Statistical Analysis Plan

NCT Number: NCT02955355

Title: Long-Term Tolerability and Safety of Immune Globulin Infusion 10% (Human) With Recombinant Human Hyaluronidase (HYQVIA/HyQvia) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Study Number: 161505

Document Version and Date: Version 3.0, 13 October 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: 161505

Long-Term Tolerability and Safety of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Phase: IIIb

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Author: [redacted] **and** [redacted]

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REVISION HISTORY

Version	Date		Primary Rationale for Revision
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Final 1.0	2022-04-25	[redacted]	Minor updates to align with main study 161403.
Amendment 1	2022-05-23	[redacted]	Minor clarifications to variables. Main changes: • Clarification for derivation of date of relapse if subject has multiple increases in INCAT over time (Section 6.5) • Addition of AEs to exclude from local adverse event definition (Section 6.6.1) • Extension of windowing for assessments that occur every 24 weeks (Section 9.2.4) • Addition of formula for conversion of dose unit calculation (Section 9.2.14)
Amendment 2	2023-10-13	[redacted]	Minor clarifications. Main changes: • Clarification for which R-ODS scores (raw summed or centile) will be used for certain analysis (Section 6.5) • Clarification for defining infusions related to one or more AEs (Section 6.6.1) • Remove ECG analysis as not collected per protocol (Section 6.6.5) • Sections renumbered following removal of ECG (Section 6.6.5) • Clarification for defining binding anti-rHuPH20 antibodies and cross reactivity with Hyal-1, 2, and 4 (Section 6.6.6)

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ABBREVIATIONS

AE	adverse event
AR	adverse reaction
BL	Baseline
BMI	body mass index
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CSR	clinical study report
CTMS	Clinical Trial Management System
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EQ-5D-3L	EuroQOL 5-Dimension 3-Level
FDA	Food and Drug Administration
HRU	Healthcare Resources Utilization
IA	interim analysis
ICH	*International Council for Harmonisation* of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IGI	Immune Globulin Infusion (Human), 10% Solution
INCAT	Inflammatory Neuropathy Cause and Treatment disability score
IP	investigational product
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
OLE	open-label extension
PCS	potentially clinically significant
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PRO	patient-reported outcome
PT	Preferred Term (MedDRA)
R-ODS	Rasch-built Overall Disability Scale
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SD	standard deviation
SF-36	Short Form 36
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication, version 9
WHO	World Health Organization

1. OBJECTIVES, ENDPOINTS AND ESTIMANDS

This study is a Phase IIIb, open-label, multicenter study to assess the long-term safety, tolerability, and immunogenicity of HYQVIA/HyQvia (IGI, 10% with rHuPH20 administered subcutaneously) for maintenance therapy to prevent relapse. This study is an extension of Baxalta Clinical Study 161403, a Phase III Efficacy, Safety, and Tolerability Study of HYQVIA/HyQvia and GAMMAGARD LIQUID/KIOVIG in CIDP.

One interim analysis will be performed, based on an interim data cut-off to occur within 30 days after the last subject in Study 161403 had their last visit in Epoch 1. The interim analysis results will become part of the HyQvia regulatory registrations.

This document is the statistical analysis plan (SAP) for both the interim and final analyses of Study 161505. This SAP will be approved prior to unblinding Study 161403 Epoch 1.

1.1. Objectives

The purpose of this study is to assess the long-term safety, tolerability, and immunogenicity of the SC treatment with IGSC facilitated with rHuPH20 (HYQVIA/HyQvia) in subjects with CIDP who have completed Baxalta Clinical Study 161403 Epoch 1 without CIDP worsening.

1.1.1. Primary Objective

1. *To evaluate the long-term safety, tolerability, and immunogenicity of HYQVIA/HyQvia.*

1.1.2. Exploratory Objective(s)

1. *To assess the long-term effect of HYQVIA/HyQvia on clinical outcome measures, including prevention of relapse, change in functional ability, hand grip strength, and muscle strength.*
2. *To assess the long-term effect of HYQVIA/HyQvia on quality of life, health utility, health resource utilization (HRU), treatment satisfaction, treatment preference, and subject global impression of change.*
3. *To evaluate improvement in functional impact on everyday tasks as measured by a pre-specified subscore of R-ODS.*

1.2. Endpoints

1.2.1. Primary Outcome Measures

Safety/Tolerability

1. *Number (percentage) of subjects experiencing any treatment-emergent SAEs and/or AEs, regardless of causality*
2. *Number (percentage) of subjects experiencing causally related SAEs and/or AEs*
3. *Number (percentage) of subjects with serious and/or non-serious adverse reactions (ARs) plus suspected ARs*

4. *Rate of AEs that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other factors, expressed as number of events per infusion and per subject-year*
5. *Number (percentage) of treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality*
6. *Number (percentage) of causally related SAEs and/or AEs associated with infusions*
7. *Number (percentage) of AEs temporally associated with infusions (defined as AEs occurring during or within 72 hours after completion of an infusion)*
8. *Number (percentage) of serious and/or non-serious ARs plus suspected ARs associated with infusions*
9. *Number (percentage) of infusions associated with 1 or more systemic AEs*
10. *Number (percentage) of infusions associated with 1 or more local infusion site reactions*
11. *Number and proportion of infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs*
12. *Rates of systemic and local AEs, regardless of causality, expressed as number of events per infusion, per subject, and per subject-year*
13. *Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year*
14. *Rates of systemic and local ARs plus suspected ARs, expressed as number of events per infusion, per subject, and per subject-year*
15. *Number of subjects with an AE(s) that led to discontinuation from study*
16. *Number and rate per infusion of moderate or severe AEs that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other factors*
17. *Number (percentage) of subjects experiencing treatment-emergent local infusion site reactions. All local infusion site treatment-emergent AEs are to be reported as adverse reactions*
18. *Number (percentage) of subjects with treatment-emergent with local tolerability* events during the first 8 weeks of open-label Extension Study 161505 among subjects originally randomized to placebo (no ramp up), versus during the 8 week-ramp-up period for subjects originally randomized to HYQVIA in double-blind Study 161403. * Subjects for which infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.*
19. *Number (percentage) of subjects with local infusion reactions, as a function of dosing interval, infusion rate per site, and infusion volume per site*

20. *Number (percentage) of subjects whose anti-hyaluronidase antibody titers rise by ≥ 4-fold from the original baseline value from study 161403 using combined data from both studies (161403 and 161505).*

Immunogenicity

1. *Incidence of binding antibodies to rHuPH20*
2. *Incidence of neutralizing antibodies to rHuPH20*
3. *Number of subjects with a decline of anti-rHuPH20 antibody titers to the antibody titer level at baseline in Study 161403 and/or to <160 at the study completion or early discontinuation*
4. *For subjects who have >10,000 titer of binding antibodies to rHuPH20: neutralizing antibodies and cross reactivity with Hyal-1,2 and 4.*

1.2.2. Exploratory Outcome Measures

Efficacy

1. *Relapse rate (proportion of subjects who experience a worsening of functional disability defined as an increase of ≥1 point relative to baseline in 2 consecutive adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability scores).*
2. [redacted]
3. *Time to relapse*
4. *Change in Rasch-built Overall Disability Scale (R-ODS) score ≥ 4 points from baseline*
5. *Change in adjusted INCAT disability score from baseline*
6. *Percentage of subjects with change in hand grip strength score ≥ 8 kPa from baseline*
7. *Change in Medical Research Council (MRC) sum score from baseline*
8. *Change from baseline in functional impact on everyday tasks as measured by RODS sub-components*

Patient Reported Outcomes

1. *Short Form-36 (SF-36) scores and changes from baseline over various time periods.*
2. *EuroQoL (Quality of Life)-5 Dimensions (EQ-5D-3L) scores and changes from baseline over various time periods*

3. *HRU, including days off school/work, unscheduled physician visits, hospitalization, and emergency room visits, plus the total number of acute physician visits (office and emergency room due to CIDP exacerbation, any CIDP-related issue, any cause), over various time periods*
4. *Treatment satisfaction*
5. *Treatment preference*
6. *Subject global impression of change*

Other

1. *Trough serum IgG levels*

1.3. Estimands

The Estimand Framework is not applicable to this study. According to ICH E9(R1) "Estimands should be defined and explicitly specified in the clinical trial protocol". ICH E9(R1) came into effect on 30th July 2020 (step 5 of the ICH process) whereas the original protocol was finalized prior to this date (20th January 2016).

2. STUDY DESIGN

This study is a Phase IIIb, open-label, multicenter study to assess the long-term safety, tolerability, and immunogenicity of HYQVIA/HyQvia (IGI, 10% with rHuPH20 administered subcutaneously) for maintenance therapy to prevent relapse. This study is an extension of Baxalta Clinical Study 161403, a Phase III Efficacy, Safety, and Tolerability Study of HYQVIA/HyQvia and GAMMAGARD LIQUID/KIOVIG in CIDP.

Enrollment into this study is open to subjects who have completed Study 161403 Epoch 1 without CIDP worsening and who have provided informed consent. Enrollment may take place prior to or during the subject's study completion visit in Study 161403. The termination visit of Study 161403 is to serve as the baseline visit for the Extension Study. It is estimated that a maximum of 88 subjects will be eligible for study participation.

In this Extension Study, eligible subjects will receive HYQVIA/HyQvia in an open-label fashion until relapse or until predetermined study end for the specific country from which the subject is participating. Subjects will continue to receive the same dose and dosing regimen of HYQVIA/HyQvia in the Extension Study as the subject's full dose received in Epoch 1 of the Phase III Study 161403.

The study product components of HYQVIA/HyQvia will be administered sequentially. SC infusion of rHuPH20 solution at a dose of 80 U/g Immunoglobulin G (IgG) will be administered first, to be followed by SC infusion of IGI, 10% within 10 minutes of completion of the infusion of rHuPH20 solution.

After the first 12 weeks of treatment in the Extension Study, the dosing interval of HYQVIA/HyQvia may be adjusted for subject preference provided that it is safe to do so at the investigator's discretion. If medically necessary, the interval and/or dose may be changed at any time, at the investigator's discretion.

An interim analysis will be performed based on a data cut-off to occur within 30 days after the last subject in Study 161403 has its last visit in Epoch 1.

3. STATISTICAL HYPOTHESES AND DECISION RULES

3.1. Statistical Hypotheses

There are no statistical hypotheses to be tested and no planned statistical testing.

3.2. Statistical Decision Rules

Not applicable.

3.3. Multiplicity Adjustment

No multiplicity adjustment will be applied.

4. SAMPLE-SIZE DETERMINATION

This study is an extension to Study 161403. The purpose of this study is to assess the long-term safety, tolerability, and immunogenicity of HYQVIA in subjects with CIDP who have completed Study 161403 Epoch 1 without CIDP worsening. Enrollment in Study 161505 is open to subjects who have completed Study 161403 Epoch 1 without CIDP worsening and who have provided informed consent.

5. ANALYSIS SETS

Enrolled Set

The Enrolled Set will consist of all subjects who signed the informed consent.

Safety Analysis Set

The Safety analysis set will include all subjects who are enrolled in the Extension Study and who received at least one dose of study medication. This will be the primary analysis set for all analyses, unless otherwise specified.

Per-Protocol Analysis Set

Not applicable.

Pharmacokinetic Analysis Set

Not applicable. Pharmacokinetic (PK) analysis described in this SAP is limited to trough serum IgG levels only for which the Safety analysis set will be used (Section 6.7).

6. STATISTICAL ANALYSIS

6.1. General Considerations

The baseline value is the last available result prior to the first infusion for 505 and after the last infusion for 403, unless otherwise specified for an analysis.

For this extension study, the treatment cohorts are defined based on a combination of the treatments received in Study 161403 and Study 161505. Subjects who received HYQVIA/HyQvia in Study 161403 will be assigned to the "HyQvia - HyQvia" treatment cohort and subjects who received the Placebo with rHuPH20 in Study 161403 will be assigned to the "Placebo – HyQvia" treatment cohort.

Where applicable, descriptive statistics will be presented by treatment cohort and overall. Unless otherwise specified, summaries of continuous variables will display the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum, maximum. Means, medians and quartiles (if applicable) will be presented to 1 more decimal place than the recorded data. SDs will be presented to 2 more decimal places than the recorded data. Calculated data points (for example, BMI) will be rounded to 1 decimal place for reporting.

Summaries of categorical and count variables will display the following: number of subjects (n), percentage (%) of subjects in the category, and number of outcomes/events/occurrences. Where applicable, 'Missing' may be displayed as a category to represent missing data. Each summary containing a percentage will include a footnote stating the denominator that was used in calculating the percentage, unless the percentage is self-explanatory. Percentages will be displayed with 1 more significant digit than the raw (actual) data. No percentages will be displayed if the number of subjects is 0.

Missing data due to the COVID-19 pandemic will not be handled any differently than missing data for other reasons.

6.1.1. Analysis Approach for Continuous Variables

Generally, continuous endpoints will be summarized descriptively (no inferential statistical analysis) unless otherwise stated.

6.1.2. Analysis Approach for Binary Variables

Binary endpoints will be summarized descriptively.

6.1.3. Analysis Approach for Time-to-Event Variables

Median time to relapse will be presented for each treatment cohort and overall using the Kaplan-Meier method. Additionally, survival functions for each treatment cohort and overall will be estimated using Kaplan-Meier curves.

6.2. Disposition of Subjects

Disposition summaries will be presented by treatment cohort and overall and will include, but are not limited to, number and percentage of subjects in the categories listed below.

- Subjects from Study 161403 who enrolled in Study 161505
- Subjects who did not meet all selection criteria in Study 161505
- Dosed with IP (Safety analysis set)
- Completed study
- Discontinued study prematurely
- Discontinuations by primary reason for early discontinuation

The number of subjects by country and site will also be summarized by treatment cohort and overall for the Safety analysis set. Additionally, the following listings will be presented:

- Disposition (Enrolled Set)
- All subjects who prematurely discontinued the study will be listed for the Enrolled Set and the listing will include the primary reason for discontinuation. All AEs for subjects who prematurely discontinued will be presented.

As a further supplementary analysis, time to discontinuation will be presented graphically. Time to discontinuation/completion will be calculated as:

- Date of discontinuation/completion – date of initial dose of IP in Study 161505 + 1

Subjects who are ongoing in Study 161505 at the time of the data snapshot for the Interim Analysis will be counted as right-censored. The corresponding cumulative incidence (1-survival) function for each treatment cohort will be estimated using Kaplan-Meier curves, where the vertical axis will represent the cumulative risk of discontinuation and the number of subjects at-risk over time will be displayed.

Duration of enrolment and the number of dosed and completed subjects will be presented overall and by country and site.

6.2.1. Protocol Deviations

Protocol deviations will be recorded in the IQVIA Clinical Trial Management System (CTMS) and will be classified as critical, major or minor by the site staff, CRA and/or medical monitor. Such protocol deviations will be determined prior to data lock. Critical/major/minor protocol deviations will be summarized by site, treatment cohort and overall and category for the Safety analysis set. Protocol deviations will also be listed by subject and by site for the Safety analysis set. Deviation categories will be included as part of the CTMS protocol deviations log and may include any of the following categories:

- Informed consent
- Eligibility and entry criteria
- Concomitant medication criteria
- Laboratory assessment criteria
- Study procedures criteria
- Serious AE criteria
- Visit schedule criteria
- Investigational product compliance
- Administrative criteria
- Source document criteria
- Regulatory or ethics approval criteria
- Other criteria

6.2.2. COVID-19

A separate table and listing of protocol deviations related to the COVID-19 pandemic will be presented. Missing data due to the COVID-19 pandemic will not be handled any differently than missing data for other reasons.

6.3. Demographic and Other Baseline Characteristics

6.3.1. Demographics

Descriptive summaries of demographic and baseline characteristics will be presented by actual treatment cohort and overall for the Safety analysis set.

Demographic and baseline characteristics will include age (years), age group (≤55 years, >55 years), sex, race, and ethnicity. Characteristics at baseline will include height (cm), weight (kg) and body mass index (BMI; Underweight <18.5, Normal 18.5 to <25, Overweight 25 to <30, Obese ≥30; kg/m^2). INCAT disability score will also be included as a baseline characteristic.

6.3.2. Medical History and Concurrent Medical Conditions

Pre-existing diseases that are present before entry into the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

Any abnormal conditions that are detected during the physical examination at baseline will be described on the medical history CRF. Additionally, any ongoing TEAE that occurred during Study 161403 will be reported in the continuation study as medical history. If this specific ongoing AE becomes worse after the first infusion in the continuation study, this AE will be reported as a new TEAE.

Subject medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 18.1 or higher). The number of subjects with any relevant past and current medical conditions/diseases will be tabulated by MedDRA system organ class (SOC) and preferred term (PT), by treatment cohort and overall, for the Safety analysis set. A subject will only be counted once within a particular SOC (or PT) even if he/she has multiple conditions/diseases in the same SOC (or PT). Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending frequency in the overall column.

Listings of medical history will be provided using the Safety analysis set.

6.3.3. Baseline Characteristics

A descriptive summary of CIDP history at baseline will be presented by treatment cohort and overall. This summary will include time since first CIDP symptoms (years), time since CIDP diagnosis (years), subject age at first diagnosis of CIDP, dosing schedule (2, 3 or 4 weeks) and final dose (per kg of subject body weight) from 161403.

A listing of CIDP history will be presented using the Safety analysis set.

6.4. Medications, Non-Drug Therapies and Procedures

Medication history (e.g., use of steroid and/or immunomodulatory/immunosuppressive agents) and/or non-drug therapies (e.g., PE) related to the treatment of CIDP from 6 months (or 3 months for PE) prior to baseline throughout the study will be recorded on the appropriate CRF(s).

Prior and concomitant medications will be presented separately for the Safety analysis set. For data presentation purposes, prior and concomitant medications are defined as follows ('time' implies date and time):

Prior medication: Any medication which began **prior to** first dose of IP in Study 161505. Prior non-drug therapies and procedures are defined similarly.

Concomitant medication: Any medication which began **at or after** first dose of IP in Study 161505, OR medications which began **prior to** first dose of IP and continuing at or after first dose of IP. Concomitant non-drug therapies and procedures are defined similarly.

Note that medications with start time prior to time of IP administration and stop time after time of IP administration will be counted as both prior and concomitant medications.

For medications with partial onset times, non-missing date parts will be used to determine if the medication is a concomitant or prior medication. If a determination cannot be made using the non-missing date parts as to when the medication occurred relative to the date of IP administration, then the medication will be classified as a concomitant medication.

6.4.1. Prior Medications

Prior and concomitant medications, non-drug therapies and procedures will be summarized by treatment cohort and overall for the Safety analysis set. Medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version September 2015 or later. Procedures will be coded using MedDRA, version 18.1 or higher.

Listings of prior and concomitant medications, non-drug therapies and procedures will be presented using the Safety analysis set.

6.4.2. Concomitant Medications

Concomitant medications and non-drug therapies and procedures (simply referred to as concomitant medications) will be summarized by treatment and overall for the Safety Analysis Set. Concomitant medications where type is 'procedure' will be coded using MedDRA, version 18.1 or higher, and concomitant medications where type is not 'procedure' (i.e., concomitant medication and non-drug therapies) will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version September 2015 or later.

6.5. Efficacy Analysis

All analyses of efficacy outcome measures in this non-comparative study will be exploratory and will focus on estimation and descriptive statistics overall for all subjects in the Safety analysis set. Summaries will be presented by 161403 Epoch 1 actual treatment and overall, where applicable. There are no statistical hypotheses to be tested and no planned statistical testing.

1. *Relapse (defined as a worsening of functional disability defined as an increase of ≥1 adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability scores in 2 consecutive timepoints, relative to baseline).*

At any time during the treatment period, unscheduled visit(s) may take place for a subject whose CIDP is worsening to assess whether the subject has an increase in the adjusted INCAT disability score by ≥ 1 point relative to the baseline score. INCAT assessment will be repeated to confirm the subject's adjusted INCAT disability score has increased by ≥ 1 point relative to the baseline score. This confirmatory INCAT assessment can be performed as early as the same day of the first INCAT assessment and no later than prior to the next scheduled infusion and by the same rater. In case of multiple INCAT assessments over time for a subject, date of relapse is defined as the first occurrence of an increase in the adjusted INCAT disability score by ≥ 1 point relative to the baseline score when confirmed by an INCAT assessment as early as the same day of this INCAT assessment and no later than prior to the next scheduled infusion and by the same rater.

A sensitivity analysis will be performed to assess the robustness of estimated relapse rates relating to the requirement for a confirmatory INCAT assessment to be performed as early as the same day of the first INCAT assessment and no later than prior to the next scheduled infusion by using a stricter requirement for the confirmatory assessment. For this sensitivity analysis, the confirmatory INCAT assessment can be performed as early as the same day of the first INCAT assessment and no later than 7 days after the first INCAT evaluation.

An additional sensitivity analysis will be performed to assess the robustness of estimated relapse rates relating to the requirement for a confirmatory INCAT assessment. For this sensitivity analysis, relapse is alternatively defined as an increase in adjusted INCAT disability score by ≥ 1 point relative to the baseline score, on a single INCAT assessment. In case of multiple INCAT assessments over time for a subject, date of relapse is defined as the first occurrence of an increase in the adjusted INCAT disability score by ≥ 1 point relative to the baseline score. This sensitivity analysis removed the requirement for the increase by ≥ 1 point relative to the baseline score to be confirmed at a confirmatory INCAT evaluation in order to classify a subject as having relapsed.

Subject relapse rates will be characterized by 6-month and cumulative relapse rates at the end of each consecutive 6-month study period and at the end of the study. The statistics reported will include but are not limited to:

- number of subjects included in the analysis (by treatment cohort),
- number (%) of subjects included in the analysis who relapsed (by treatment cohort),
- two-sided 95% CIs for the estimated relapse rates (by treatment cohort).

CIs for relapse rates will be computed using the Wilson score method (Wilson, 1927).

Additionally, a listing of relapse status will be presented for the Safety analysis set.

No imputation will be performed as these are exploratory analyses. The definition of missing relapse outcome is provided in Section 9.2.3.

[redacted]

3. Time to relapse

Time to relapse is defined as the total time (in days) from the first dose of IP in Study 161505 to the date of relapse. For subjects who relapsed, time to relapse will be calculated as:

date of relapse – date of initial dose of IP in Study 161505 + 1.

Note: Date of relapse is as defined in relapse endpoint section above.

Subjects who did not relapse will be censored with time to censoring calculated as:

date of discontinuation/completion – date of initial dose of IP in Study 161505 + 1.

The statistics presented will include but are not limited to:

- number of subjects included in the analysis (by treatment cohort),
- number of subjects with event (by treatment cohort),
- number of subjects censored (by treatment cohort),
- percentiles (25th, 50th and 75th, if calculable) for the cumulative incidence (1-survival) function, estimated using the Kaplan-Meier method.

Additionally, the cumulative incidence (1-survival) function for each treatment cohort will be estimated using Kaplan-Meier curves, where the vertical axis will represent the cumulative risk of experiencing a relapse and the number of subjects at-risk over time will be displayed.

4. *Percentage of subjects with change from baseline in R-ODS ≥ 4 points*

The R-ODS score will be calculated following the rules defined by the developers of the instrument (van Nes et al., 2011). The change in raw and centile R-ODS from baseline to any post-infusion visit value will be calculated as the post-infusion value that is closest to the visit target day minus the baseline.

The statistics reported will include but are not limited to:

- number of subjects included in the analysis (by treatment cohort),
- number (%) of subjects included in the analysis who had change in raw R-ODS score by ≥ 4 points from baseline (by treatment cohort),
- two-sided 95% CIs for the estimated rates of ≥ 4 points decrease in raw R-ODS from baseline (by treatment cohort).

CIs for the estimated rates will be computed using the Wilson score method (Wilson, 1927).

Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) will be presented for centile R-ODS scores and change from baseline by visit, treatment cohort, and overall. Additionally, the estimated mean change from baseline and two-sided 95% CIs (by treatment cohort) will be reported.

A plot of mean change from baseline by treatment cohort and visit and a listing for centile R-ODS score and derived endpoints will also be presented for the Safety analysis set.

5. *Change from baseline in adjusted INCAT disability score*

Change from baseline in adjusted INCAT disability score will be summarized by visit, treatment cohort, and overall using descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum).

Plots of mean change from baseline in adjusted INCAT disability score by treatment cohort and timepoint will be presented, using the Safety analysis set. A listing for adjusted INCAT disability score will also be presented for the Safety analysis set.

6. *Percentage of subjects with change in maximum hand grip strength of the more affected hand by ≥ 8 kPa from baseline*

The within-hand change in hand grip strength from baseline to any post-infusion visit value will be calculated as the post-infusion value that is closest to the visit target day minus the baseline.

The statistics reported will include but are not limited to:

- number of subjects included in the analysis (by treatment cohort),
- number (%) of subjects included in the analysis who had change in maximum hand grip strength of the more affected hand by ≥ 8 kPa points from baseline (by treatment cohort),
- two-sided 95% CIs for the estimated rates of ≥ 8 kPa decrease in maximum hand grip strength of the more affected hand from baseline (by treatment cohort).

CIs for the estimated rates will be computed using the Wilson score method (Wilson, 1927).

Observed values and changes from baseline in maximum hand grip strength will also be summarized by visit, treatment cohort, and overall using descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum). Results will be presented separately for the more and less affected hand which will be determined at the baseline visit. For each hand, the maximum of three measurements on each hand will be used to determine the hand grip strength score at each visit.

Plots of mean change from baseline in hand grip strength by treatment cohort and visit will be presented, using the Safety analysis set. A listing for hand grip strength will also be presented for the Safety analysis set.

7. Change in Medical Research Council (MRC) Sum Score from Baseline

MRC sum score and change from baseline will be summarized by visit, treatment cohort, and overall using descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum).

Plots of mean change from baseline in MRC sum score by treatment cohort and visit will be presented, using the Safety analysis set. A listing for MRC sum score will also be presented for the Safety analysis set.

8. Change from baseline in RODS sub-components

The RODS overall and subcomponent scores and changes from baseline will be summarized by treatment cohort and timepoint, using the Safety analysis set. A plot of mean change from baseline in R-ODS overall score by treatment and timepoint will be presented for the safety analysis set. A listing for R-ODS score and derived endpoints will be presented for the safety analysis set.

9. Alternative R-ODS Score

An alternative scoring scheme for the standard R-ODS will be determined using the data collected in the 161403 study. This alternative scoring will be obtained after deletion of six items that were identified through protocol driven qualitative research following ISPOR guidelines (Walton et al., 2015) that included elicitation of the patient's experience and debriefing of the concepts included in the R-ODS. The results of this qualitative study will be documented prior to data lock. The six items identified as possibly not appropriate in this context of use were: "Reading a book", "Eating", "Going to the GP", "Doing the shopping", "Traveling by public transportation", and "Dancing". Supportive information on the measurement properties of this alternative scoring will be generated using blinded study data. These psychometric analyses will be specified in a separate PSAP. The scoring algorithm will be finalized and reported prior to data lock.

Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) will be presented for the alternative R-ODS score overall and change from baseline by treatment and timepoint. Missing values will not be imputed.

A plot of mean change from SC baseline in alternative R-ODS score overall and by treatment and timepoint will be presented for the safety analysis set. A listing for R-ODS score and derived endpoints, including the alternative R-ODS score, will be presented for the safety analysis set.

6.6. Safety Analysis

Safety outcome measures include adverse events, immunogenicity, clinical laboratory assessments and vital signs. All safety presentations will be based on the Safety analysis set. Continuous safety data (e.g., change from baseline in a lab parameter) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, maximum value.

Categorical safety data (e.g., occurrence of AE) will be summarized in terms of number and percentage of subjects in the category, and, where applicable, number of outcomes/events/occurrences in the category.

6.6.1. Adverse Events

All AE summaries will be presented overall and by treatment cohort. Safety outcome measures are presented in Section 1.2.1.

Any TEAE that is recorded by the investigator as "possibly related" or "probably related" to IP or if relationship is missing will be considered IP-related AE, and any AE recorded as "unlikely related" or "not related" will be considered unrelated AE. For AEs temporally associated with infusions (defined as AEs occurring during or within 72 h after completion of an infusion), a time period of 3 calendar days after IP administration (including the day of administration) will be used if time of IP administration or AE onset is unavailable. An AR/suspected AR is defined as an AE that is considered by the investigator to be possibly or probably related to IP administration, or for which the causality is indeterminate or missing, or that begins during infusion of IP or within 72 hours following the end of IP infusion. If the time of IP administration or AE onset is unavailable, then a time period of 3 calendar days after IP administration (including the day of administration) will be used. Any AE with the MedDRA High-Level Group Term (HLGT) = "Administration site reactions" will be considered a local AE. In addition, any AE with a preferred term (PT) not in the above HLGT that include the phrase "infusion site" or "injection site" will be considered a local AE. Any AE with PT that include the phrase "not at infusion site" or "not at injection site" will not be considered a local AE. In addition, any AE with PT that includes the phrase "vaccination" or "vaccine" will not be considered a local AE. All other AE's will be considered a systemic AE.

Infusions associated with one or more AEs are defined as follows: if an AE occurs after an infusion but prior to the next infusion that infusion is associated with that AE.

All AEs will be coded using MedDRA version 18.1 or higher and then reported by MedDRA SOC and PT, and overall.

Only TEAEs will be analyzed. Non-TEAEs will be listed only. Pre-treatment events (captured on the AE form that occurred prior to the first dose of investigational product) will be listed by

subject for all subjects who were treated with IP for the Safety analysis set. In addition, AEs of subjects who were never treated with IP will be listed for the Safety analysis set.

Note: TEAE and AE hereafter are used interchangeably.

The following summaries will be provided (no statistical hypothesis testing is planned):

- Number and percentage of subjects with TEAEs by SOC and PT, and overall
- Number of TEAEs: SOC and PT, and overall

The following approaches will be used, where applicable:

- Overall summary: Any TEAE, TEAE related to IP, severe TEAE, severe TEAE related to IP, serious TEAEs, serious TEAE related to IP, TEAE leading to discontinuation, and any TEAE leading to death.
- Summaries by SOC and PT: In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency in the Total column (i.e., the Total column will be sorted in descending order after the sorting by SOC and PT).
- Summaries by PT only: In the summaries, PT will be sorted in decreasing frequency in the table Total column.
- In AE incidence summaries, subjects with multiple events in the same category will be counted only once in the AE category. Subjects with events in more than one category will be counted once in each of the categories.
- In AE count summaries, multiple occurrences of the same AE will be counted multiple times.
- Note that, in addition to standard AE listings, the following subject data listing will be provided per regulatory request (FDA request, Item 6 in Preliminary Responses, dated 7 December 2018): Subjects who prematurely discontinued from the study, and all their treatment-emergent adverse events. The listing will be based on the Enrolled Set and display demographics, first and last dose dates (if known), withdrawal date, duration in study, primary reason for premature withdrawal, and adverse event data.

6.6.1.1. Descriptive Analysis of Adverse Events per Infusion, per Subject, per Subject-Year

The following summaries will be provided (no statistical hypothesis testing is planned):

- Number of AEs per infusion, by SOC and PT
- Number of AEs per subject, by SOC and PT
- Number of AEs per 1000 subject-years, by SOC and PT

AEs per subject-year summary adjusts for differences in subjects' durations in the study and differential dropout rates between treatment cohorts.

For number of AEs, multiple occurrences of the same AE in the same subject will be counted multiple times.

Number of AEs and AEs per 1000 subject-years (SYs) will be provided for all AEs (if analyzable), by primary SOC and PT for each treatment cohort and overall,

The following calculations apply, where applicable:

- AEs per infusion = number of AEs / total number of infusions administered to subjects in the analysis set
- AE per subject = number of AEs / total number of subjects in the analysis set
- AEs per subject-year (SY) = number of AEs / total number of days of exposure, i.e., the sum of duration of treatment for all subjects in the analysis set, converted into years.
- AEs per 1000 SYs = 1000 × (Total Number of AEs for all subjects in the treatment cohort / Total SYs in the treatment cohort).
- Total SYs will be calculated by summing subjects' durations in the study. Each subject's duration will be calculated as: (last date – date of initial dose of IP + 1) / 365.2425. If the subject's last date is missing, then the date of last dose of IP will be used if available.

6.6.2. Adverse Events of Special Interest

AEs of special interest will be reported by MedDRA PT, and overall. AEs of special interest include AEs that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other factors. Codes for uncoded terms, if any, will be assigned by the study Global Safety Lead and applied via statistical programming.

Descriptive analysis of AEs of special interest will be performed and limited to number and percentage of subjects with TEAEs, by treatment cohort, PT and overall.

Adverse events of special interest (Protocol Section 12.7.11) include:

- Allergic reactions
  - Urticaria
  - New-onset bronchospasm
  - Oedema of tongue, lips, face (angioedema)
  - Anaphylaxis
  - Stevens-Johnson syndrome
  - Erythema multiforme
  - Toxic epidermal necrolysis
- Immune complex mediated reactions – Local
  - Induration/nodule at the site of administration that persists for more than 48 hours
  - Excessive inflammation at the site of administration - severe redness, heat, swelling, and/or pain
  - Tissue necrosis/ulceration at the site of administration
  - Dystrophic or fibrotic changes at the site of administration
  - Pigmented skin changes at the site of drug administration

- Immune complex mediated reactions – Systemic
  - Arthritis
  - Vasculitis (purpuric rash)
  - Glomerulonephritis, as indicated by hematuria, red cell casts in urine, and/or progressive renal dysfunction
- Thrombotic and Embolic Events
  - Arterial
  - Venous
  - Vessel unspecified/unknown.

6.6.3. Clinical Laboratory Data

Clinical laboratory endpoints are not explicitly stated in the study protocol as endpoints but are included in this SAP for further assessment of the safety profile of HYQVIA. Raw (actual) clinical laboratory values (in SI units) and changes in raw values from baseline at each post-baseline assessment time point will be summarized as continuous variables. Shift-from-baseline to each assessment timepoint will be provided for categorical variables. Results will be presented by treatment cohort and overall. The following laboratory variables/parameters will be summarized, and the data will be listed in the subject data listings, as indicated.

Data Type	Description	Type of Analysis
Hematology	The hematology panel will consist of hemoglobin (HGB), hematocrit (HTC), erythrocytes (i.e., red blood cell [RBC] count), and leukocytes (i.e., white blood cell [WBC] count) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts, as well as absolute neutrophil count, and absolute lymphocyte account.	Summary and Listing
Clinical Chemistry	The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine, amylase, lipase, aldolase, and glucose.	Summary and Listing
Hemolytic Panel	The hemolytic panel includes hemoglobin [HGB], LDH, serum haptoglobin, plasma-free (unbound) HGB, serum direct anti-globulin (direct Coomb's) test, reticulocyte count, and urine hemosiderin.	Listing only

Data Type	Description	Type of Analysis
Hemoglobin A1C	Hemoglobin A1C is collected for subjects who have a known diagnosis of diabetes mellitus.	Listing only
Iron Panel	Serum iron, ferritin, and total iron binding capacity (TIBC) are included in the iron panel.	Listing only
Viral Serology	Serum samples may be collected for viral serology testing for HAV antibody, hepatitis B surface antigen (HBsAg), HCV antibody, and HIV-1/HIV-2 antibody. Additional tests, such as hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and/or nucleic acid tests, may be performed as considered necessary by the PI.	Listing only
Urinalysis	Color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocyte esterase will be recorded, and a microscopic examination will be done. Urinalysis should be completed before the first IP dose is given.	Listing only
Pregnancy Test	For female subjects of childbearing potential, a urine pregnancy test will be performed, unless a serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.	Listing only

Summaries of shift-from-baseline (shift tables) will be produced for each parameter that has a reference range, using the categories: low (below the lower limit of the reference range), normal (within the reference range), high (above the upper limit of the reference range), and missing. Missing data will not be imputed.

In addition, shift-from-baseline summaries will be produced by toxicity grade. Summaries will display number and percent of subjects whose laboratory values were assessed as Grade < 3, Grade 3, Grade 4, or Missing at baseline, and at the post-baseline maximum Grade.

Laboratory parameters will be summarized tabularly and/or graphically using boxplots or scatterplots as follows: boxplots of blood chemistry values by parameter, treatment cohort and visit; scatterplots of ALT, AST, and bilirubin post-baseline versus baseline comparisons to normal range limits by parameter, treatment cohort and visit; boxplots of hematology values by parameter, treatment cohort and visit.

The following will be provided in subject data listings.

- Listing of abnormal hematology results with investigator assessment of clinical significance
- Hematology values for subjects who met toxicity Grade ≥3 criteria for any hematology parameter

- Listing of abnormal blood chemistry results with investigator assessment of clinical significance
- Blood chemistry values for subjects who met toxicity Grade ≥3 criteria for any blood chemistry parameter
- Hemolytic parameters panel
- Hemolytic parameters panel for only the subjects who showed a reduction in Hgb level of 1 g/dL or more at any time after the first dose of IP.

6.6.4. Vital Signs

Vital signs endpoints are not explicitly mentioned in the study protocol as endpoints but are included in this SAP to further assess the safety of HYQVIA. Raw (actual) values for vital signs and their changes from baseline at each post-baseline assessment time point will be summarized by treatment cohort, overall and by visit. Vital signs will also be summarized graphically (boxplots).

A vital sign value will be considered potentially clinically significant (PCS) if it meets both the observed value criteria and the change from baseline criteria listed in Table 1. The number and percentage of subjects with PCS post-baseline values will be tabulated. Percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCS post-baseline vital sign value in the specified period.

Table 1 : Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Post-Baseline Value	Change from Baseline
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15
Pulse rate (beats per minute)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15
Weight (kg)	High	-	Increase of ≥7%
	Low	-	Decrease of ≥7%

[a] A post-baseline value is considered as a PCS value if its meets both criteria for observed value and change from baseline.

6.6.5. Physical Examination

Physical examination (PE) data will be listed in the subject listing only. Note that clinically significant, treatment-emergent changes in PEs will be recorded in the study database as AEs.

6.6.6. Anti-rHuPH20 Antibody Development

The immunogenicity outcome measures corresponding to the immunology safety objective include:

- Anti-rHuPH20 antibody titers, specifically subjects with:
  - A decline of anti-rHuPH20 antibody titers to the antibody titer level at baseline in Study 161403 and/or to <160 at the study completion or early discontinuation
  - A rise in anti-rHuPH20 antibody titers by ≥ 4-fold from the original baseline value in Study 161403
- Binding and/or neutralizing antibodies to rHuPH20, specifically subjects with:
  - Neutralizing antibodies,
  - Binding antibodies,
  - >10,000 titer of binding antibodies: neutralizing antibodies and cross reactivity with Hyal-1, 2 and 4

Antibody titers may be reported as direct titers (positive integers) or as the inverse of the amount of diluent that is required to abolish a positive test result. Higher direct antibody titer means more antibody is made, an unfavorable outcome.

Binding antibodies are defined as an anti-rHuPH20 antibody titer ≥ 160. Cross reactivity with Hyal-1, 2 and 4 is classified as positive if any one of the three values are positive and is classified as negative if all three values are negative.

Anti-rHuPH20 antibody development will be summarized (number and percentage by category: declined, neutralizing, binding) by treatment cohort and overall, and by visit.

Additionally, AEs experienced by each of the titer groups will be summarized:

- Subjects with any treatment emergent abnormal titer or rises above baseline in anti-rHuPH20 antibody titer
  - AEs before any abnormal or rise
  - AEs after any abnormal or rises

6.6.7. Extent of Exposure and Compliance

Exposure to IP and compliance will be summarized by treatment cohort and overall. Exposure to IP will be determined from infusion data, which will be collected in a hand-held device regardless of location (i.e., home, clinic, other) of infusion administration.

Descriptive summaries of exposure and compliance will include, but will not be limited to, the following:

- number of infusions including interrupted/stopped or rate reduced,
- number of infusions excluding interrupted/stopped or rate reduced,

- number of infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability,
- treatment duration (months, as defined below),
- infusion compliance (total number of administered infusions including completed, interrupted, and stopped infusions for each subject during the study divided by the number of expected infusions if subject completed the study, multiplied by 100),
- infusion compliance (total number of administered infusions including completed, interrupted, and stopped infusions for each subject during the study divided by the number of actual scheduled infusions, multiplied by 100),
- dosing compliance (the number of infusions within 10% of the planned dose divided by the total number of administered infusions, including completed, interrupted, and stopped infusions).

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) or number of subjects and percentage, as applicable, will be presented by dose, dosing regimen, treatment cohort and overall.

Exposure is defined as the total duration of treatment with IP (in days), calculated as:

Date of last dose of IP – date of initial dose of IP + 1.

Treatment duration will be summarized both as a continuous variable and using the following categories

- <6 months
- 6 - <12 months
- 12 - <18 months
- 18 - <24 months
- ≥6 months
- ≥12 months
- ≥18 months
- ≥24 months

Listings of investigational product exposure and compliance will be provided using the Safety analysis set. A listing of Investigational Product Accountability will also be provided.

6.7. Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

Analyses for trough serum IgG are described in Section 6.9. Additional PK/PD analysis is outside the scope of this SAP, and will be described in a separate analysis plan, if deemed necessary.

6.8. Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

1. Short Form-36 (SF-36) scores and changes from baseline over various time periods

The SF-36 scores will be computed according to the developer's scoring algorithm (Version 2, Ware et al., 2000). Scores and change from baseline will be summarized using descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) by visit, overall and treatment cohort for each of the following: the eight SF-36 domain scores (physical functioning, role limitations due to physical health, role limitations due to emotional problems, vitality, bodily pain, social functioning, mental health, and general health), the physical component score and the mental component score.

A listing for SF-36 score data will be presented for the Safety analysis set.

2. EQ-5D-3L scores and changes from baseline over various time periods

Scores and change from baseline will be summarized using descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) by visit, overall and treatment cohort for the following EQ-5D-3L (The EuroQol Group, 1990) variables:

- Individual EQ-5D-3L item scores,
- Visual analogue score for the subject's self-rated health.

Additionally, descriptive statistics (number and percentage of subjects within each category) will be presented at baseline and post-baseline visit for the number of subjects at each level of each EQ-5D-3L dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by treatment cohort and overall.

A listing for EQ-5D-3L score data will be presented for the Safety analysis set.

3. HRU (such as days off school/work, unscheduled physician visits, hospitalization, and emergency room visits) over various time periods

Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) for all HRU endpoints will be presented by visit, treatment cohort, relapse status and overall, i.e. for the following categories:

- Treatment cohort (irrespective of relapse status),
- Treatment cohort and relapsed,
- Treatment cohort and did not relapse,
- Relapsed (irrespective of treatment cohort),
- Did not relapse (irrespective of treatment cohort).

Descriptive summaries of HRU data for each of the above categories will include but are not limited to:

- Number of unscheduled doctor visits.

- Number of unscheduled doctor visits in subjects with at least one unscheduled doctor visit.
- Number of days off from school/work per subject.
- Number of days off from school/work per subject in subjects who have had at least one day off from school/work.
- Number of hospitalizations per subject.
- Number of hospitalizations per subject in subjects who have had at least one hospitalization.
- Number of hospitalizations related to CIDP per subject.
- Number of hospitalizations related to CIDP per subject in subjects who have had at least one hospitalization related to CIDP.
- Number of ER visits per subject.
- Number of ER visits per subject in subjects who have had at least one ER visit.
- Number of ER visits related to CIDP per subject.
- Number of ER visits related to CIDP per subject in subjects who have had at least one ER visit related to CIDP.
- Number of ER visits lasting longer than 24 hours per subject.
- Number of ER visits lasting longer than 24 hours per subject in subjects who have had at least one ER visit lasting longer than 24 hours.
- Number of ER visits lasting longer than 24 hours related to CIDP per subject.
- Number of ER visits lasting longer than 24 hours related to CIDP per subject in subjects who have had at least one ER visit related to CIDP.

A listing for HRU data will be presented for the Safety analysis set.

4. Treatment satisfaction.

Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum for continuous items and number of subjects and percentage for categorical items) will be presented for baseline and post-baseline visits in overall treatment satisfaction score, as measured by the Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9), domains (Effectiveness, Convenience, Global Satisfaction) and individual items, and will be presented overall and by treatment cohort.

A listing for TSQM-9 data will be presented for the Safety analysis set.

5. Treatment preference

The number and percentage of subjects responding to each category for each of the treatment preference items will presented for baseline and the last non-missing post-baseline outcome overall and by treatment cohort.

A listing of the treatment preference data will be presented for the Safety analysis set.

6. PGIC

The number and percentage of subjects at each level of the patient global impression of change (PGIC) will be presented for each visit, overall and by treatment cohort. A listing for PGIC data will be presented for the Safety analysis set.

6.9. Other Analyses

1. Trough serum concentrations of IgG

Analyses of serum trough concentrations of IgG will include subjects in the Safety analysis set. Serum trough concentrations of IgG will be summarized overall and by treatment cohort and visit using descriptive statistics (n, mean, SD, median, minimum, maximum, geometric mean, SD of the geometric mean).

In addition, the relationship between serum IgG trough levels after day 120 or at the time of CIDP symptom relapse and relapse status (relapse, no relapse) will be assessed as an exploratory analysis. Serum trough concentrations of IgG will be summarized by treatment and relapse status and overall using descriptive statistics (n, mean, SD, median, minimum, maximum, geometric mean, SD of the geometric mean).

A listing of serum trough concentrations of IgG will be presented for the Safety analysis set.

6.10. Interim Analyses

An interim analysis will be performed based on an interim data cut-off to occur within 30 days after the last subject in Study 161403 had its last visit in Epoch 1.

Data to be analyzed descriptively will include but may not be limited to:

- Number and percentage of subjects with a relapse, and annual rate of relapse.
- Time to relapse
- Percentage of subjects with change in R-ODS score by ≥ 4 points from baseline
- Change in adjusted INCAT disability score from baseline
- Percentage of subjects with change in hand grip strength score by ≥ 8 kPa from baseline
- Change in MRC sum score from baseline
- Treatment-emergent serious and non-serious AEs
- Treatment-Emergent Adverse Events That Occurred During or Within 72 Hours Post-Infusion, Per Infusion, Subject, and Subject-Year, by System Organ Class and Preferred Term
- Rates of systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year

- Infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs, for both local and systemic AEs
- Anti-rHuPH20 binding and neutralizing antibody titers
- Any relevant information that may support safety evaluation

Key data are expected to be clean for these analyses. A data cutoff date and reporting timeline will be established by the study team for the unblinding of Study 161403.

An agreed list of the planned outputs will be provided with the mock shells document. Safety data will be summarized descriptively by treatment cohort and overall for the Safety analysis set.

The data for all interim analyses conducted prior to unblinding Study 161403 (Epoch 1) will be analyzed by a separate unblinded statistical team which is located at a different geographical site than the main study team. The unblinded statistical team will not be involved with study conduct or data cleaning decisions. The main study team will not become unblinded to subject treatment due to any interim analysis that is conducted prior to the Study 161403 (Epoch 1) database lock.

6.11. Data Monitoring Committee/Internal Review Committee/Other Data Review Committees

An independent, external DMC has been tasked with monitoring subject safety and identifying any safety or medical concerns in Study 161403 and Extension Study 161505. Details are provided in the Study 161505 protocol. Procedural information is provided in the DMC Charter. It is anticipated that DMC data review meetings will be scheduled via teleconference approximately biannually (approximately every 6 months) during study conduct.

The two studies are monitored jointly. Ideally, Study 161403 and Study 161505 data will be reviewed concurrently (+/-3 days if needed). The meeting dates will be driven by the Study 161403 requirements. Study data will be presented to the DMC in tables, figures, and listings. The DMC will review the materials and recommend one of the following actions to the study sponsor:

- Study may continue without modifications
- Study may continue with modifications
- Study should be paused pending resolution of a specific issue
- Study should be stopped
- More data are required for review, or other changes.

7. REFERENCES

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8. CHANGES TO PROTOCOL PLANNED ANALYSES

- An Enrolled Subjects set was added to support the disposition table.
- Further clarification was added regarding the calculation and presentation of grip strength results: 1) presented for both the more affected and the less affected hand at baseline, 2) the maximum of three measurements is to be used to determine hand -grip strength at each timepoint.
- Analyses of the rise in anti-rHuPH20 antibody titers by ≥ 4-fold from the original baseline value in Study 161403 was added to support the immunology safety objective.
- Two sensitivity analyses were added to the exploratory efficacy endpoint: Relapse, to assess the robustness of the estimated relapse rates and to align with study 161403.

9. APPENDIX

9.1. Changes from the Previous Version of the SAP

There are no changes made from the previous version of the SAP that have a **material impact to the planned statistical analysis methods.** Clarifications to variable definitions are described in the revision history table.

9.2. Data Handling Conventions

9.2.1. General Data Reporting Conventions

Datasets will be constructed using the IQVIA implementation of CDISC standards, based on the SDTM IG v3.2 and the ADaM IG v1.1.

TFLs will follow Takeda or Shire standards, where applicable, except that footnotes will be printed at the bottom of every output page. IQVIA SOPs and work instructions will apply to all statistical programming, unless otherwise specified in this SAP or the corresponding TFL shells document. Listings will be sorted by study site, and subject identification number, unless otherwise specified. Both derived and non-derived data, if available, will be displayed in listings.

9.2.2. Definition of Baseline

In general, the Baseline visit will be the End of Study Visit in Study 161403. If no value is available from the Baseline visit, then the most recent non-missing measurement prior to the first dose of investigational product in Study 161505 and after the last dose of investigational product in Study 161403 will be used. Events collected on the administration day are not considered as baseline.

9.2.3. Definition of Missing Relapse Outcome

For the exploratory analysis of relapse, missing relapse outcome is defined as:

- Missing Baseline INCAT assessment, or
- No post-baseline INCAT assessments, or
- Missing confirmatory INCAT in the presence of an abnormal INCAT (≥ 1 point relative to baseline).

9.2.4. Definition of Visit Windows

For statistical analysis purposes, all efficacy-like and PRO assessments will be assigned to an analysis visit window. Unless otherwise specified for an analysis, the following will apply:

- Assessments will be assigned based on the date the assessment was performed regardless of the completed CRF page.
- Study day will be calculated as: date of assessment – date of first dose + 1
- If two or more assessments fall within the same visit window, then the assessment that is closest to the target study day will be used for analysis. If two or more assessments are

equidistant from a planned target study day, then the most recent assessment will be used for analysis.

- If there is no assessment within a visit window, then the assessment for that planned study visit will be a considered as missing.
- If two or more assessments fall on the same day and which coincides with an infusion visit, then the assessments performed closest to the start of infusion will be used for analysis (prior to the start of infusion for Baseline).

Analysis visit windows are presented for:

- Infusion data (Table 2)
- Efficacy and PRO assessments (Table 3)

Table 2: Analysis Visit Windows for Infusions in Subjects with Dosing every 2/3/4 Weeks

Infusion number	Target Day	Protocol-Accepted Start Day	Protocol-Accepted End Day	Analysis window start day	Analysis window end day	Other Assignment Criteria
2-week dosing frequency						
1	1	1	3	1	8	Exception [a]
2	15 (+/-3)	12 to 18	12 to 18	9	22	
3	29 (+/-3)	26 to 32	26 to 32	23	36	
4	43 (+/-3)	40 to 46	40 to 46	37	50	
<etc>	<etc>	<etc>	<etc>	Earliest accepted start -3 days	Latest accepted end +4 days	
3-week dosing frequency						
1	1 (+/-3)	1	3	1	11	Exception [a]
2	22 (+/-3)	19 to 25	19 to 25	12	32	
3	43 (+/-3)	40 to 46	40 to 46	33	55	
4	64 (+/-3)	61 to 67	61 to 67	54	74	
<etc>	<etc>	<etc>	<etc>	Earliest accepted start -7 days	Latest accepted end +7 days	
4-week dosing frequency						
1	1	1	3	1	15	Exception [a]
2	29	26 to 32	26 to 32	16	43	
3	57	54 to 60	54 to 60	44	71	
4	85	82 to 88	82 to 88	72	99	
<etc>				Earliest accepted start -10 days	Latest accepted end +11 days	

- [a] The first dosing window is an exception to the general rule described for each actual dosing frequency.

Table 3: Analysis Visit Windows for PRO Assessments in Subjects with Dosing every 2/3/4 Weeks

Analysis Visit	Relative Target Day	Relative Start Day	Relative End Day	Other Assignment Criteria
INCAT / Hand Grip Strength / MRC Sum Score / R-ODS				
BASELINE (2W/3W/4W)	-14	-14	1	If relative day is missing and collected visit indicates BASELINE
OL WEEK 12	85 (+/-3)	2	88	If relative day is missing and collected visit indicates 0 < week number ≤ 12
OL WEEK 24	169 (+/-3)	89	172	If relative day is missing and collected visit indicates 12 < week number ≤ 24
OL WEEK 36	253 (+/-3)	173	256	If relative day is missing and collected visit indicates 24 < week number ≤ 36
OL WEEK 48	337 (+/-3)	257	340	If relative day is missing and collected visit indicates 36 < week number ≤ 48
OL WEEK 60	421 (+/-3)	341	424	If relative day is missing and collected visit indicates 48 < week number ≤ 60
OL WEEK 72	505 (+/-3)	425	508	If relative day is missing and collected visit indicates 60 < week number ≤ 72
OL WEEK 84	589 (+/-3)	509	592	If relative day is missing and collected visit indicates 72 < week number ≤ 84
OL WEEK 96	673 (+/-3)	593	676	If relative day is missing and collected visit indicates 84 < week number ≤ 96
OL WEEK xx (every 12 weeks)	(xx*7)+1 (+/-3)	(xx*7)-79	(xx*7)+4	If relative day is missing and collected visit indicates 96 < week number ≤ xx
SF-36, EQ-5D-3L, Treatment Satisfaction, Treatment Preference				
BASELINE	-14	-14	1	If relative day is missing and collected visit indicates BASELINE
OL WEEK 24	169 (+/-3)	2	172	If relative day is missing and collected visit indicates 0 < week number ≤ 24
OL WEEK 48	337 (+/-3)	173	340	If relative day is missing and collected visit indicates 24 < week number ≤ 48
OL WEEK 72	505 (+/-3)	341	508	If relative day is missing and collected visit indicates 48 < week number ≤ 72
OL WEEK 96	673 (+/-3)	509	676	If relative day is missing and collected visit indicates 72 < week number ≤ 96
OL WEEK xx (every 24 weeks)	(xx*7)+1 (+/-3)	(xx*7)-163	(xx*7)+4	If relative day is missing and collected visit indicates 96 < week number ≤ xx

9.2.5. Repeated or Unscheduled Assessments of Safety Parameters

If a subject has a repeated assessment before initial dose of IP, then the most recent assessment value prior to initial dose of IP will be used as baseline in analysis/summaries involving baseline.

If a subject has repeated assessments after initial dose of IP (repeated post-baseline assessments), then the most recent assessment value within an analysis visit window will be used in analysis/summaries involving post-baseline.

Unscheduled assessments (i.e., assessments not done at a planned visit) will be used only in summaries of abnormalities or toxicities (not otherwise).

All assessments, including repeated and unscheduled assessments, will be presented in the subject data listings.

9.2.6. Handling of Missing, Unused, and Spurious Data

This section provides a general plan for handling of missing data, unused and spurious data. Specific endpoint analysis sections provide handling details.

Data that appear to be spurious (e.g., outliers, incompatible with life) will be queried by Clinical Data Management and then either corrected or explained in the CSR if not correctable. Outliers will not be excluded from analysis unless otherwise specified. Any exclusion of data from analysis will be appropriately footnoted in the relevant output.

9.2.7. Missing Date of Investigational Product

If the date of the last dose of IP is missing for a subject in the Safety analysis set, then all efforts will be made by the study sponsor, or on behalf of the sponsor, to obtain the date from the study investigator. If the date cannot be obtained despite all efforts, then the last visit date when IP was dispensed will be used in the calculation of treatment duration. That is, if last dose date is missing, then last visit date will be used.

9.2.8. Missing Date Information for Prior or Concomitant Medications, Therapies, and Procedures, Medical History

For prior or concomitant medications (and/or therapies/procedures), incomplete (fully or partially missing) start date and/or stop date of medication will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first using the imputation approach described in the subsequent sections.

9.2.8.1. Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of IP, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of IP, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP, then the day of the date of the first dose of IP will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of IP, or if both years are the same but the month is before the month of the date of the first dose of IP, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of IP, or if both years are the same but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day.

9.2.8.2. Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of IP is missing, then replace it with the last visit date. If the imputed stop date is before the (imputed or non-imputed) start date, then the imputed stop date will be equal to the start date.

If imputation of an incomplete stop date is required for calculating duration, and both the start date and the stop date are incomplete for a subject, then the start date will be imputed first.

A completely missing stop date will be interpreted as ongoing.

Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of IP, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of IP, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP, then the day of the date of the last dose of IP will be assigned to the missing day.
- If the year is before the year of the date of the last dose of IP, or if both years are the same but the month is before the month of the date of the last dose of IP, then the last day of the month will be assigned to the missing day.
- If the year is after the year of the last dose of IP, or if both years are the same but the month is after the month of the date of the last dose of IP, then the first day of the month will be assigned to the missing day.

9.2.9. Missing Date Information for Adverse Events

The following approaches will be applied:

- To facilitate categorization of AEs as treatment emergent, imputation of dates can be used.
- If an AE start date is completely missing, then the AE will be considered treatment-emergent.
- For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to IP (eg, AE start year and month are the same as the year and month of the first dose of IP), then the AE will be classified as treatment-emergent.
- For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol.
- If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

9.2.9.1. Incomplete Start Date

Rules in Section 9.2.8.1 apply.

9.2.9.2. Incomplete Stop Date

Rules in Section 9.2.8.2 apply.

9.2.10. Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of IP, then a severity of "Severe" will be assigned.

If a subject experiences more than one AE categorized under the same preferred term, where one of them is categorized as "severe" and one of them is categorized as "unknown", then the severity of this AE will be counted as "severe".

If a subject experiences more than one AE categorized under the same preferred term, where one of them is categorized as "mild" or "moderate" and one of them is categorized as "unknown", then the severity of this AE will be counted as "unknown".

The imputed values for severity assessment will be used for summaries, while both the actual and the imputed values will be used in subject data listings.

9.2.11. Missing Seriousness of Adverse Events

AEs of unknown seriousness will be tabulated as SAEs in summaries; however, every effort will be made to avoid study data lock with AEs for which a determination of seriousness is missing.

9.2.12. Missing Relationship to Investigational Product for Adverse Events

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP, then a causality of "related" will be assigned. The imputed values for relationship to IP will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

9.2.13. Character Values of Clinical Laboratory Variables

Laboratory measurements will be presented in SI units, unless otherwise specified for an analysis. If a laboratory result is expected to have a numeric value, but the data which are received include a special character such as ">" or "<", then the result will be assumed to lie outside the range of quantitation.

Tables based on a dichotomous or categorical grouping, including but not limited to shift tables, will place such data appropriately prior to removal of the special character, so that particularly low or high values remain recognized as such. For quantitative summaries by time-point or visit, the numeric part of such a result will be used, unless the table is designed to include explicit tabulation of results that are outside the range of quantitation.

9.2.14. Conversion of Dose Units

If the infusion volume of either study drug is collected in g/kg of bodyweight, the following conversion to mL will be applied:

For IGI 10%:

1. Dose in g = (Dose in g/kg of bodyweight) * (subject weight in kg prior to infusion)
2. Round dose in g to nearest gram
3. Dose in mL = Dose in g * 10 mL/g

For rHuPH20:

1. Dose in g IG = (Dose in g/kg of bodyweight) * (subject weight in kg prior to infusion)
2. Round dose in g IG to nearest gram
3. Dose in mL = Dose in g IG * 0.5 mL/g [1]

[1]Note: standard rHuPh20 injection strength is 160 U/mL and rHuPH20 dose is 80 U/g IG = 0.5 mL/g

Subject weight is the latest available value prior to infusion.

9.3. Analysis Software

All statistical analyses will be performed using SAS® Version 9.4 or higher.

9.4. Study Flow Chart

Figure 1: Study Flow Chart for Study 161505