[a]
Biochemistry	• Phosphate • Calcium • Haptoglobin • Chloride • Cystatin C • Creatinine • C-reactive protein • Albumin • Direct bilirubin • Protein • Creatine kinase • Bilirubin • Creatinine clearance • Glucose • Total bilirubin • Alanine aminotransferase • Alkaline phosphatase • Aspartate aminotransferase • Blood urea nitrogen or Urea • Gamma glutamyl transferase • Thyroid stimulating hormone[b] • Lactate dehydrogenase • Morning cortisol level[b]
Other Screening Tests	**Viral Serology:** Blood samples are to be tested for the absence of HBV, HCV and HIV. **Follicle-stimulating hormone:** As needed in women of nonchildbearing potential only. **Urine Sodium**[b]

Retention Sample	Day 1 and Week 25 before first dose of IMP and after all study infusions have been completed at the EOT visit: retention sample for possible future assessment of unspecified viral agents

aPTT = activated partial thromboplastin time; β-hCG = beta-human chorionic gonadotropin; ECG = electrocardiogram; EOT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IMP = investigational medicinal product; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.

[a] Collected for all subjects at Screening only.

[b] For subjects where these tests have not already been completed and assessed as normal after symptom onset.

8.3.1. Clinical Safety Laboratory Assessments

- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of IMP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Sponsor's Medical Monitor.
  - If clinically significant values do not return to normal / baseline within a time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.
  - All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).
  - If laboratory values from nonprotocol-specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the subject's source documents.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Events

AEs and SAEs are defined in Section 10.2.1.

No AEs of special interest are defined for this study.

The investigator and any qualified delegates are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up.

The methods of reporting, recording, evaluating, and assessing causality of AEs, SAEs, and other significant AEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

8.5. Pharmacokinetics

Blood samples for IgG level determination will be collected pre-dose at baseline and study visits indicated in the Schedule of Activities (Section 1.3).

Additional blood samples for IgG levels will be collected in a subset of subjects (N = approximately 25) during the Open-label Treatment Period for serial PK sampling starting at Week 41. The additional samples will be collected at the following time points:

- Week 41, Day 2 (24 h ± 3 h after the start of Day 1 infusion)
- Week 41, Day 3 (48 h ± 3 h after the start of Day 1 infusion)
- Week 41, Day 4 (72 h ± 3 h after the start of Day 1 infusion)
- Week 41, Day 6 (120 h ± 3 h after the start of Day 1 infusion)

The samples for total serum IgG concentrations will be analyzed by a centralized bioanalytical laboratory. IgG concentrations during the Double-blind Treatment Period will not be disclosed prior to unblinding.

8.6. Biomarkers

8.6.1. Autoantibodies and Disease Biomarkers in Blood

Blood samples (serum /plasma) will be collected for the measurement of autoantibodies and disease biomarkers (eg, cytokines) that may be related to post-COVID POTS and will be assessed to determine baseline cytokine levels as well as proportion of autoantibody-positive subjects. Additional samples will be collected post-treatment as indicated in the Schedule of Activities (Section 1.3) to determine change from baseline, and to assess the relationship between change from baseline and efficacy.

The assessments of disease biomarkers may include, but are not limited to, the following: alpha 1 adrenergic receptor antibody, muscarinic receptor antibody, and anti-nuclear antibodies. Autoantibodies and disease biomarkers, including additional markers of proinflammatory response (eg, IL-6, IL-8 and other cytokines previously described as elevated in POTS) may be measured as exploratory research analysis, and will be included in an exploratory biomarker report, but will not be included in the clinical study report.

Blood samples for autoantibody and cytokine assessment are collected at the time points specified in the Schedule of Activities (Section 1.3).

Samples may be retained for up to 15 years and then destroyed.

8.6.2. Optional Blood Transcriptomics Analysis

In subjects who consent, whole blood samples will be collected and stored for RNA sequencing and transcriptomic analysis of changes in inflammatory pathways in peripheral blood and potential biomarkers of treatment response, disease activity, comorbid conditions and safety. The results of RNA transcriptomics analysis will be part of an exploratory research analysis and will be included in an exploratory biomarker report, which will not be included in the clinical study report.

8.6.3. Optional Future Research

Subjects may optionally consent for future research samples (blood) and residual samples (including PK) to be used for future research. Such research is directed at better understanding disease and the activity and interaction of IgPro20 with related molecular pathways, drug pharmacology, insight into the mechanisms of AEs, and the discovery of new therapeutic targets. Samples may also be used to facilitate biomarker innovation, developing new testing methodology and statistical analysis. Samples may be retained for up to 15 years and then destroyed.

8.7. Genomics

Genomics will not be evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity will not be evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics will not be evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study is designed to test the null (H_{01}) versus the alternative (H_{11}) hypothesis of the primary endpoint for the proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test (ie, no longer experiencing HR increase of ≥ 30 bpm, in the absence of orthostatic hypotension [ie, sustained 20 mmHg decrease of SBP]) at the end of the Double-blind Treatment Period.

$$H_{01}: P_{IgPro20} \leq P_{Placebo} \quad \text{versus}$$

$$H_{11}: P_{IgPro20} > P_{Placebo}$$

Where $P_{IgPro20}$ and $P_{Placebo}$ indicate the proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test in the IgPro20 and placebo group, respectively. The test for superiority will be performed at a 1-sided alpha level of 2.5% using a Farrington-Manning test.

Hypothesis for the key secondary endpoints are:

$$H_{02}: \mu_{IgPro20} \geq \mu_{Placebo} \quad \text{versus}$$

$$H_{12}: \mu_{IgPro20} < \mu_{Placebo}$$

Where, $\mu_{IgPro20}$ and $\mu_{Placebo}$ correspond to the treatment group means of interindividual changes in OI score of COMPASS-31 for IgPro20 and placebo, respectively. The test for superiority will be performed using a *t*-test.

$$H_{03}: \mu_{IgPro20} \geq \mu_{Placebo} \quad \text{versus}$$

$$H_{13}: \mu_{IgPro20} < \mu_{Placebo}$$

Where $\mu_{IgPro20}$ and $\mu_{Placebo}$ correspond to the treatment group means of interindividual changes in COMPASS-31total score for IgPro20 and placebo, respectively. The test for superiority will be performed using a *t*-test.

$$H_{04}: \mu_{IgPro20} \geq \mu_{Placebo} \quad \text{versus}$$

$$H_{14}: \mu_{IgPro20} < \mu_{Placebo}$$

Where $\mu_{IgPro20}$ and $\mu_{Placebo}$ correspond to the treatment group means of interindividual changes in HR for IgPro20 and placebo, respectively. The test for superiority will be performed using a *t*-test.

Testing will be performed accounting for multiplicity as outlined in Section 9.4.3 to preserve the alpha level of 2.5%.

9.2. Sample Size Determination

Based on the rationale presented in Section 4.3, assuming the proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test at the end of the Double-blind Treatment Period. Sample size assumptions are based on the 30% and 60% response for the placebo and IgPro20 group, respectively; under

these assumptions, at least 126 subjects will be required to provide 90% power (2:1 randomization) to detect a 30% difference in proportion of responders using a Farrington-Manning test for a 1-sided alpha of 2.5%. An additional 18 subjects will be randomized to account for a futility analysis at 54 subjects, and an additional 33 subjects will be randomized to ensure > 100 subjects treated with IgPro20 for >1 year will be achieved considering approximately 20% early drop out. Therefore, the final number of patients to be randomized is 177 (118:59).

For hypothesis testing, an alpha of 2.5% (1-sided) will be used. Randomization will be continued if the dropout rate is over 10%.

9.3. Analysis Sets

All decisions regarding definition of analyses sets will be made prior to unblinding.

9.3.1. Screened Analysis Set

The Screened Analysis Set consists of all subjects who provided written informed consent.

9.3.2. Intention-to-Treat Analysis Set

The Intention-to-Treat (ITT) analysis set consists of all subjects in the Screened Analysis Set who were randomized into the study. This analysis set will be analyzed using the treatment to which the subject was randomized regardless of the treatment actually received.

9.3.3. Per-Protocol Analysis Set

The Per-protocol (PP) set will consist of all subjects who satisfy the ITT criteria and have no major protocol deviations that impact the primary efficacy endpoint (as defined in the SAP).

Subjects in the PP set will be analyzed using the ITT principle (ie, according to randomized treatment assignment).

9.3.4. Safety Analysis Set

The Safety Analysis Set consists of all subjects in the ITT Analysis Set who received any IMP. The Safety Analysis Set will be analyzed using the treatment that the subject actually received.

9.3.5. Pharmacokinetic Analysis Set

The PK Analysis Set consists of all subjects in the Safety Analysis Set with at least 1 quantifiable PK concentration of IgG after administration.

The PK Substudy Analysis Set includes all subjects in the Safety Analysis Set who enrolled into the PK Substudy and have intensive concentration data to provide interpretable results for the specific parameters of interest for IgG.

9.4. Statistical Analyses and Methods

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints.

9.4.1. General Considerations

All statistical tests will be 2-sided and will be performed at the 5% level of significance, unless otherwise stated.

In general, continuous variables will be summarized using descriptive statistics (number of observations [n], mean, standard deviation [SD], median, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages. For repeated observations of continuous variables, change from baseline will also be summarized. Summary statistics will be described separately for each treatment group.

Baseline refers to the last measurement or the last calculated value before the first administration of IgPro20. For COMPASS-31, the assessment at the Screening visit will be used as baseline value (for total as well for all domains).

Missing dates / times in AE and concomitant therapies data will be handled as described in the SAP. There will be no imputation schemes applied to missing data unless otherwise specified in the SAP. Values that are below the limit of quantification in the PK data will be handled as described in the SAP.

9.4.2. Efficacy Analyses

All efficacy analyses will be conducted using the ITT Analysis Set except otherwise. The details of all analyses, as well as by visit analysis, will be defined in the SAP.

9.4.2.1. Primary Estimand and Analysis of Primary Efficacy Endpoint

The subject's response status of no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test (ie, no longer experiencing HR increase of ≥ 30 bpm, in the absence of 20 mmHg decrease of HR [orthostatic hypotension]) will be assessed as the primary endpoint.

A subject is considered a responder if

$$HRw_{25,10min} - HRw_{25,0min} < 30 \text{ bpm} \quad \textit{and}$$

$$BPw_{25,as} - BP_{W25,bs} > -20 \text{ mmHg}$$

Where, $HR_{W25,10min}$ indicates the average of the 2 highest HR measures (bpm) within 10 minutes after start of the standing test at W25, $HR_{W25,0min}$ indicates the HR measure (bpm) at start of the standing test at W25, $BP_{W25,as}$ indicates the systolic blood pressure measure (mmHg) at any time point within 10 minutes after start of the standing test at W25, and $BP_{W25,bs}$ indicates the systolic blood pressure measure at the start of the standing test at W25.

Consequently, a subject is considered a non-responder, if

$$HRw_{25,10min} - HRw_{25,0min} \geq 30 \text{ bpm} \quad \textit{or}$$

$$BPw_{25,as} - BP_{W25,bs} \leq -20 \text{ mmHg}$$

Response rates [%] will be determined for placebo and IgPro20.

For each treatment group point estimates and 95% Wilson Score confidence intervals will be provided, for the difference between treatment groups (IgPro20 – placebo) the point estimate, 95% Farrington-Manning confidence interval and 1-sided p-value will be provided.

To show the magnitude of the HR increase at baseline ($HR_{10min, baseline} - HR_{0min, baseline}$) and at W25 ($HR_{10min, W25} - HR_{0min, W25}$), the proportion of subjects within the following categories will be analyzed. This analysis will show the proportion of the subjects with normal HR increase after the standing test at the end of the treatment period.

- HR increase < 10 bpm
- 10 bpm ≥ HR increase < 15 bpm
- 15 bpm ≥ HR increase < 20 bpm
- 20 bpm ≥ HR increase < 25 bpm
- 25 bpm ≥ HR increase < 30 bpm
- 30 bpm ≥ HR increase < 35 bpm
- 35 bpm ≥ HR increase < 40 bpm
- 40 bpm ≥ HR increase < 45 bpm
- 45 bpm ≥ HR increase < 50 bpm
- HR increase ≥ 50 bpm

9.4.2.1.1. Detail of Primary Estimand

The primary comparison of interest is to quantify the treatment effect of IgPro20 versus placebo. The treatment effect of interest is the difference in the proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test (no longer experiencing HR increase of ≥ 30 bpm in the absence of 20 mmHg decrease of SBP [orthostatic hypotension]).

The attributes of the primary estimand, as defined in the ICH E9(R1) guidance, are provided in Table 5.

Table 5: Attributes of Primary and Key Secondary Estimand

Estimand Attribute	Subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test.
Population	Adults (≥ 18 years of age) with post-COVID-19 Postural Orthostatic Tachycardia Syndrome (POTS)
Treatment	Randomized IMP (blinded IgPro20 or blinded placebo)

Endpoint	Primary: Proportion of subjects no longer meeting diagnostic criteria of post-COVID POTS as measured by standardized standing test. Key secondary: • Change from baseline in orthostatic intolerance score (OI) of COMPASS-31 at the end of the Double-blind Treatment Period. Change from baseline in COMPASS-31 total score (TS) at the end of the Double-blind Treatment Period. • Change from baseline in HR increase within 10 minutes of standing test at the end of the Double-blind Treatment Period.		
Intercurrent Event	***Strategy***	***Description***	***Imputation details***
Treatment (IMP) discontinuation due to LoE, related adverse event or lack of compliance	Composite / Hypothetical	Discontinuation due to lack of efficacy will be treated as a failure. Only data collected prior to treatment (IMP) discontinuation will be analyzed	Primary endpoint: non-responder Key secondary endpoints: MI based on placebo group after ICE
Treatment discontinuation (not due to LoE, related AE nor lack of compliance)	Hypothetical	Depending on the subject's status until the last known visit and specific intercurrent event that contributed to the lost to follow-up, the relevant above intercurrent events will be considered for analyses.	Primary endpoint: MI based on randomized treatment Key secondary endpoints: MI based on randomized treatment
Stop of IMP but continues the study up to end of the Double-blind Treatment Period	Treatment-policy	The occurrence of missing IMP will be ignored, and data analyzed as planned to determine response status.	No action needed
Prohibited therapies	Composite / Hypothetical	Data after the intake of prohibited medication with a potential effect on the primary or key secondary endpoints will be disregarded.	Primary endpoint: non-responder Key secondary endpoints: MI based on placebo group after ICE
Concomitant therapies	Treatment policy	Data will be collected and analyzed regardless of whether an allowed concomitant therapy is given.	No action needed
Death not related to IMP or disease	Composite	Depending on the subject's status until the last known visit and specific intercurrent event that contributed to the lost to follow-up, the relevant above intercurrent events will be considered for analyses. No data beyond the date of death will be imputed.	Primary endpoint: MI based on placebo group Key secondary endpoints: MI based on placebo group

Intercurrent Event	***Strategy***	***Description***	***Imputation details***
Death related to IMP or disease	Composite	Death will be considered as treatment failure. No data beyond the date of death will be imputed.	Primary endpoint: non-responder Key secondary endpoints: imputing worst score / highest HR observed
Lost to follow-up	Hypothetical	Depending on the subject's status until the last known visit and specific intercurrent event that contributed to the lost to follow-up, the relevant above intercurrent events will be considered for analyses.	Primary endpoint: MI based on randomized treatment Key secondary endpoints: MI based on randomized treatment
Population-level Summary	Primary: Point estimate and 95% CI for the difference in proportions. Key secondary: Point estimate and 95% CI for difference in means.		

CI = confidence interval; ICE = intercurrent event; IMP = investigational medicinal product; LoE = lack of efficacy; MI = multiple imputation; POTS = Postural Orthostatic Tachycardia Syndrome

9.4.2.1.2. Sensitivity Analysis

The following sensitivity analyses are planned for the primary efficacy endpoint:

- Using the PP analysis set.
- Using a tipping point analysis: for subjects with an ICE (see Section 9.4.2.1.1 for further details), the HR after the ICE will be imputed using a multiple imputations approach (see Section 9.4.4 for further details).

9.4.2.2. Analysis of Key Secondary Endpoints

To further evaluate the efficacy of IgPro20 in adult subjects with post-COVID POTS, the following key secondary endpoints will be conducted:

1. Change from baseline in OI score of COMPASS-31 at the end of Double-blind Treatment Period

   For each subject $OI_{change} = OI_{W25} - OI_{baseline}$ will be calculated, where OI_{W25} corresponds to the OI score of COMPASS-31 at Week 25 and baseline, respectively. Descriptive statistics of the individual changes will be calculated by treatment group, including means and 95% CIs. Treatment group means will be tested for superiority by using a *t*-test. Hypothesis testing as outlined in Section 9.1 will be done.

2. Change from baseline in TS of COMPASS-31 at the end of the Double-blind Treatment Period

   For each subject $TS_{change} = TS_{W25} - TS_{baseline}$ will be calculated, where TS_{W25} corresponds to the TS of COMPASS-31 at Week 25 and baseline, respectively. Descriptive statistics of the individual changes will be calculated by treatment group, including means and 95% CIs. Treatment group means will be tested for superiority by using a *t*-test. Hypothesis testing as outlined in Section 9.1 will be done.

3. Change from baseline in HR increase within 10◦minutes of standing test at the end of the Double-blind Treatment Period:

   For each subject $HR_{change} = (HR_{W25,10min} - HR_{W25,0min}) - (HR_{baseline,10min} - HR_{baseline,0min})$ will be calculated, where $HR_{W25,10min}$ indicates the average of the two highest HR measures (bpm) within 10 minutes after start of the standing test at W25, $HR_{W25,0min}$ indicates the HR measure (bpm) at start of the standing test at Week 25, and likewise for baseline. Descriptive statistics of the individual changes will be calculated by treatment group, including means and 95% CIs. Treatment group means will be tested for superiority by using a *t*-test. Hypothesis testing as outlined in Section 9.1 will be done.

Additional analyses

To show the magnitude of the improvement of OI score of COMPASS-31, OI scores at baseline ($OI_{baseline}$) and at W25 (OI_{W25}), the proportion of subjects within the following categories will be analyzed. This analysis will show the proportion of the subjects with OI symptom score improvement at the end of the treatment period.

- OI Score ≥ 36
- 33 ≥ OI Score < 36
- 30 ≥ OI Score < 33
- 27 ≥ OI Score < 30
- 24 ≥ OI Score < 27
- 21 ≥ OI Score < 24
- 18 ≥ OI Score < 21
- 15 ≥ OI Score < 18
- 12 ≥ OI Score < 15
- OI Score < 12

To show the magnitude of the improvement of TS score of COMPASS-31, TS scores at baseline ($TS_{baseline}$) and at W25 (TS_{W25}), the proportion of subjects within the following categories will be analyzed. This analysis will show the proportion of the subjects with TS symptom score improvement at the end of the treatment period.

- Total Score ≥ 91
- 86 ≥ Total Score < 91
- 81 ≥ Total Score < 86
- 76 ≥ Total Score < 81
- 71 ≥ Total Score < 76
- 66 ≥ Total Score < 71

- 61 ≥ Total Score < 66
- 56 ≥ Total Score < 61
- 50 ≥ Total Score < 56
- Total Score < 50

To show the proportion of subjects with normal HR after 24 weeks of treatment also had improvement in their OI and TS of COMPASS-31, the correlation between HR and OI as well as TS will be done using the Spearman correlation. Sensitivity Analysis of Key Secondary Endpoints

The following sensitivity analyses are planned for the key secondary efficacy endpoints:

- using the PP analysis set
- using a tipping point analysis: for subjects with an ICE the HR and COMPASS-31 after the ICE (see Section 9.4.2.1.1 for further details) will be imputed using a multiple imputation (see Section 9.4.4).

9.4.3. Multiplicity

Issues related to multiplicity arising from testing the primary endpoint and key secondary endpoints will be addressed using pre-defined hierarchical testing procedure of the primary and key secondary endpoints with following order at an alpha level of 2.5%:

1. Hypothesis tested: primary endpoint
2. Hypothesis tested: 1stkey secondary endpoint; change from baseline in OI domain of the COMPASS-31
3. Hypothesis tested: 1st key secondary endpoint; change from baseline in COMPASS-31 total score
4. Hypothesis tested: 2nd key secondary endpoint; change from baseline in HR increase

9.4.4. Multiple Imputation

For subjects with an ICE (see Section 9.4.2.1.1) that considers multiple imputation data after the ICE will be disregarded (if applicable) and be imputed using a multiple imputations approach.

Intermittent missing replacement step: If intermittent values are missing for any of the data included in the multiple imputation analysis, the intermittent values will be imputed first using a Markov Chain Monte Carlo method 50 times to create 50 data sets with only monotone missing. The corresponding data sets will be used as input data sets for replacement of the post-ICE missing values using monotone regression; as the preceding step led already to 50 data sets, the number of imputations in this step is to be set to 1.

Imputation step: Replacement of missing values for $HR_{,W5,0min}$, $HR_{W5,10min}$, $HR_{W9,0min}$, $HR_{W9,10min}$, $HR_{W13,0min}$, $HR_{W13,10min}$, $HR_{W17,0min}$, $HR_{W17,10min,}$ $HR_{W21,0min}$, $HR_{W21,10min,}$ $HR_{W25,0min}$, and $HR_{W25,10min}$, OI_{W5}, OI_{W9}, and OI_{W25} as well as TS_{W5}, TS_{W9}, and TS_{W25} (if

applicable), will be done using multiple imputations based on monotone regression with the covariates treatment, country, HR at baseline, COMPASS-31TS and OI at baseline and HR and COMPASS-31 TS and OI values from previous weeks by SAS® PROC MI for 50 imputations with a seed of 7562032. The HR value at the end of the standing test will be considered as the average of the two highest values within 10 minutes after start of the standing test.

Analysis step: For each of the 50 analyses of the primary and key secondary endpoints will be performed as outlined in Section 9.4.2.1 and Section 9.4.2.2.

For the primary endpoint, each subject's response status will be derived as in Section 9.4.2.1.

For the first key secondary endpoint, the imputed HR will be used.

For the second and third key secondary endpoints, the imputed COMPASS-31 values will be used.

Combination step: The corresponding results across the data sets are combined for overall inference using SAS® PROC MIANALYZE according to Rubin's rule to give the 1-sided p-values for hypothesis testing, and the corresponding measures (responder rate, mean, 95% CIs, as applicable).

9.4.5. Tipping Point Analysis

A tipping point analysis will be done to assess the robustness of the assumptions for the multiple imputation and will be done only if primary analysis has a p-value < 0.025 (1-sided).

For each of the primary and key secondary endpoints, the treatment differences (D) are obtained from the main analysis as $HR_{IgPro20,W25,0min}$ - $HR_{placebo,W25,0min}$ and $HR_{IgPro20,W25,10min}$ - $HR_{placebo,W25,10min}$ (for primary and third key secondary endpoint) and $OI_{IgPro20,W25} - OIp_{placebo,W25}$ as well as $TS_{IgPro20,W25} - TS_{placebo,W25}$ (for the first and second key secondary endpoints) from the primary analyses. The HR value at the end of the standing test will be considered as the average of the two highest values within 10 minutes after start of the standing test.

For each λ =0.05 to1 (by 0.05) steps, subtract $\lambda \times \Delta$ from the imputed values of the IgPro20 treatment group in each of the 50 imputed datasets from the primary analysis. Continue with the analysis and combination step as described above for each λ.

9.4.6. Exploratory Analysis

The proportion of subjects with orthostatic hypotension, the change in Malmö Symptom score, EQ-5D-5L utility scores and visual analog scale, WPAI total and domain scores, SF-12 domain score, the remaining domains of COMPASS-31 and the proportion of patients who achieved the clinically meaningful improvement in OI and total domains of COMPASS-31 at the end of the Double-blind Treatment Period for IgPro20 vs placebo will be summarized.

9.4.7. Safety Analyses

All safety analyses will be performed by treatment group using the Safety Analysis Set. Adverse events will be coded using the Medical Dictionary for Regulatory Activities.

Treatment-emergent AEs (TEAEs) are defined as AEs reported at or after the start of IMP administration. The number and percentage of subjects with TEAEs will be reported. Frequency counts and percentages will also be presented for subjects with treatment-emergent SAEs, TEAEs leading to withdrawal or discontinuation of investigational product, TEAEs by severity, and TEAEs by relationship to investigational product. All AEs will be listed.

Analyses of other safety assessments such as ECGs, vital signs, and clinical laboratory safety markers will be described in the SAP.

9.4.8. Pharmacokinetics Analyses

IgG concentrations will be listed for individual subjects and summarized by nominal (planned) visit and timepoints, as well as by treatment group (IgPro20 vs placebo). Individual concentration-time profiles and mean (± SD) profiles will be plotted using actual time points for individual plots and nominal (planned) time points for mean profiles on both log-linear and linear scales.

$C_{troughs}$ will be measured for all subjects. Other parameters, including $AUC_{0\text{-}tau}$ (tau=Day 7), C_{max} and T_{max}, will be derived for the subjects with serial sampling on Week 41 using noncompartmental methods. The PK parameters will be listed individually and summarized.

Additional information on the analyses of PK parameters will be provided in the SAP. The PK Analysis Set or PK Substudy Analysis Set will be used.

The IgG concentration data may be used, possibly in combination with IgPro20 data from previous studies, to further develop the population PK model.

9.4.9. Pharmacodynamic and Biomarker Analyses

If applicable, additional exploratory biomarker analyses will be described in a separate biomarker SAP and may be reported outside of the SAP and clinical study report.

9.4.10. Pharmacokinetic / Pharmacodynamic Analyses

Relationships between trough concentrations and other PD/biomarker endpoints may be explored through graphical and statistical regression analyses as appropriate. Details will be provided in the SAP.

9.4.11. Other Analyses

Subgroup Analyses of Primary Endpoint

Internal consistency of observed treatment effect across major subgroups on the primary endpoint will be investigated. Subgroup factors are shown in the list below:

- Subjects received a COVID-19 vaccine
  - Yes
  - No

- Age
  - ≥18 – <20 Years
  - ≥20 – <26 Years
  - ≥26 – <46 Years
  - ≥46 – <65 Years
  - ≥ 65 Years
- Sex:
  - Female
  - Male
- Baseline total COMPASS-31 score:
  - ≥40 – <46
  - ≥46 – <51
  - ≥51 – <56
  - ≥ 56

Subgroup analysis will use the same analytical approach as in the primary endpoint analysis.

9.4.12. Interim Analysis

Simulation within EAST software was used to determine time point and operating characteristics of an interim analysis for futility using a gamma family alpha spending function. There is neither a plan for sample size re-estimation during the trial nor for early stopping for efficacy. For a futility boundary of 10% (ie, if response rate with IgPro20 IgPro20 – response rate with placebo is < 10%) there is a probability to stop under H0 (no treatment effect) of 75.8% and to stop the study under H1 (assumed treatment effect of 30%) of 7.4% at the time the futility analysis is performed (when 54 subjects have completed the first 24 weeks of treatment). Please see below for further scenarios (total N of 177). This boundary and timepoint for the interim analysis was considered suitable considering recruitment.

The detailed of boundaries and timepoint for the interim analysis will be described in IDMC SAP and IDMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Clinical Trial Research Agreement

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

10.1.2. Regulatory and Ethics Considerations

This study will be conducted in accordance with the Clinical Study Protocol (CSP) and with the following:

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki.

- Applicable ICH GCP Guidelines.
- Applicable laws and regulations.
- The CSP, CSP amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) / Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB / IEC before the study is initiated.
- Any CSP amendments will require IRB / IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- CSP and CSP amendments will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB / IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB / IEC.
- Notifying the IRB / IEC of SAEs or other significant safety findings as required by IRB / IEC procedures.

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB / IEC, European Clinical Trials Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.3. Informed Consent Process

Informed consent will be obtained from all subjects or legally authorized representatives, if appropriate, before any study-related procedures are performed.

The investigator or delegate will explain the nature of the study to the subject or their legally authorized representative and answer all questions regarding the study.

Subjects or their legally authorized representative must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent, either via paper or electronic means, that meets the applicable requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, and the IRB / IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects or their legally authorized representative must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or their legally authorized representative.

OR

The ICF will contain a separate section or addendum that addresses the use of samples for optional exploratory research. The investigator or authorized delegate will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4. Data Protection

Measures used to protect individual subject data include the following:

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that their personal study-related data will be used by the Sponsor in accordance with all applicable data protection laws. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the ICF.

The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Information and Data

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

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

This CSP will be made public following study completion with results posting in any applicable public registry (eg, ClinicalTrials.gov). Company confidential information within the CSP and personal protected data may be redacted as defined by regulatory authorities.

10.1.6. Data Quality Assurance

All subject data relating to the study will be recorded either through the IRT system or on printed or eCRFs unless transmitted to the Sponsor or delegate electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of eCRFs will be provided in the eCRF.

The investigator must permit study-related monitoring, audits, IRB / IEC review, and regulatory agency inspections, and provide direct access to source data documents.

The Sponsor or delegate is responsible for the data management of this study including quality checks of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the timeline outlined in the Clinical Trial Research Agreement.

Quality tolerance limits, where appropriate, will be predefined in the Quality Risk Management Plan to identify systematic issues that can impact participant safety and / or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the quality tolerance limits and remedial actions taken may be summarized in the clinical study report.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk-Based Quality Management), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan and Quality Risk Management Plan.

10.1.7. Patient Recruitment

As part of this clinical trial, patients will be recruited using digital ads on social media platforms. Images and text used in the ads require IRB or EC approval prior to use.

Once a potential participant clicks on the digital ad, they will be directed to a landing page where they will review and accept a Privacy Policy and Terms of Use detailing the purpose of data collection, what data will be collected, how it will be used, and their rights under applicable data privacy laws. Should they choose to proceed, the potential participant is then directed to a pre-screening questionnaire to answer a few questions about their condition and their contact information.

Once the pre-screening questionnaire is completed, these responses are reviewed by the patient referral vendor. Potential participants confirm their potential eligibility, their interest in potential participation, and consent to sharing their information with the clinical research site. Once the patient referral vendor shares the information with the clinical research site, the investigator will directly confirm initial eligibility and interest with the potential participant.

10.1.8. Committees Structure

10.1.8.1. Independent Data Monitoring Committee

An unblinded IDMC will monitor the safe conduct of the study. An IDMC charter outlines the roles and responsibilities of the committee and guides its operations. The IDMC consists of qualified POTS clinical experts and scientists who are not investigators in the study and not otherwise associated with the Sponsor. The IDMC responsibilities include the following:

- Review the safety data at planned intervals and identify if significant safety concerns arise during the study.
- Provide recommendations to the Sponsor regarding study conduct matters that affect safety.
- Request an interim safety review whenever one is warranted.
- Recommend modifications to study conduct or early study termination, if warranted due to safety concerns.
- Review efficacy and safety data and make recommendations regarding study progression or termination due to futility (see Section 10.1.10).

10.1.9. Source Documents

Source documents (including eCOA / eDiary) provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

The definition of what constitutes source data can be found in the Clinical Trial Research Agreement.

Data reported through the IRT system or entered into the eCRF that are transcribed from source documents must be consistent with the source documents. If there are data

discrepancies, the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must also be available.

The investigator must maintain accurate documentation (source data) to support the information entered into the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Premature Site Closure and Study Termination

The Sponsor or delegate reserves the right to close the study site prematurely or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for premature site closure include, but are not limited to:

- Failure of the investigator to comply with the CSP, the requirements of the IRB / IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Enrollment target achieved earlier than expected.
- The reason for study termination may include, but is not limited to, discontinuation of IMP development for any reason. If the study is terminated or suspended, the Sponsor will promptly notify the investigators, the IRBs / IECs, the regulatory authorities, and any contract research organization(s) used in the study and provide the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator will promptly inform the subject and should ensure that they are properly transitioned out of the study.

10.1.11. Publication Policy

The rights and obligations of investigators and the Sponsor 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 Research Agreement for the study.

10.2. Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definitions

10.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered an investigational product and that 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 observation period for AEs is defined in Section 10.2.4.

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a preexisting condition. Preexisting conditions should be recorded on the Medical History eCRF and only 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 and before IMP administration.
- Intercurrent illnesses with an onset after administration of IMP.

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 related to preexisting conditions that have not worsened.
  - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).
  - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy).
- Overdose of IMP or any concomitant therapy that does not result in any adverse signs or symptoms.

For laboratory and other safety parameters (eg, vital signs), any instances of absolute values or changes at any visit after study start that are considered by the investigator as clinically significant must be recorded on the AE eCRF. In addition, at the investigator's discretion,

any changes or trends over time in laboratory parameters may be recorded on the AE eCRF if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

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

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

10.2.1.2. 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 inpatient hospitalization or prolongation of existing hospitalization** – 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 considered by the investigator to potentially jeopardize the subject or to require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

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

10.2.2. Assessment of Severity

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

Table 6: Definitions of Adverse Event Severity

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.

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

10.2.3. Assessment of Causality

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

The degree of certainty with which an AE is attributed to IMP, the medical device (constituent), or the combination of device and IMP 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.
- 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 IMP, drug withdrawal, or reproduced on rechallenge).

10.2.4. 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 dose or until resolution of an ongoing AE.

If the investigator becomes aware of an SAE that has started after the observation period has ended, and there is at least a possible causal relationship with IMP, the event must be reported to the Sponsor (Section 10.2.6.2).

10.2.5. Follow-up of Adverse Events

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

10.2.6. Adverse Event Reporting

10.2.6.1. Adverse Events

At each study visit, the investigator (or delegate) will inquire and determine whether any AEs have occurred. All AEs are to be recorded directly on the eCRF and must be consistent with the source documents, if available. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs, laboratory findings, and / or symptoms.

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

10.2.6.2. Serious Adverse Events

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Guideline 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 directly in the eCRF and must be consistent with the source documents, if available.

All SAEs that occur during the study, whether or not causally related to IMP, **must be entered into the eCRF immediately and must be sent to the Sponsor within 24 hours of the investigator becoming aware of the event.**

Adverse events occurring between the subject's written informed consent and the first exposure to IMP, and that meet at least 1 of the criteria for seriousness, must be entered into the eCRF in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the EOS Visit that is considered to be causally related to IMP must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to the Sponsor.** Such events are not entered into the CRF.

The minimum requirements for the reporting of SAEs are:

- Subject identification number.
- Suspected medicinal product and / or procedure.
- Event term.
- Identity of reporting source (ie, subject, caregiver, treating physician, investigator).

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

In addition, the investigator must:

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

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

10.2.6.3. Adverse Events of Special Interest

No adverse events of special interest are defined for this study.

10.2.6.4. Other Significant Events

10.2.6.5. Overdose

Any overdose that occurs in association with an adverse sign or symptom must be entered into the eCRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 10.2.6.2).

The details (ie, volume, location of infusions, infusion rate) of an overdose of the IMP (defined in Section 6.11) must be recorded into the appropriate CRF. Details of an overdose of any concomitant therapy must be recorded on the concomitant therapies CRF.

10.2.6.6. Pregnancy and Breastfeeding

A female subject or female partner of a male subject who becomes pregnant while participating in the study, or up to and including 5 times the half-life of IMP after the last dose of IgPro20, must notify the investigator within 24 hours of a positive pregnancy result.

If a female subject becomes pregnant, she must discontinue treatment with IgPro20, 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 (ie, receiving study drug), her participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in Section 7).

The investigator must notify the Sponsor within 5 days of becoming aware of the pregnancy.

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

All abnormal pregnancies and neonatal outcomes (eg, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly) will meet the criteria for SAE classification. The investigator should follow the procedure for reporting these events as SAEs (see Section 10.2.6.2).

10.2.7. IRB / IEC Reporting Requirements

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

10.3. Contraceptive Guidance

10.3.1. Definitions

Woman of Childbearing Potential

Women are considered women of childbearing potential (ie, fertile) from the time of menarche until becoming postmenopausal unless permanently sterile.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IMP, additional evaluation should be considered.

Woman of Nonchildbearing Potential

Women are considered women of nonchildbearing potential if they are postmenopausal or premenopausal and permanently sterile.

Postmenopausal

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence

of 12 months of amenorrhea, confirmation with more than 1 follicle-stimulating hormone measurement is required.

- Women on HRT and whose menopausal status is in doubt
  - will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study.
  - must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanently Sterile

Permanent sterilization methods (for the purpose of this study) include:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than those listed above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be exercised when determining the subject's eligibility for enrollment in the study.

Note: Documentation can come from the site personnel's review of the subject's medical records, physical examination, or medical history interview.

10.3.2. Contraception Guidance

Contraceptive use by males or females should be consistent with local regulations regarding the use of contraceptive methods in clinical studies.

Table 7: Contraceptives Allowed During the Study

Method	Failure Rate	Type
Highly Effective [a] Low User Dependency	< 1%	• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [a] • Intrauterine device • Intrauterine hormone-releasing system [a] • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has*

Method	Failure Rate	Type
		been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days Note: documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview
Highly Effective User Dependent [a]	< 1%	• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [b] o oral o intravaginal o transdermal o injectable • Progestogen-only hormone contraception associated with inhibition of ovulation o oral o injectable • Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
Effective Methods [c] **Not Considered Highly Effective**	≥ 1%	• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods) [d]

[a] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[b] If hormonal contraception efficacy is potentially decreased due to interaction with investigational product, add: Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with

Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

[c] Considered effective, but not highly effective – failure rate of ≥ 1% per year. Periodic abstinence (calendar, symptothermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

[d] Male condom and female condom should not be used together (due to risk of failure from friction).

10.4. Study Assessment and Procedure Considerations

10.4.1. Optional, On-demand Alternative Visit Modalities

The following alternative visit modalities may be implemented with Sponsor approval as per the Schedule of Activities (Section 1.3): phone or video conference calls at home for safety follow-up, including assessment of AEs and concomitant therapies, and hematology, biochemistry, and pregnancy blood sampling at a local laboratory, where possible.

Telemedicine or virtual study visits may be performed by qualified, designated study site personnel if approved by the Sponsor.

Home health visits may be performed by a qualified medical provider approved by the Sponsor.

A local laboratory may be used to collect and analyze protocol-required assessments.

Electronic clinical outcomes assessment (eCOA) solutions may also be offered directly to the subject to ensure that subjects can enter data remotely. In case alternative visit modalities are used in the study, data will continue to be protected and stored securely without disruption.

Table 8: Optional, On-demand Alternative Visit Modalities

Activity	Visit Day / Number	Permitted Visit Modality
Weight and BP		Home Health
PK Collection		Home Health
IMP Dispensing		Direct to Patient Shipment

BP = blood pressure; IMP = investigational medicinal product; PK = pharmacokinetic

10.4.2. Use of Electronic Clinical Outcomes Assessment Solution

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

The eCOA solution captures electronic source data in a controlled and consistent way and provides 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 always under the control of the investigator.

The investigator (or delegate) will have access to all eCOA data entered at site and / or all data reported within the subject eDiary 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 the Sponsor's Clinical Data Warehouse at a predefined frequency via a secure data channel for systematic review by the Sponsor's clinical team.

The eCOA provider engaged for this study is responsible for providing a solution that conforms to all pertinent regulations. The solution is never intended to be a substitute for normal medical care of the subject. The vendor hosts the eCOA data on behalf of the investigators, until each investigator receives a certified archive copy of all diary data relating to subjects at that site and has confirmed that it is readable.

10.4.3. Genomics: Use and Analysis of DNA

Not applicable

10.5. Country-specific Requirements

Not applicable

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APPENDIX 1. CLINICAL STUDY PROTOCOL AMENDMENT HISTORY

Not applicable

APPENDIX 2. PRINCIPAL INVESTIGATOR SIGNATURE

SIGNATURE OF PRINCIPAL INVESTIGATOR

Study Title: Double-blind, Randomized, Placebo-controlled Phase 3 Study Evaluating Efficacy and Safety of IgPro20 (subcutaneous immunoglobulin, HIZENTRA®) in post-COVID-19 Postural Orthostatic Tachycardia Syndrome (POTS)

Study Number: IgPro20_3010 **Site Number:**

I have read the Clinical Study Protocol (CSP) version 1.0 titled "Double-blind, Randomized, Placebo-controlled Phase 3 Study Evaluating Efficacy and Safety of IgPro20 (subcutaneous immunoglobulin, HIZENTRA®) in post-COVID-19 Postural Orthostatic Tachycardia Syndrome (POTS)".

By signing this CSP, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the CSP, the standards of Good Clinical Practice (as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use), ethical principles that have their origin in the Declaration of Helsinki, and applicable regulatory requirements.

Changes to the CSP will only be implemented after written approval is received from the Sponsor 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 CSP.

_____ _____

(Signature) Date (DD Month YYYY)

_____

(Printed name)

_____

(Title)

Signature Page

IgPro20_3010 - Protocol - 11Apr2024

Signed By	Date (GMT)
PPD	24-Apr-2024 14:47:37
Approved-PPD	
PPD	24-Apr-2024 14:48:20
Approved-PPD	
PPD	24-Apr-2024 14:53:26
Approved-PPD	

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