Statistical Analysis Plan

NCT Number: NCT02549170

Title: A Phase III Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Study Number: 161403

Document Version and Date: Statistical Analysis Plan Version 2.0, 25-APR-2022

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

Epoch 1 Final Analysis ('Formal Interim Analysis') and Epoch 2 Final Analysis

Study Number: 161403

A Phase III Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Phase: III

Version: 2.0

Date: 25-Apr-2022

Prepared by: [redacted]

Based on:

Protocol Version: Amendment 6

Protocol Date: 20-May-2021

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
0.2 Draft	[Not applicable]	Original draft version was based on Protocol Amendment 1 and, since protocol Amendment 6, randomization will be stopped earlier than originally planned.
0.3 Stable Draft	18-June-2021	Stable Draft
Final1.0	20-Oct-2021	Minor updates to include team comments following review of TLF shells. Main changes: • Epoch 1: Descriptive summaries for all planned timepoints by dosing regimen added for R-ODS (secondary endpoint), INCAT, hand-grip, MRC sum score, alternative R-ODS (tertiary endpoint). • Additional details relating to the determination of hand grip strength in Epoch 1 and Epoch 2.
Amendment 1	25-Apr-2022	Minor clarifications to variables. Main changes: • Edit Epoch 1 secondary endpoint: Proportion of Subjects who experience a worsening of CIDP to align with Protocol Section 8.4.1.2 (Section 1.2.1.2 and Section 6.5.1.2) • Add clarification for which Wilcoxon survival test used for Epoch 1 secondary endpoint: Time to Relapse (Section 6.5.1.2) • Minor editorial updates (numbering of Epoch 1 secondary efficacy endpoints 6.5.1.2) • Edit regression to the mean implication for Epoch 2 Primary Endpoint Exploratory analysis to indicate correct direction for adjusted INCAT for relapse in Epoch 1 and response in Epoch 2 (Section 6.5.2.1.3) • Add clarification for identifying local versus systemic Adverse events (Section 6.6.1) • Add Thrombotic/Embolic events to Adverse Events of Special Interest (AESI) (Section 6.6.2) • Add clarification of definition of Missing Relapse Outcome (Section 9.2.3) • Add clarification for R-ODS windowing timepoints for Epoch 1 (Section 9.2.4) • Add clarification for efficacy assessments coinciding with infusion visit (Section 9.2.4) • Edit Epoch 2 windowing timepoints for E2W25/EOE2T to align with Epoch 1 windowing timepoints for EOE1T (Section 9.2.4) • Add clarification for incomplete/missing date of medical history (Section 9.2.8)

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ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
BL	baseline
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
COVID-19	coronavirus disease 2019
CP	conditional power
CRA	clinical research associate
DA	demyelinating abnormalities
DMC	Data Monitoring Committee
EDX	electrodiagnostic
HLGT	High-Level Group Terms (MedDRA)
HR	hazard ratio
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
IVIG	intravenous immunoglobulin G
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intention-to-treat
MCAR	missing completely at random
MNAR	missing not at random
MMRM	mixed model for repeated measures
PRO	patient-reported outcome
PSAP	psychometric and statistical analysis plan
PK	pharmacokinetic
PT	Preferred Term (MedDRA)
R-ODS	Rasch-built Overall Disability Scale
REML	restricted maximum likelihood

rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SC	subcutaneous
SCIG	subcutaneous immune globulin
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

The study is a Phase III, prospective, multicenter study to evaluate the efficacy, safety, and tolerability of HYQVIA/HyQvia (IGI, 10% with rHuPH20 administered subcutaneously) for maintenance therapy to prevent relapse and GAMMAGARD LIQUID/KIOVIG (IGIV 10% administered intravenously) for the treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). This study will enroll adult subjects with a confirmed diagnosis of CIDP who have remained on a stable dosing regimen (monthly equivalent dose of 0.4 to 2.4 g/kg body weight (BW) with a dosing interval of 2 to 6 weeks) of IV immunoglobulin G (IGIV) therapy for at least 12 weeks prior to screening.

Two interim analyses are planned (Section 6.10):

- Interim Safety Analysis, which is Epoch 1 and Epoch 2 safety analysis,
- Formal Interim Analysis, which is the final analysis of Epoch 1 data.

This document is the statistical analysis plan (SAP) for both the Epoch 1 final analysis (Formal Interim Analysis) and Epoch 2 final analysis and is planned to be approved before data lock and unblinding of Epoch 1. The statistical analyses for the Interim Safety Analysis are described in a separate SAP and have already been executed as of the writing of the current document. The development methods for an alternative targeted subscale for the Rasch-built Overall Disability Scale (R-ODS), which measures impact on ability to complete everyday tasks, will be described in a psychometric and statistical analysis plan (PSAP). This R-ODS targeted subscale is an Epoch 1 tertiary endpoint and comparative analyses based on this endpoint are described in this SAP.

1.1 Objectives

1.1.1 Epoch 1

Primary Objective

1. *To evaluate the efficacy of HYQVIA/HyQvia as a maintenance therapy for CIDP to prevent relapse of neuromuscular disability and impairment.*

Secondary Objectives

1. *To assess the time to CIDP relapse during maintenance therapy with HYQVIA/HyQvia, compared to placebo.*
2. *To assess the effect of HYQVIA/HyQvia on activities of daily living (ADL).*
3. *To assess the safety and tolerability of HYQVIA/HyQvia.*

4. *To monitor for the presence of binding and neutralizing anti-rHuPH20 antibodies following HYQVIA/HyQvia administration.*

Tertiary Objectives

1. *To evaluate the effects of HYQVIA/HyQvia on additional clinical outcome measures, including change in functional ability, hand grip strength, and muscle strength.*
2. *To evaluate improvement in functional impact on everyday tasks as measured by a pre-specified subscore of R-ODS*
3. *To assess the effect of HYQVIA/HyQvia on quality of life, health utility, health resource utilization (HRU), treatment satisfaction, treatment preference, and patient global impression of change (PGIC).*
4. *To assess the effect of HYQVIA/HyQvia on the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.*

1.1.2 Epoch 2

Primary Objective

1. *To evaluate the efficacy of GAMMAGARD LIQUID/KIOVIG for the treatment of CIDP to improve neuromuscular disability and impairment.*

Secondary Objectives

1. *To assess the safety and tolerability of GAMMAGARD LIQUID/KIOVIG.*
2. *To assess the effect of GAMMAGARD LIQUID/KIOVIG on ADL.*

Tertiary Objectives

1. *To assess the time to improvement during GAMMAGARD LIQUID/KIOVIG treatment.*
2. *To evaluate the effects of GAMMAGARD LIQUID/KIOVIG on additional clinical outcome measures, including change in functional ability, ADL, hand grip strength, and muscle strength in subjects with CIDP.*
3. *To assess the effect of GAMMAGARD LIQUID/KIOVIG on quality of life, health utility, HRU, treatment satisfaction, treatment preference, and patient global impression of change.*
4. *To assess the effect of GAMMAGARD LIQUID/KIOVIG on the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.*

1.2 Endpoints

1.2.1 Epoch 1

1.2.1.1 Primary Endpoint

1. *Relapse rate (proportion of subjects who experience a worsening of functional disability defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores)*

1.2.1.2 Secondary Endpoints

Efficacy

1. *Proportion of subjects who experience a worsening of functional disability defined as one or more of the following: an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores; who experience CIDP worsening (defined as a ≥8 kPa decrease in the hand grip strength in the more affected hand); ≥4 points decrease in R-ODS relative to the pre-SC treatment baseline score(at the time of withdrawal from the SC treatment period)*
2. *Time to relapse*
3. *Change from pre-SC treatment baseline in R-ODS*

Safety

1. *Number (percentage) of subjects experiencing any treatment-emergent serious and/or nonserious adverse events (SAEs and/or AEs, respectively), regardless of causality*
2. *Number (percentage) of subjects experiencing causally related SAEs and/or AEs*
3. *Number (percentage) of subjects with serious and/or nonserious adverse reactions (ARs) plus suspected ARs*
4. *Number (percentage) with treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality*
5. *Number (percentage) of causally related SAEs and/or AEs associated with infusions*
6. *Number (percentage) of AEs temporally associated with infusions (defined as AEs occurring during or within 72 h after completion of an infusion)*
7. *Number (percentage) of serious and/or nonserious ARs plus suspected ARs associated with infusions*
8. *Number (percentage) of treatment-emergent systemic AEs associated with infusions*

9. *Number (percentage) of treatment-emergent local infusion site reactions associated with infusions*
10. *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*
11. *Rates of systemic and local AEs, regardless of causality, expressed as number of events per infusion, per subject, and per subject-year*
12. *Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year*
13. *Rates of systemic and local ARs plus suspected ARs, expressed as number of events per infusion, per subject, and per subject-year*
14. *Number of subjects who have developed binding and/or neutralizing antibodies to rHuPH20*

Note: Adverse events in this section refer to treatment-emergent AEs, if not specified.

1.2.1.3 Tertiary Endpoints

Efficacy

1. *Change from pre-SC treatment baseline in adjusted INCAT disability score*
2. *Change from pre-SC treatment baseline in hand grip strength score*
3. *Change from pre-SC treatment baseline in functional impact on everyday tasks as measured by R-ODS sub-components*
4. *Change from pre-SC treatment baseline in MRC sum score*
5. *Change from prescreen baseline in the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.*

Patient Reported Outcomes

1. *Change from pre-SC treatment baseline in SF-36 scores*
2. *Change from pre-SC treatment baseline in EQ-5D scores*
3. *HRU (such as days off school/work, unscheduled physician visits, hospitalization, and emergency room visits)*
4. *Treatment satisfaction*
5. *Treatment preference*
6. *PGIC*

Other
Trough serum IgG levels.

1.2.2 Epoch 2

1.2.2.1 Primary Endpoint

1. *Responder rate (proportion of subjects with clinically meaningful improvement in functional ability defined as a decrease of ≥1 point in the adjusted INCAT disability score at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score).*

1.2.2.2 Secondary Endpoints

Safety

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 nonserious ARs plus suspected ARs*
4. *Number (percentage) of treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality*
5. *Number (percentage) of causally related SAEs and/or AEs associated with infusions*
6. *Number (percentage) of AEs temporally associated with infusions (defined as AEs occurring during or within 72 h after completion of an infusion)*
7. *Number (percentage) serious and/or nonserious ARs plus suspected ARs associated with infusions*
8. *Number (percentage) of treatment-emergent systemic AEs associated with infusions*
9. *Number (percentage) of treatment-emergent local infusion site reactions associated with infusions*
10. *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*
11. *Rates of systemic and local AEs, regardless of causality, expressed as number of events per infusion, per subject, and per subject-year*
12. *Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year*
13. *Rates of systemic and local ARs plus suspected ARs, expressed as number of events per infusion, per subject, and per subject-year*

Note: Adverse events in this section refer to treatment-emergent AEs, if not specified.

Efficacy

1. *Proportion of subjects with clinically meaningful improvement in functional ability defined as a decrease of ≥1 point in the adjusted INCAT disability score at 2 consecutive time points OR who experience CIDP improvement (defined as ≥8 kPa increase in the hand grip strength in the more affected hand OR ≥4 points increase in R-ODS) at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score*

1.2.2.3 Tertiary Endpoints

Efficacy

1. *Proportion of subjects whose adjusted INCAT disability score has returned to pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥1 point during Epoch 1*
2. *Proportion of subjects whose hand grip strength in the more affected hand has returned to pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥8 kPa during Epoch 1*
3. *Proportion of subjects whose R-ODS score has returned to the pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥4 points during Epoch 1*
4. *Time to improvement in functional ability (defined as a decrease of ≥1 point in the adjusted INCAT score)*
5. *Change from pre-IV treatment baseline in adjusted INCAT disability score*
6. *Change from pre-IV treatment baseline in R-ODS*
7. *Change from pre-IV treatment baseline in hand grip strength score*
8. *Change from pre-IV treatment baseline in MRC sum score*
9. *Proportion of subjects who require an increase in IGIV 10% dose due to worsening of CIDP*
10. *Proportion of subjects who returned to pre-randomization adjusted INCAT disability score*
11. *Change from pre-IV baseline in the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.*

Patient Reported Outcomes

1. *Change from pre-IV treatment baseline in SF-36 scores*
2. *Change from pre-IV treatment baseline in EQ-5D scores*
3. *HRU (such as days off school/work, unscheduled physician visits, hospitalization, and emergency room visits)*
4. *Treatment satisfaction*
5. *Treatment preference*
6. *PGIC*

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 (27th May 2015).

2.0 STUDY DESIGN

This is a Phase III, prospective, multicenter study to evaluate the efficacy, safety, and tolerability of HYQVIA/HyQvia (IGI, 10% with rHuPH20 administered subcutaneously) for maintenance therapy to prevent relapse and GAMMAGARD LIQUID/KIOVIG (IGIV 10% administered intravenously) for the treatment of CIDP. This study will enroll adult subjects with a confirmed diagnosis of CIDP and who have remained on a stable dosing regimen (monthly equivalent dose of 0.4 to 2.4 g/kg BW with a dosing interval of 2 to 6 weeks) of IV immunoglobulin G (IGIV) therapy for at least 12 weeks prior to screening. Randomization to Epoch 1 will be stopped by the sponsor prior to achieving the originally planned total of 174 randomized subjects. At least 120 subjects will be randomized and dosed so that adequate statistical power (90%) will still be achieved, based on revised sample size assumptions. It is estimated that 15% of subjects will be prematurely discontinued from the study.

The overall study design is illustrated in Section 9.4- Study Flow Chart. Epoch 1 is randomized, double-blind, placebo-controlled phase of the study, in which eligible subjects will be randomized in a 1:1 ratio to receive either HYQVIA/HyQvia or the 0.25% albumin placebo solution with rHuPH20 in a double-blind fashion for a period of 6 months or until relapse. *The dosing regimen for HYQVIA/HyQvia or 0.25% albumin placebo with rHuPH20 will be the same as the subject's pre-randomization monthly equivalent IgG dose (or at matching infusion volume for subjects in the placebo group) when administered at a dosing frequency of every 2, 3, or 4 weeks (see Protocol Amendment 6 Section 8.7.4.1 for more information).*

Epoch 2 is the open-label phase of this study that aims to provide evidence for the use of GAMMAGARD LIQUID/KIOVIG as an IV immunoglobulin treatment option in patients with CIDP. *Subjects will receive GAMMAGARD LIQUID/KIOVIG (all subjects at non-US sites) or GAMUNEX®-C[1] [Immune Globulin Injection (Human) 10%] (subjects at US sites only). IGIV treatment will consist of an induction dose of 2 g/kg BW, followed by maintenance infusions at the same monthly dose as the subject's pre-randomization IGIV dosing regimen when administered every 3 weeks for a total of 6 months. The dose level of IGIV treatment may be adjusted at the discretion of the investigator, as medically necessary and/or as tolerated by the subject. Adjustment to the dosing interval of every 3 weeks is not allowed. All subjects will be asked to return to the study site every 3 weeks (i.e., every infusion visit) until study completion or early discontinuation, for follow-up monitoring of their functional ability as well as other clinical, safety, PRO measures, and trough serum IgG levels.*

Two interim analyses are planned (Section 6.10)*:*

- *Interim Safety Analysis, which is Epoch 1 and Epoch 2 safety analysis,*
- *Formal Interim Analysis, which is the final analysis of Epoch 1 data.*

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

3.1.1 Epoch 1

The primary objective of Epoch 1 is to evaluate the efficacy of HYQVIA/HyQvia as a maintenance therapy for CIDP to prevent relapse of neuromuscular disability and impairment. The null hypothesis of no difference in relapse rates between HYQVIA/HyQvia and placebo with rHuPH20 treatment will be tested against a two-sided alternative:

H_0: HYQVIA/HyQvia relapse rate = Placebo with rHuPH20 relapse rate,

H_1: HYQVIA/HyQvia relapse rate ≠ Placebo with rHuPH20 relapse rate.

3.1.2 Epoch 2

The primary objective of Epoch 2 is to evaluate the efficacy of GAMMAGARD LIQUID/KIOVIG for the treatment of CIDP to improve neuromuscular disability and impairment. The null hypothesis is that the response rate to GAMMAGARD LIQUID/KIOVIG among subjects who relapsed in Epoch 1 while on placebo with rHuPH20 treatment of the current study is not higher than 24%. If the lower limit of the two-sided 95% Wilson Score CI of the responder rate in the E1:Placebo Relapse / E2:GGL/KIOVIG set exceeds the assumed historical-control placebo response rate of 24%, then the null hypothesis will be rejected and the current study will be interpreted as providing evidence of the efficacy of GAMMAGARD LIQUID/KIOVIG. This analysis will be performed on the E1:Placebo Relapse – E2: GGL/KIOVIG analysis set as the primary analysis set. Justification for the assumed historical-control placebo response rate of 24% is given in Section 4.2.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

No multiplicity adjustment will be applied.

4.0 SAMPLE-SIZE DETERMINATION

4.1 Epoch 1

4.1.1 Summary

The original planned sample size of 174 randomized subjects was estimated on the basis of the treatment effect observed in the GAMUNEX®-C pivotal (ICE) study (Hughes et al., 2008) and an assumed remission rate of 45% (Viala et al., 2010).

[redacted]

As discussed in Protocol Section 8.6, randomization to Epoch 1 will be stopped by the sponsor prior to achieving the original planned sample size of 174 randomized subjects. It is expected that at least 120 subjects will be randomized and dosed which, based on the revised sample size assumptions using more recent scientific literature, will be sufficient to achieve 90% power.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[1] www.fda.gov/media/146188/download

[redacted]

[redacted] *based on additional information provided by more recent scientific literature, the original sample size assumptions are no longer considered to be accurate and a larger difference in relapse rates of 29% is now expected compared with the originally assumed 18%. Whilst the assumed relapse rates still remain close to the original assumptions, the percentage of subjects on long-term IgG therapy that no longer need therapy (the "remission rate") has been revised from 45% to 19%, leading to an increase in the expected treatment effect.* [redacted]

4.1.3 Power calculation

[redacted] *the difference in the relapse rates between the HYQVIA/HyQvia and placebo groups is expected to be 29%, where a sample size of 120 randomized and dosed subjects (60 subjects per group) will provide 90% power. This power estimate is based on a continuity-corrected chi-squared test, equal allocation, a 15% drop-out rate, a two-sided 5% significance level and a difference in relapse rates of 29% (39% Placebo – 10% HYQVIA/HyQvia = 29%) and was derived based on 100,000 simulation runs and with dropouts imputed as no relapse, as per the planned primary analysis.*

4.1.4 Assumptions of Screen Failure Rate and Dropout Rates

The following screening and dropout rate assumptions are made:

- ***a)*** ***Screening****: A 25% screen failure rate is assumed based on the screen failure rates reported in the following clinical studies:*
  - *(1) In the Privigen® PRIMA study (Léger et al., 2013), 3 of 31 (10%) enrolled subjects were excluded during screening;*
  - *(2) In the ICE study (Hughes et al., 2008), 31 of 148 (21%) enrolled subjects were*

excluded during screening.

(3) In the PATH study (van Schaik et al., 2018), 31 of 276 (11%) enrolled subjects were excluded during screening

(4) In the FORCIDP study (Hughes et al., 2018), 53 of 159 (33%) enrolled subjects were excluded during screening

b) Dropout Rate: *A 15% dropout rate in the treatment period is assumed based on the following clinical studies:*

(1) In the PRIMA study (Léger et al., 2013), 3 of 28 (11%) subjects were prematurely discontinued from the study due to serious adverse events and insufficient clinical response.

(2) In the ICE study (Hughes et al., 2008), 21 of 74 (28%) subjects who initially responded to IGIV treatment in the first period and cross-over periods were prematurely discontinued during the extended treatment period due to relapse or insufficient response, AE, and other reasons.

(3) In the PATH study (van Schaik et al., 2018), 16 of 172 (9%) subjects were prematurely discontinued from the study due to serious adverse events and withdrawal of consent for other reasons.

(4) In the FORCIDP study (Hughes et al., 2018), 9 of 106 (8%) subjects were prematurely discontinued from the study due to serious adverse events, protocol violation, and withdrawal of consent for other reasons.

4.2 Epoch 2

4.2.1 Upper Limit of Response Rate from Historical Control

In Epoch 2 (the IV treatment period), the primary efficacy *population will comprise of IGIV experienced subjects who have relapsed while on the placebo control during Epoch 1 (the SC treatment period). Therefore, the historical control should match those conditions. The historical placebo response rate observed in the subset of treatment -experienced subjects in the GAMUNEX®-C pivotal (ICE) study has been chosen (Hughes et al., 2008). In the ICE study, none of the 12 IGIV-experienced subjects randomized to placebo were responders- representing a responder rate of 0% (0/12). The upper bound of the two-sided 95% CI using the Wilson score method is 24%. Therefore, the CI limit to exceed for the present study is 24%.*

4.2.2 Power Calculation

Assuming that 19% of enrolled IGIV-pretreated subjects are in remission (and thus would not relapse upon withdrawal of treatment) and based on the probability of relapse of 48% for the placebo group, a relapse rate of 39% ([1 - 0.19] × 48%) in the SC placebo treatment group is

assumed. These remission and placebo relapse rate estimates are based on random effect meta-analyses of the relevant literature, as detailed for the Epoch 1 sample size calculation (Section 4.1).

Randomization to Epoch 1 will be stopped by the sponsor prior to achieving the originally planned total of 174 randomized subjects. At least 120 subjects will be randomized and dosed in Epoch 1. Therefore, with at least 60 subjects randomized to the SC placebo treatment group in Epoch 1, and allowing for a 15% drop-out rate in Epoch 1, it is expected that 19 or more subjects (60 x [1–0.15] x 0.39) will relapse and subsequently receive GAMMAGARD LIQUID/KIOVIG treatment in Epoch 2. Assuming a responder rate of 65% to GAMMAGARD LIQUID/KIOVIG based on responder rates of 55% and 77% observed in the subset of treatment-experienced subjects in the ICE study (Hughes et al., 2008) and the PRIMA study (Léger et al., 2013), respectively, the estimated sample size of at least 19 subjects will provide more than 90% power to reject the null hypothesis that the responder rate is at most 24% at the two-sided 5% significance level and allowing for a 15% drop-out rate in Epoch 2.

5.0 ANALYSIS SETS

5.1 Epoch 1

Enrolled Set

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

Safety Analysis Set

The Epoch 1 Safety Set will include all subjects who received any double-blind study medication. Analyses based on the Epoch 1 Safety Set will use the actual treatment that a subject received during Epoch 1.

Modified Intent-to-Treat Analysis Set

A Modified Intent-to-Treat (MITT) analysis set will include all randomized subjects who received any double-blind study medication; this will be the primary efficacy analysis set for Epoch 1 data. Analyses based on the MITT analysis set will use the Epoch 1 planned (ie, as randomized) treatment.

Per-Protocol Analysis Set

A Per-Protocol (PP) analysis set will include all randomized subjects who received any double-blind study medication, and had no major or critical *protocol deviations during Epoch 1 that may have a significant impact on the primary outcome measure; this will be used for sensitivity and/or supportive analyses. Analyses based on the PP analysis set will use the Epoch 1 planned (ie, as randomized) treatment.*

Major or critical protocol deviations during Epoch 1 that may have a significant impact on the primary outcome measure include, but are not limited to:

- Did not meet all inclusion/exclusion criteria,
- Incorrect treatment applied,
- IP not taken in compliance with protocol (Section 12.1.), e.g., Overdose / Underdose route of administration/timing of infusion. For this purpose, underdose is defined as >20% of the scheduled doses (4 doses in 2 week schedule, 3 in 3-week schedule, 2 in 4-week schedule) after the ramp-up which are missed or interrupted without completion where less than 80% of the calculated dose was administered, or administered > 3 days after the scheduled infusion day).

- IP administration visit performed outside of window (outside of ±3 day window),
- Confirmatory relapse assessment performed later than 7 days after the initial INCAT assessment,
- Rater performing study rating scale clinical assessments (INCAT) not certified/trained,
- Rater performing study rating scale clinical assessments (INCAT) exposed to other patient data including Adverse Event information,
- Rater performing INCAT assessment after study treatment infusion,
- Subject met criteria for "will be discontinued" study withdrawal (Section 9.3), but was not discontinued.

The PP analysis set will be discussed and approved at a data review meeting prior to Epoch 1 data lock.

Pharmacokinetic Analysis Set

Not applicable. Epoch 1 pharmacokinetic (PK) analysis described in this SAP is limited to trough serum IgG levels only for which the MITT analysis set will be used (Section 6.9.1).

Additional analysis sets

Not applicable

5.2 Epoch 2

Enrolled Set

The Epoch 2 Enrolled Set includes all subjects who had a relapse in Epoch 1 and entered Epoch 2.

Safety Analysis Set

The Epoch 2 Safety Set will include all subjects who had a relapse in Epoch 1, entered Epoch 2, and received IGIV treatment with either GAMMAGARD LIQUID/KIOVIG or GAMUNEX®-C in Epoch 2.

Modified Intent-to-Treat Analysis Set

Not applicable.

Per-Protocol Analysis Set

Not applicable.

Pharmacokinetic Analysis Set

Not applicable. Epoch 2 pharmacokinetic (PK) analysis is limited to trough serum IgG levels, where the applicable analysis sets are described in Section 6.9.2.

Additional analysis cohorts

The E1:Placebo Relapse / E2:GGL/KIOVIG Set will include a subset of subjects who had a relapse while on placebo in Epoch 1, entered Epoch 2, and were treated with GAMMAGARD LIQUID/KIOVIG in Epoch 2. This is the primary analysis set for Epoch 2 (the IV treatment period) non-safety data.

The E1:Placebo Relapse / E2:IGIV Set will include all subjects who had a relapse while on placebo in Epoch 1, entered Epoch 2, and were treated with IGIV (GAMMAGARD LIQUID/KIOVIG or GAMUNEX®-C). This is a secondary analysis set for Epoch 2 (the IV treatment period) non-safety data.

The E1: HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG Set will include all subjects who had a relapse while on HYQVIA/HyQvia in Epoch 1, entered Epoch 2, and were treated with GAMMAGARD LIQUID/KIOVIG in Epoch 2. This is an exploratory analysis set for Epoch 2 (the IV treatment period) non-safety data.

The E1:HYQVIA/HyQvia Relapse / E2:IGIV Set will include all subjects who had a relapse while on HYQVIA/HyQvia in Epoch 1, entered Epoch 2, and were treated with IGIV (GAMMAGARD LIQUID/KIOVIG or GAMUNEX®-C) in Epoch 2. This is an exploratory analysis set for Epoch 2 (the IV treatment period) non-safety data.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Epoch 1 baseline value is defined as the pre-SC treatment baseline visit value, if non-missing. If missing, then the Screening visit value will be used (if non-missing).

Epoch 2 baseline value is the pre-IV treatment/Epoch 2 Week 1 visit value, if non-missing. If missing, then the last non-missing assessment prior to administration of the first dose of IP in Epoch 2 (GAMMAGARD or GAMUNEX®-C) will be used.

For some analyses, data are summarized at the Epoch 1 Interim Visit. As detailed in Protocol Section 21.2, the timing of the Epoch 1 Interim Visit depends on dosing frequency: Epoch 1 week 15 for the 2 weeks dosing regimen, Epoch 1 week 14 for the 3 weeks dosing regimen or Epoch 1 week 16 for the 4 weeks dosing regimen.

Change from baseline will be calculated as the end of treatment outcome minus the baseline value, within the relevant epoch. End of treatment outcome is defined as the last non-missing post-baseline value within epoch.

Hypothesis tests and 95% confidence intervals (CIs) will be 2-sided. All p-values reported will be 2-tailed and rounded to 3 decimal places. P-values which are less than 0.001 will be displayed as '<0.001' and p-values which are greater than 0.999 will be displayed as '>0.999'. Determination of statistical significance will be based on the p-value and corresponding alpha threshold before rounding.

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. BMI, averaged laboratory results (eg, diastolic/systolic blood pressure) and pulse (when taken in triplicate), and derived scores 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 presented to 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 Handling of Treatment Misallocations

For Epoch 1, appropriate treatment allocation for each analysis will be determined by the applicable analysis set (Section 5.1).

6.1.2 Analysis Approach for Continuous Variables

Epoch 1
Generally, continuous endpoints will be summarized descriptively (no inferential statistical analysis) unless otherwise stated.

Epoch 2
Continuous endpoints will be summarized descriptively (no inferential statistical analysis) unless otherwise stated.

6.1.3 Analysis Approach for Binary Variables

Epoch 1
All statistical analyses of binary endpoints will be analyzed using a continuity-corrected chi-square test unless otherwise stated. Analysis approaches for safety events are described in Section 6.6.

Epoch 2
The analysis approach for the primary endpoint of responder rate is described in Section 6.5.2. Other binary endpoints will be summarized descriptively (Section 6.1).

6.1.4 Analysis Approach for Time-to-Event Variables

Epoch 1
Time to relapse (Section 6.5.1.2) will be compared between treatment groups using the Wilcoxon survival test. Additionally, survival functions for each treatment will be estimated using Kaplan-Meier curves. The time-to-event analysis approach for safety endpoints is described in Section 6.6.1.2.

Epoch 2

Time to functional improvement will be presented using the Kaplan-Meier method, as described in Section 6.5.2.3.

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 for each epoch, where applicable.

Epoch 1

- Screened
- Screen failed
- Enrolled (Epoch 1 Enrolled Set)
- Randomized
- Randomized and dosed with IP (Epoch 1 MITT Set)
- Dosed with IP (Epoch 1 Safety Set)
- Completed study
- Discontinued study prematurely
- Primary reason for premature discontinuation
- Relapsed and entered Epoch 2

Epoch 2

- Subjects who relapsed in Epoch 1
- Subjects who relapsed and did not enter Epoch 2
- Subjects who relapsed and entered Epoch 2 (Epoch 2 Enrolled Set)
- Subjects who received IP (Epoch 2 Safety Set)
- Subjects who completed study
- Subjects who discontinued study prematurely
- Primary reason for premature discontinuation

The number of subjects by country and site will also be summarized by treatment/cohort and overall for the Safety Analysis Sets. Additionally, the following listings will be presented for each epoch:

- Disposition (Enrolled Set)
- Listing of all screen failures (i.e., subjects that have signed the informed consent, but did not pass screening),
- Randomization assignment data listing (Randomized Subjects) will be provided for subjects that were randomized to a treatment group and actual treatment received based on the kit identification assignment will be included,
- 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 Epoch 1 discontinuation/completion – date of initial dose of IP in Epoch 1 + 1

and all subjects will be counted as having the event (i.e. no subjects will be censored). The corresponding cumulative incidence (1-survival) function for each planned treatment group 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 randomized, 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 the respective data lock for epochs 1 and 2. Critical/major/minor protocol deviations will be summarized by site, treatment and category for the Epoch 1 and 2 Safety Analysis Sets. Protocol deviations will also be listed by subject and by site for the Safety Analysis Sets. 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

Additionally, for each epoch, a separate table and listing of protocol deviations related to the COVID-19 pandemic will be presented (Section 6.2.2). Protocol deviations which relate to the Epoch 1 Per-Protocol analysis set are described in Section 5.1.

6.2.2 COVID-19

A separate table and listing of protocol deviations related to the COVID-19 pandemic will be presented for each epoch. 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, baseline and screening characteristics will be presented separately for Epoch 1 and Epoch 2. Demographic and baseline characteristics will include age (years), age group (≤55, >55), sex, race and ethnicity. Characteristics at screening 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). Demographic, baseline and screening characteristic summaries will be presented for the following analysis sets / cohorts:

Epoch 1

- MITT,
- Per-protocol,
- Safety,

by treatment and overall, in addition to:

- Screen failures.

Epoch 2

- E1:Placebo Relapse / E2:GGL/KIOVIG,
- E1:Placebo Relapse / E2:IGIV,
- E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG,
- E1:HYQVIA/HyQvia Relapse / E2:IGIV.

In addition, overall results will be presented for the following combined cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG and E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG combined,
- E1:Placebo Relapse / E2:IGIV and E1:HYQVIA/HyQvia Relapse / E2:IGIV combined.

Listings of the demographic, baseline and screening characteristics will be provided separately for the Epoch 1 and Epoch 2 Safety Analysis Sets.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history and prior procedures (hereafter simply referred to as medical history) data will be presented separately for the Epoch 1 and Epoch 2 Safety Analysis Sets. 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 arm 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 pooled treatment arms.

Listings of medical history will be provided using the Epoch 1 and Epoch 2 Safety Analysis Sets.

6.3.3 Baseline Characteristics

Descriptive summaries of CIDP history at screening will be presented separately for Epoch 1 and Epoch 2 using the analysis sets detailed in Section 6.3.1. These summaries 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 subject usage (yes, no) of any IgG product, plasma exchange or corticosteroids within 6 months prior to screening.

Listings of CIDP history will be presented using the Epoch 1 and Epoch 2 Safety Analysis Sets.

6.4 Medication History and Concomitant Medications

Prior and concomitant medications will be presented separately for Epoch 1 and Epoch 2 Safety Analysis Sets. 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** Epoch 1 IP administration. Prior non-drug therapies and procedures are defined similarly.
- **Concomitant medication**: Any medication which began **at or after** investigational product administration within the specified Epoch, OR medications which began **prior to** first investigational product administration within the Epoch and continuing at or after the first investigational product administration within the Epoch. Concomitant non-drug therapies and procedures are defined similarly.

Note that medications with start time prior to time 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 concomitant medication.

6.4.1 Prior Medications

Prior medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version September 2015 or later. Prior medications, non-drug therapies and procedures (simply referred to as prior medications) will be summarized separately by treatment and overall for the Epoch 1 and Epoch 2 Safety Analysis Sets.

Listings of prior and concomitant medications will be presented using the Epoch 1 and Epoch 2 Safety Analysis Sets.

6.4.2 Concomitant Medications

Concomitant medications and non-drug therapies and procedures (simply referred to as concomitant medications) will be summarized separately for Epoch 1 and 2, by treatment and overall for the Safety Analysis Sets. 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.

Listings of prior and concomitant medications will be presented using the Epoch 1 and Epoch 2 Safety Analysis Sets.

6.5 Efficacy Analysis

6.5.1 Epoch 1

6.5.1.1 Primary Endpoint Analysis

The primary analysis for Epoch 1 is based on a comparison of relapse rates between HYQVIA/ HyQvia and Placebo with rHuPH20 using the MITT analysis set. A continuity-corrected chi-square test will be used to compare relapse rates and will be conducted at the two-sided 5% level of statistical significance, and with missing outcomes imputed as no relapse. Example SAS code for a continuity-corrected chi-square test is provided in Section 9.3.1. The statistics reported will include but are not limited to:

- number of subjects included in the analysis (by planned treatment),
- number (%) of subjects included in the analysis who relapsed (by planned treatment),
- two-sided p-value,
- two-sided 95% CIs for the estimated relapse rates (by planned treatment),
- the risk difference and two-sided 95% CI.

CIs for relapse rates will be computed using the Wilson score method (Wilson, 1927), and CIs for the difference in relapse rates will be determined using Newcombe's approach based on the Wilson score confidence limits for each of the two individual proportions (Newcombe, 1998). It should be noted that the CI for the risk difference is included for descriptive purposes only and may not correspond exactly to the two-sided p-value from the continuity-corrected chi-square test, which will be used for formal assessment of statistical significance.

Additionally, a listing for Epoch 1 relapse status will presented for the MITT analysis set.

6.5.1.1.1 Derivation of Endpoint

A relapse is defined as a worsening of functional disability such that there is an increase of ≥1 point relative to the pre-SC treatment baseline visit score in 2 consecutive adjusted INCAT disability scores. For the primary analysis missing outcomes will be imputed as no relapse.

At any time during the SC 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 pre-SC treatment baseline score. INCAT assessment will be repeated during the pre-IV treatment baseline visit or early termination visit, as

applicable, to confirm the subject's adjusted INCAT disability score has increased by ≥1 point relative to the pre-SC treatment baseline score, at which time the final determination of whether a subject has met relapse criteria will be made. If INCAT evaluation indicates relapse during the SC treatment, the second confirmatory INCAT evaluation (Pre-IV BL Epoch 2) can be performed as early as the same day of the first INCAT evaluation and no later than 7 days after the first INCAT evaluation and by the same rater.

The definition of missing relapse outcome is provided in Section 9.2.3.

6.5.1.1.2 Sensitivity Analysis

Sensitivity analyses to assess the robustness of inferences from the Epoch 1 primary analysis relating to imputing missing as "no relapse" are addressed in sensitivity analyses 1 and 2, and sensitivity analyses to assess the robustness of inferences from the Epoch 1 primary analysis relating to protocol deviations and the requirement for a confirmatory INCAT assessment is addressed in sensitivity analyses 3 and 4, respectively:

1. *MITT analysis set with missing outcome in subjects who participated in Epoch 1 imputed as a relapse,*
2. *MITT Observed Cases analysis with missing outcome in subjects who participated in Epoch 1 excluded,*
3. *PP analysis set with missing outcome in subjects who participated in Epoch 1 imputed as no relapse,*
4. *MITT analysis set with missing imputed as no relapse, where relapse is alternatively defined as an increase in adjusted INCAT disability score of ≥1 point relative to the pre-SC treatment baseline score, on a single INCAT assessment; this sensitivity analysis removes the requirement for the increase by ≥1 point relative to the pre-SC treatment baseline score to be confirmed at a secondary confirmatory INCAT evaluation (to be performed as early as the same day of the first INCAT evaluation and no later than 7 days afterwards) in order to classify a subject as having relapsed.*

As for the primary analysis, a continuity-corrected chi-square test will be used to compare relapse rates between treatment groups for these sensitivity analyses. Two-sided p-values will be reported in addition to the estimated relapse rates for each planned treatment group and associated two-sided 95% CIs, as well as the risk difference and the corresponding two-sided 95% CI. CIs will be determined using the same methods as for the primary analysis (Section 6.5.1.1) and are included for descriptive purposes only. Example SAS code for a continuity-corrected chi-square test is provided in Section 9.3.1.1.

The definition of missing relapse outcome for these sensitivity analyses are provided in Section 9.2.3.

6.5.1.2 Secondary Endpoints Analysis

All Epoch 1 secondary efficacy endpoint analyses will be based on the MITT analysis set.

1. *Proportion of subjects who experience a worsening of functional disability*

Worsening of functional disability is defined as one or more of the following: an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores; who experience CIDP worsening (defined as a ≥8 kPa decrease in the hand grip strength in the more affected hand); ≥4 points decrease in R-ODS relative to the pre-SC treatment baseline score (at the time of withdrawal from the SC treatment period). This endpoint will be analyzed using a continuity-corrected chi-square test approach, as described for the Epoch 1 primary analysis (Section 6.5.1.1), with no imputation of missing values. Example SAS code is provided in Section 9.3.1.1. The null hypothesis of no difference in the proportion of subjects who experience a worsening of functional disability between HYQVIA/HyQvia and placebo with rHuPH20 treatment will be tested against a two-sided alternative:

H_0: HYQVIA/HyQvia proportion experiencing worsening =

Placebo with rHuPH20 proportion experiencing worsening,

H_1: HYQVIA/HyQvia proportion experiencing worsening ≠

Placebo with rHuPH20 proportion experiencing worsening.

Additionally, the number and percentage of subjects meeting each component of worsening will be presented. A listing for worsening of functional disability will be presented for the MITT analysis set.

2. *Time to relapse*

Time to relapse is defined as time from the date of the first SC administration of HYQVIA/HyQvia or placebo with rHuPH20 to the date of relapse (where relapse is defined as in Section 6.5.1.1.1). For subjects who relapsed in Epoch 1, time to relapse will be calculated as:

date of relapse – date of initial dose of IP in Epoch 1 + 1.

Subjects who did not relapse in Epoch 1 will be censored with time to censoring calculated as:

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

Time to relapse will be compared between treatment groups using the Wilcoxon survival test (i.e., Gehan's generalized Wilcoxon survival test). The null hypothesis of no difference in time to relapse between HYQVIA/HyQvia and placebo with rHuPH20 treatment will be tested against a two-sided alternative:

H_0: HYQVIA/HyQvia time to relapse = Placebo with rHuPH20 time to relapse,

H_1: HYQVIA/HyQvia time to relapse ≠ Placebo with rHuPH20 time to relapse.

The statistics presented will include but are not limited to:

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

Additionally, the cumulative incidence (1-survival) *function for each treatment arm 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.

3. *Change from pre-SC treatment baseline in R-ODS*

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 ADL (R-ODS) from baseline to the end of the treatment period will be analyzed using an analysis of covariance (ANCOVA) model to test the treatment effect, with baseline R-ODS score as a covariate* (baseline is defined in Section 6.1). *The last non-missing change in Epoch 1 will be used for subjects who discontinued early*. For subjects with no post-baseline R-ODS data, no imputation of post-baseline data will be conducted and these subjects will not contribute to the analysis. The null hypothesis of no difference in mean change from pre-SC treatment baseline in R-ODS between HYQVIA/HyQvia and placebo with rHuPH20 treatment will be tested against a two-sided alternative:

H_0: HYQVIA/HyQvia mean change from pre-SC treatment baseline in R-ODS = Placebo with rHuPH20 mean change from pre-SC treatment baseline in R-ODS,

H_1: HYQVIA/HyQvia mean change from pre-SC treatment baseline in R-ODS ≠ Placebo with rHuPH20 mean change from pre-SC treatment baseline in R-ODS.

Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) will be presented for R-ODS at baseline, the end of treatment period (last non-missing post-baseline outcome) and change from baseline, overall and by treatment. Additionally, the statistics reported will include but are not limited to:

- estimated mean change from baseline and two-sided 95% CIs (by planned treatment),
- estimated mean difference between treatment groups and two-sided 95% CI,
- two-sided p-value for the effect of treatment.

An additional descriptive summary of R-ODS by timepoint and planned treatment will be presented for all timepoints (weeks) as well as a plot of mean change from SC baseline by planned treatment and timepoint (week), using the MITT analysis set. Descriptive summaries by dosing regimen and planned treatment will also be presented. Listings for R-ODS score and derived endpoints will also be presented for the MITT analysis set.

[redacted]

[redacted]

6.5.1.2.2 Supplementary analysis

Not applicable.

6.5.1.3 Tertiary Endpoints Analysis

6.5.1.3.1 Efficacy

All Epoch 1 tertiary efficacy endpoint analyses will be based on the MITT analysis set.

1. *Change from pre-SC treatment baseline in adjusted INCAT disability score*
2. *Change from pre-SC treatment baseline in hand grip strength score*
3. *Change from pre-SC treatment baseline in MRC sum score*

Changes from pre-SC treatment baseline in adjusted INCAT disability scores, hand grip strength scores and MRC sum scores will be summarized by planned treatment group using descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum). For hand grip strength, results will be presented separately for the more and less affected hand which will be determined at the Epoch 1 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.

Summaries will be based on the following timepoints: baseline, the Epoch 1 Interim Visit and the end of treatment period (last non-missing post-baseline outcome). Descriptive summaries by dosing regimen, planned treatment and regimen-specific planned timepoint will also be presented. Missing values will not be imputed.

Plots of mean change from SC baseline in adjusted INCAT disability score, hand grip strength score (more and less affected hand, separately) and MRC sum score by planned treatment and timepoint will be presented, using the MITT analysis set. Listings for adjusted INCAT disability score, hand grip strength score and MRC sum score will also be presented for the MITT analysis set.

4. *Change from pre-SC treatment baseline in functional impact on everyday tasks as measured by R-ODS sub-components*

An alternative scoring scheme for the R-ODS will be determined using the data collected in the study, prior to Epoch 1 being unblinded. 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 which will be finalized prior to Epoch 1 data lock.

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 by planned treatment and timepoint. Descriptive summaries by dosing regimen, planned treatment and regimen-specific planned timepoint will also be presented. Missing values will not be imputed.

A plot of mean change from SC baseline in alternative R-ODS score by planned treatment and timepoint will be presented, using the MITT analysis set. Listings for R-ODS score and derived endpoints, including the alternative R-ODS score, will also be presented for the MITT analysis set.

5. *Change from prescreen baseline in the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.*

The following electrodiagnostic (EDX) variables will be summarized by planned treatment group using descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum):

- The total number of demyelinating abnormalities (DA) at Epoch-1 screening,
- The total number of DA at Epoch 1 exit (end of the treatment period),
- Change in total number of DA at the Epoch 1 exit EDX assessment compared to Epoch 1 EDX baseline assessment,
- The number of new DA at the Epoch 1 exit EDX assessment.

Only subjects with complete EDX Epoch 1 data will be included in these analyses (i.e. bilateral tibial, peroneal, median and ulnar measurements at both baseline and exit EDX studies).

Additional descriptive summaries for all EDX measurements and change from screening values will be presented. These summaries will not be limited to those subjects with complete data.

A listing for EDX data will be presented for the MITT analysis set.

6.5.1.4 Subgroup Analyses

Subgroup analyses will be presented for the Epoch 1 primary endpoint only. The purpose of subgroup analyses for the primary efficacy endpoint is to explore relapse rates across subgroups and assess possible exploratory evidence of differential treatment effects. All subgroup analyses should be interpreted with caution, particularly if the number of relapses within any subgroup is small.

A comparison of relapse rates between planned treatment groups in the MITT analysis set using the methods described for the Epoch 1 primary analysis (Section 6.5.1.1) will be conducted for the following subgroups:

Age group:

- ≤55 years
- >55 years

Sex:

- Female
- Male

Race

- White
- Black or African American
- Asian
- Native Hawaiian or Other Pacific Islander
- American Indian or Alaska Native
- Other
- Not reported

Dosing regimen:

- 2 weeks
- 3 weeks
- 4 weeks

Geographic region

- North America
- South America
- Europe

The statistics presented will include but are not be limited to:

- number of subjects included in the analysis (by subgroup and planned treatment),
- number (%) of subjects included in the analysis who relapsed (by subgroup and planned treatment),
- two-sided 95% CIs for the estimated relapse rates (by subgroup and planned treatment),
- the risk difference and two-sided 95% CI for the comparison of relapse rates (by subgroup),
- two-sided p-value for the comparison of treatments within each subgroup using the continuity-corrected chi-square test.

However, if for any subgroup there are 5 subjects or less within either treatment group then no inferential statistics (p-values or confidence intervals) will be presented. CIs will be determined using the same methods as for the Epoch 1 primary analysis (Section 6.5.1.1). Within-subgroup analyses are included for descriptive purposes only.

To assess whether there is exploratory evidence of a potential differential effect of treatment across subgroup categories, within each subgroup variable, a Firth logistic regression model (Firth D., 1993) will be fitted with relapse as the outcome variable and randomized treatment, subgroup and the treatment-by-subgroup interaction as explanatory variables (example SAS code is provided in Section 9.3.1.3). In addition to the statistics outlined above, the Type III p-value from the Firth logistic regression model for the treatment-by-subgroup interaction term from these interaction models will be presented, where a p-value of <10% will be considered as potential exploratory evidence of a differential treatment effect across subgroups and where a graphical display of the subgroup analyses using forest plots showing the risk difference and two-sided 95% CI for the comparison of relapse rates by subgroup will be used to assess the clinical relevance of any potential treatment-by-subgroup interaction.

TEAE summaries to be presented by subgroup are described in Section 6.6.1. Additional descriptive summaries by dosing regimen are described in Section 6.5.1.2 and 6.5.1.3.

6.5.2 Epoch 2

6.5.2.1 Primary Endpoint Analysis

The primary endpoint analysis *will be performed on the E1:Placebo Relapse – E2: GGL/KIOVIG analysis set. The primary outcome measure in Epoch 2 is the response rate (where the definition of responder is provided in Section 6.5.2.1.1). The null hypothesis is that the response rate to GAMMAGARD LIQUID/KIOVIG among subjects who relapsed in Epoch 1 while on placebo with rHuPH20 treatment of the current study is not higher than 24%. If the lower limit of the two-sided 95% Wilson Score CI of the responder rate in the E1:Placebo Relapse / E2:GGL/KIOVIG set exceeds the assumed historical-control placebo response rate of 24%, then the null hypothesis will be rejected and the current study will be interpreted as providing evidence of the efficacy of GAMMAGARD LIQUID/KIOVIG.* This analysis is a complete case analysis implicitly based on the missing completely at random (MCAR) premise where subjects with a missing response status at the completion of the IV treatment period (6 months) or the last study visit of the IV treatment period will not be imputed.

The statistics presented will include but are not limited to:

- number of subjects included in the analysis,
- number (%) of subjects included in the analysis who were responders,
- two-sided 95% Wilson Score CI for the estimated response rate.

Additionally, a listing for response status will presented for the Epoch 2 Safety Analysis Set.

6.5.2.1.1 Derivation of Endpoint(s)

A responder is defined as a subject who demonstrated an improvement of functional disability by ≥1 point (decrease) in the adjusted INCAT disability score at the completion of IV treatment period (6 months) or the last study visit of the IV treatment period, relative to pre-IV treatment baseline.

6.5.2.1.2 Sensitivity Analyses

To assess the robustness of inferences from the Epoch 2 primary analysis relating to the normal approximation to the binomial distribution inherent in the Wilson score interval, a sensitivity analysis for the Epoch 2 primary analysis in the E1:Placebo Relapse – E2: GGL/KIOVIG analysis set will be conducted, where the two-sided 95% CI for the responder rate will be determined using the Clopper-Pearson method (Clopper and Pearson, 1934). This analysis was requested by FDA in an interaction dated March 28th 2016.

To assess the robustness of inferences from the Epoch 2 primary analysis to departures from the MCAR premise, a sensitivity analysis based on the missing not at random (MNAR) premise will be performed. For this analysis, subjects with missing response status at the completion of the IV treatment period (6 months) or the last study visit of the IV treatment period will be imputed as non-responders.

6.5.2.1.3 Supplementary Analyses

The overall responder rates will also be presented for the following analysis cohorts:

- E1:Placebo Relapse / E2:IGIV,
- E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG,
- E1:HYQVIA/HyQvia Relapse / E2:IGIV.

In addition, overall results will be presented for the following combined cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG and E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG combined,
- E1:Placebo Relapse / E2:IGIV and E1:HYQVIA/HyQvia Relapse / E2:IGIV combined.

Two-sided 95% Wilson Score CIs will not be presented for any cohort with less than or equal to 5 subjects. No statistical comparison with historical control values will be made for these analysis sets.

An additional exploratory analysis to assess the potential impact of regression to the mean in Epoch 2 will be conducted using the E1:Placebo Relapse – E2: GGL/KIOVIG analysis set. Regression to the mean would imply that patients with the largest increase in adjusted INCAT in Epoch 1 would experience the largest drop in Epoch 2. An exploratory stratified estimation of the response rate using the methodology for a stratified Wilson Score interval introduced by Yan and Su (2010) will be applied. Two strata will be defined:

(a) Epoch 1 change in adjusted INCAT ≤ 2,

(b) Epoch 1 change in adjusted INCAT > 2.

The stratified proportion will be estimated as

$$\hat{p}_{strat} = \sum_{i=1}^{2} w_i \hat{p}_i, \tag{1}$$

where w_i are the stratum-specific weights (discussed below), $\sum_{i=1}^{2} w_i = 1$, and $\hat{p}_i$ are the estimated stratum-specific response rates. Estimated stratum-specific response rates are given by $\hat{p}_i = x_i/n_i$, and where x_i and $n_i$are the number of responders and subjects within each stratum, respectively. The lower (L) and upper (U) limits for the confidence interval for the stratified proportion are given by:

$$(L,U) = \sum_{i=1}^{2} w_i \left(\frac{\hat{p}_i + z_\gamma^2/2n_i}{1 + z_\gamma^2/n_i} \pm \frac{z_\gamma}{1 + z_\gamma^2/n_i} \sqrt{\frac{\hat{p}_i(1-\hat{p}_i)}{n_i} + \frac{z_\gamma^2}{4n_i^2}} \right). \tag{2}$$

The required normal percentile, z_γ, so that the overall confidence level is equal to $1-\alpha$ can be obtained, is given by

$$z_\gamma = \left\{ \sqrt{\sum_{i=1}^{2} w_i^2 \frac{\hat{p}_i(1-\hat{p}_i)}{n_i}} \Big/ \sum_{i=1}^{2} w_i \sqrt{\frac{\hat{p}_i(1-\hat{p}_i)}{n_i}} \right\} z_{1-\alpha/2}, \tag{3}$$

where $z_{1-\alpha/2}$ is the $1-\alpha/2$ percentile of the standard normal distribution; $\alpha = 0.05$. Yan and Su (2010) demonstrate how inverse-variance weights with a continuity correction can be chosen so that the weighted squared length of the confidence interval is minimized. These stratum-specific weights can be estimated by

$$\widehat{w}_i = \frac{\left(1+z_\gamma^2/n_i\right)^2}{\hat{p}_i(1-\hat{p}_i)/n_i + z_\gamma^2/4n_i^2} \Bigg/ \sum_{i=1}^{2} \frac{\left(1+z_\gamma^2/n_i\right)^2}{\hat{p}_i(1-\hat{p}_i)/n_i + z_\gamma^2/4n_i^2}, \quad (4)$$

for $i = 1,2$. However, since z_γ (Equation (3)) and $\widehat{w}_i$ (Equation (4)) are interdependent, an iterative process is needed:

1. Choose the initial normal percentile as $z_{1-\alpha^{1/2}}$ and use Equation (4) to compute initial weights, w_i^0.
2. Use w_i^0's and Equation (3) to compute the new normal percentile, z_γ^0.
3. Use z_γ^0 and Equation (4) to calculate the new weights, $\widehat{w}_i$'s.
4. Use updated $\widehat{w}_i$'s and Equation (3) to compute the new normal percentile z_γ.

The estimated stratified proportion (Equation (1)) and its confidence interval (Equation (2)) can then be determined.

6.5.2.2 *Secondary Endpoint Analysis*

1. *Proportion of subjects with clinically meaningful improvement in functional ability*

A clinically meaningful improvement in functional ability is *defined as a decrease of ≥1 point in the adjusted INCAT disability score at 2 consecutive time points OR who experience CIDP improvement (defined as ≥8 kPa increase in the hand grip strength in the more affected hand OR ≥4 points increase in R-ODS) at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score.* Missing values will not be imputed. Descriptive statistics (number and percentage of subjects within each category) will be presented for the following analysis cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG,
- E1:Placebo Relapse / E2:IGIV,
- E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG,

- E1:HYQVIA/HyQvia Relapse / E2:IGIV.

In addition, overall results will be presented for the following combined cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG and E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG combined,
- E1:Placebo Relapse / E2:IGIV and E1:HYQVIA/HyQvia Relapse / E2:IGIV combined.

Two-sided 95% Wilson Score CIs will also be presented for all cohorts with greater than 5 subjects.

A listing of Epoch 2 adjusted INCAT disability scores will be presented for the Epoch 2 Safety Analysis Set.

6.5.2.3 Tertiary Endpoints Analysis

Tertiary endpoint analyses will be presented for the following analysis cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG,
- E1:Placebo Relapse / E2:IGIV,
- E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG,
- E1:HYQVIA/HyQvia Relapse / E2:IGIV.

In addition, overall results will be presented for the following combined cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG and E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG combined,
- E1:Placebo Relapse / E2:IGIV and E1:HYQVIA/HyQvia Relapse / E2:IGIV combined.

1. *Proportion of subjects whose adjusted INCAT disability score has returned to pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥1 point during Epoch 1*
2. *Proportion of subjects whose hand grip strength in the more affected hand has returned to pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥8 kPa during Epoch 1*

3. *Proportion of subjects whose R-ODS score has returned to the pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥4 points during Epoch 1*

For all Epoch 2 binary tertiary endpoints based on a return to pre-SC baseline after previous worsening in Epoch 1, summaries will include but are not limited to:

- Number and percentage of subjects who worsened during Epoch 1,
- Number and percentage of subjects who did not worsen during Epoch 1,
- Number, percentage (and two-sided 95% Wilson Score CI) of subjects who worsened during Epoch 1 but whose value returned to pre-SC baseline or better in Epoch 2 (during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period)
- Number and percentage of subjects who worsened during Epoch 1 but whose value did not return to pre-SC baseline or better in Epoch 2 (during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period)

Missing values will not be imputed. Two-sided 95% Wilson Score CIs will not be presented for any cohort with less than or equal to 5 subjects.

Listings of Epoch 2 adjusted INCAT disability scores, hand grip strength scores and R-ODS scores will be presented for the Epoch 2 Safety Analysis Set.

4. *Time to improvement in functional ability (defined as a decrease of ≥1 point in the adjusted INCAT score)*

Time to improvement in functional ability is defined as the time from the date of the first IV administration in Epoch 2 to a decrease of ≥1 point in the adjusted INCAT score compared with pre-IV treatment baseline. For subjects whose functional ability improved, time to improvement will be calculated as:

date of improvement – date of first IV administration in Epoch 2 + 1.

Subjects whose functional ability did not improve will be censored with time to censoring calculated as:

date of Epoch 2 discontinuation/completion – date of first IV administration in Epoch 2 + 1.

The cumulative incidence (1-survival) function, estimated using the Kaplan-Meier method, will be presented, where the vertical axis will represent the cumulative incidence of improvement in functional ability and the number of subjects at-risk over time will be displayed. Additional statistics presented will include but are not limited to:

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

A listing of adjusted INCAT disability scores will be presented for the Epoch 2 Safety Analysis Set.

5. *Change from pre-IV treatment baseline in adjusted INCAT disability score*
6. *Change from pre-IV treatment baseline in R-ODS*
7. *Change from pre-IV treatment baseline in hand grip strength score*
8. *Change from pre-IV treatment baseline in MRC sum score*

For the adjusted INCAT disability score, hand grip strength score and MRC sum score endpoints, descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) will be presented at pre-IV treatment baseline, Epoch 2 Interim Visit, end of treatment period (last non-missing post-baseline outcome) and change from baseline to these timepoints. For R-ODS, observed values and change from baseline values will be presented for all planned timepoints (weeks). For hand grip strength, results will be presented separately for the more and less affected hand which will be determined at the Epoch 2 pre-IV treatment 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. Missing values will not be imputed.

Plots of mean change from pre-IV treatment baseline in adjusted INCAT disability score, R-ODS, hand grip strength score (more and less affected hand, separately) and MRC sum score by treatment and timepoint will be presented.

Listings of adjusted INCAT disability scores, R-ODS score, hand grip strength score and MRC sum score will be presented for the Epoch 2 Safety Analysis Set.

9. *Proportion of subjects who require an increase in IGIV 10% dose due to worsening of CIDP*

10. Proportion of subjects who returned to pre-randomization adjusted INCAT disability score

Descriptive statistics (number of subjects and percentage) and two-sided 95% Wilson Score CIs will be presented for the proportion of subjects who required an increase in IGIV 10% dose due to worsening of CIDP and the proportion of subjects who returned to pre-randomization adjusted INCAT disability score. Missing values will not be imputed. Two-sided 95% Wilson Score CIs will not be presented for any cohort with less than or equal to 5 subjects.

Listings of IGIV dose and adjusted INCAT disability scores will be presented for the Epoch 2 Safety Analysis Set.

11. Change from pre-IV baseline in the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies

The following Epoch 2 EDX data will be summarized using descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum):

- The total number of DA at Epoch 2 baseline,
- The total number of DA at Epoch 2 exit EDX assessment (end of the treatment period),
- Change in total number of DA at the Epoch 2 exit EDX assessment compared to Epoch 2 EDX baseline assessment,
- The number of new DA at the Epoch 2 exit EDX assessment.

Only subjects with complete EDX Epoch 2 data will be included in these analyses (i.e. bilateral tibial, peroneal, median and ulnar measurements at both baseline and exit EDX studies).

A listing for Epoch 2 EDX data will be presented for the Epoch 2 Safety Analysis Set.

6.5.2.4 Subgroup Analyses

Subgroup analyses will be presented for the Epoch 2 primary endpoint only, using the E1:Placebo Relapse – E2: GGL/KIOVIG analysis cohort. The purpose of subgroup analyses for the primary efficacy endpoint is to explore response rates across key subgroups. All subgroup analyses should be interpreted with caution, particularly if the number of subjects and/or responders within any subgroup is small. The response rate for the following subgroups will be presented:

Age group:

- ≤55 years
- >55 years

Sex:

- Female
- Male

Race

- White
- Black or African American
- Asian
- Native Hawaiian or Other Pacific Islander
- American Indian or Alaska Native
- Other
- Not reported

Two-sided 95% Wilson Score CIs will be presented for subgroups with greater than 5 subjects.

TEAE summaries to be presented by subgroup are described in Section 6.6.1.

6.6 Safety Analysis

Safety analyses are applicable to both Epoch 1 and Epoch 2. Safety endpoints corresponding to the Epoch 1 safety objective cover adverse events, immunogenicity, clinical laboratory assessments and vital signs in Epoch 1. Safety endpoints corresponding to the Epoch 2 safety objective cover adverse events. All safety presentations will be based on the Safety Analysis Sets. Continuous safety data (eg, 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 (eg, 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.

For Epoch 1 only, Time-to-event AE data will be analyzed using Cox regression, to account for both the occurrence and timing of the event. These analyses are for purely descriptive purposes and therefore no formal statistical hypothesis testing will be performed.

6.6.1 Adverse Events

All AE summaries will be presented overall and by treatment, separately for the Epoch 1 and 2 Safety Analysis Sets. Safety endpoints are presented in Sections 1.2.1.2 and 1.2.2.2 for Epoch 1 and Epoch 2, respectively.

Any TEAE that is recorded by the investigator as "possibly related" or "probably related" to IP 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. 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. All other AE's will be considered a systemic 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, separately for the Epoch 1 and Epoch 2 Safety Analysis Sets. In addition, AEs of subjects who were never treated with IP will be listed, separately for the Epoch 1 and Epoch 2 Safety Analysis Sets.

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

TEAE summaries will also be presented by sex, age and race (with subgroups defined as in Section 6.5.1.4). The following approaches will be used, where applicable:

- Overall summary: Overall summary: Any TEAE, TEAE related to IP, severe TEAE, severe TEAE related to IP, serious TEAEs, serious TEAE related to IP, and TEAE leading to discontinuation for the epoch, 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 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 groups.

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 group 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 = 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 in Epoch 1 = 1000 × (Total Number of AEs in Epoch 1 for all subjects in the treatment group / Total SYs in Epoch 1 in the treatment group).
- Total SYs in Epoch 1 will be calculated by summing subjects' durations in Epoch 1 through the end of Epoch 1. Each subject's duration will be calculated as: (last date of Epoch 1– date of initial dose of IP in the Epoch 1 + 1) / 365.2425. If the subject's last date in the Epoch is missing, then the date of last dose of IP will be used if available.

6.6.1.2 Analysis of Time-to-Adverse Event

Time-to-event AE analyses will only be presented for Epoch 1 data.

6.6.1.2.1 Definition

To account for both the occurrence and timing of the first TEAE, time-to-event analysis will be performed. For analysis purposes, event time is defined as date of initial dose of IP (the time origin) to date of first occurrence of the event of interest, calculated as: date of the first occurrence - date of initial dose + 1. Note: Time origin is date of initial dose.

6.6.1.2.2 Censoring

Subjects may fall into 1 of 3 categories: Subjects experienced the event and hence their event times are observed, or withdrew prematurely without experiencing the event and hence their event times are right censored (not observed), or are lost to follow-up without experiencing the event and hence their event times are right censored (not observed).

The applicable observational period is the start of initial dose through the end of Epoch 1. For each subject who prematurely withdraws from Epoch 1 without having the TEAE (event = 0, time is right censored): Event time will be censored at date of premature withdrawal, and the censored time will be calculated as: date of the premature withdrawal in Epoch 1 – date of initial dose of IP in Epoch 1 +1.

For each subject who is lost to follow up without having the TEAE (event = 0, time is censored): Event time will be censored at date of last visit date, and the censored time will be calculated as: date of the last visit – date of initial dose of IP in Epoch 1 +1.

6.6.1.2.3 Handling of Missing Dates

If the date of premature withdrawal is missing, then the non-missing date of last visit in Epoch 1 will be used in calculating the censored time. If the last visit date is missing, then the date of last dose of IP will be used in calculating the censored time. If the date of last dose of IP is missing, then the censored time will be set missing.

6.6.1.2.4 Analysis approach

In order to estimate the treatment effect on AE incidence, appropriately accounting for exposure time, a Cox regression analysis of time to first occurrence of the AE in Epoch 1 will be performed using a Cox proportional hazards model with treatment as a main effect. Tied event times will be handled using the exact method. Cox regression analysis of time to first occurrence of the AE in Epoch 1 will be performed, regardless of the AE incidence in Epoch 1; non-estimable values will be presented as 'ND' (Not done). Exposure time will be calculated as: date of assessment – date of first dose + 1.

An overall HR for the main effect of treatment (HYQVIA versus Placebo) for each of the AEs will be provided, as well as a HR for treatment within time intervals in order to assess risk of AE from interval to interval (increasing relative hazard, decreasing, constant). In addition, two-sided 95% CIs will be reported. The time intervals are: 0 to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, and >12 weeks. The analysis aims to address the potential impact of differential exposure time on occurrence of AE, and to characterize the relationship of AEs to treatment, overall by time interval. For analyses within time intervals, subjects who experience an event in a particular interval will not be included in the at-risk set for subsequent intervals.

Cox regression analysis is purely descriptive, and therefore no formal statistical hypothesis testing will be performed. The following statistics will be provided in summarizing results from analysis:

- Overall HR (HYQVIA vs. Placebo for each TEAE).
- Time-interval-specific HRs (HYQVIA vs. placebo in time interval).
- Two-sided 95% CIs for each HR.

6.6.2 Adverse Events of Special Interest

AEs of special interest will be reported by MedDRA PT, and overall. 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 actual treatment, PT and overall.

Adverse events of special interest (source: Section 12.7.12 of the study protocol) 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, and were included in the Interim Safety Analysis 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-pre-SC baseline to each assessment timepoint will be provided for categorical variables. Results will be presented by treatment group and, where applicable, overall. The following laboratory variables/parameters will be summarized, and the data will be listed in the subject data listing, as indicated.

Hematology	The hematology panel will consist of hemoglobin (HOB), 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-glut amyl-transferase (GET), lactate dehydrogenase (LDH), creating phosphokinase (CAP), blood urea nitrogen (BUN), creatinine, and glucose.	Summary and Listing
Hemolytic Panel	The hemolytic panel includes hemoglobin [HOB], LD., serum haptoglobin, plasma-free HGB, serum direct anti-globulin (direct Coombs) test, reticulocyte count, and urine hemosiderin. If indicated, LDH isoenzymes and antibody elution may also be done. Certain determinations depend on a review of the on-treatment hemoglobin change from E1W1 value. If the E1W1 hemoglobin is missing, then the screening value will be used for required comparisons.	Listing only
Hemoglobin A1C	Hemoglobin A1C is collected at the Screening, E1W1, E1INT, and EOE1T visits for subjects who have a known diagnosis of diabetes mellitus. Results will be listed. Summaries will not be provided.	Listing only
Iron Panel	Serum iron, ferritin, and total iron binding capacity (TIBC) are included in the iron panel.	Listing only
Urinalysis	Urine 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 was only performed at Screening.	Listing only
Pregnancy Test	Positive pregnancy tests	Listing only

Summaries of shift-from-pre-SC 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-pre-SC 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 the pre-SC baseline, and at the post-baseline maximum Grade during Epoch 1.

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

The following will be provided in subject data listings.

- Hematology values for subjects who met toxicity Grade ≥3 criteria for any hematology parameter
- Blood chemistry values for subjects who met toxicity Grade ≥3 criteria for any blood chemistry parameter
- Hemolytic parameters panel
- Hemolytic parameters panel for subjects who showed a reduction in Hgb level of 1 g/dL or more at any time after the first full dose of IP treatment during the epoch

6.6.4 Vital Signs

Vital signs endpoints are not explicitly mentioned in the study protocol as endpoints but are included in this SAP, and were included in the Interim Safety Analysis SAP, to further assess the safety of HYQVIA. Raw (actual) values for vital signs and their changes from pre-SC baseline at each post-baseline assessment time point will be summarized by treatment group, 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 (pre-SC) baseline criteria listed in Table 1. Number and percentage of subjects with PCS post-baseline values in Epoch 1 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[b]
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.

[b] Pre-SC baseline for Epoch 1 data, pre-IV baseline for Epoch 2 data.

6.6.5 Electrocardiogram

Electrocardiogram (ECG) data (overall interpretation) will be provided in subject listing only. Note that clinically significant, treatment-emergent changes in ECGs will be recorded in the study database as AEs.

6.6.6 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.

6.6.7 Anti-rHuPH20 Antibody Development

Immunogenicity in Epoch 1 is of key clinical and regulatory interest in this study. The immunogenicity endpoints corresponding to the immunology safety objective include:

- Anti-rHuPH20 antibody titers, specifically subjects with:
    - Positive titers (≥1:160),
    - Negative titers (<1:160),
    - Any abnormal titers or rises above baseline,
    - Elevated titers.

A subject is defined as having elevated anti-rHuPH20 antibody titers if the subject has two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers.

- Binding and/or neutralizing antibodies to rHuPH20, specifically subjects with:
    - Neutralizing antibodies,
    - High-binding antibodies,
    - Low-binding antibodies.

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.

Subjects who have two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers will be classified as experiencing treatment-emergent development of anti-rHuPH20 antibodies at the first of the two time points.

Anti-rHuPH20 antibody development will be summarized (number and percentage by category: elevated, neutralizing, high-binding, low binding) by treatment group and overall, and by visit.

All treatment-emergent AEs and related AEs in subjects with anti-rHuPH20 antibody titers >= 1:160 will be summarized and presented in a subject data listing.

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

- Subjects with positive anti-rHuPH20 antibody titers (≥ 1:160)
    - AEs before positive titer
    - AEs after positive titers
- Subjects with only negative anti-rHuPH20 antibody titers (< 1:160)
    - AEs before negative titer
    - AEs after negative titers
- 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
- AEs for subjects with elevated titers

If at least 5 subjects in each treatment group have elevated titers, then the descriptive analysis will be conducted to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs of interest. This analysis relates to a regulatory request (FDA request, dated 17 April 2019)

6.6.8 Extent of Exposure and Compliance

Exposure to investigational product and compliance will be summarized separately for the Epoch 1 and Epoch 2 Safety Analysis Sets, by treatment/cohort and overall. Exposure to IP in Epoch 1 will be determined from infusion data, which will be collected in a hand-held device regardless of location (ie, home, clinic, other) of infusion administration. For Epoch 2, infusions will be performed in the clinic.

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

- needle length at baseline (6 mm, 9 mm, 12 mm, 14 mm),
- 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 applied infusions including completed, interrupted, and stopped infusions for each subject during the study divided by the number of expected infusions if subject had completed Epoch 1, multiplied by 100),
- infusion compliance (total number of applied 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 applied 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 group and overall. Needle length will also be cross-tabulated against BMI categories (as defined in Section 6.3.1).

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

- <1 month
- 1 - <3 months
- 3 - <6 months
- ⩾1 month
- ⩾3 months
- ⩾6 months

Listings of investigational product exposure and compliance will be provided using the Epoch 1 and Epoch 2 Safety Analysis Sets. Listings of Investigational Product Accountability will also be provided for Epoch 1 and Epoch 2 separately.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Analyses for trough serum IgG are described in Section 6.9. Additional analysis may be conducted and will be described in a separate pharmacokinetic/pharmacodynamic data analysis plan if applicable.

6.7.2 Pharmacodynamic Analysis

Not applicable.

6.7.3 Biomarker Analysis

Not applicable.

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

6.8.1 Epoch 1

All Epoch 1 PRO and healthcare resources utilization (HRU) endpoint analyses will be based on the MITT Analysis Set. Further exploratory analyses of PRO data maybe specified in a separate PRO-specific analysis plan.

1. *Change from pre-SC treatment baseline in SF-36 scores*

The SF-36 scores will be computed according to the developer's scoring algorithm (Version 2, Ware et al., 2000). Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) for baseline, end of treatment period (last non-missing post-baseline outcome) and the change from baseline will be presented for SF-36 overall and by planned treatment arm 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 (PCS) and the mental component score (MCS).

A listing for Epoch 1 SF-36 score data will be presented for the MITT Analysis Set.

2. *Change from pre-SC treatment baseline in EQ-5D scores*

Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) for baseline, end of treatment (last non-missing post-baseline outcome) and the change from baseline will be presented overall and by planned treatment for the following EQ-5D (EQ-5D-3L, The EuroQol Group, 1990) variables:

- Individual EQ-5D 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 end of treatment (last non-missing post-baseline outcome) for the number of subjects at each level of each EQ-5D dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by planned treatment group and overall.

A listing for Epoch 1 EQ-5D score data will be presented for the MITT Analysis Set.

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

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

- Hyqvia (irrespective of relapse status),
- Placebo (irrespective of relapse status),
- Hyqvia and relapsed,
- Placebo and relapsed,
- Hyqvia and did not relapse,
- Placebo and did not relapse,

- Relapsed (irrespective of planned treatment),
- Did not relapse (irrespective of planned treatment).

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 during Epoch 1.
- Number of days off from school/work per subject during Epoch 1 in subjects who have had at least one day off from school/work during Epoch 1.
- Number of hospitalizations per subject during Epoch 1.
- Number of hospitalizations per subject during Epoch 1 in subjects who have had at least one hospitalization during Epoch 1.
- Number of hospitalizations related to CIDP per subject during Epoch 1.
- Number of hospitalizations related to CIDP per subject during Epoch 1 in subjects who have had at least one hospitalization related to CIDP during Epoch 1.
- Number of ER visits per subject during Epoch 1.
- Number of ER visits per subject during Epoch 1 in subjects who have had at least one ER visit during Epoch 1.
- Number of ER visits related to CIDP per subject during Epoch 1.
- Number of ER visits related to CIDP per subject during Epoch 1 in subjects who have had at least one ER visit related to CIDP during Epoch 1.
- Number of ER visits lasting longer than 24 hours per subject during Epoch 1.
- Number of ER visits lasting longer than 24 hours per subject during Epoch 1 in subjects who have had at least one ER visit lasting longer than 24 hours during Epoch 1.
- Number of ER visits lasting longer than 24 hours related to CIDP per subject during Epoch 1.
- Number of ER visits lasting longer than 24 hours related to CIDP per subject during Epoch 1 in subjects who have had at least one ER visit related to CIDP during Epoch 1.

A listing for Epoch 1 HRU data will be presented for the MITT 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 the end of treatment period (last non-missing post-baseline outcome) 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 planned treatment.

A listing for Epoch 1 TSQM-9 data will be presented for the MITT 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 end of treatment period (last non-missing post-baseline outcome) overall and by planned treatment.

A listing for Epoch 1 treatment preference data will be presented for the MITT 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 the end of treatment period (last non-missing post-baseline outcome) overall and by planned treatment.

A listing for Epoch 1 PGIC data will be presented for the MITT Analysis Set.

6.8.2 Epoch 2

All Epoch 2 PRO and HRU endpoints will be presented for the following analysis cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG,
- E1:Placebo Relapse / E2:IGIV,
- E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG,
- E1:HYQVIA/HyQvia Relapse / E2:IGIV.

In addition, overall results will be presented for the following combined cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG and E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG combined,

- E1:Placebo Relapse / E2:IGIV and E1:HYQVIA/HyQvia Relapse / E2:IGIV combined.

1. Change from pre-IV treatment baseline in SF-36 scores

The SF-36 scores will be computed according to the developer's scoring algorithm (Version 2, Ware et al. 2000). Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) for baseline, end of treatment period (last non-missing post-baseline outcome) and the change from baseline will be presented for SF-36 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 (PCS) and the mental component score (MCS).

A listing for Epoch 2 SF-36 score data will be presented for the Epoch 2 Safety Analysis Set.

2. Change from pre-IV treatment baseline in EQ-5D scores

Descriptive statistics (n, mean, median, SD, first and third quartiles, minimum, maximum) for baseline, end of treatment period (last non-missing post-baseline outcome) and the change from baseline will be presented for the following EQ-5D (EQ-5D-3L, EuroQol, 1990) variables:

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

Additionally, descriptive statistics (number and percentage of subjects) will be presented for the number of subjects at each level of each EQ-5D dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at baseline and end of treatment (last non-missing post-baseline outcome).

A listing for Epoch 2 EQ-5D score data will be presented for the Epoch 2 Safety Analysis Set.

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

Descriptive summaries (n, mean, median, SD, first and third quartiles, minimum, maximum) 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 during Epoch 1.

- Number of days off from school/work per subject during Epoch 1 in subjects who have had at least one day off from school/work during Epoch 1.
- Number of hospitalizations per subject during Epoch 1.
- Number of hospitalizations per subject during Epoch 1 in subjects who have had at least one hospitalization during Epoch 1.
- Number of hospitalizations related to CIDP per subject during Epoch 1.
- Number of hospitalizations related to CIDP per subject during Epoch 1 in subjects who have had at least one hospitalization related to CIDP during Epoch 1.
- Number of ER visits per subject during Epoch 1.
- Number of ER visits per subject during Epoch 1 in subjects who have had at least one ER visit during Epoch 1.
- Number of ER visits related to CIDP per subject during Epoch 1.
- Number of ER visits related to CIDP per subject during Epoch 1 in subjects who have had at least one ER visit related to CIDP during Epoch 1.
- Number of ER visits lasting longer than 24 hours per subject during Epoch 1.
- Number of ER visits lasting longer than 24 hours per subject during Epoch 1 in subjects who have had at least one ER visit lasting longer than 24 hours during Epoch 1.
- Number of ER visits lasting longer than 24 hours related to CIDP per subject during Epoch 1.
- Number of ER visits lasting longer than 24 hours related to CIDP per subject during Epoch 1 in subjects who have had at least one ER visit related to CIDP during Epoch 1.

A listing for Epoch 2 HRU data will be presented for the Epoch 2 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 at baseline and the end of treatment period (last non-missing post-baseline outcome) for overall treatment satisfaction score, as measured by the TSQM-9, and individual items.

A listing for Epoch 2 TSQM-9 data will be presented for the Epoch 2 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 at baseline and the end of treatment period (last non-missing post-baseline outcome).

A listing for Epoch 2 treatment preference data will be presented for the Epoch 2 Safety Analysis Set.

6. PGIC

Descriptive statistics (number and percentage of subjects) for the end of treatment period (last non-missing post-baseline outcome) for each level of the PGIC will be presented.

A listing for Epoch 2 PGIC data will be presented for the Safety Analysis Set.

6.9 Other Analyses

6.9.1 Epoch 1

1. Trough plasma concentrations of IgG

Analyses of serum trough concentrations of IgG will include subjects in the Epoch 1 MITT Analysis Set. Serum trough concentrations of IgG will be summarized overall and by planned treatment using descriptive statistics (n, mean, SD, median, minimum, maximum, geometric mean, SD of the geometric mean) for the following timepoints: pre-SC baseline, Epoch 1 Week 1, Epoch 1 Interim Visit and the end of Epoch 1 treatment visit or early termination visit.

In addition, the relationship between serum IgG trough levels after day 120 (every 2-week dosing E1W27/EOE1T; every 3-week dosing E1W26/EOE1T, every 4-week dosing E1W28/EOE1T) or at the time of CIDP symptom relapse (E1ET or Pre-IV BL/E2W1) and relapse status (relapse, no relapse) will be assessed as an exploratory analysis. Serum trough concentrations of IgG will be summarized by planned treatment and relapse status and overall using descriptive statistics (n, mean, SD, median, minimum, maximum, geometric mean, SD of the geometric mean).

A listing for Epoch 1 serum trough concentrations of IgG will be presented for the MITT Analysis Set.

6.9.2 Epoch 2

1. Trough plasma concentrations of IgG

Analyses of serum trough concentrations of IgG for Epoch 2 will be presented for the following analysis cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG,
- E1:Placebo Relapse / E2:IGIV,
- E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG,
- E1:HYQVIA/HyQvia Relapse / E2:IGIV.

In addition, overall results will be presented for the following combined cohorts:

- E1:Placebo Relapse – E2: GGL/KIOVIG and E1:HYQVIA/HyQvia Relapse / E2:GGL/KIOVIG combined,
- E1:Placebo Relapse / E2:IGIV and E1:HYQVIA/HyQvia Relapse / E2:IGIV combined.

Serum trough concentrations of IgG will be summarized using descriptive statistics (n, mean, SD, median, minimum, maximum, geometric mean, SD of the geometric mean) for the following timepoints: pre-IV baseline, Epoch 2 Week 13 Interim Timepoint and the end of Epoch 2 treatment visit or early termination visit.
A listing for Epoch 2 serum trough concentrations of IgG will be presented for the Safety Analysis Set.

6.10 Interim Analyses

Two interim analyses are planned:

- Interim Safety Analysis, which is Epoch 1 and Epoch 2 safety analysis.
- Formal Interim Analysis, which is the final analysis of Epoch 1 data.

The purpose and timing of each analysis are defined below.

6.10.1 Interim Safety Analysis

An interim safety analysis was performed during early conduct of the study in order to closely monitor safety and determine the anti-rHuPH20 antibody response in CIDP subjects. Data from the interim safety analysis was independently reviewed by the DMC, and the Interim Safety Analysis Report along with the DMC recommendation was used to update regulatory authorities.

The interim safety analysis was planned to include a minimum of 30 subjects treated with HYQVIA/HyQvia (ie, a total of approximately 60 randomized subjects), and followed up for a minimum of 30 days following the second full-dose administration. Full details of the planned analyses for the interim safety analysis are described in a separate Interim Safety Analysis SAP.

6.10.2 Formal Interim Analysis (Epoch 1 Final Analysis)

Formal Interim Analysis (Epoch 1 Final Analysis) *will be performed to evaluate the efficacy of HyQvia versus placebo as a maintenance therapy for CIPD to prevent relapse of neuromuscular disability and impairment. All of the following will apply:*

- *Analysis will be performed when all subjects have completed participation in Epoch 1.*
- *Definition of completed participation: Any subject who completes Epoch 1, or discontinues prematurely from Epoch 1, irrespective of reason for withdrawal, is considered as having completed participation in Epoch 1.*
- *At the completion of Epoch 1, all Epoch 1 data will be locked, treatment assignment will be unblinded, and all Epoch 1 data will be analyzed as preplanned in the study SAP. The analysis will be considered the final analysis of Epoch 1 data. All available Epoch 2 data will be included in subject data listings along with Epoch 1 data and will not be analyzed.*
- *The study SAP will be finalized and approved prior to Epoch 1 data lock and treatment unblinding.*

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

The safety of subjects in Study 161403 and Extension Study 161505 is monitored jointly by an independent, external DMC. Details are provided in the Study 161403 protocol, and procedural information is provided in the DMC Charter. Two DMC analyses will be performed: periodic DMC analysis of Epoch 1 and Epoch 2 (approximately every 6 months), and a 30-subject DMC analysis of Epoch 1 and Epoch 2. Study data, presented in tables, figures and listings, will be submitted to the DMC, established to monitor the study for any safety or medical concerns, and, based on their review of the data, may recommend to the study Sponsor one of the following: 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 stopping.

The periodic DMC analyses are performed approximately every 6 months until clinical database lock for the study final analysis, and mainly for the purpose of subject safety monitoring. The 30-subject DMC analysis was performed for the purpose of early regulatory submission to update authorities regarding safety. The analysis was completed prior to finalization of Interim Safety Analysis SAP and was performed when a minimum of 15 subjects were treated with HYQVIA (ie, a total of approximately 30 randomized subjects, 1:1 randomization ratio), and followed up for a minimum of 30 days following the second full-dose administration (ie, 30 subjects with 2 full doses, plus 30 days of follow-up). Note that the 30-subject DMC analysis, though not worded in the Study 161403 protocol as such, is one of the periodic DMC analyses but focused on approximately 30 subjects.

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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Changes to protocol-specified analyses have been made in this SAP, as follows:

- Epoch 1 and Epoch 2 Enrolled Subjects Sets were added to support disposition summaries (Section 5.0).
- The definition of the Epoch 1 per-protocol analysis set was updated to additionally exclude subjects who had 'critical' protocol deviations (Section 5.1) – whereas in the protocol only 'major' protocol deviations are referred to. Protocol deviation categories relevant to the PP analysis set are also describe in this SAP but were not described in the study protocol.
- Clinical laboratory endpoints are not explicitly stated in the study protocol as endpoints but are included in this SAP, and the Interim Safety Analysis SAP, for further assessment of the safety profile of HYQVIA.
- 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.
- Infusion parameters are not explicitly specified in the study protocol as data for analysis, but are included in this SAP to further assess the safety and tolerability of HYQVIA.
- Cox regression analysis hazard ratio content was clarified to better reflect the analysis plan to be performed as per the Interim Safety Analysis SAP.
- In the study protocol it is stated: "The median time to response will be presented for the GAMMAGARD LIQUID/KIOVIG Placebo Relapse analysis set." To incorporate possible censoring, percentiles for time to response (functional improvement) will be estimated using the Kaplan-Meier method, as described in Section 6.5.2.3.
- [redacted]
- Subgroup analyses for the Epoch 1 and Epoch 2 primary endpoints were added to assess for exploratory evidence of a differential treatment effect across key subgroups (Sections 6.5.1.4 and 6.5.2.4). Note that the sponsor agreed to present safety and effectiveness data by gender, age and racial subgroup and to identify any modifications of dose or dose interval needed for any specific subgroups in a pre-IND response to FDA written response dated 20 April 2015.

- Epoch 1 trough plasma concentrations of IgG will be based on the MITT Analysis Set (Section 6.9.1), not the Safety Analysis Set as described in the study protocol (Protocol Section 14.1.4.3).
- To assess the robustness of inferences from the Epoch 2 primary analysis to departures from the MCAR premise, a sensitivity analysis based on the missing not at random (MNAR) premise was added. For this analysis, subjects with missing response status at the completion of the IV treatment period (6 months) or the last study visit of the IV treatment period will be imputed as non-responders.
- A sensitivity analysis for the Epoch 2 primary analysis in the E1:Placebo Relapse – E2: GGL/KIOVIG analysis set will be conducted, where the two-sided 95% confidence interval for the responder rate will be determined using the Clopper-Pearson method. The Clopper-Pearson approach was recommended by the FDA in an interaction dated March 28th 2016.
- An Epoch 2 exploratory analysis to assess regression to the mean for the primary endpoint of responder rate will be conducted. This analysis was added following an EMA scientific advice letter dated 22nd Jan 2015 – however the method of (Yan and Su, 2010) will be applied, rather than the ad-hoc method described in the EMA interaction.
- Further clarification was added regarding the calculation and presentation of grip strength results: 1) presented for both more affected and less affected hand at respective baselines for each epoch, 2) the maximum of three measurements is to be used to determine hand - grip strength at each timepoint. A cross-tabulation of needle size with BMI was added (Section 6.6.8).

9.0 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. In addition, there were textual changes purely to improve the flow, organization and clarity.

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 country, 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

Epoch 1 baseline value is defined as the pre-subcutaneous treatment baseline visit value, if non-missing. If missing, then the Screening visit value will be used (if non-missing).

Epoch 2 Baseline value is the pre-intravenous treatment/Epoch 2 Week 1 visit value, if non-missing. If missing, then the last non-missing assessment prior to administration of the first dose of IP in Epoch 2 (GAMMAGARD or GAMUNEX®-C) will be used.

9.2.3 Definition of Missing Relapse Outcome

For the Epoch 1 primary endpoint analysis and associated sensitivity analyses (1, 2, and 3), 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 the pre-SC treatment baseline) within 7 days.

For the Epoch 1 primary endpoint sensitivity analysis 4 (alternate relapse definition), missing relapse outcome is defined as:

- Missing Baseline INCAT assessment, or
- No post-baseline INCAT assessments.

9.2.4 Definition of Visit Windows

For statistical analysis purposes, all efficacy 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:

- Epoch 1 Infusion data (Table 2),
- Epoch 1 Efficacy and PRO assessments:
  - 2-week regimen (Table 3),
  - 3-week regimen (Table 4),
  - 4-week regimen (Table 5),
- Epoch 2 Efficacy and PRO assessments (Table 6).

Table 2: Epoch 1 Analysis Windows for Infusion data

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	9	Exception [a]
2	15 (+/-3)	12 to 18	12 to 21	10	23	
3	29 (+/-3)	26 to 32	26 to 35	24	37	
4	43 (+/-3)	40 to 46	40 to 49	38	51	
<etc>	<etc>	<etc>	<etc>	Earliest accepted start -2 days	Latest accepted end +2 days	
3-week dosing frequency						
1	1 (+/-3)	1	3	1	13	Exception [a]
2	22 (+/-3)	19 to 25	19 to 28	14	34	
3	43 (+/-3)	40 to 46	40 to 49	35	55	
4	64 (+/-3)	61 to 67	61 to 70	56	76	
<etc>	<etc>	<etc>	<etc>	Earliest accepted start -5 days	Latest accepted end +6 days	
4-week dosing frequency						
1	1	1	3	1	16	Exception [a]
2	29	26 to 32	26 to 35	17	44	
3	57	54 to 60	54 to 63	45	72	
4	85	82 to 88	82 to 91	73	100	
<etc>				Earliest accepted start -9 days	Latest accepted end +9 days	

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

Table 3: Epoch 1 Analysis Windows for Efficacy and PRO Assessments in Subjects with SC Dosing Every 2 Weeks

Analysis Visit	Epoch 1 Relative Target Day	Epoch 1 Relative Start Day	Epoch 1 Relative End Day	Other Assignment Criteria
INCAT				
SCREENING	-42 (+/-28)	-70	-18	If E1 relative day is missing and collected visit indicates SCREENING
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1INT	105 (+/-3)	2	108	If E1 relative day is missing and collected visit indicates E1 and week number ≤ 15
EOE1T	189 (+/-3)	109	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number > 15
Hand Grip Strength, MRC Sum Score				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1INT	105 (+/-3)	2	108	If E1 relative day is missing and collected visit indicates E1 and week number ≤ 15
EOE1T	189 (+/-3)	109	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number > 15
SF-36, EQ-5D, Treatment Satisfaction, Treatment Preference				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
EOE1T	189 (+/-3)	2	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number ≥ 1
Patient Global Impression of Change				
EOE1T	189 (+/-3)	2	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number ≥ 1
R-ODS				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1W1	7	2	10	If E1 relative day is missing and collected visit indicates E1 and week number 1
E1W2	14	11	17	If E1 relative day is missing and collected visit indicates E1 and week number 2
E1W3	21	18	24	If E1 relative day is missing and collected visit indicates E1 and week number 3
E1W4	28	25	31	If E1 relative day is missing and collected visit indicates E1 and week number 4
E1W5	35	32	38	If E1 relative day is missing and collected visit indicates E1 and week number 5
E1W6	42	39	45	If E1 relative day is missing and collected visit indicates E1 and week number 6
E1W7	49	46	52	If E1 relative day is missing and collected visit indicates E1 and week number 7
E1W8	56	53	59	If E1 relative day is missing and collected visit indicates E1 and week number 8

Table 3: Epoch 1 Analysis Windows for Efficacy and PRO Assessments in Subjects with SC Dosing Every 2 Weeks

Analysis Visit	Epoch 1 Relative Target Day	Epoch 1 Relative Start Day	Epoch 1 Relative End Day	Other Assignment Criteria
E1W9	63	60	66	If E1 relative day is missing and collected visit indicates E1 and week number 9
E1W10	70	67	73	If E1 relative day is missing and collected visit indicates E1 and week number 10
E1W11	77	74	80	If E1 relative day is missing and collected visit indicates E1 and week number 11
E1W12	84	81	87	If E1 relative day is missing and collected visit indicates E1 and week number 12
E1W13	91	88	94	If E1 relative day is missing and collected visit indicates E1 and week number 13
E1W14	98	95	101	If E1 relative day is missing and collected visit indicates E1 and week number 14
E1W15/E1INT	105	102	108	If E1 relative day is missing and collected visit indicates E1 and week number 15
E1W16	112	109	115	If E1 relative day is missing and collected visit indicates E1 and week number 16
E1W17	119	116	122	If E1 relative day is missing and collected visit indicates E1 and week number 17
E1W18	126	123	129	If E1 relative day is missing and collected visit indicates E1 and week number 18
E1W19	133	130	136	If E1 relative day is missing and collected visit indicates E1 and week number 19
E1W20	140	137	143	If E1 relative day is missing and collected visit indicates E1 and week number 20
E1W21	147	144	150	If E1 relative day is missing and collected visit indicates E1 and week number 21
E1W22	154	151	157	If E1 relative day is missing and collected visit indicates E1 and week number 22
E1W23	161	158	164	If E1 relative day is missing and collected visit indicates E1 and week number 23
E1W24	168	165	165	If E1 relative day is missing and collected visit indicates E1 and week number 24
E1W25	175	172	178	If E1 relative day is missing and collected visit indicates E1 and week number 25
E1W26	182	179	185	If E1 relative day is missing and collected visit indicates E1 and week number 26
E1W27/EOE1T	189	186	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number 27

Table 4: Epoch 1 Analysis Windows for Efficacy and PRO Assessments in Subjects with SC Dosing Every 3 Weeks

Analysis Visit	Epoch 1 Relative Target Day	Epoch 1 Relative Start Day	Epoch 1 Relative End Day	Other Assignment Criteria
INCAT				
SCREENING	-42 (+/-28)	-70	-18	If E1 relative day is missing and collected visit in SCREENING
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1INT	98 (+/-3)	2	101	If E1 relative day is missing and collected visit indicates E1 and week number ≤ 14
EOE1T	182 (+/-3)	102	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number > 14
Hand Grip Strength, MRC Sum Score				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1INT	98 (+/-3)	2	101	If E1 relative day is missing and collected visit indicates E1 and week number ≤ 14
EOE1T	182 (+/-3)	102	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number > 14
SF-36, EQ-5D, Treatment Satisfaction, Treatment Preference				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
EOE1T	182 (+/-3)	102	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number ≥ 1
Patient Global Impression of Change				
EOE1T	182 (+/-3)	2	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number ≥ 1
R-ODS				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1W1	7	2	10	If E1 relative day is missing and collected visit indicates E1 and week number 1
E1W2	14	11	17	If E1 relative day is missing and collected visit indicates E1 and week number 2
E1W3	21	18	24	If E1 relative day is missing and collected visit indicates E1 and week number 3
E1W4	28	25	31	If E1 relative day is missing and collected visit indicates E1 and week number 4
E1W5	35	32	38	If E1 relative day is missing and collected visit indicates E1 and week number 5
E1W6	42	39	45	If E1 relative day is missing and collected visit indicates E1 and week number 6
E1W7	49	46	52	If E1 relative day is missing and collected visit indicates E1 and week number 7
E1W8	56	53	59	If E1 relative day is missing and collected visit indicates E1 and week number 8
E1W9	63	60	66	If E1 relative day is missing and collected visit indicates E1 and week number 9
E1W10	70	67	73	If E1 relative day is missing and collected visit indicates E1 and week number 10

Table 4: Epoch 1 Analysis Windows for Efficacy and PRO Assessments in Subjects with SC Dosing Every 3 Weeks

Analysis Visit	Epoch 1 Relative Target Day	Epoch 1 Relative Start Day	Epoch 1 Relative End Day	Other Assignment Criteria
E1W11	77	74	80	If E1 relative day is missing and collected visit indicates E1 and week number 11
E1W12	84	81	87	If E1 relative day is missing and collected visit indicates E1 and week number 12
E1W13	91	88	94	If E1 relative day is missing and collected visit indicates E1 and week number 13
E1W14/E1Int	98	95	101	If E1 relative day is missing and collected visit indicates E1 and week number 14
E1W15	105	102	108	If E1 relative day is missing and collected visit indicates E1 and week number 15
E1W16	112	109	115	If E1 relative day is missing and collected visit indicates E1 and week number 16
E1W17	119	116	122	If E1 relative day is missing and collected visit indicates E1 and week number 17
E1W18	126	123	129	If E1 relative day is missing and collected visit indicates E1 and week number 18
E1W19	133	130	136	If E1 relative day is missing and collected visit indicates E1 and week number 19
E1W20	140	137	143	If E1 relative day is missing and collected visit indicates E1 and week number 20
E1W21	147	144	150	If E1 relative day is missing and collected visit indicates E1 and week number 21
E1W22	154	151	157	If E1 relative day is missing and collected visit indicates E1 and week number 22
E1W23	161	158	164	If E1 relative day is missing and collected visit indicates E1 and week number 23
E1W24	168	165	165	If E1 relative day is missing and collected visit indicates E1 and week number 24
E1W25	175	172	178	If E1 relative day is missing and collected visit indicates E1 and week number 25
E1W26	182	179	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number 26

Table 5: Epoch 1 Analysis Windows for Efficacy and PRO Assessments in Subjects with SC Dosing Every 4 Weeks

Analysis Visit	Epoch 1 Relative Target Day	Epoch 1 Relative Start Day	Epoch 1 Relative End Day	Other Assignment Criteria
INCAT				
SCREENING	-42 (+/-28)	-70	-18	If E1 relative day is missing and collected visit in SCREENING
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1INT	112 (+/-3)	2	115	If E1 relative day is missing and collected visit indicates E1 and week number ≤ 16
EOE1T	196 (+/-3)	116	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number > 16
Hand Grip Strength, MRC Sum Score				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1INT	112 (+/-3)	2	115	If E1 relative day is missing and collected visit indicates E1 and week number ≤ 16
EOE1T	196 (+/-3)	116	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number > 16
SF-36, EQ-5D, Treatment Satisfaction, Treatment Preference				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
EOE1T	196 (+/-3)	2	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number ≥ 1
Patient Global Impression of Change				
EOE1T	196 (+/-3)	2	E1 Last Visit	If E1 relative day is missing and collected visit indicates E1 and week number ≥ 1
R-ODS				
E1BL	-14 (+/-3)	-17	1	If E1 relative day is missing and collected visit indicates BASELINE
E1W1	7	1	10	If E1 relative day is missing and collected visit indicates E1 and week number 1
E1W2	14	11	17	If E1 relative day is missing and collected visit indicates E1 and week number 2
E1W3	21	18	24	If E1 relative day is missing and collected visit indicates E1 and week number 3
E1W4	28	25	31	If E1 relative day is missing and collected visit indicates E1 and week number 4
E1W5	35	32	38	If E1 relative day is missing and collected visit indicates E1 and week number 5
E1W6	42	39	45	If E1 relative day is missing and collected visit indicates E1 and week number 6
E1W7	49	46	52	If E1 relative day is missing and collected visit indicates E1 and week number 7
E1W8	56	53	59	If E1 relative day is missing and collected visit indicates E1 and week number 8
E1W9	63	60	66	If E1 relative day is missing and collected visit indicates E1 and week number 9
E1W10	70	67	73	If E1 relative day is missing and collected visit indicates E1 and week number 10

Table 5: Epoch 1 Analysis Windows for Efficacy and PRO Assessments in Subjects with SC Dosing Every 4 Weeks

Analysis Visit	Epoch 1 Relative Target Day	Epoch 1 Relative Start Day	Epoch 1 Relative End Day	Other Assignment Criteria
E1W11	77	74	80	If E1 relative day is missing and collected visit indicates E1 and week number 11
E1W12	84	81	87	If E1 relative day is missing and collected visit indicates E1 and week number 12
E1W13	91	88	94	If E1 relative day is missing and collected visit indicates E1 and week number 13
E1W14	98	95	101	If E1 relative day is missing and collected visit indicates E1 and week number 14
E1W15	105	102	108	If E1 relative day is missing and collected visit indicates E1 and week number 15
E1W16/E1Int	112	109	115	If E1 relative day is missing and collected visit indicates E1 and week number 16
E1W17	119	116	122	If E1 relative day is missing and collected visit indicates E1 and week number 17
E1W18	126	123	129	If E1 relative day is missing and collected visit indicates E1 and week number 18
E1W19	133	130	136	If E1 relative day is missing and collected visit indicates E1 and week number 19
E1W20	140	137	143	If E1 relative day is missing and collected visit indicates E1 and week number 20
E1W21	147	144	150	If E1 relative day is missing and collected visit indicates E1 and week number 21
E1W22	154	151	157	If E1 relative day is missing and collected visit indicates E1 and week number 22
E1W23	161	158	164	If E1 relative day is missing and collected visit indicates E1 and week number 23
E1W24	168	165	165	If E1 relative day is missing and collected visit indicates E1 and week number 24
E1W25	175	172	178	If E1 relative day is missing and collected visit indicates E1 and week number 25
E1W26	182	179	185	If E1 relative day is missing and collected visit indicates E1 and week number 26
E1W27	189	186	192	If E1 relative day is missing and collected visit indicates E1 and week number 27
E1W28/EOE1T	193	193	E1 Last Visit	

Table 6: Epoch 2 Analysis Windows for Efficacy and PRO Assessments (IVIG Dosing Every 3 Weeks)

Analysis Visit	Epoch 2 Relative[a] Target Day	Epoch 2 Relative Start Day	Epoch 2 Relative End Day	Other Assignment Criteria
INCAT, Hand Grip Strength, MRC Sum Score				
E2BL	1(+/-3)	-3	3	If E2 relative day is missing and collected visit indicates EOE1T or (E2 and week number 1)
E2W1	7(+/-3)	4	14	If E2 relative day is missing and collected visit indicates E2 and week number 1
E2W3	21(+/-3)	15	24	If E2 relative day is missing and collected visit indicates E2 and week number 3
E2W4	28(+/-3)	25	38	If E2 relative day is missing and collected visit indicates E2 and week number 4
E2W7	49(+/-3)	39	59	If E2 relative day is missing and collected visit indicates E2 and week number 7
E2W10	70(+/-3)	60	80	If E2 relative day is missing and collected visit indicates E2 and week number 10
E2W13/E2INT	91(+/-3)	81	101	If E2 relative day is missing and collected visit indicates E2INT or (E2 and week number 13)
E2W16	112(+/-3)	102	122	If E2 relative day is missing and collected visit indicates E2 and week number 16
E2W19	133(+/-3)	123	143	If E2 relative day is missing and collected visit indicates E2 and week number 19
E2W22	154(+/-3)	144	164	If E2 relative day is missing and collected visit indicates E2 and week number 22
E2W25/E2EOT	175 (+/-3)	165	E2 Last Visit	If E2 relative day is missing and collected visit indicates EOE2T or (E2 and week number 25)
SF-36, EQ-5D, Treatment Satisfaction, Treatment Preference, Patient Global Impression of Change				
E2BL	1(+/-3)	-3	3	If E2 relative day is missing and collected visit indicates EOE1T or (E2 and week number 1)
E2W25/EOE2T	175(+/-3)	4	E2 Last Visit	If E2 relative day is missing and collected visit indicates EOE2T or (E2 and week number 25)
R-ODS[a]				
E2BL	-1	-7	-1	If E2 relative day is missing and collected visit indicates BASELINE
E2W1	7	1	10	If E2 relative day is missing and collected visit indicates E2 and week number 1
E2W2	14	11	17	If E2 relative day is missing and collected visit indicates E2 and week number 2
E2W3	21	18	24	If E2 relative day is missing and collected visit indicates E2 and week number 3
E2W4	28	25	31	If E2 relative day is missing and collected visit indicates E2 and week number 4
E2W5	35	32	38	If E2 relative day is missing and collected visit indicates E2 and week number 5
E2W6	42	39	45	If E2 relative day is missing and collected visit indicates E2 and week number 6
E2W7	49	46	52	If E2 relative day is missing and collected visit indicates E2 and week number 7
E2W8	56	53	59	If E2 relative day is missing and collected visit indicates E2 and week number 8

Table 6: Epoch 2 Analysis Windows for Efficacy and PRO Assessments (IVIG Dosing Every 3 Weeks)

Analysis Visit	Epoch 2 Relative[a] Target Day	Epoch 2 Relative Start Day	Epoch 2 Relative End Day	Other Assignment Criteria
E2W9	63	60	66	If E2 relative day is missing and collected visit indicates E2 and week number 9
E2W10	70	67	73	If E2 relative day is missing and collected visit indicates E2 and week number 10
E2W11	77	74	80	If E2 relative day is missing and collected visit indicates E2 and week number 11
E2W12	84	81	87	If E2 relative day is missing and collected visit indicates E2 and week number 12
E2W13	91	88	94	If E2 relative day is missing and collected visit indicates E2 and week number 13
E2W14	98	95	101	If E2 relative day is missing and collected visit indicates E2 and week number 14
E2W15	105	102	108	If E2 relative day is missing and collected visit indicates E2 and week number 15
E2W16	112	109	115	If E2 relative day is missing and collected visit indicates E2 and week number 16
E2W17	119	116	122	If E2 relative day is missing and collected visit indicates E2 and week number 17
E2W18	126	123	129	If E2 relative day is missing and collected visit indicates E2 and week number 18
E2W19	133	130	136	If E2 relative day is missing and collected visit indicates E2 and week number 19
E2W20	140	137	143	If E2 relative day is missing and collected visit indicates E2 and week number 20
E2W21	147	144	150	If E2 relative day is missing and collected visit indicates E2 and week number 21
E2W22	154	151	157	If E2 relative day is missing and collected visit indicates E2 and week number 22
E2W23	161	158	164	If E2 relative day is missing and collected visit indicates E2 and week number 23
E2W24	168	165	171	If E2 relative day is missing and collected visit indicates E2 and week number 24
E2W25/EOE2T	175	172	E2 Last Visit	If E2 relative day is missing and collected visit indicates EOE2T or (E2 and week number 25)

[a] Epoch 2 relative day is based on the date of the first Epoch 2 infusion; the day of the first infusion is E2 Day 1.

9.2.5 Repeated or Unscheduled Assessments of Safety Parameters

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

Unscheduled assessments (i.e., assessments not done at a planned visit) will 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. Specifics regarding handling are addressed in specific endpoint analysis sections.

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 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/Procedures/Medical History)

For prior or concomitant medications (and/or therapies/procedures/medical history), incomplete (fully or partially missing) start date and/or stop date of medication (and/or therapies/procedures/medical history) 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.

9.2.8.1.1 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.

9.2.8.1.2 Missing Month Only

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

9.2.8.1.3 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.

9.2.8.2.1 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.

9.2.8.2.2 Missing Month Only

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

9.2.8.2.3 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 in Epoch 1.
- 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.

9.3 Analysis Software

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

9.3.1 Example SAS® code

9.3.1.1 Continuity-corrected chi-squared test

The following example SAS® code can be utilized for a continuity-corrected chi-squared test which is required for the primary efficacy and sensitivity analyses:

```
ods output ChiSq = chisq(where = (statistic = "Continuity Adj. Chi-
Square")) PdiffCLs = riskdiffcl;

proc freq data = <input data set>;
  table trt*aval / missing nopercent chisq sparse binomial(cl = score)
riskdiff(column = <1 or 2> cl = newcombe);

run;
```

```
ods output close;
```

where the input data set contains only those subjects in the relevant analysis set and where '`aval`' represents a binary relapse outcome variable which equals 1 if the subject relapsed and 0 if the subject did not relapse (with missing values handled according to the specifications for the analysis, Section 6.5.1) and '`trt`' represents planned treatment. A value for the `column` option should be chosen so that the risk difference reflects the difference in relapse rates for Hyqvia versus Placebo.

[redacted]

9.3.1.3 Firth logistic regression for subgroup analyses

Firth logistic regression models will be used for Epoch 1 subgroup analyses to explore possible differential treatment effects across subgroups (Section 6.5.1.4). The following example SAS® code can be utilized:

```
ods output ModelANOVA = type3(where = (parameter = "trt*subgrp"));
proc logistic data=<input data set>;
  class aval trt(ref="Placebo") subgrp / param=ref;
  model aval(event='1') = trt subgrp trt*subgrp / firth;
```

```
run;
ods output close;
```

where '`aval`' represents a binary relapse outcome variable which equals 1 if the subject relapsed and 0 otherwise, '`trt`' represents randomized treatment and '`subgrp`' represents the applicable subgroup variable.

9.4 Study Flow Chart

Figure 1: Study Design for Clinical Study 161403