STATISTICAL ANALYSIS PLAN (SAP)

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)

Investigational Medicinal Product: IgPro20 (Hizentra®)

Protocol Number: IgPro20_3010

Version: 2.0

Version Date: 27 August 2025

Sponsor: CSL Behring, LLC

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1. MODIFICATION HISTORY

Version	Effective Date	Author of Modification	Reason for Change
1.0	11 April 2024		N/A – First Version
2.0	27 August 2025	PPD	Premature termination of the study

2. LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
ADaM	Analysis data model
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BP	Blood pressure
BDRM	Blinded data review meeting
BMI	Body mass index
CM	Concomitant medication
C_{max}	Maximum concentration
C_{trough}	Trough concentration
COMPASS-31	Composite Autonomic Symptom Score 31
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
ECG	Electrocardiogram
EOS	End of Study
EQ-5D-5L	EuroQol-5 dimension-5 levels
GI	Gastrointestinal
HR	Heart rate
ICE	Intercurrent event
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IRT	Interactive Response Technology
ITT	Intention-to-treat
OHQ	Orthostatic Hypotension Questionnaire
OI	Orthostatic intolerance
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
POTS	Postural Orthostatic Tachycardia Syndrome
PRO	Patient-reported outcomes

Abbreviation	Term
PROMIS	Patient-reported Outcomes Measurement Information System
PT	Preferred Term
QoL	Quality of Life
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDTM	Study Data Tabulation Model
SF-12	Short Form – 12 Item
SOC	System Organ Class
TEAE	Treatment emergent adverse event
WPAI:SHP	Work Productivity & Activity Impairment: Specific Health Problems

3. PURPOSE

This statistical analysis plan (SAP) provides a detailed and complete description of the planned statistical analyses for the primary, key secondary, and all other analyses to be presented in Clinical Study Reports (CSRs). Mock tables, listings, and figures shells are provided in separate supporting documents.

This SAP complies with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials.

This Statistical Analysis Plan has been updated as CSL Behring made the decision to terminate the study on May 13, 2025. The decision was based on persistent recruitment challenges and extended development timelines. The decision was not related to any safety concern of Hizentra. By May 13, 2025, 16 of the planned 177 subjects had been randomized.

Section 4 of the SAP describes the initially planned design according to the CSP. Section 5 provides an overview of the changes to the planned analyses.

4. STUDY DESIGN

4.1. Study 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

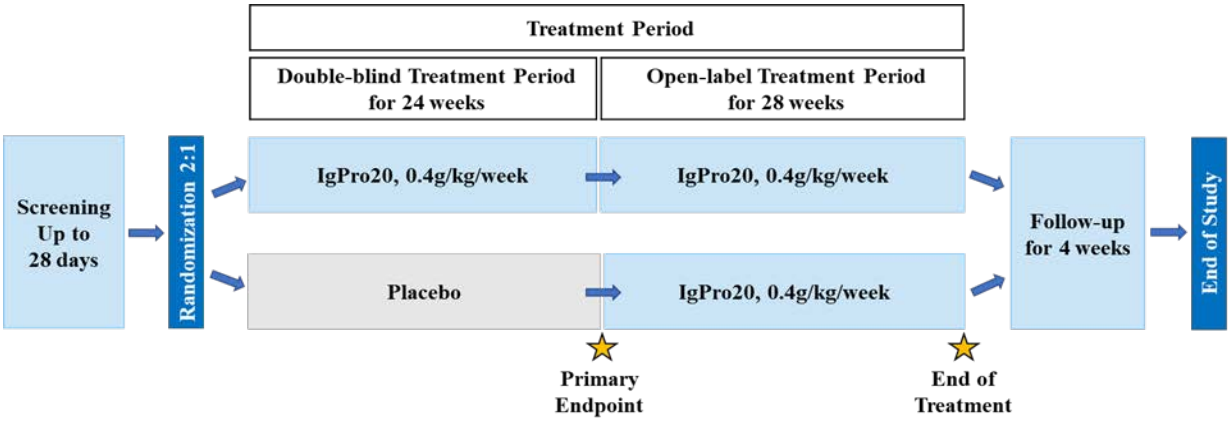
subjects with post SARS-CoV-2 infection 2019 postural orthostatic tachycardia syndrome (post Coronavirus Disease 2019 [COVID-19] POTS, hereafter referred to as post-COVID POTS).

Planned enrollment for the study was approximately 177 subjects with a confirmed diagnosis of post-COVID POTS as defined in the protocol who are 18 years or older at the time of providing written informed consent.

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 Independent Data Monitoring Committee (IDMC) recommendation after futility analysis review has been received and reviewed by the Sponsor.

Eligible subjects will be randomized in a 2:1 ratio to receive subcutaneous (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.

Figure 1: Study Scheme



4.2. Objectives and Endpoints

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

To further evaluate the efficacy of IgPro20 in comparison with placebo in adults with post-COVID POTS the following key secondary endpoints will be evaluated:

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

Table 1: Study Objectives, Endpoints, Estimands, and Summary Measures for Primary and Secondary Endpoints

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 Table 5 of the CSP **Population:** Intent-To-Treat **Treatment:** IgPro20 vs. placebo **Population Summary:** Point estimate and 95% CI for the difference in proportions.
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 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 orthostatic intolerance score of COMPASS-31 at the end of the Double-blind Treatment Period. Intercurrent events: See Table 5 of the CSP **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

Objectives	Endpoints and Estimands
	of interest is differences from baseline in COMPASS-31 total score at the end of the Double-blind Treatment Period. For intercurrent events: See Table 5 of the CSP **3. Endpoint**: Change from baseline in HR increase within 10 minutes of standardized 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 standardized standing test at the end of the Double-blind Treatment Period. For intercurrent events: See Table 5 of the CSP
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 (shift) from baseline at Week 25 and Week 53.
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)
	  ○ C_{max}
	  ○ T_{max}
	  ○ C_{min}
	  ○ AUC_{0-7d}
	  ○ AUC_{0-last}

To further evaluate the efficacy of IgPro20 in comparison with placebo in adults	• 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.

Objectives	Endpoints and Estimands
with post-COVID POTS	• Change from baseline in Mental Component Score, and Physical Component at the end of the Double-blind Treatment Period. • Change from baseline in remaining domains of COMPASS-31 at the end of 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 global and 2 domains of the OHQ score.

$AUC_{0\text{-}1}$ = Area under the concentration-time curve from time point 0 to the last quantifiable time point; $AUC_{0\text{-}7d}$ = Area under the concentration-time curve from time point 0 to day 7; $AUC_{0\text{-}last}$ = 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; EQ-5D-5L = EuroQol-5 dimension-5 level; HR = heart rate; IgG = Immunoglobulin G; PK = pharmacokinetic; POTS = Postural Orthostatic Tachycardia Syndrome; PROMIS = Patient-reported Outcomes Measurement Information System; SBP = systolic blood pressure; SF-12 = Short Form – 12-item; TEAE = treatment-emergent adverse event; T_{max} = time to reach maximum concentration; WPAI:SH = Work Productivity & Activity Impairment: Specific Health Problems

4.2.1. Primary Study Hypothesis

The primary study objective is to test the superiority of IgPro20 relative to placebo. The study is designed with the objective of testing the null and the alternative hypotheses for the responder rates as defined below:

$$H_{01}: \pi_{IgPro20} \leq \pi_{Pbo} \text{ versus}$$
$$H_{11}: \pi_{IgPro20} > \pi_{Pbo}$$

Where $\pi_{IgPro20}$ and π_{Pbo} represent the responder rates with IgPro20 and placebo, respectively.

Under the null hypothesis, the assumption is that no beneficial effect is afforded by IgPro20 while the alternative hypothesis states that IgPro20 is effective in increasing the responder rate compared to the placebo arm. Statistical significance will be assessed using the one-sided alpha level of 0.025.

4.2.2. Key Secondary Endpoints Hypotheses

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

1. Change from baseline in orthostatic intolerance (OI) score of COMPASS-31 at the end of the Double-blind Treatment Period:

$$H_{02}: \mu_{OI,IgPro20} \geq \mu_{OI,Pbo} \quad \text{versus}$$
$$H_{12}: \mu_{OI,IgPro20} < \mu_{OI,Pbo}$$

2. Difference between treatment groups in change from baseline in total score (TS) score of COMPASS-31 at the end of the Double-blind Treatment Period:

$$H_{03}: \mu_{TS,IgPro20} \geq \mu_{TS,Pbo} \quad \text{versus}$$
$$H_{13}: \mu_{TS,IgPro20} < \mu_{TS,Pbo}$$

3. Difference between treatment groups in change from baseline in HR increase within 10 minutes of standardized standing test at the end of the Double-blind Treatment Period

$$H_{04}: \mu_{HR,IgPro20} \geq \mu_{HR,Pbo} \quad \text{versus}$$
$$H_{14}: \mu_{HR,IgPro20} < \mu_{HR,Pbo}$$

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, considering multiple testing procedure (see Section 4.2.3).

4.2.3. Multiplicity

For issues related to multiplicity refer to CSP Section 9.4.3.

4.3. Study Treatments

Subjects will be randomized 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 where all subjects will receive CCI g/kg/week of IgPro20 for 28 weeks as depicted in Figure 1. The study duration for an individual subject will be up to 60 weeks.

4.4. Randomization Procedures and Blinding

Eligible subjects will be randomized to 1 of the 2 double-blind treatments by means of Interactive Response Technology (IRT). The IRT will assign the Investigational medicinal product (IMP) to each subject and the correct dose volume based on the subject's body weight. Randomization will be done centrally and CSL Behring will supply the investigator with a user guide for the IRT.

4.5. Determination of the Sample Size

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 is 30% and 60% for the placebo and IgPro20 group, respectively, 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 will be randomized to ensure > 100 subjects treated with Hizentra for >1 year will be achieved considering approximately 20% early drop out. Therefore, the final number of subjects 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%.

4.6. Interim Analyses

An interim futility analysis will be conducted after 54 subjects have completed 24 weeks of treatment. 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 – 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). This boundary and timepoint for the interim analysis were considered suitable considering recruitment. The details of the boundaries and timepoint for the interim analysis are presented in Appendix 1 and will be described in the IDMC SAP and IDMC charter.

4.6.1. Independent Data Monitoring Committee (IDMC) Reviews

The IDMC will monitor the safety data as well as the result of the futility analysis generated during the study to conduct unblinded assessments of the safety and futility of the IgPro20 in post COVID POTS population.

The composition, activities, and responsibilities of the IDMC will be described in the IDMC charter. The analyses to support the IDMC data review activities during the study will be detailed in a separate IDMC SAP.

5. CHANGES IN THE CONDUCT OF PLANNED ANALYSES

The study was terminated prematurely (see Section 3) due to persistent recruitment challenges and extended development timelines. As less than 10% of the planned subjects (16 of 177) had been randomized at the time of discontinuation and those subjects were at different stages of the study, the originally planned analyses will not be done. The scope of the analyses will be restricted to a descriptive analysis of the following:

- Disposition of subjects.
- Demographic and baseline characteristics.
- Efficacy endpoints.
  - Descriptive efficacy analysis by visit for the double-blind period restricted to the following endpoints
    - Primary and key secondary endpoints
      Due to the premature termination of the study, the planned multiple imputation strategy for handling missing data for the primary and key secondary endpoints will not be performed. The actual sample size and the sparse data render these methods inappropriate and unreliable for generating meaningful inference. As a consequence only observed data are presented and all analyses are descriptive in nature.
    - PROs: only Malmö Symptom score, OHQ score, and Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) for OI symptoms.
  - The originally planned sensitivity analysis or subgroup analysis will not be done.
- Adverse events.
  - Summarizing analysis will be performed for the Double-blind Treatment Period. TEAEs starting in the Open-Label Treatment Period will be included in listings.
  - Annualized TEAE rates will not be calculated.
- Other data will not be summarized but provided in the SDTM data sets only.

6. STUDY ANALYSIS SETS

Screened Analysis Set – SCR

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

Intention-to-Treat Analysis Set – ITT

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.

Safety Analysis Set – SAF

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.

7. GENERAL CONSIDERATIONS

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

SAS version 9.4 or higher will be used to perform all data analyses and to generate tables, figures, and listings.

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum. Other descriptive statistics (eg, coefficient of variation, geometric mean) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics required identified with the analysis in the applicable SAP section.

All listings will include subject number, treatment sequence, and randomized treatment of the respective treatment sequence. Unless otherwise stated, all listings will be sorted by treatment sequence, subject number, and then by numeric visit date and time. If any of these variables do not apply to a listing, then that listing will use only those that do in the order given here.

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

Formatting for dates and times will be:

Dates only – ddmmmyyyy

- Times only – hh:mm or hh:mm:ss (as appropriate)
- Dates and times – ddmmmyyyy hh:mm or ddmmmyyyy hh:mm:ss (as appropriate)

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

Planned times will be used in the descriptive summaries of IgG levels.

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

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

7.1. Treatment and Visit Descriptors

The Double-blind Treatment Period will be Week 1 to Week 25 and the Open-label Treatment Period will be Week 25 to end of Week 52. The "Baseline" visit comprises all baseline assessments which is not necessarily identical to the summary of all assessments from the Baseline visit.

7.2. Multiple Comparisons and Multiplicity

Not applicable.

8. DATA HANDLING CONVENTIONS

8.1. Missing Data

8.1.1. Imputation of Non-Date Missing Data

As the study is terminated early, the originally planned imputation for missing data for the primary and the key secondary endpoints will not be done.

8.1.2. Imputation of Partial Dates

Imputed dates will not be used to derive study day, duration (eg, duration of adverse events), or elapsed time variables. Imputed dates will be displayed in listings and identified as imputed.

Partial date imputation will follow Analysis Data Model (AdaM) conventions. The AdaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

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

Blank indicates that no imputation was done

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

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

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

8.1.3. Adverse Events

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. They will not be used to calculate duration of adverse events (AEs). If an AE start or end date is missing, then the duration of the AE will be set to missing.

As a rule, the missing start date elements will be imputed with following priorities:

- The event is counted as TEAE for IgPro20 with the earliest onset possible.
- The event is counted as TEAE for placebo with the earliest onset possible.

For subjects randomized to Placebo in the Double-blind Treatment Period who have already transitioned to the Open-label Treatment Period, if due to missing elements the event qualifies to either IgPro20 or placebo, the event is assigned to be treatment-emergent in the IgPro20 Open-label Treatment Period.

Table 2: Imputation of Missing Dates for AEs

Date	Missing Element	Rule
Start Date	day, month, and year	Do not impute completely missing AE start dates. **Double-blind Treatment Period** • The AE will be deemed treatment-emergent during the Double-blind Treatment Period (Week 1-25) if the AE end date does not indicate that the AE ended prior to IMP start date (Week 1), • otherwise, the AE will be deemed not treatment emergent. **Open-label Treatment Period** • The AE will be deemed treatment-emergent during the Open-label Treatment Period (Week 25-53) if the AE end date does not indicate that the AE ended prior to IMP start date (Week 25), • else the AE will be deemed treatment-emergent in the Double-blind Treatment Period (Week 1-25) if the AE end date does not indicate that the AE ended prior to IMP start date (Week 1), • otherwise, the AE will be deemed not treatment emergent.
Start Date	day, month only	**Double-blind Treatment Period** • If the year of AE start date is the same as the year of IMP start date (Week 1), and the AE end date indicates the AE ended after IMP start date (Week 1), then set AE start date to IMP start date (Week 1), • otherwise set AE month and day to January 1st **Open-label Treatment Period** • If the year of AE start date is the same as the year of IMP start date (Week 25), and the AE end date indicates the AE ended after IMP start date (Week 25), and IMP start date (Week 25) is not missing then set AE start date to IMP start date (Week 25), • else if the year of AE start date is the same as the year of IMP start date (Week 1), and the AE end date indicates the AE ended after IMP start date (Week 1) then set AE start date to IMP start date (Week 1), • otherwise set AE month and day to January 1st
	day only	**Double-blind Treatment Period** • If the month/year of AE start date is the same as the month/year of IMP start date (Week 1), and the AE end date indicates the AE ended after IMP start date (Week 1) then set AE start date to IMP start date (Week 1), • otherwise set day of AE start date to 1 **Open-label Treatment Period** • If the month/year of AE start date is the same as the month/year of IMP start date (Week 25), and the AE end date indicates the AE ended after IMP start date (Week 25), and IMP start date

Date	Missing Element	Rule
		(Week 25) is not missing then set AE start date to IMP start date (Week 25), • else if the month/year of AE start date is the same as the month/year of IMP start date (Week 1), and the AE end date indicates the AE ended after IMP start date (Week 1) then set AE start date to IMP start date (Week 1),
End Date	any date element	No imputation for completely or partially missing AE end dates; as applicable, report the AE as ongoing and the AE duration as missing.

8.1.4. Medical History

Missing dates for medical history will not be imputed.

8.1.5. Initial Diagnosis of Post-COVID POTS

Table 3: Imputation of Missing Dates for Diagnosis of Post-COVID POTS

Missing Element	Rule
day, month, and year	No imputation for completely missing dates. Time since first diagnosis will be set to missing.
Day, month only	Set the date to January 1st.
day only	Set the date to 1.

8.1.6. Concomitant Medication

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

As a rule, the missing start date elements will be imputed with following priorities:

1. The medication is ‘concomitant’ to IMP
2. The medication is ‘prior’ to IMP

Table 4: Imputation of Missing Dates for Concomitant Medication

Date	Missing Element	Rule
Start Date	day, month, and year	Completely missing medication start dates will not be imputed and all values that depend on this date will be set to missing. The medication will be considered 'concomitant'.
End Date	day, month, and year	Medication is considered ongoing at the end of the study.
	Day, month only	• If the year of concomitant medication (CM) start date is the same as the year of IMP start date (Week 1), and the CM end date indicates the CM ended after IMP start date (Week 1) then set CM start date to IMP start date (Week 1), • otherwise set CM month and day to January 1st
	day only	• If the month/year of CM start date is the same as the month/year of IMP start date (Week 1), and the CM end date indicates the CM ended after IMP start date (Week 1) then set CM start date to IMP start date (Week 1), • otherwise set day of CM start date to 1
	Day, month only	Set CM end month and day to December 31st
	day only	Set day of CM end date to the last day of the month.

8.2. Derived Variables

The following sections provide a general description of the derived and transformed variables to be used in data analyses. Separate analysis dataset specifications provide full details on all data derivations and transformations.

In this study, an Electronic Clinical Outcomes Assessment (eCOA) device will be used to collect data for several outcomes.

8.2.1. Reference Dates

Reference dates are used to assign study periods relative to treatment. The reference date is the date of the start of the period (Section 8.3).

8.2.2. Heart Rate and Change in Heart Rate During Standardized Standing Test

Heart rate for standing test will be measured at the end of the 10 minutes in supine position and at 1, 3, 5, 7, and 10 minutes of standing.

The change in heart rate during the standing test is calculated as the difference of the average of the two highest heart rate measures (bpm) within 10 minutes of standing and the heart rate measure (bpm) at the end of the 10 minutes in supine position.

If in one subject the standardized standing test was repeated at a visit results of the last standing test will be used for the summarizing analysis.

8.2.3. Systolic Blood Pressure and Change in Systolic Blood Pressure During Standardized Standing Test

Blood pressure for standing test will be measured at the end of the 10 minutes in supine position and at 1, 3, 5, 7, and 10 minutes of standing.

The change in systolic blood pressure during the standing test is calculated as the difference of the minimum of all systolic blood pressures (mmHg) within 10 minutes of standing and the systolic blood pressures (mmHg) at the end of the 10 minutes in supine position.

If in one subject the standardized standing test was repeated at a visit results of the last standing test will be used for the summarizing analysis.

8.2.4. Study Day

If the date of interest occurs on or after the date of the start of first IMP infusion, then the study day will be calculated as (date of interest – date of the start of first IMP infusion) + 1. If the date of interest occurs before the date of the start of first IMP infusion, then the study day will be calculated as (date of interest – date of the start of first IMP infusion). There is no study day 0.

8.2.5. Study Week

The start of a study week is the day of the first infusion of IMP in that week as recorded in the infusion diary. Events that occur after premature discontinuation of IMP will not be assigned to a specific week.

End date of last study treatment week =
minimum of (Date of last visit, date of 1st infusion in last study week + 6 days)

The end of a study week is the day before the start of the next study week. In case of longer treatment interruptions planned weeks will be considered.

8.2.6. Baseline Definition

Baseline is defined as the most recent, non-missing value prior to the start date and time of the first IMP infusion. Results from repeat test prior to the start date and time of the first IMP infusion will be considered.

For COMPASS-31, the assessment at the Screening visit will be used as baseline value (for total as well as for all domains). Therefore, if the assessment at the Screening visit is missing, COMPASS-31 will be considered missing.

If the time of assessment is after the time of the first IMP infusion, then this assessment is NOT considered baseline.

8.2.7. Change from Baseline or Reference Visit

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

change from baseline = visit value – baseline value.

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

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

8.2.8. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during data set creation). Unscheduled data will not be included in by-visit summaries but may contribute to the End of Study (EOS) value.

For data included in the summarizing analyses, data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

8.2.9. Actual Treatment

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

8.2.10. Body Mass Index (BMI)

BMI will be calculated using the following formula:

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

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

8.2.11. Patient-Reported-Outcome Assessments

All patient-reported outcomes (PRO) measurements will be performed at the time points specified in the Schedule of Activities and recommended to be administered BEFORE any other study activities unless otherwise specified. All assessments will be administered electronically unless otherwise specified. The mode of administration can be changed for exceptional circumstances after the consultation with the Sponsor. The scoring will be performed based on the scoring manual of each instrument below.

COMPASS-31

The COMPASS-31 is a self-reported questionnaire that measures autonomic symptoms related to six 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 subjects have severe autonomic dysfunction. The OI subscale was chosen as its own key secondary endpoint as OI symptoms were found to be most prominent to differentiate between POTS and other dysautonomias, covering the most burdensome and frequent symptoms reported by POTS subjects.

Table 5: COMPASS-31

1. In the past 7 days, have you ever felt faint, dizzy, "goofy", or had difficulty thinking soon after standing up from a sitting or lying position?	Yes=1; No=0
2. When standing up, how frequently do you get these feelings or symptoms?	Rarely = 0 Occasionally = 1 Frequently = 2 Almost always = 3
3. How would you rate the severity of these feelings or symptoms?	Mild = 1 Moderate = 2 Severe = 3
4. In the past 7 days, have these feelings or symptoms that you have experienced:	Gotten much worse =3 Gotten somewhat worse = 2 Staying about the same = 1 Gotten somewhat better = 0 Gotten much better = 0 Completely gone = 0
Total Orthostatic Intolerance score	Sum(Q1 – Q4) *4
5. In the past 7 days, have you ever noticed color changes in your skin, such as red, white, or purple? (If you answer no, please skip to question 8)	Yes=1; No=0
6. What parts of your body are affected by these color changes?	Hands = 1 Feet = 1 Hands and Feet = 2
7. Have these changes in your skin color:	Getting much worse =3 Getting somewhat worse = 2 Staying about the same = 1 Getting somewhat better = 0 Getting much better = 0 Completely gone = 0
Total Vasomotor score	Sum(Q5 – Q7) *0.83333333
8. In the past 7 days, what changes, if any, have occurred in your general body sweating?	I sweat much more than I used to = 1 I sweat somewhat more than I used to = 0 I haven't noticed any changes in my sweating = 0 I sweat somewhat less than I used to = 1 I sweat much less than I used to = 2
9. Do your eyes feel excessively dry?	Yes=1; No=0
10. Does your mouth feel excessively dry?	Yes=1; No=0
11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, has this symptom:	Getting much worse =3 Getting somewhat worse = 2 Staying about the same = 1 Getting somewhat better = 0 Getting much better = 0 Completely gone = 0 I have not had any of these symptoms = 0
Total Secretomotor score	Sum(Q8 – Q11) *2.1428571

12. In the past 7 days, have you noticed any changes in how quickly you get full when eating a meal?	I get full a lot more quickly now than I used to = 2 I get full more quickly now than I used to = 1 I haven't noticed any change = 0 I get full less quickly now than I used to = 0 I get full a lot less quickly now than I used to = 0
13. In the past 7 days, have you felt excessively full or persistently full (bloated feeling) after a meal?	Never = 0 Sometimes = 1 A lot of the time = 2
14. In the past 7 days, have you vomited after a meal?	Never = 0 Sometimes = 1 A lot of the time = 2
15. In the past 7 days, have you had a cramping or colicky abdominal pain?	Never = 0 Sometimes = 1 A lot of the time = 2
16. In the past 7 days, have you had any bouts of diarrhea? (If you answer no, please skip to question 20)	Yes=1; No=0
17. How frequently does this occur?	Rarely = 0 Occasionally = 1 Frequently = 2 Almost always = 3
18. How severe are these bouts of diarrhea?	Mild = 1 Moderate = 2 Severe = 3
19. Have your bouts of diarrhea gotten:	Much worse =3 Somewhat worse = 2 Stayed about the same = 1 Somewhat better = 0 Much better = 0 Completely gone = 0
20. In the past 7 days, have you been constipated? (If you answer no, please skip to question 24)	Yes=1; No=0
21. How frequently are you constipated?	Rarely = 0 Occasionally = 1 Frequently = 2 Almost always = 3
22. How severe are these episodes of constipation?	Mild = 1 Moderate = 2 Severe = 3
23. Has your constipation gotten:	Much worse =3 Somewhat worse = 2 Staying about the same = 1 Somewhat better = 0 Much better = 0 Completely gone = 0
Total Gastrointestinal score	Sum(Q12 – Q23) *0.8928571
24. In the past 7 days, have you ever lost control of your bladder function?	Never = 0 Occasionally = 1 Frequently = 2 Constantly = 3
25. In the past 7 days, have you had difficulty passing urine?	Never = 0 Occasionally = 1 Frequently = 2 Constantly = 3

26. In the past 7 days, have you had trouble completely emptying your bladder?	Never = 0 Occasionally = 1 Frequently = 2 Constantly = 3
Total Bladder score	Sum(Q24 – Q26) *1.1111111
27. In the past 7 days, without sunglasses or tinted glasses, has bright light bothered your eyes? (If you mark never, please skip to question 29)	Never = 0 Occasionally = 1 Frequently = 2 Constantly = 3
28. How severe is this sensitivity to bright light?	Mild = 1 Moderate = 2 Severe = 3
29. In the past 7 days, have you had trouble focusing your eyes? (If you mark never, please skip to question 31)	Never = 0 Occasionally = 1 Frequently = 2 Constantly = 3
30. How severe is this focusing problem?	Mild = 1 Moderate = 2 Severe = 3
31. Has the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) gotten:	Much worse =3 Somewhat worse = 2 Stayed about the same = 1 Somewhat better = 0 Much better = 0 Completely gone = 0 I have not had any of these symptoms = 0
Total Pupillomotor score	Sum(Q27 – Q31) *0.3333333
Total COMPASS-31 Score	Sum (Total Orthostatic Intolerance score, Total Vasomotor score, Total Secretomotor score, Total Gastrointestinal score, Total Bladder score, Total Pupillomotor score)

Malmö Symptom Score

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). The scores for each symptom are summed to give a total score, which ranges from 0 to 120.

Table 6: Malmö

1. Dizziness in upright position while standing up										
0	1	2	3	4	5	6	7	8	9	10
2. Dizziness, feeling you are going to faint										
0	1	2	3	4	5	6	7	8	9	10
3. Palpitations, high pulse, or feeling heart beating irregularly										
0	1	2	3	4	5	6	7	8	9	10
4. Difficult breathing/dyspnoea, both at effort and rest										
0	1	2	3	4	5	6	7	8	9	10
5. Chest pain										
0	1	2	3	4	5	6	7	8	9	10
6. Headache										
0	1	2	3	4	5	6	7	8	9	10
7. Concentration difficulties and/or problems with thinking										
0	1	2	3	4	5	6	7	8	9	10
8. Muscle pain										
0	1	2	3	4	5	6	7	8	9	10
9. Nausea										
0	1	2	3	4	5	6	7	8	9	10
10. Gastrointestinal problems										
0	1	2	3	4	5	6	7	8	9	10
11. Abnormal tiredness that persists after rest										
0	1	2	3	4	5	6	7	8	9	10
12. Insomnia										
0	1	2	3	4	5	6	7	8	9	10

Short Form – 12 Item (SF-12)

Data of the SF-12 will not be summarized but provided in the SDTM data sets.

Orthostatic Hypotension Questionnaire (OHQ)

The OHQ 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, items 1 to 6 in Table 7) and Orthostatic

Hypotension Daily Activity Scale (OHDAS) (4 items, items 7 to 10 in Table 7). Higher score indicates more severe symptoms. The instructions to the OHQ were 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.

The OHQ composite score is the sum of the scores from both the OHSA and OHDAS components, resulting in a total score that ranges from 0 to 100.

Table 7: OHQ

	1. Dizziness, lightheadedness, feeling faint, or feeling like you black out											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	3. Weakness											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	4. Fatigue											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	5. Trouble concentrating											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	6. Head and neck discomfort											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	7. Activities that require standing for a short time											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	8. Activities that require standing for a long time											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	9. Activities that require walking for a short time											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible
	10. Activities that require walking for a long time											
none	0	1	2	3	4	5	6	7	8	9	10	Worst possible

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

Data of EQ-5D-5L will not be summarized but provided in the SDTM data sets.

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

Data of WPAI:SHP will not be summarized but provided in the SDTM data sets.

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

Table 8: PGI-S and PGI-C

Patient Global Impression of Severity (overall) Considering all the ways POTS affects you, please choose the response below that best describes the severity of your overall symptoms over the past month	None Mild Moderate Severe Very Severe
Patient Global Impression of Change (overall) Considering all the ways POTS affects you, how would you rate the change in your overall symptoms since you started taking the study medication?	Much Improved A Little Bit Improved No change A Little Bit Worse Much Worse
Patient Global Impression of Severity (Orthostatic Intolerance) Please choose the response below that best describes the severity of your discomfort when you are in the upright position over the past month	None Mild Moderate Severe Very Severe
Patient Global Impression of Change (Orthostatic Intolerance) How would you rate the change in your ability to remain upright without experiencing discomfort since you started taking the study medication?	Much Improved A Little Bit Improved No change A Little Bit Worse Much Worse

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. Responses to PGI-S and PGI-C for OI symptoms will be summarized by treatment group.

PROMIS Cognitive Functioning Short Form 6a

Data of PROMIS Cognitive Functioning Short Form 6a will not be summarized but provided in the SDTM data sets.

8.2.12. Study Drug Exposure

Duration of exposure to study medication will be summarized by treatment groups for the Double-blind Treatment Period as well as for the Open-label Treatment Period.

8.3. Study Periods Relative to Treatment

Definitions of the start and end of the Double-blind and Open-label Treatment Periods and reference visits are presented in Table 9.

Table 9: Duration and Reference Visits for Double-blind Treatment Period and Open-label Treatment Period

Period	Start of period	Reference visit of period	End of period
For efficacy analysis:			
Week 1 – Week 25 (Week 1 – End of Double-blind Treatment Period)	Start date and time of the first IMP infusion	Baseline (before infusion of IMP)	Week 25 (before infusion of IMP)
Week 25 – Week 53[b] (Week 25 – End Open-label Treatment Period)	Start date and time of the first IMP infusion at Week 25	Baseline (before infusion of IMP)	Week 52
For safety analysis:			
Week 1 – Week 25 (Week 1 – End of Double-blind Treatment Period)	Start date and time of the first IMP infusion	Baseline (before infusion of IMP)	Week 25 (before infusion of IMP)
Week 25 – Week 57[b] (Week 25 – End of Open-label Treatment Period)	Start date and time of the first IMP infusion at Week 25	Baseline (before infusion of IMP)	Week 57
Week 1- End of Open-label Treatment Period	Start date and time of the first IMP infusion	Baseline (before infusion of IMP)	Week 57

8.3.1. Study Time Periods for Adverse Events

Adverse events (AEs) with onset date/ time after start of first infusion of IMP are TEAEs. Assessment whether an AE is considered treatment-emergent, will take place after imputation of partially missing dates (see Section 8.1.2).

The TEAE analysis will be done for both treatment periods. An AE will be counted for the analysis of a period if the onset of the event falls within the period. For the definition of start and end of the periods see Table 9.

8.3.2. Study Time Periods for Concomitant Medications

The following classification of concomitant medication related to start date and the end date of IMP will be applied. Each medication belongs to one of the following categories:

- Assign to ‘Prior’ if the medication end date is before the date of the first IMP infusion.
- Assign to ‘Concomitant in Double-blind Treatment Period’ if the medication start date is at or before start of first IMP infusion at Week 25 or the medication start date

is at or before the end of the last IMP infusion in the Double-blind Treatment Period AND the medication end date is at or after start of first IMP infusion at Week 1.

- Assign to 'Concomitant in Open-label Treatment Period' if the medication start date is at or before start of first IMP infusion at Week 53 or the medication start date is at or before the end of the last IMP infusion in the Open-label Treatment Period AND the medication end date is at or after start of first IMP infusion at Week 25.
- Assign to 'Post' if the medication start date is after the date of the last IMP infusion.

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

8.3.3. Study Time Periods for Medical History

Prior medical conditions are those which end before the start of first infusion of IMP. All other Medical History entries are Concomitant medical conditions, including those with missing end date.

8.4. Values of Potential Clinical Importance

Not applicable.

9. STUDY POPULATION

Unless otherwise stated, all tables and listings in this section will be based on the ITT analysis set, and all summaries and data listings will use treatment labels.

9.1. Disposition of Subjects

The following summaries will be provided by treatment group, treatment period and overall:

- Subjects in each of the analysis sets described in Section 6.
- Subject status, including:
  - subjects screened,
  - screen failures (including the reason),
  - subjects randomized,
  - completed IMP,
  - discontinued IMP (including the primary reason)
  - completed the study
  - withdrawals from the study (including the primary reason).

Reasons for study withdrawal and IMP discontinuation will be presented in the order they are displayed in the electronic Case Report Form (eCRF).

The following listing will be provided:

- Reasons for study withdrawal including the date of withdrawal.

9.2. Protocol Deviations

The following summaries will be provided by treatment group:

- All major protocol deviations during the Screening or Double-blind Treatment including inclusion and exclusion.

The following listing will be provided:

- All protocol deviations.

9.3. Demographic and Baseline Characteristics

All demographic and Baseline characteristics summaries will be based on the ITT analysis set. They will be presented in summary tables by treatment sequence. Continuous data will be summarized by descriptive statistics and categorical data will be summarized by frequency distributions. Age will be described as both a continuous and a discrete variable. By-subject listings will be provided for demographic and Baseline characteristic data.

The following summaries will be provided by treatment group and overall, for ITT analysis set:

- Demographic characteristics
  - Age (years)
  - Age group (18-19, > 19 years)
  - Sex
  - Ethnicity
  - Race and racial combinations
  - Body weight, baseline assessment (kg)
  - Height (cm)
  - BMI, baseline assessment (kg/m^2)
  - Prior IgG treatment (identified by ATC 3 = “IMMUNOGLOBULINS”)
- Disease characteristics at Screening

The following listings will be provided:

- Demographic characteristics
- Disease characteristics at Screening
- Medical history

9.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug Dictionary Enhanced (WHO-DDE) 2022/2023 or more recent version, and listed.

9.5. Non-Pharmacological Interventions and Physiotherapy

Non-pharmacological intervention data and physiotherapy will be provided in the SDTM data sets.

10. EFFICACY

This section describes the planned restricted analyses of efficacy endpoints after the premature discontinuation of the study. The analysis will be done on the ITT analysis set.

10.1. 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 of 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.

10.2. Primary Estimand and Analysis of Primary Efficacy Endpoint

10.2.1. Detail of Primary Estimand

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

The protocol-defined attributes of the primary estimand, as defined in the ICH E9(R1) guidance, are provided in Table 5 of the CSP. Due to the premature discontinuation of the study the

primary estimand cannot be assessed; only observed data are presented and all analyses are descriptive in nature (see Section 5).

10.2.2. Analysis of Primary 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 SBP [orthostatic hypotension]) will be assessed as the primary endpoint.

A subject is considered a responder if,

$$HRw_{25,10min} - HRw_{25,0min} < 30 \text{ bpm} \quad \textit{and}$$
$$SBPw_{25,as} - SBP_{W25,bs} > -20 \text{ mmHg}$$

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 heart rate measure (bpm) at start of the standing test at W25, $SBP_{W25,as}$ indicates the systolic blood pressure measure (mmHg) at any time point within 10 minutes after start of the standing test at W25, and $SBP_{W25,bs}$ indicates the systolic blood pressure measure at the start of the standing test at W25.

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

$$HRw_{25,10min} - HRw_{25,0min} \geq 30 \text{ bpm} \quad \textit{or}$$
$$SBPw_{25,as} - SBP_{W25,bs} \leq -20 \text{ mmHg}$$

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

Due to the premature termination of the study not all randomized subjects completed the Double-blind Treatment Period, thus the assessment of response at Week 25 is not always possible. For that reason, response will be assessed by visit based on the available data at each of the following visits, ie., Week 5, Week 9, Week 13, Week 17, Week 21 and Week 25. The multiple imputation strategies as planned in the study protocol for handling missing data will not be performed (see Section 5). For the following intercurrent events, the composite strategy will be applied, and the subject will be considered non-responder for all visits following the ICE:

Table 10: Definition of response for specific ICEs

Intercurrent Event	***Strategy***	***Description***	***Imputation details for response***
Treatment (IMP) discontinuation due to LoE, related adverse event or lack of compliance	Composite	Discontinuation due to lack of efficacy, related adverse event or lack of compliance will be treated as a failure.	For all visits following ICE: non-responder
Prohibited therapies	Composite	Data after the intake of prohibited medication with a potential effect on the primary endpoint will be treated as failure.	For all visits following ICE: non-responder
Death related to IMP or disease	Composite	Death will be considered as treatment failure.	For all visits following ICE: non-responder

All symptoms that have been collected during the standardized standing test will be listed.

10.2.3. Sensitivity and Supplementary Analyses of Primary Endpoint

Not applicable.

10.2.4. Subgroup Analyses of Primary Endpoint

Not applicable.

10.3. Key Secondary Estimand

According to the study protocol, the key secondary interest was to quantify the treatment effect of IgPro20 under the hypothetical situation where no subjects withdraw from treatment or the study before Week 25 with the key secondary estimand details provided in CSP Section 9.4.2.1.1. Due to the premature termination of the study not all randomized subjects completed the double-blind period, thus the assessment of the key secondary endpoints at Week 25 is not always possible. For that reason the key secondary endpoints as defined in Section 10.3.1 will be assessed based on the available data at each of the following visits: Week 5, Week 9, Week 13, Week 17, Week 21 and Week 25 and for each treatment group the respective descriptive statistics will be provided by visit. The multiple imputation strategies as planned in the study protocol for handling missing data will not be performed (see Section 5).

10.3.1. Analysis of Key Secondary Endpoints

The following key secondary efficacy endpoints are defined:

1. Change from baseline in OI score of COMPASS-31 at the end of the 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.

2. Change from baseline in TS score 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} / $TS_{baseline}$ correspond to the TS score of COMPASS-31 at Week 25 and baseline, respectively. Descriptive statistics of the individual changes will be calculated by treatment group.

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.

10.3.2. Sensitivity Analyses of Key Secondary Endpoints

Not applicable.

10.3.3. Subgroup Analyses of Key Secondary Endpoints

Not applicable.

10.4. Analysis of Secondary Efficacy Endpoint

Not applicable.

10.5. Multiplicity

Not applicable.

10.6. Multiple Imputation

The originally planned multiple imputation process will not be done due to the low sample size and the sparseness of the data (see Section 5).

10.7. Tipping Point Analysis

Not applicable.

10.8. Analysis of Exploratory Endpoints

The following exploratory endpoints will be summarized descriptively similarly to secondary efficacy endpoints. No comparison between treatment sequences will be done.

10.8.1. Analysis of Patient Reported Outcomes

Analysis of additional PROs will be restricted to the Malmö Symptom score and the OHQ score. The responses to each question will be summarized by assessment point and treatment group. The absolute mean changes from baseline in all total (if available) and domain (if available) scores assessments will be summarized. The following scores will be summarized for each assessment time:

- Change in Malmö Symptom score.

- Change from baseline in the 2 domains of the OHQ score and in the OHQ composite score.
- Responses to PGI-S and PGI-C for OI symptoms.

10.8.2. PK parameters

Not applicable.

11. SAFETY ANALYSES

All Safety analyses will be performed for the following period and analysis set:

- Double-blind treatment period: Week 1 – Week 25 by treatment groups (SAF)

11.1. Extent of Exposure

Exposure to the IMP will be descriptively summarized by treatment groups:

- Duration of exposure (days) per subject.
- Number of infusions (partial or complete) administered per subject.
- Number of days with infusions per subject.
- Total dose received (g) per subject.
- Total volume received (mL) per subject.

Extent of exposure will also be described for subjects treated with IgPro20 in any treatment period.

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

11.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 or higher. TEAEs are defined as AEs started after the start of the first infusion of IMP. All AEs regardless of when they were reported will be listed.

An AE will be counted in the respective analysis if the onset of the event falls within the period. For the definition of start and end of the periods see Table 9.

- An overview summary of TEAEs, including number of subjects, percentages of subjects, the number of events, including the following:
  - Any TEAE.
  - TEAEs related to IMP.
  - Temporally associated TEAEs (defined as an AE with an onset between the start of the IMP infusion and up to 72 hours after the end of IMP infusion).

- TEAEs leading to permanent discontinuation of IMP.
- TEAEs leading to withdrawal from study.
- TEAEs leading to IMP dose interruptions.
- Serious TEAEs.
- Serious TEAEs related to the IMP.
- Temporally associated serious TEAEs.
- Fatal serious TEAEs.

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

- TEAEs by System Organ Class (SOC) and Preferred Term (PT).
- TEAEs by SOC, PT, and maximum severity (presenting number and percentages of subjects).
- Causally related TEAEs by SOC and PT.
- Temporally associated TEAEs by SOC and PT.
- All AE summaries presented by SOC and preferred term will include a virtual SOC comprising of local reactions, ie, all AEs reported within the MedDRA High level terms “Administration site reactions NEC” or “Infusion site reactions” or “Injection site reactions”. Local reactions will be analyzed by using a virtual SOC called “local adverse events”.

All tables will be displayed in descending order of total incidence by preferred term and by SOC and PT, respectively.

Number of events are counted within the respective period and treatment group.

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

The following listings will be provided:

- All Adverse Events
- All serious TEAEs

11.3. Pregnancies

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE as described in the

protocol. If any subject becomes pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

11.4. Clinical Laboratory Evaluations

Results of laboratory tests will be provided in SDTM datasets.

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

11.5. Other Safety Measures

11.5.1. Vital Signs

Vital signs will be provided in SDTM datasets.

11.5.2. Electrocardiograms (ECG)

ECG data will be provided in SDTM datasets.

11.5.3. Physical Examination

Physical Exam data will be provided in SDTM datasets.

12. PHARMACOKINETIC ANALYSES

Serum samples for IgG level determination will be collected at Screening and at specified study visits. Only IgG trough levels were assessed in this study, due to the early termination of the study no subject had PK samples in Week 41.

12.1. Drug Concentration Measures

IgG concentrations will be listed for individual subjects and summarized by nominal (planned) time points.

12.2. Deriving and Summarizing Pharmacokinetic Parameters

Not applicable.

12.3. Pharmacokinetics Statistical Analyses

Not applicable.

13. REFERENCES

ICH E9. Statistical Principles in Clinical Trials. International Conference on Harmonization. 1998.

ICH E9 (R1). Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principals for Clinical Trials. International Conference on Harmonization. 2020.

Finucane C, van Wijnen VK, Fan CW, Soraghan C, Byrne L, Westerhof BE, et al. A practical guide to active stand testing and analysis using continuous beat-to-beat non-invasive blood pressure monitoring. Clinical Autonomic Research. 2019;29:427-441.

APPENDIX 1. FUTILITY INTERIM ANALYSIS BOUNDARY

Futility boundary	Placebo response rate	Active Response rate	N at interim	Interim Analysis information fraction	Boundary Crossing Probability	
					Futility und H0	Futility under H1
10%	30%	55%	27	15.0%	0.698	0.227
10%	30%	55%	36	20.0%	0.713	0.188
10%	30%	55%	45	25.0%	0.738	0.163
10%	30%	55%	54	30.0%	0.758	0.14
10%	30%	55%	93	52.6%	0.833	0.082
20%	30%	55%	27	15.0%	0.845	0.411
20%	30%	55%	36	20.0%	0.869	0.385
20%	30%	55%	45	25.0%	0.896	0.373
20%	30%	55%	54	30.0%	0.917	0.362
20%	30%	55%	93	52.6%	0.827	0.028
10%	30%	60%	27	15.0%	0.7	0.156
10%	30%	60%	36	20.0%	0.711	0.117
10%	30%	60%	45	25.0%	0.736	0.092
10%	***30%***	***60%***	***54***	***30.0%***	***0.758***	***0.074***
10%	30%	60%	63	35.0%	0.776	0.059
10%	30%	60%	72	40.0%	0.795	0.048
10%	30%	60%	93	52.6%	0.827	0.028
20%	30%	60%	27	15.0%	0.846	0.316
20%	30%	60%	36	20.0%	0.867	0.275
20%	30%	60%	45	25.0%	0.898	0.258
20%	30%	60%	54	30.0%	0.918	0.238

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IgPro20_3010 - Statistical Analysis Plan - 27Aug2025

Signed By:	Date (GMT):
PPD	02-Sep-2025 05:04:58
Approved-PPD Approval	
PPD	28-Aug-2025 13:14:15
Approved-PPD Approval	
PPD	28-Aug-2025 14:59:27
Approved-PPD Approval	

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