Clinical Study Protocol

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: Protocol Amendment #6, 20-MAY-2021

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.

A summary of changes to previous protocol versions is appended to the end of the document.

PROTOCOL: 161403

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)
SHORT TITLE:	Phase III Efficacy, Safety, and Tolerability Study of HYQVIA/HyQvia and GAMMAGARD LIQUID/KIOVIG in CIDP
STUDY PHASE:	*Phase 3*
DRUG:	Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG)
IND NUMBER:	014381
EUDRACT NUMBER:	2014-005496-87
NCT Number:	NCT02549170
SPONSOR:	Takeda Development Center Americas, Inc. 95 Hayden Ave, Lexington, MA 02421, USA AND Baxalta Innovations GmbH* Industriestrasse 67, A-1221 Vienna * Baxalta is now part of Shire, a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited
PRINCIPAL/ COORDINATING INVESTIGATOR:	N/A
PROTOCOL HISTORY:	**AMENDMENT 6: 2021 MAY 20** ***Replaces****:* AMENDMENT 5: 2019 MAY 10 **ALL VERSIONS:** Amendment 6: 2021 MAY 20 Amendment 5: 2019 MAY 10 Amendment 4: 2019 FEB 13 Amendment 3: 2018 JAN 31 Amendment 2: 2016 APR 22 Amendment 1: 2015 AUG 25 Original: 2015 MAY 27

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted] MD	**Date:** May 20, 2021

Investigator's Acknowledgement

I have read this protocol for Study 161403.

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)

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Plasma Derived Therapies
Takeda Development Center Americas

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (eg, investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs, INCLUDING SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS), ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

Drug Safety contact information: see SAE Report form
Refer to SAE Protocol Sections and the study team roster for further information

For definitions and information on the assessment of these events, refer to the following:

- Adverse events (AE), Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product(s) (IP[s])	1. Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20; HYQVIA/HyQvia[i]) 2. Immune Globulin Infusion (Human), 10% Solution (IGI, 10%; GAMMAGARD LIQUID/KIOVIG[ii]; IGI, 10% when administered intravenously is also referred to as IGIV 10%) 3. 0.25% human albumin in Lactated Ringer's (LR) solution (placebo) with rHuPH20
Name(s) of Active Ingredient(s)	1. Immune Globulin Infusion 10% (Human) for HYQVIA/HyQvia 2. Immune Globulin Infusion (Human), 10% Solution for GAMMAGARD LIQUID/KIOVIG (The active ingredient is identical in both IPs.)
CLINICAL CONDITION/INDICATION • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	
PROTOCOL ID	161403
PROTOCOL 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)
Short Title	Phase III Efficacy, Safety, and Tolerability Study of HYQVIA/HyQvia and GAMMAGARD LIQUID/KIOVIG in CIDP
STUDY PHASE	Ph3
PLANNED STUDY PERIOD	
Initiation	Q4 2015
Primary Completion	Q1 2022
Study Completion	Q1 2022
Duration	The maximum overall duration of this study is estimated to be approximately 72 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit), including: • An enrollment period of approximately 64 months • A screening/baseline period of up to 8 weeks • Epoch 1 (subcutaneous [SC] treatment period) of 6 months • Epoch 2 (intravenous [IV] treatment period) of 6 months for subjects who relapse during Epoch 1

[i] HYQVIA and HyQvia are registered trademarks of Takeda Development Center Americas / Baxalta Innovations GmbH

[ii] GAMMAGARD LIQUID and KIOVIG are registered trademarks of Takeda Development Center Americas / Baxalta Innovations GmbH

STUDY OBJECTIVES AND PURPOSE

Study Purpose

- The purpose of this study is to provide evidence for the use of HYQVIA/HyQvia as a maintenance therapy option that enables self-infusion of a full therapeutic dose every 2 to 4 weeks in patients with CIDP.
- In addition, this study aims to provide evidence for the use of GAMMAGARD LIQUID/KIOVIG as an IV immunoglobulin treatment option in patients with CIDP.

Study Objectives

Epoch 1: SC Treatment Period with HYQVIA/HyQvia vs Placebo with rHuPH20

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.

Epoch 2: IV Treatment Period with GAMMAGARD LIQUID/KIOVIG

Primary Objective

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

Secondary Objective

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.	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy, Safety, Tolerability
Control Type	Epoch 1 (SC treatment period) – Concurrent (Placebo) Epoch 2 (IV treatment period) – No control
Study Indication Type	Treatment
Intervention model	Parallel
Blinding/Masking	Epoch 1 (SC treatment period) – Double-blind Epoch 2 (IV treatment period) – Open-label
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 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. 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 21.1 Study Flow Chart. Schematics for study assessments and visits are detailed in Section 21.2. Details on the procedures to be performed at each study visit can be found in Section 21.2 Schedule of Study Procedures and Assessments and Section 21.3 Clinical Laboratory Assessments. After informed consent has been obtained, subjects will undergo screening and baseline procedures for the determination of eligibility. During the screening/baseline period, subjects will continue to receive their own IGIV treatment at the same dose and dosing frequency as prescribed prior to their entry into this study.

	Epoch 1: SC Treatment Period In this double-blind, placebo-controlled phase of the study (Epoch 1), eligible subjects will be randomized in a 1:1 ratio to receive either HYQVIA/HyQvia or 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 immunoglobulin G (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.[iii] No conversion factor will be applied when switching from pre-randomization IGIV to HYQVIA/HyQvia (or 0.25% albumin placebo solution with rHuPH20) treatment; that is, the monthly IgG dose of HYQVIA/HyQvia (or matching infusion volume for subjects in the placebo group) will be the same as the subject's pre-randomization monthly dose of IGIV. The number of infusion visits and clinic visits during the SC treatment period will vary across subjects depending on whether their infusion cycles are every 2, 3, or 4 weeks (see Table 21-1, Table 21-2, and Table 21-3). The study product components of HYQVIA/HyQvia (or 0.25% albumin placebo solution with rHuPH20) will be administered sequentially. SC infusion of rHuPH20 solution at a dose of 80 U/g IgG (or its equivalent at 80 U/10 mL of the 0.25% albumin placebo solution) will be administered first, to be followed by SC infusion of IGI, 10% or placebo solution within 10 minutes of completion of the infusion of rHuPH20 solution. To gradually increase the SC infusion volume, a dose ramp-up schedule will be employed until the subject's full dose is reached (see Table 8-3). The first SC administration will take place 2 weeks (±3 days) following the subject's last pre-randomization IGIV administration. Initial SC infusions (during the ramp-up period and, at a minimum, the first full-dose infusion) will be administered at the study site or infusion center to monitor for safety and tolerability, to determine the infusion rate and infusion volume per infusion site that can be tolerated by the subject, and to provide training to the subject (and/or, as applicable, a caregiver who may assist the subject with self -administration) on self-infusion procedures.

[iii] Subjects receiving pre-randomization IGIV treatment every 2, 3, or 4 weeks will receive HYQVIA/HyQvia or placebo with rHuPH20 administration at the same IgG dose (or matching infusion volume for subjects in the placebo group) and dosing frequency during the study. Adjustment to dosing interval as a subject's treatment is being switched from pre-randomization IGIV to SC IGI, 10% or placebo infusion will not be allowed, except for (i) subjects with pre-randomization IGIV dosing every 5 or 6 weeks (for these subjects the dosing interval in the study will be converted to 2, 3, or 4 weeks while maintaining the same monthly equivalent IgG dose [or matching infusion volumes for subjects in the placebo group]), or (ii) subjects for whom the IgG dose (or matching infusion volume for subjects in the placebo group) that is to be administered exceeds a SC maximum infusion volume that a subject can tolerate.

	At the investigator's discretion, the remainder of the SC infusions may take place at the study site, infusion center, or at the subject's home or other suitable location, as acceptable per local regulations and standard practices of the study site. The ability of the subject (and/or caregiver) to perform infusion procedures independently is a prerequisite for self-administration. Training and the investigator/designee's evaluation of the subject's (and/or caregiver's) proficiency in independently self-administering infusions must be documented. Assessments will be conducted to monitor for changes in the subject's functional ability (Inflammatory Neuropathy Cause and Treatment [INCAT] disability score (Hughes et al., 2001)) and other clinical outcome measures, including ADL (Rasch-built Overall Disability Scale [R-ODS] (van Nes et al., 2011)), hand grip strength (Merkies et al., 2000), and muscle strength (Medical Research Council [MRC] sum score (Kleyweg et al., 1991)); to collect trough serum IgG levels; as well as for safety laboratory assessments. Additionally, patient reported outcome (PRO) measures will be collected, including quality of life (Short Form-36 [SF-36] (Ware et al., 2000)), health utility status (EuroQoL [Quality of Life]-5 Dimensions [EQ-5D] scores (The EuroQol Group, 1990)), HRU, treatment satisfaction, treatment preference, and PGIC. An electronic diary (DIARYpro) will be utilized to capture data records related to infusions, adverse events (AEs), concomitant medications, and PRO measures such as the R-ODS and HRU. At any time during the SC treatment period, unscheduled visit(s) for INCAT assessments will be allowed for subjects who experience CIDP worsening, in order to determine whether the worsening meets the definition of relapse (ie, worsening in functional disability by ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores[iv] (Hughes et al., 2008). Open label treatment with IGIV will be provided for any subjects (regardless of their treatment assignment in Epoch 1) who meet the definition of relapse and enter into Epoch 2, in order to restore functional ability. An INCAT assessment will be performed at the time the subject is being evaluated for relapse, and again just prior to initiation of IGIV treatment in Epoch 2. The pre-IV treatment baseline INCAT assessment will be used 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. Subjects who relapse during Epoch 1 may choose not to enter into- Epoch 2. For these subjects, INCAT assessment will be repeated during the early termination visit, and this INCAT disability score will serve to confirm whether the subject has met the relapse criteria.

[iv] The adjusted INCAT disability score is identical to the INCAT disability score with the exception that upper extremity score changes from 0 (normal) to 1 (minor symptoms) or from 1 to 0 are excluded in determining the adjusted score, given that these changes do not reflect functional motor disability.

	Epoch 2: IV Treatment Period Epoch 2 is the open-label phase of this study with the aim of providing IGIV treatment for subjects who meet relapse criteria during Epoch 1, in order to restore functional ability. • Subjects will receive GAMMAGARD LIQUID/KIOVIG (all subjects with the exception of those at US sites) or GAMUNEX®-C[v] (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 (ie, 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.
Planned Duration of Subject Participation	Approximately 8 to 14 months Study participation duration will be approximately 8 months for subjects who complete the SC treatment period (Epoch 1) without relapse. Study participation may be extended by 6 months for those subjects who relapse during the SC treatment period and undergo IV treatment (Epoch 2).

Epoch 1: SC Treatment Period

Primary Outcome Measure

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)

Secondary Outcome Measures

Efficacy

1. 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 **OR** who experience CIDP worsening (defined as a ≥8 kPa decrease in the hand grip strength in the more affected hand) **OR** ≥4 points decrease in R-ODS relative to the pre-SC treatment baseline score at 2 consecutive time points (at the time of withdrawal from the SC treatment period)
2. Time to relapse
3. Change from pre-SC treatment baseline in R-ODS

[v] GAMUNEX®-C is approved for the treatment of CIDP and is a registered trademark of Grifols Therapeutics Inc.

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.

Tertiary Outcome Measures

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

1. Trough serum IgG levels.

Epoch 2: IV Treatment Period

Primary Outcome Measure

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)

Secondary Outcome Measures

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) 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

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

Tertiary Outcome Measures

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

INVESTIGATIONAL PRODUCTS, DOSE AND MODE OF ADMINISTRATION	
Active Treatment	**Epoch 1: HYQVIA/HyQvia** (Sequential SC administration of rHuPH20 solution followed by IGI, 10%) **1. rHuPH20** **Dose:** 80 U/g IgG **Dosing Frequency:** Every 2, 3, or 4 weeks, except during the ramp-up period (see Table 8-3 for IP administration schedule during the ramp-up period) **Dosage form**: Injection, solution **Mode of Administration:** The rHuPH20 solution will be administered **s**ubcutaneously via a peristaltic infusion pump with programmable infusion rates and infusion volumes at 1, 2, or 3 infusion sites per infusion day. Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US only) will be the Q Core – Sapphire pump. The Body Guard 323 pump and pump tubing will continue to be used in EU/ROW. Details on the infusion parameters will be noted in the Investigator Site Infusion Manual. **2. IGI, 10%/ IGIV 10%** IGI, 10% when administered intravenously is also referred to as IGIV 10%. **Dose:** Same monthly equivalent dose as the individual subject's pre-randomization IgG treatment **Dosing Frequency**: Every 2, 3, or 4 weeks[iii], except during the ramp-up period (see Table 8-3 for IP administration schedule during the ramp-up period) **Dosage form**: Injection, solution **Mode of Administration:** The SC infusion of IGI, 10% solution will begin within 10 minutes of completion of SC infusion of rHuPH20 solution via a peristaltic infusion pump with programmable infusion rates and infusion volumes at 1, 2, or 3 infusion sites per infusion day. A step-wise infusion rate escalation regimen is suggested (see Section 8.7.3, Table 8-1, and Table 8-2) Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US only) will be the Q Core – Sapphire pump. The Body Guard 323 pump and pump tubing will continue to be used in EU/ROW. Details on the infusion parameter will be noted in the Investigator Site Infusion Manual.

	If a subject's total IgG dose on a given day exceeds 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg, or exceeds the SC maximum infusion volume the subject can tolerate, the HYQVIA/HyQvia dose may be administered over multiple days as divided doses with 48 to 72 h between doses (eg, Day 1 and Day 3 of a given infusion cycle) to allow absorption of infusion fluid at infusion site(s). **Epoch 2: GAMMAGARD LIQUID/KIOVIG** **1. GAMMAGARD LIQUID/KIOVIG (IGI 10%) (for all subjects with the exception of those at US sites)** **Dose:** Induction dose of 2 g/kg BW, followed by maintenance infusions at the same monthly equivalent dose as the individual subject's pre-randomization IGIV treatment. The IG dose may be adjusted at the discretion of the investigator, as medically necessary and/or as tolerated by the subject, with a maximum dose of 100 g/1000 mL/day. **Dosing Frequency:** Every 3 weeks (adjustment to the dosing interval is not allowed) **Dosage form**: Injection, solution **Mode of Administration:** IV infusion (to be administered via a peristaltic variable rate infusion pump). Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US only) will be the Q Core – Sapphire pump. The Body Guard 323 pump and pump tubing will continue to be used in EU/ROW. Details on the infusion parameters will be noted in the Investigator Site Infusion Manual. The recommended starting infusion rate is 0.5 mL/kg BW/h, which may be gradually increased up to 5.4 mL/kg BW/h as tolerated by the subject. Induction dose (2 g/kg BW) is to be administered over 2 to 5 consecutive days. Maintenance infusions at the same monthly equivalent dose as the individual subject's pre-randomized IGIV doses are to be administered over 2 to 5 consecutive days, every 3 weeks. Note: For subjects at the US sites, GAMUNEX®-C will be used. GAMUNEX®-C will be used as the IGIV treatment for subjects at US sites who relapse in Epoch 1 and enter into Epoch 2. Please refer to GAMUNEX®-C Prescribing Information for directions for use and storage instructions. **Dose:** Induction dose of 2 g/kg BW, followed by maintenance infusions at the same monthly equivalent dose as the individual subject's pre-randomization IGIV treatment. The IG dose may be adjusted at the discretion of the investigator, as medically necessary and/or as tolerated by the subject, with a maximum dose of 100 g/1000 mL/day.

	Dosing Frequency: Every 3 weeks (adjustment to the dosing interval is not allowed) **Dosage form**: Injection, solution **Mode of Administration:** IV infusion (to be administered via a peristalic variable rate infusion pump). The recommended initial infusion rate is 2 mg/kg/min (0.02 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min);see GAMUNEX-C Prescribing Information. For patients judged to be at risk for renal dysfunction or thrombosis, GAMUNEX-C is recommended to be administered at the minimum infusion rate practicable. Induction dose (2 g/kg BW) is to be administered over 2 to 4 consecutive days, maintenance infusion of 1 g/kg (10 mL/kg) administered over 1 day or divided into 2 doses of 0.5 g/kg (5 mL/kg) given on 2 consecutive days, every 3 weeks. EU/ROW -Maximum infusion rate is 500 mL/hr when using the Body Guard pump.
Placebo Treatment	**Epoch 1: Placebo (0.25% human albumin in LR solution) with rHuPH20** (Sequential SC administration of rHuPH20 solution followed by 0.25% human albumin solution in LR solution) **1. rHuPH20** **Dose:** 80 U/10 mL of the 0.25% albumin placebo solution **Dosing Frequency:** Every 2, 3, or 4 weeks[iii], except during the ramp-up period (see Table 8-3 for IP administration schedule during the ramp-up period) **Dosage form**: Injection, solution **Mode of Administration:** The rHuPH20 solution will be administered **s**ubcutaneously via a peristaltic infusion pump with programmable infusion rates and infusion volumes at 1, 2, or 3 infusion sites per infusion day Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US only) will be the Q Core – Sapphire pump. The Body Guard 323 pump and pump tubing will continue to be used in EU/ROW. Details on the infusion parameters will be noted in the Investigator Site Infusion Manual. **0.25% Human albumin in LR Solution** **Dose:** At matching infusion volume as the subject's pre-randomization monthly equivalent IgG dose **Dosing Frequency:** Every 2, 3, or 4 weeks[iii], except during the ramp-up period (see Table 8-3 for IP administration schedule during the ramp-up period)

	Dosage form: Injection, solution **Mode of Administration:** SC infusion of 0.25% albumin placebo solution will begin within 10 minutes of completion of SC infusion of rHuPH20 solution via a peristaltic infusion pump with programmable infusion rates and infusion volumes at 1, 2, or 3 infusion sites per infusion day. A step-wise infusion rate escalation regimen is suggested (see Section 8.7.3, Table 8-1, and Table 8-2) Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US only) will be the Q Core – Sapphire pump. The Body Guard 323 pump and pump tubing will continue to be used in EU/ROW. Details on the infusion parameters will be noted in the Investigator Site Infusion Manual. If a subject's total placebo dose (ie, infusion volume of the 0.25% albumin placebo solution) on a given day exceeds 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg, or exceeds the SC maximum infusion volume the subject can tolerate, placebo dose may be administered over multiple days as divided doses with 48 to 72 h between doses (eg, Day 1 and Day 3 of a given infusion cycle) to allow absorption of infusion fluid at infusion site(s).
SUBJECT SELECTION	
Targeted Accrual	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.
Number of Groups/Arms/ Cohorts	Epoch 1 (SC treatment period) –2 groups (HYQVIA/HyQvia vs 0.25% albumin placebo with rHuPH20) Epoch 2 (IV treatment period) – 1 group (open-label GAMMAGARD LIQUID/KIOVIG for all subjects with the exception of those at US sites, or GAMUNEX®-C for subjects at the US sites)
Inclusion Criteria Subjects who meet **ALL** of the following criteria are eligible for this study: 1. Males or females of age ≥18 years old at the time of screening. 2. Subject has a documented diagnosis of definite or probable CIDP (focal atypical CIDP and pure sensory atypical CIDP will be excluded), as confirmed by a neurologist specializing/experienced in neuromuscular diseases to be consistent with the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria (European Federation of Neurological Societies, 2010). Fulfillment of electrodiagnostic criteria must be confirmed by an independent qualified/experienced central reader.	

3. Subject has responded to IgG treatment in the past (partial or complete resolution of neurological symptoms and deficits), and must currently be on stable doses of IGIV treatment within the dose range equivalent to a cumulative monthly dose of 0.4 to 2.4 g/kg BW (inclusive) administered intravenously for at least 12 weeks prior to screening. The dosing interval of IGIV treatment must be between 2 and 6 weeks (inclusive). Variations in the dosing interval of up to ±7 days or monthly dose amount of up to ±20% between subject's pre study IgG infusions are within acceptable limits.
4. INCAT disability score between 0 and 7 (inclusive). Subjects with INCAT scores of 0, 1 (whether from upper or lower extremities), or 2 (if at least 1 point is from an upper extremity) at screening and/or baseline will be required to have a history of significant disability as defined by an INCAT disability score of 2 (must be exclusively from the lower extremities) or greater documented in the medical record. Subjects will be eligible if one of the below eligibility criteria are met:
   a. Screening and Baseline INCAT disability score of between 3 and 7 inclusive.
   b. Screening and/or Baseline INCAT disability score of 2 (both points are from lower extremities)
   c. Screening and/or Baseline INCAT disability score of 2 (both points are not from lower extremities)
      AND has at least a score of 2 or greater documented in the medical record prior to screening. If a score was greater than 2 documented in the medical record prior to screening at least 2 points must be from lower extremities.
   d. Screening and/or Baseline INCAT disability score of 0 or 1 AND has at least a score of 2 or greater (both from lower extremities) documented in the medical record prior to screening, at least 2 points must be from lower extremities.
5. If female of childbearing potential, the subject must have a negative pregnancy test at screening and agree to employ a highly effective contraceptive measure throughout the course of the study and for at least 30 days after the last administration of investigational product (IP).
6. Subject is willing and able to sign an Informed Consent Form (ICF).
7. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet **ANY** of the following criteria are NOT eligible for this study:

1. Subjects with focal atypical CIDP or pure sensory atypical CIDP.
2. Any neuropathy of other causes, including:
   a. Hereditary demyelinating neuropathies, such as hereditary sensory and motor neuropathy (HSMN) (Charcot-Marie-Tooth [CMT] disease), and hereditary sensory and autonomic neuropathies (HSANs).
   b. Neuropathies secondary to infections, disorders, or systemic diseases such as Borrelia burgdorferi infection (Lyme disease), diphtheria, systemic lupus erythematosus, POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, lymphoma, and amyloidosis.
   c. Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
   d. Multifocal motor neuropathy (MMN)
   e. Drug-, biologic-, chemotherapy-, or toxin-induced peripheral neuropathy

3. Immunoglobulin M (IgM) paraproteinemia, including IgM monoclonal gammopathy with high titer antibodies to myelin-associated glycoprotein.
4. Presence of prominent sphincter disturbance.
5. Any central demyelinating disorders such as multiple sclerosis.
6. Any chronic or debilitating disease, or central nervous disorder that causes neurological symptoms or may interfere with assessment of CIDP or outcome measures, including (but not limited to) arthritis, stroke, Parkinson's disease, and diabetic peripheral neuropathy. (Subjects with clinically diagnosed diabetes mellitus who do not have diabetic peripheral neuropathy and who have adequate glycemic control with hemoglobin A1C [HbA1C] level of <7.5% at screening will be eligible for the study, provided the electrodiagnostic criteria are consistent with the diagnosis of a definite or probable CIDP consistent with the EFNS/PNS 2010 criteria and the subject agrees to maintain adequate glycemic control.)
7. Congestive heart failure (New York Heart Association [NYHA] class III/IV), unstable angina, unstable cardiac arrhythmias, or uncontrolled hypertension (defined as diastolic blood pressure >100 mmHg and/or systolic blood pressure >160 mmHg).
8. History of deep vein thrombosis or thromboembolic events (eg, cerebrovascular accident, pulmonary embolism) within 12 months prior to screening.
9. Condition(s) which could alter protein catabolism and/or IgG utilization (eg, protein-losing enteropathies, nephrotic syndrome).
10. Known history of chronic kidney disease, or glomerular filtration rate (GFR) of <60 mL/min/1.73m^2 estimated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009) at the time of screening.
11. Subject with active malignancy requiring chemotherapy and/or radiotherapy, or history of malignancy with less than 2 years of complete remission prior to screening. Exceptions to this exclusion are: adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and stable prostate cancer not requiring treatment.
12. Clinically significant anemia that precludes repeated blood sampling during the study, or hemoglobin (Hgb) level of <10.0 g/dL at the time of screening.
13. Known history of hypersensitivity or ARs such as urticaria, breathing difficulty, severe hypotension, or anaphylaxis following administration of human blood products such as human IgG, albumin, or other blood components.
14. Known allergy to hyaluronidase of human (including recombinant human hyaluronidase) or animal origin (such as bee or wasp venom).
15. Known history of or immunoglobulin A (IgA) deficiency (<8 mg/dL) at the time of screening.
16. Abnormal laboratory values at screening meeting any one of the following criteria:
    a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN)
    b. Platelet count <100,000 cells/µL
    c. Absolute neutrophil count (ANC) <1000 cells/µL
17. Ongoing/active infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) Type 1/2 infection at the time of screening. (Subjects with immunity to hepatitis B from either active vaccination or from previous natural infection are eligible to participate in the study.)

18. The subject has received or is currently receiving treatment with immunomodulatory/immunosuppressive agents within 6 months prior to screening.
19. The subject has received or is currently receiving treatment with any corticosteroids dose within 8 weeks prior to screening, regardless of indication.
20. The subject has undergone plasma exchange (PE) within 3 months prior to screening.
21. The subject has any disorder or condition that in the investigator's judgment may impede the subject's participation in the study, pose increased risk to the subject, or confound the results of the study.
22. The subject is nursing or intends to begin nursing during the course of the study.
23. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment, or is scheduled to participate in another clinical study (with the exception of the HYQVIA/HyQvia extension study in CIDP) involving an IP or investigational device during the course of this study.
24. The subject is a family member or employee of the investigator.
25. Subjects with acquired or inherited thrombophilic disorders. These will include the specific types of acquired or inherited thrombophilic disorders that could put subjects at risk of developing thrombotic events. Examples include
    a. Hereditary Thrombophilias:
        i. Factor V Leiden mutation
        ii. Prothrombin 20210A mutation
        iii. Protein C deficiency
        iv. Protein S deficiency
        v. Antithrombin deficiency
    b. Acquired thrombophilias
        i. Antiphospholipid antibody syndrome
        ii. Activated protein C Resistance acquired
        iii. Homocystinemia

STATISTICAL ANALYSIS

This statistical analysis section provides:

- Sample size estimation (along with the underlying assumptions) and the planned statistical analysis for HYQVIA/HyQvia during the placebo-controlled, randomized, SC treatment period.
- Sample size estimation (along with the underlying assumptions) and the planned statistical analysis for GAMMAGARD LIQUID/KIOVIG during the open-label, IV treatment period.

Epoch 1: SC Treatment with HYQVIA/HyQvia vs Placebo with rHuPH20

Sample Size and Power

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]

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] 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]

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.

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

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 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.

Planned Statistical Analysis

Analysis Sets

The Epoch 1 Safety Set will include all subjects who received any double-blind study medication.

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.

A Per-Protocol (PP) analysis set will include all randomized subjects who received any double-blind study medication, and had no major 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.

Analysis of Primary Outcome Measure

A relapse is defined as worsening of functional disability by ≥1 point (increase) relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores.

The null hypothesis is that relapse rates are not different between the HYQVIA/HyQvia and placebo with rHuPH20 treatment groups. The primary efficacy outcome measure is the Epoch 1 relapse rate in the MITT analysis set. The primary analysis is a comparison of relapse rates in the two treatment groups,

using a continuity-corrected chi-square test conducted at the 5% level of statistical significance, with missing outcomes imputed as no relapse. The estimated relapse rates will be presented for each planned treatment group, along with the 95% confidence interval (CI) computed using the Wilson score method. Sensitivity analyses will include comparisons of the relapse rates in (1) the MITT analysis Set with missing imputed as a relapse, (2) an MITT Observed Cases analysis (missing outcomes excluded), (3) the PP Set with missing imputed as no relapse, and (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. These sensitivity analyses will use similar statistical methods to the primary analysis.

Analysis of Secondary Outcome Measures

Efficacy

Clinical worsening of CIDP, defined as subject relapse or ≥8 kPa decrease in the hand grip strength in the more affected hand OR ≥4 points decrease in R-ODS relative to the pre-SC treatment baseline score at 2 consecutive time points at the time of withdrawal from the SC treatment period, will be analyzed using the same methods as the primary endpoint.

Time to relapse, defined as time from the date of the first SC administration of HYQVIA/HyQvia or placebo with rHuPH20 to the date of relapse, will be compared between treatment groups using the Wilcoxon survival test. Additionally, the survival function will be estimated using the Kaplan-Meier curve. The analysis will be performed using data from the MITT analysis set with the planned Epoch 1 treatment.

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 as a covariate. The last non-missing change in Epoch 1 will be used from subjects who discontinued early. If an analysis of overall discontinuation rates shows a differential dropout rate between treatments that is significant at the 5% level, then a repeated-measures analysis of the change in ADL (R-ODS) will be used to investigate the robustness of results of the ANCOVA with last observation carried forward (LOCF) imputation in the MITT analysis set. The repeated-measure analysis will employ a restricted maximum likelihood (REML)-based, mixed-model repeated measure (MMRM) model which contains fixed terms for treatment group and planned timepoint, with baseline R-ODS as a covariate and subject as a random factor; additional details will be provided in the statistical analysis plan (SAP). These analyses will be performed in the MITT population.

Safety

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and reported by body system, preferred term, and treatment group. Clinically significant, treatment-emergent changes in physical exams, vital signs, electrocardiograms (ECGs), and clinical laboratory measurements will be recorded as AEs; therefore, safety analyses will be primarily based on analysis of AEs, including ARs plus suspected ARs. Safety endpoints will be summarized descriptively in the Epoch 1 Safety Set using actual treatment.

Treatment-emergent AEs (TEAEs), serious TEAEs, and other AE-related outcome measures will be described by the number and percentage of subjects in each treatment group who experienced a particular type of event. Additionally, event rates will be expressed as number of events (reports) per infusion, per subject, and per subject-year. Both systemic event and events that are localized to the infusion site(s) will be examined. The relationship of AEs to infusions will be described further in terms of the number and proportion of infusions that were associated with an AE, and the number and proportion of infusions that were not completed as planned (interrupted, discontinued) due to an AE.

The first occurrence of any TEAE and the first occurrence of any treatment-emergent SAE will be analyzed using a Cox PH model to obtain an overall hazard ratio (HR) for treatment, adjusted for time in study (ie, duration of treatment). Separate HR's for the relationship of AEs with treatment will be computed for subjects who had total treatment durations of 0 to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, and 13 to 26 weeks at the time of the data cut-off. These analyses will address the potential impact of any imbalance in AE rates due to differential dropout rates in Epoch 1 between HYQVIA/HyQvia and placebo with rHuPH20, and will characterize the relationship of AEs to treatment, overall and over time. Point estimates and CIs will be reported.

Similar analyses will be performed for ARs plus suspected ARs.

Summaries of subject deaths during study (if any) and of AEs leading to discontinuation will be provided.

For laboratory measurements, data will be summarized by treatment group and time point. Summaries of continuous measurements will include sample size, mean, standard deviation (SD), minimum, and maximum. For categorical measurements, the proportion of observations in each category will be presented.

Subjects are defined as having elevated rHuPH20 antibody titers if they have two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers.
If at least 5 subjects in each treatment group have elevated titers, then an exploratory 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. In addition, an exploratory analysis of any treatment emergent *abnormal titer or rises above* baseline in anti-rHuPH20 antibody titer will be performed to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs.

Analysis of Tertiary Outcome Measures

Treatment satisfaction, treatment preference, PGIC, HRU (such as days off school/work, unscheduled physician visits, hospitalization, and emergency room visits) and changes from pre-IV treatment baseline in adjusted INCAT disability scores, hand grip strength scores, MRC sum scores, SF-36 scores, and EQ-5D scores will be summarized in the MITT analysis set, by planned treatment group, using descriptive statistics (sample size, mean, SD, median, minimum, maximum) for continuous measures or the number and percentage of subjects for categorical measures.

Improvement in functioning in daily tasks will be evaluated using subset of R-ODS scores. The subset scoring will be outlined in the SAP. In addition, a separate psychometric statistical plan (PSAP) will be finalized prior to Epoch 1 data lock to confirm the targeted subscale is fit-for-purpose and the subset scoring's validity and reliability.

Trough plasma concentrations of IgG will be summarized for the Safety set, by actual treatment, using the sample size, mean, SD, median, minimum, maximum, geometric mean, and SD of the geometric mean.

In addition, potential correlation between serum IgG trough levels on or after day 120 or at the time of CIDP symptom relapse and relapse status (relapse, no relapse) will be assessed as an exploratory analysis.

Electrodiagnostic (EDX) studies obtained before and after Epoch-1 (Epoch-1 baseline and exit) will be used to determine resolution of previously identified demyelinating abnormalities (DA) or occurrence of new DA. The total number of DA at Epoch-1 baseline and Epoch-1 exit, as well as their change, and the number of new DA in exit EDX will be summarized using descriptive statistics (sample size, mean, SD, median, minimum, maximum) for continuous measures or the number and percentage of subjects for categorical measures.

Epoch 2: IV Treatment with GAMMAGARD LIQUID/KIOVIG

Sample Size Calculation

Historical Responder Rate for Placebo: In the ICE study (Hughes et al., 2008), 0 out of 12 treatment-experienced patients in the placebo group responded to treatment, yielding an estimated responder rate of 0% with the upper bound of the two-sided 95% CI of 24%, based on the Wilson score method. Therefore, for comparison to historical controls, the placebo rate is at most 24% with 97.5% confidence.

Sample Size: 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.

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 (or Gammunex-C in the US) 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.

Planned Statistical Analysis

Analysis Sets

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.

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.

Analysis of Primary Outcome Measure

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 the pre-IV treatment baseline.

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.

Analysis of Secondary Outcome Measures

Safety

Epoch 2 safety set, including SAEs, TEAEs, ARs plus suspected ARs, deaths, and discontinuations due to AE will be analyzed using methods similar to Epoch 1. Analyses will be performed in the Epoch 2 Safety Set using the actual treatment. Safety endpoints will be summarized descriptively by IGIV treatment (ie, GAMMAGARD LIQUID/KIOVIG and GAMUNEX®-C separately).

Efficacy

Clinically meaningful improvement of CIDP, defined as one or more of the following: subject response (response defined as a decrease of ≥1 point in the adjusted INCAT disability score) at 2 consecutive time points; ≥8 kPa increase in the hand grip strength in the more affected hand; ≥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, will be presented using descriptive statistics.

Analysis of Tertiary Outcome Measures

All tertiary outcome measures will be summarized descriptively.

Planned Interim Analyses of the Study

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.

Interim Safety Analysis

An interim safety analysis will be performed during the early conduct of the study to provide a preliminary assessment of potential immune response to rHuPH20 in CIDP subjects.

The interim safety analysis will include a minimum of 30 subjects who have been 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.

Formal Interim Analysis (Epoch 1 Final Analysis)

Formal Interim Analysis will be performed to evaluate the efficacy of HyQvia versus placebo as a maintenance therapy for CIDP 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.
- No multiplicity adjustment for the control of Type 1 error (false positive conclusion) will be made, as the analysis of Epoch 1 data will include all Epoch 1 data for all subjects who have completed participation in Epoch 1.
- The study SAP will be finalized and approved prior to Epoch 1 data lock and treatment unblinding.

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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR(s)	Adverse reaction(s)
AST	Aspartate aminotransferase
BW	Body weight
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Peak or maximum concentration
CRF(s)	Case report form(s)
CTA	Clinical Trial Agreement
DIARYpro	Electronic diary
DMC	Data monitoring committee
EC(s)	Ethics committee(s)
ECRF/eCRF	Electronic case report form
EFNS/PNS	European Federation of Neurological Societies/Peripheral Nerve Society
EQ-5D	EuroQoL (Quality of Life)-5 Dimensions
FDA	Food and Drug Administration
GAMMAGARD LIQUID/KIOVIG	Immune Globulin Infusion (Human), 10% Solution
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
H	Hour
HAV	Hepatitis A virus
HbA1C	Hemoglobin A1C; also known as glycosylated or glycated hemoglobin
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus

Abbreviation	Definition
HR	Hazard ratio
HRQOL	Health-related quality of life
HRU	Health Resource Utilization
HYQVIA/HyQvia	Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20)
IB	Investigator's brochure
ICH	International Council for Harmonisation
IgA	Immunoglobulin A
IGI, 10%	Immune Globulin Infusion (Human), 10% Solution
IGIV or IVIg	Intravenous immunoglobulin G
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGSC	Subcutaneous immunoglobulin G
INCAT	Inflammatory Neuropathy Cause and Treatment disability scale
IP(s)	Investigational product(s)
IRT	Interactive Response Technology System
IV	Intravenous
LDH	Lactate dehydrogenase
LR	Lactated Ringer's
MADSAM	Multifocal acquired demyelinating sensory and motor neuropathy
MITT	Modified Intent-to-Treat
MMN	Multifocal motor neuropathy
MMRM	Mixed-model repeated measure
MRC	Medical Research Council
NMC	Non-medical complaint
PE	Plasma exchange
PGIC	Patient Global Impression of Change
PID	Primary immunodeficiency disease
PK	Pharmacokinetic(s)
PP	Per-Protocol
PRO	Patient Reported Outcome
RBC	Red blood cell
rHuPH20	Recombinant human hyaluronidase
R-ODS	Rasch-built Overall Disability Scale
SAE(s)	Serious adverse event(s)

Abbreviation	Definition
SAER	Serious adverse event report
SAP	Statistical analysis plan
SC	Subcutaneous
Scr	Serum creatinine
SD	Standard deviation
SF-36	Short Form-36 health survey
SIC	Subject identification code
SUSAR(s)	Suspected unexpected serious adverse reaction(s)
TEAE(s)	Treatment-emergent adverse event(s)
TIBC	Total Iron Binding Capacity
T_{max}	Time to maximum concentration
TSQM-9	Abbreviated treatment satisfaction questionnaire for medication
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

6. BACKGROUND INFORMATION

Purified human immunoglobulin G (IgG) preparations were first used in 1952 for the treatment of patients with primary immunodeficiency disease (PID), a class of disorders that result in increased susceptibility to infection including both recurrent pyogenic infections secondary to defects of humoral immunity and opportunistic infections resulting from defects in cell-mediated immunity (Bruton, 1952, Rosen et al., 1995). Individuals with these disorders require replacement therapy with immunoglobulin products to prevent or reduce the severity of infections. In addition to PID syndromes, immunoglobulin preparations have been indicated for secondary immunodeficiencies, such as B-cell chronic lymphocytic leukemia, acquired immunodeficiency syndrome (AIDS), and immunodeficiency after bone marrow transplantation (Abdel-Mageed et al., 1999, Griffiths and Chapel, 1997, Rechtman, 1997, Wolin and Gale, 1997). Immunoglobulins are also effective in the management of autoimmune disorders, such as idiopathic thrombocytopenic purpura (ITP) (George and Raskob, 1998, Imbach et al., 1995, McMillan, 2000), Kawasaki syndrome (Barron et al., 1990, Rosenfeld et al., 1995), and multifocal motor neuropathy (MMN) (Hahn et al., 2013). Clinical studies in neurological indications have also shown significant results with intravenous (IV) immunoglobulin G (IGIV) preparations in the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Hughes et al., 2008, Léger et al., 2013).

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired progressive chronic sensory and motor neuropathy with a relapsing and remitting or progressive course of more than 2 months, characterized by proximal weakness, positive sensory symptoms, areflexia without wasting, and impaired sensation with a preferential loss of vibration or joint position sense (European Federation of Neurological Societies, 2010, Köller et al., 2005). Worldwide estimates of the prevalence of CIDP range from 1.9 to 8.9/100,000 with an annual incidence of 0.15 to 1.6/100,000 (Iijima et al., 2008, Laughlin et al., 2009, Lunn et al., 1999, McLeod et al., 1999, Mygland and Monstad, 2001). A report in Neurology in 2009 cited a United States (US) prevalence of CIDP of 8.9/100,000 and an annual incidence of 1.6/100,000 new cases each year (Laughlin et al., 2009). CIDP has an estimated prevalence in Europe of 3.7/100,000 (Orphanet Report Series, 2014).

European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guidelines published in 2010 utilize clinical, electrodiagnostic, and supportive criteria for the diagnosis of CIDP (European Federation of Neurological Societies, 2010). CIDP is defined as having either a typical or an atypical clinical presentation. Typical CIDP presents as a symmetric proximal and distal weakness with sensory involvement of all extremities. The clinical course is either slowly progressive or relapsing and remitting. Tendon reflexes are diminished or absent in all extremities. Cranial nerve involvement is less commonly seen. Balance can be impaired due to loss of proprioception (Koski, 2002). Sensory symptoms may include numbness, tingling and painful paresthesias (Dyck et al., 1975, McCombe et al., 1987). Atypical CIDP, according to the EFNS/PNS guidelines, includes CIDP with pure motor or pure sensory impairment or with distal, multifocal, or focal distributions (European Federation of Neurological Societies, 2010). Atypical presentations of CIDP may include the presence of normal tendon reflexes in unaffected limbs. CIDP with a predominantly distal presentation is described as distal acquired demyelinating symmetric neuropathy (DADS) (DADS without immunoglobulin M [IgM] paraprotein is generally considered to be a variant of CIDP). Lewis-Sumner Syndrome, also known as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), is the asymmetric variant of CIDP. For this study, pure sensory CIDP (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron), and focal CIDP (eg, involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb) will be exclusionary; the study outcome measures are not fitting to assess clinical change in patients with those variants of CIDP. In order to meet the clinical diagnostic criteria for CIDP (whether typical or atypical), other causes for a neuropathy must be excluded (European Federation of Neurological Societies, 2010).

The EFNS/PNS guidelines and the American Academy of Neurology (AAN) require electrodiagnostic testing with findings consistent with demyelination for a diagnosis of CIDP (Cornblath et al., 1991, European Federation of Neurological Societies, 2010, Hahn et al., 2005, Köller et al., 2005). Major electrodiagnostic features consistent with CIDP include one or more of the following: prolonged distal motor latencies, reduced motor conduction velocity, delay or absence of F waves, partial motor conduction block, abnormal temporal dispersion, and distal compound motor action potential (CMAP) increase (European Federation of Neurological Societies, 2010, Köller et al., 2005, Koski, 2002). Supportive criteria in the diagnosis of CIDP may include findings from examination of cerebrospinal fluid, magnetic resonance imaging, nerve biopsy and/or response to immunotherapy treatment (European Federation of Neurological Societies, 2010).

While CIDP can occur in all ages, it occurs more often in the middle-aged and elderly population with a male predominance (Hughes, 2003). The peak incidence of CIDP is between the ages of 30 to 60 years (Dalakas, 2011). Approximately 60% of patients have a chronic progressive form and are typically older. Approximately 30% have a relapsing remitting course and these patients tend to be younger.

There is a significant burden of disease associated with CIDP. Patients with CIDP have weakness and gait disturbances that result in tripping and falling, difficulty with stairs, difficulty rising from a seat, and difficulty with maintaining balance. Walking may require a cane or a walker or the patient may be confined to a wheelchair or bed. Weakness and clumsiness of the upper extremities results in impaired dexterity in carrying out task such as personal hygiene, dressing, buttoning a shirt, or picking up objects. Patients can have difficulty showering or going to the bathroom. Paresthesias can result in painful symptoms such as aching, jabbing, and searing or burning pain (Ulane and Brannagan, 2012).

Although the exact etiology of CIDP is unknown, it is regarded as an autoimmune disorder. On nerve biopsy, a demyelinating neuropathy is seen with inflammatory changes and infiltration of macrophages and T-cells. Demyelination, remyelination and onion bulb formation is present (Hughes, 2003, Köller et al., 2005, Koski, 2002). Axonal loss can also be seen. Long term demyelination leads to axonal loss and it is the amount of axonal loss that determines the level of disability and long term prognosis (Köller et al., 2005, Koski, 2002, Ulane and Brannagan, 2012). Treatment is recommended for all CIDP patients who demonstrate significant clinical symptoms in order to prevent continuing demyelination and secondary axon loss leading to permanent disability (Köller et al., 2005).

Conventional therapy for CIDP includes corticosteroids, plasma exchange (PE) and IGIV. IGIV has been the most studied treatment and the only approved therapy for CIDP for both induction and maintenance therapy (Eftimov et al., 2013, Harbo et al., 2009b, Hughes et al., 2001, Hughes et al., 2008, Kuitwaard et al., 2010, Léger et al., 2013, Mendell et al., 2001, Nobile-Orazio et al., 2012, Patwa et al., 2012, van Schaik et al., 2002). In clinical guidelines for treatment of CIDP, corticosteroids (Eftimov et al., 2012, Hughes et al., 2001, Nobile-Orazio et al., 2012, van Schaik et al., 2010) and PE (Dyck et al., 1986, Hahn et al., 1996, Mehndiratta and Hughes, 2012) are also first-line therapies for induction therapy and maintenance therapy (European Federation of Neurological Societies, 2010, Patwa et al., 2012).

The EFNS/PNS 2010 guidelines recommend that either corticosteroids or IGIV should be considered for the initial treatment of CIDP. PE may be similarly effective, but less tolerated because associated adverse events (AEs) are not uncommon. Since IGIV may provide rapid improvement, it is often the first choice. If the response is inadequate to the initial treatment or there is a problem with tolerability of maintenance treatment, the EFNS/PNS 2010 guidelines recommend that the other first-line therapies (IGIV, steroids, or PE) be tried before considering combination treatments. Adding an immunosuppressant or immunomodulatory drug may be considered, but there is insufficient evidence to recommend a particular immunosuppressant/immunomodulatory agent (Cocito et al., 2011a, European Federation of Neurological Societies, 2010). However, while corticosteroids are effective in treating the symptoms of CIDP, there are significant problems with safety and tolerability associated with corticosteroid treatment, particularly when given chronically (Gorson, 2012).

Subcutaneous (SC) administration of immunoglobulin G (IGSC) has been the predominant mode in the Scandinavian countries for many years (Gardulf et al., 1991), and has become increasingly widespread with tens of thousands of SC infusions given during the last decade in patients with primary and secondary antibody deficiencies (Grunebaum et al., 2002). To date, several publications have reported the therapeutic efficacy of IGSC administration in patients with CIDP (Cocito et al., 2014, Cocito et al., 2011b, Köller et al., 2006, Lee et al., 2008, Markvardsen et al., 2013, van Schaik et al., 2018). This now includes long-term safety and efficacy IGSC up to 48 weeks and consistent with PATH study (van Schaik et al., 2019). The meta-analysis of Five studies, compassing 176 placebo subjects, measured maintained stability or deterioration as the primary endpoint results found deterioration was observed in 57% of these subjects randomized to placebo, but 43% (95% CI: 35, 50) did not relapse (placebo effect) (Lewis et al., 2020). IGSC replacement therapy is considered to be effective, safe, and also highly appreciated by patients and to have a low risk of systemic adverse reactions (ARs) (Gardulf et al., 1995, Gardulf et al., 1993, Gardulf et al., 1991). Some of the proposed advantages of IGSC over IGIV include: 1) superior systemic adverse event profile and improved tolerability, 2) an alternative for patients with poor venous access, 3) option for home treatment, and thus reduced burden on resources and healthcare costs (Gardulf and Hammarström, 1996), 4) improved health-related quality of life (HRQOL), 5) ease of administration and flexibility of dosing, and 6) increased convenience and compliance. The main disadvantages with conventional IGSC therapy are: 1) the limited volume of fluid that can be delivered subcutaneously, and 2) the low bioavailability (65%-69%) (Berger et al., 2013) of the conventional IGSC therapy.

These limitations in turn require more frequent dosing typically to be weekly to several times a week (Markvardsen et al., 2014) and, in the case of large doses, administration at multiple sites to deliver the entire dose (Harbo et al., 2009a, Harbo et al., 2010, Markvardsen et al., 2014).

Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20; tradenames: HYQVIA/HyQvia) was developed to address the major limitation of conventional IGSC therapy. HYQVIA/HyQvia significantly enhances SC administration in PID by offering improved bioavailability (as compared to conventional IGSC therapy) without requiring greater doses than those administered by IV (Schiff et al., 2008). In addition, HYQVIA/HyQvia allows the SC administration of standard PID monthly dosing volumes, and the utilization of infusion rates equal to IV administration while preserving the advantages of SC administration (Schiff et al., 2008). These advantages may be particularly relevant to neurology indications, including immune-medicated neuropathies for IgG usage, that require immunomodulatory doses up to five-times higher than immune replacement doses.

This clinical study is being performed to investigate rHuPH20-facilitated IGSC therapy in patients with CIDP (Epoch 1) as well as to study the efficacy of GAMMAGARD LIQUID/KIOVIG in CIDP (Epoch 2).

The COVID-19 pandemic has disrupted on-going drug development efforts including this study. More importantly it has resulted in several new issues directly impacting the treatment of dysimmune neuropathies (Eftimov et al., 2020).

6.1 Description of Investigational Products

6.1.1 Epoch 1

6.1.1.1 HYQVIA/HyQvia

HYQVIA/HyQvia is a product that contains both Immune Globulin Infusion 10% (Human) (IGI, 10%) and recombinant human hyaluronidase (rHuPH20) packaged as two separate vials. The Immune Globulin Infusion, 10% (Human) component of HYQVIA/HyQvia is manufactured by the same process and at the same manufacturing facilities as GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10%.

Further information is provided in the Investigator's Brochure (IB) for Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20).

6.1.1.1.1 Recombinant Human Hyaluronidase (rHuPH20)

[redacted]

6.1.1.1.2 Immune Globulin Infusion 10% (Human) (IGI, 10%)

Immune Globulin Infusion 10% (Human) (IGI, 10%), the therapeutically active component of HYQVIA/HyQvia, is identical to that in GAMMAGARD LIQUID/KIOVIG.

[redacted]

6.1.1.2 Placebo Control

Human albumin 0.25% in Lactated Ringer's (LR) solution (also known as Ringer's Lactate or Hartmann's solution or Compound Sodium Lactate Solution for Infusion in some participating countries) will be used as the placebo control for IGI, 10% in this study. The placebo solution will be administered in the same sequential manner with rHuPH20 solution as for HYQVIA/HyQvia.

Lactated Ringer's solution is a physiological, isotonic solution that will be better tolerated in the SC tissue at a large volume than other crystalloid solutions such as normal saline. Human albumin at a very low concentration (0.25%) is added to match the appearance (eg, color) and foaming characteristics to that of IGI, 10% solution. Human albumin is compatible with LR. Human albumin is not known to have any therapeutic activity for the treatment of CIDP.

6.1.2 Epoch 2

6.1.2.1 GAMMAGARD LIQUID/KIOVIG

GAMMAGARD LIQUID/KIOVIG Immune Globulin Infusion (Human), 10% Solution; IGI, 10% is a liquid solution containing 10% human normal immunoglobulin. IGI, 10% when administered intravenously is also referred to as IGIV 10%.

Note: For subjects at the US sites, GAMUNEX®-C will be used.

Please see Section 6.1.1.1.2 for product description. Further information is provided in the IB for Immune Globulin Infusion (Human), 10% Solution (IGI, 10%).

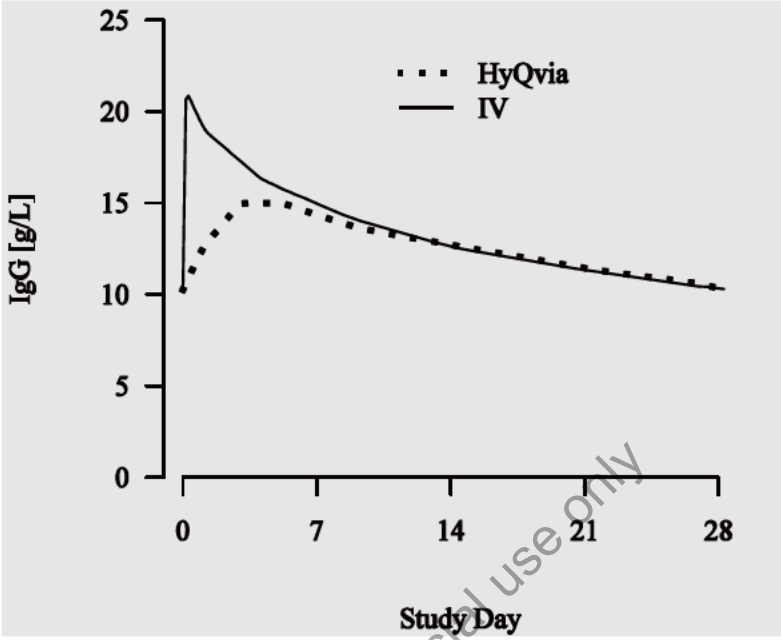
6.1.3 Dose Justification

6.1.3.1 Epoch 1

In Epoch 1 (SC treatment period), the IgG dosing regimen for HYQVIA/HyQvia or the 0.25% albumin placebo with rHuPH20 will be the same as the subject's pre-randomization monthly equivalent IGIV 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.

A concentration-time profile of mean serum IgG levels at steady-state following administration of GAMMAGARD LIQUID/KIOVIG or HYQVIA/HyQvia administered every 4 weeks is shown in Figure 6-1. HYQVIA/HyQvia infusions were given at an adjusted dose of 108% of IV dose to provide equivalent area under the IgG concentration-time curve (AUC) at steady state. This illustrates (a) the expected difference in C_{max} and T_{max} for the two modes of administration, (b) the superimposition of IgG concentration-time curves during the elimination phase following SC and IV administration, and (c) comparable trough IgG levels after SC and IV administration. For this reason, no dose conversion factor will be applied; that is, subjects entering the study will receive the same IgG monthly equivalent dose as their own pre-study IGIV treatment regimen that was effective in maintaining the subject's CIDP condition.

Figure 6-1. Pharmacokinetic Comparison of Mean IgG Concentration-Time Profiles of IGI, 10% Following rHuPH20-Facilitated SC (HYQVIA/HyQvia) or IV (GAMMAGARD LIQUID/KIOVIG) Administration



6.1.3.2 Epoch 2

An open-label IGIV treatment period (Epoch 2) is included in this study in order to restore subjects' functional ability following a relapse and deterioration in functional ability. When patients with CIDP relapse, there is neuroinflammation and active demyelination which can lead to further axonal loss with potential for irreparable nerve damage and permanent disability (Köller et al., 2005, Koski, 2002, Ulane and Brannagan, 2012). IGIV is the only approved first line of therapy for the treatment in CIDP, with improvement often noted within a few weeks or even as early as 10 days after initiation of therapy. Per the 2010 EFNS/PNS guidelines (European Federation of Neurological Societies, 2010) on the management of CIDP, the recommended IGIV dosing regimen consists of an induction dose of 2 g/kg BW administered intravenously over 2 to 5 days, followed by 1 g/kg over 1 day every 3 weeks. This dosing regimen has been demonstrated to be effective and safe for the treatment of CIDP in IgG treatment-naïve and treatment-experienced patients in a double-blind, randomized, placebo-controlled international study (ICE study) (Hughes et al., 2008) and an open-label study (PRIMA study) (Léger et al., 2013) in European centers. The EFNS/PNS guidelines recommend that, following stabilization on maintenance IGIV therapy, the dose and/or dosing frequency of IGIV should be reduced periodically to establish the need for ongoing therapy because patients may need less IGIV than they receive or possibly none at all.

In Epoch 2, subjects will receive GAMMAGARD LIQUID/KIOVIG[vii]. The first infusion will be given at 2 g/kg BW, followed by maintenance infusions at the same monthly equivalent dose that the subject had been stabilized on prior to enrollment into this study. Adjustments in the IGIV dose based on clinical response and/or subject's tolerability are allowed. The Epoch 2 IGIV treatment regimen with provision for dose adjustments is consistent with the recommendations provided in the EFNS/PNS 2010 guidelines on the management of CIDP.

6.2 Clinical Condition/Indication

- Epoch 1: For maintenance therapy of CIDP to prevent relapse of neuromuscular disability and impairment.
- Epoch 2: For the treatment of CIDP to improve neuromuscular disability and impairment.

6.3 Population To Be Studied

This study will enroll adult CIDP patients who have demonstrated a response to IGIV therapy and who remain on stable doses of IGIV. The study will evaluate the efficacy of HYQVIA/HyQvia as a maintenance therapy in Epoch 1 (SC treatment phase) of the study. Eligible subjects must have:

1. a documented diagnosis of definite or probable typical/ atypical CIDP (with the exclusion of focal atypical CIDP or pure sensory atypical CIDP), in accordance with the EFNS/PNS 2010 guidelines (European Federation of Neurological Societies, 2010).
2. responded to IgG treatment in the past, and must be currently on stable doses of IgG treatment within the dose range equivalent to a cumulative monthly dose of 0.4 to 2.4 g/kg BW administered IV for at least 12 weeks prior to screening.
3. an Inflammatory Neuropathy Cause and Treatment (INCAT) disability score (Hughes et al., 2001) between 0 and 7 (see more details in Section 9.1).

Epoch 2 (IV treatment phase) of the study will include subjects who relapse (see definition in Section 8.2) during the randomized "SC treatment phase", regardless of their treatment assignment in Epoch 1.

This study is not planned to enroll treatment-naïve subjects.

[vii] At US sites only, subjects who relapse in Epoch 1 will receive GAMUNEX®-C in Epoch 2.

It is estimated that 232 subjects need to be enrolled into the study in order to achieve 174 randomized subjects (assuming a 25% screen failure rate). Of the 174 randomized subjects, it is estimated that 15% of subjects could discontinue early from the study (dropout) such that approximately 148 evaluable subjects will complete the study. (See sample size calculations in Section 14.1 for more details.)

6.4 Findings from Nonclinical and Clinical Studies

Findings from nonclinical and clinical studies for HYQVIA/HyQvia are detailed in the IGI, 10% with rHuPH20 IB.

Findings from nonclinical and clinical studies for GAMMAGARD LIQUID/KIOVIG are detailed in the IGI, 10% IB.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Products to Human Subjects

6.5.1 HYQVIA/HyQvia

[redacted] Further information is provided in the IB for Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20) as well as Prescribing Information for HYQVIA and Summary of Product Characteristics (SmPC) for HyQvia.

The most common ARs observed in PID clinical trials in >5% of subjects were: local reactions, headache, antibody formation against rHuPH20, fatigue, nausea, pyrexia, and vomiting.

The safety and efficacy of chronic use of the rHuPH20 solution in HYQVIA/HyQvia has not been established in conditions other than PID. [redacted]

No clinical studies have been conducted with HyQvia in pregnant women. HyQvia should not be used by women who are pregnant or are planning to become pregnant and an alternate treatment should be considered. It is recommended that women of childbearing potential take appropriate measures to prevent pregnancy during HyQvia treatment (see Section 21.5 for a list of highly effective contraceptive measures). If a woman becomes pregnant, treatment with HyQvia should be stopped.

IGI, 10%, the therapeutically active component of HYQVIA/HyQvia, is identical to that in GAMMAGARD LIQUID/KIOVIG. See Section 6.5.2 for the known risks associated with IGI, 10%.

6.5.2 GAMMAGARD LIQUID/KIOVIG

IGI, 10% administered via IV treatment (GAMMAGARD LIQUID/KIOVIG) is efficacious and safe in the particular fields of therapeutic use and approved indications, ie, PID, ITP and MMN, as demonstrated in the clinical development program for GAMMAGARD LIQUID/KIOVIG. Please see the IB for Immune Globulin Infusion (Human), 10% Solution (IGI, 10%) for further information, as well as the Prescribing Information for GAMMAGARD LIQUID and the SmPC for KIOVIG.

Serious ARs (defined as SAEs occurring during or within 72 hours (h) of infusion or any casually related SAE occurring within the study period) which occurred in the clinical trials of GAMMAGARD LIQUID/KIOVIG were aseptic meningitis, pulmonary embolism, and blurred vision. The most common ARs observed in ≥5% of patients were:

- PID, IV administration: headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, laryngeal pain, rash, arthralgia, myalgia, oedema peripheral, pruritus, and cardiac murmur.

- PID, SC administration: infusion site (local) event, headache, fatigue, heart rate increased, pyrexia, abdominal pain upper, nausea, vomiting, asthma, blood pressure systolic increased, diarrhea, ear pain, aphthous stomatitis, migraine, oropharyngeal pain, and pain in extremity.
- MMN, IV administration: headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

Rare but serious events may occur with IGI products, including hypersensitivity, thrombosis, renal dysfunction/failure, hyperproteinemia, increased serum viscosity, and hyponatremia hemolysis, hemolysis, transfusion related acute lung injury (TRALI), and aseptic meningitis syndrome.

Thrombosis may occur with immune globulin products, including IGI, 10%. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients receiving IGIV products including IGI, 10%. Renal dysfunction and acute failure occur more commonly with IGIV products containing sucrose. IGI, 10% does not contain sucrose.

IGI, 10% contains blood group antibodies (isoagglutinins) that may cause hemolysis. Delayed hemolytic anemia can develop subsequent to IGI, 10% therapy due to enhanced red blood cell (RBC) sequestration. Acute hemolysis, consistent with intravascular hemolysis, has been reported The following risk factors may be related to the development of hemolysis: high doses (eg, ≥2 g/kg, single administration or divided over several days) and non-O blood group. Underlying inflammatory state in an individual patient may increase the risk of hemolysis but its role is uncertain.

Contraindications to IGI treatment include anaphylactic or severe systemic hypersensitivity reactions to IG and IgA deficient patients with antibodies against IgA and a history of hypersensitivity.

IGI, 10% has a high margin of safety. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and preparation. Three validated, dedicated, independent, and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, further increasing the margin of safety.

In addition, careful screening and monitoring of subjects in this study will be utilized to minimize the above and other known risks associated with IG therapy (eg, exclusion criteria, blood group typing at baseline, and laboratory monitoring for hemolysis).

Further information is provided in the Prescribing Information for GAMMAGARD LIQUID, SmPC for KIOVIG, and the IB for Immune Globulin Infusion (Human), 10% Solution (IGI, 10%).

[redacted]

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP R2, November 2016), Title 21 of the US Code of Federal Regulations, the EU Directives (2001/20/EC; 2005/28/EC), the Declaration of Helsinki (October 2013), and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to provide evidence for the use of HYQVIA/HyQvia as a maintenance therapy option that enables self-infusion of a full therapeutic dose every 2 to 4 weeks in patients with CIDP.

In addition, this study aims to provide evidence for the use of GAMMAGARD LIQUID/KIOVIG as an IV immunoglobulin treatment option in patients with CIDP.

7.2 Epoch 1: SC Treatment Period

7.2.1 Primary Objective

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

7.2.2 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.

7.2.3 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.

7.3 Epoch 2: IV Treatment Period

7.3.1 Primary Objective

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

7.3.2 Secondary Objective

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

7.3.3 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.

8. STUDY DESIGN

8.1 Brief Summary

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 (a monthly equivalent dose of 0.4 to 2.4 g/kg body weight [BW] with a dosing interval of 2 to 6 weeks) of IGIV therapy for at least 12 weeks prior to screening.

8.2 Overall Study Design

The overall study design is illustrated in Figure 21-1. Schematics for study assessments and visits are detailed in Section 21.2. Details on the procedures to be performed at each study visit can be found in Section 21.2 Schedule of Study Procedures and Assessments and Section 21.3 Clinical Laboratory Assessments.

After informed consent has been obtained, subjects will undergo screening and baseline procedures for the determination of eligibility. During the screening/baseline period, subjects will continue to receive their own IGIV treatment at the same dose and dosing frequency as prescribed prior to their entry into this study.

Epoch 1: SC Treatment Period

In this double-blind, placebo-controlled phase of the study (Epoch 1), 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 Section 8.7.4.1 for more information). No conversion factor will be applied when switching from pre-randomization IGIV to HYQVIA/HyQvia (or 0.25% albumin placebo with rHuPH20) treatment; that is, the monthly IgG dose of HYQVIA/HyQvia (or matching infusion volume for subjects in the placebo group) will be the same as the subject's pre-randomization monthly dose of IGIV. The number of infusion visits and clinic visits during the SC treatment period will vary across subjects depending on whether their infusion cycles are every 2, 3, or 4 weeks (see Table 21-1, Table 21-2, and Table 21-3).

The study product components of HYQVIA/HyQvia (or 0.25% albumin placebo with rHuPH20) will be administered sequentially. Subcutaneous infusion of rHuPH20 solution at a dose of 80 U/g IgG (or its equivalent at 80 U/10 mL of the 0.25% albumin placebo solution) will be administered first, to be followed by SC infusion of IGI, 10% or 0.25% albumin placebo solution within 10 minutes of completion of the infusion of rHuPH20 solution. To gradually increase the SC infusion volume, a dose ramp-up schedule will be employed until the subject's full dose is reached (see Table 8-3).*
The first SC administration will take place 2 weeks (±3 days) following the subject's last pre-randomization IGIV administration.

*Week 1 should be calculated from last day of dosing for an infusion dose that is to be administered over multiple days.

Initial SC infusions (ie, infusions during the ramp-up period and, at a minimum, the first full-dose infusion) must be administered at the study site or infusion center to monitor for safety and tolerability, to determine the infusion rate and infusion volume per infusion site that can be tolerated by the subject, and to provide training to the subject (and/or, as applicable, to a caregiver who may assist the subject with self-infusion) on self-infusion procedures. At the investigator's discretion, the remainder of the SC infusions may take place at the study site, infusion center, or at the subject's home or other suitable location, as acceptable per local regulations and standard practices of the study site. The ability of the subject (and/or caregiver) to perform infusion procedures independently is a prerequisite for self-administration. Training and the investigator/designee's evaluation of the subject's (and/or caregiver's) proficiency in independently self-administering infusions must be documented.

Assessments will be conducted to monitor for changes in the subject's functional ability (INCAT disability score (Hughes et al., 2001), ADL (Rasch-built Overall Disability Scale [R-ODS] (van Nes et al., 2011), hand grip strength (Merkies et al., 2000), and muscle strength (Medical Research Council [MRC] sum score (Kleyweg et al., 1991). Additional assessments will include trough serum IgG levels, as well as safety laboratory assessments. Patient reported outcome (PRO) measures will be collected including: quality of life (Short Form-36 [SF-36] (Ware et al., 2000)), health utility status (EuroQoL [Quality of Life]-5 Dimensions [EQ-5D] scores (The EuroQol Group, 1990), HRU, treatment satisfaction, treatment preference, and PGIC. An electronic diary (DIARYpro) will be utilized to capture data records related to infusions, AEs, concomitant medications, and PRO measures such as the R-ODS and HRU.

At any time during the SC treatment period, unscheduled visit(s) for INCAT assessments will be allowed for subjects who experience CIDP worsening, in order to determine whether the worsening meets the definition of relapse (ie, worsening in functional disability by ≥1 point relative to the pre-SC treatment baseline in 2 consecutive adjusted INCAT disability scores[iv],(Hughes et al., 2008). Open-label treatment with IGIV will be provided for any subjects (regardless of their treatment assignment in Epoch 1) who meet the definition of relapse and enter into Epoch 2, in order to restore functional ability. An INCAT assessment will be performed at the time the subject is being evaluated for relapse, and again just prior to initiation of IGIV treatment in Epoch 2. The pre-IV treatment baseline INCAT assessment will be used 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. Subjects who relapse during Epoch 1 may choose not to enter into Epoch 2. For these subjects, INCAT assessment will be repeated during the early termination visit and this INCAT disability score will serve to confirm whether the subject has met the relapse criteria.

Epoch 2: IV Treatment Period

Epoch 2 is the open-label phase of this study that aims to provide IGIV treatment for subjects who meet relapse criteria during Epoch 1, in order to restore functional ability.

Subjects will receive GAMMAGARD LIQUID/KIOVIG (all subjects with the exception of those at US sites) or GAMUNEX®-C[v] (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 (ie, 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.

At any time during the IV treatment period, unscheduled visit(s) for INCAT assessments will be allowed for subjects who experience CIDP worsening, in order to determine whether the worsening meets the definition of relapse (ie, worsening in functional disability by ≥1 point relative to the pre-SC treatment baseline in 2 consecutive adjusted INCAT disability scores). Subjects who relapse during Epoch 2, will have a close-out visit and terminate participation in the study, in order to have the opportunity to receive other/additional treatment.

8.3 Duration of Study Periods and Subject Participation

The maximum overall duration of this study is estimated to be approximately 72 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit), including:

- An enrollment period of approximately 64 months
- Subject participation duration of approximately 8 to 14 months from enrollment (ie, signing informed consent) to study completion (ie, last study visit), unless prematurely discontinued

For subjects who complete the SC treatment period (Epoch 1) without relapse, the duration of study participation will be approximately 8 months, including:

- A screening/baseline period of up to 8 weeks
- A SC treatment period (Epoch 1) of 6 months

For subjects who relapse during the SC treatment period and subsequently enter into the IV treatment period (Epoch 2), the duration of study participation will be approximately 14 months, including:

- A screening/baseline period of up to 8 weeks
- A SC treatment period (Epoch 1) of 6 months
- An IV treatment period (Epoch 2) of 6 months

8.4 Outcome Measures

8.4.1 Epoch 1: SC Treatment Period

8.4.1.1 Primary Outcome Measure

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)

8.4.1.2 Secondary Outcome Measures

8.4.1.2.1 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 score

8.4.1.2.2 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 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.

8.4.1.3 Tertiary Outcome Measures

8.4.1.3.1 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.

8.4.1.3.2 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. Patient global impression of change

8.4.1.3.3 Other

1. Trough serum IgG levels

8.4.2 Epoch 2: IV Treatment Period

8.4.2.1 Primary Outcome Measure

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)

8.4.2.2 Secondary Outcome Measures

8.4.2.2.1 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) 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.

8.4.2.2.2 Efficacy

1. Proportion of subjects with clinically meaningful improvement in functional ability defined as one or more of the following: a decrease of ≥1 point in the adjusted INCAT disability score at 2 consecutive time points; who experience CIDP improvement (defined as ≥8 kPa increase in hand grip strength in the more affected hand; ≥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

8.4.2.3 Tertiary Outcomes Measures

8.4.2.3.1 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.

8.4.2.3.2 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 assessed by Treatment Satisfaction Questionnaire for Medication (TSQM-9)
5. Treatment preference
6. Patient global impression of change

8.4.2.3.3 Other

1. Trough serum IgG levels

8.5 Randomization and Blinding

This study comprises of 2 epochs: a randomized, double-blind, placebo-controlled SC treatment period (Epoch 1) and an open-label IV treatment period (Epoch 2). In order to minimize/avoid bias, subjects meeting all eligibility criteria (including baseline INCAT assessment) will be randomly assigned to one of two SC treatment regimens (HYQVIA/HyQvia or 0.25% albumin placebo with rHuPH20) at a ratio of 1:1.
Each subject will be assigned a unique randomization code for the duration of the study. There will be no re-randomization for those subjects who relapse during Epoch 1 and subsequently enter into Epoch 2, as all subjects will receive open-label IGIV treatment during Epoch 2. Subjects who were withdrawn or discontinued early from the study after randomization will not be replaced. Randomization codes will be generated by the sponsor or the sponsor's representatives, and maintained by a centralized randomization service.

8.5.1 Blinding

Epoch 1 is blinded and Epoch 2 is open-label. During Epoch 1, treatment assignment will not be revealed to the subject, the investigator and site personnel, the sponsor and sponsor's representatives, except for unblinded study personnel. Unblinded personnel will be responsible for maintaining any unblinded records in a secure, access-controlled location/system. To avoid inadvertent unblinding, results of serum IgG levels obtained after exposure to IP(s) will be withheld from the subject, the investigator and site personnel, and all blinded study personnel with the sponsor and sponsor's representatives until all subjects have completed participation in Epoch 1. 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.

8.5.2 Unblinding

Access to unblinding data during study conduct will be controlled to ensure that the scientific integrity and regulatory utility of the study are appropriately maintained and protected.

Unblinding for Interim Safety Analysis:

For the interim safety analysis described in Section 14.3.1, treatment assignment will be unblinded and all data will be analyzed as preplanned in the study SAP; similarly for any other interim analysis.

Unblinding for Epoch 1 Final Analysis:

At the completion of Epoch 1, all Epoch 1 data will be locked, treatment assignment will be unblinded, and all data will be analyzed as preplanned in the study Statistical Analysis Plan (SAP). The analysis, described in Section 14.3.2 of this protocol, will be considered the final analysis of Epoch 1 data.

Unblinding for Other Purposes during Study Conduct:

Treatment assignment is not to be revealed before the study is completed/terminated, except for purposes of the Epoch 1 final analysis and the interim safety analysis, as noted above, and in emergency cases when unblinding is necessary for the clinical management of an SAE. In such events, the investigator may unblind via the Interactive Response Technology System (IRT) at any time (ie, 24 hours per day, 7 days per week) to obtain the treatment assignment. Details of unblinding procedures will be provided to study sites.

8.6 Study Stopping Rules

A Data Monitoring Committee (DMC) will be established to monitor the study for any safety or medical concerns, and may recommend stopping the study based on the criteria defined in the DMC charter (see Section 17.4). The study may be terminated by the sponsor at any time.

In addition to the threat and future uncertainty caused by the COVID-19 pandemic, the study has had considerable recruitment challenges as a result of low CIDP prevalence, unwillingness of patients to discontinue their existing effective CIDP treatments, increasing competition in the CIDP trial landscape, and the reluctance of physicians and patients to be exposed to placebo given the existence of efficacious treatments for CIDP.

As a result of these special circumstances, randomization to Epoch 1 will be stopped by the sponsor prior to achieving the originally planned total of 174 randomized subjects (i.e., such that 148 subjects would have been expected to complete Epoch 1). Based on updated sample size assumptions as a result of the changed scientific landscape since the study was originally planned, it is expected that adequate statistical power (90%) will still be achieved (Sections 14.1.1 and 14.2.1.2).

8.6.1 Operational procedures for study stopping

The following actions will be taken:

- Randomization to Epoch 1 will be closed prior to achieving the originally planned total of 174 randomized subjects.
- All subjects randomized will be permitted to complete Epoch 1 and may enter Epoch 2 if they relapse on Epoch 1, in accordance with study procedures. Any patient entering into Epoch 2 will be followed for the protocol specified time or discontinuation.

8.6.2 Trial integrity

It is important to note that the sponsor decision to stop randomization to Epoch 1 prior to achieving the originally planned target of 174 subjects is completely independent of observed study data and that trial integrity is completely maintained. This trial modification is therefore without risk of introducing bias into the interpretation of trial findings.

8.7 Investigational Products

8.7.1 Packaging, Labeling, and Storage

8.7.1.1 rHuPH20

Dosage Form: Injection, solution

Packaging: rHuPH20 drug product (160 U/mL) will be supplied as a clear, colorless, ready-for-use sterile liquid preparation in single-use glass vials. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

Labeling: The product will be labeled according to the regulatory requirements for clinical studies.

Storage: rHuPH20 drug product must be stored under refrigerated conditions (2° to 8°C or 36° to 46°F). Do not freeze the product. Do not use if expiration date is exceeded.

8.7.1.2 IGI, 10% / IGIV 10%

IGI, 10% when administered intravenously is also referred to as IGIV 10%.

Dosage Form: Injection, solution.

Packaging: IGI, 10% / IGIV 10% will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials. IGI, 10% / IGIV 10% is a clear or slightly opalescent and colorless or pale yellow solution. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

Labeling: IGI, 10% / IGIV 10% will be labeled according to regulatory requirements for clinical studies.

Storage: IGI, 10% / IGIV 10% must be stored under refrigerated conditions (2° to 8°C or 36° to 46°F). Do not freeze the product. Do not use if expiration date is exceeded.

8.7.1.3 Placebo Solution

Human albumin 0.25% in LR solution will be used as the placebo control in this study. Human albumin 0.25% solution will be prepared at the pharmacy by appropriate dilution of a concentrated human albumin product (e.g., 200 to 250 g/L or 25%) with LR solution.

Do not dilute human albumin solution with sterile water for injection.

Both human albumin product and LR solution should be inspected visually for particulate matter and discoloration. The products should not be used if particulate matter and/or discoloration is observed.

Dosage Form: Injection, solution.

Packaging: Human albumin product will be supplied as a transparent or slightly opalescent solution, which may have a greenish tint or may vary from a pale straw to an amber color in rest of world, and clear, slightly viscous solution, almost colorless, yellow to brown or green in US and Canada.

LR solution is a ready-for-use, sterile, clear, or almost colorless solution.

Labeling: Human albumin solution will be labeled according to regulatory requirements for clinical studies.

Storage: Store human albumin product according to information provided in the specific product label. Store LR solution at room temperature. Do not freeze the product. Do not use if expiration date is exceeded.

8.7.1.4 GAMUNEX®-C (US Only)

GAMUNEX®-C will be used as the IGIV treatment for subjects at US sites who relapse in Epoch 1 and enter into Epoch 2. Please refer to GAMUNEX®-C Prescribing Information for directions for use and storage instructions.

8.7.2 Preparation and Storage of Pooled Products

Vials of rHuPH20 solution and bag(s) of pooled IGI, 10%/0.25% albumin placebo solution will be supplied for infusions.

The vials of rHuPH20 must be stored under refrigerated conditions (2° to 8°C or 36° to 46°F). Prior to administration, the vials of rHuPH20 should be taken out of temperature-controlled storage to allow for equilibration to room temperature, which may take up to 60 minutes. Detailed instructions for transferring rHuPH20 solution into syringes for infusion will be provided in infusion manuals.

IGI, 10% and 0.25% albumin placebo solutions for administration must be prepared using aseptic techniques under controlled air environment in accordance with United States Pharmacopeia (USP) guideline 797 or its equivalent per regional or institutional standard practices. Administration of the pooled products must be completed within 5 days from the time of preparation. Once the pooled products are prepared, the infusion must be started within 3 h from the time of preparation. When administration of pooled products will begin more than 3 h from preparation, they must be kept at 2° to 8°C (36° to 46°F). Pooled products should be taken out of the temperature-controlled storage before administration to allow for equilibration to room temperature. It may take 60 minutes or longer for the pooled products to reach room temperature. The infusion shall be started no later than 3 h after removal from the temperature-controlled storage.

In case IGI, 10% solutions for administration have to be prepared using aseptic techniques without controlled air environment (Laminar Flow hood) in accordance with USP guideline 797 or its equivalent per regional or institutional standard practices and within the Pharmacy Manual, the study drug must only be administered to study subjects at the study site and immediately following preparation and after reaching room temperature.

All solutions for infusion must be administered at room temperature.

All solutions for infusion will be labeled according to regulatory requirements for clinical studies.

For instructions on preparation and administration of GAMUNEX®-C, please refer to the GAMUNEX®-C Prescribing Information.

8.7.3 Administration

8.7.3.1 Epoch 1

Mode of administration:

The rHuPH20 solution will be administered **s**ubcutaneously via a peristaltic infusion pump with programmable infusion rates and infusion volumes at 1, 2, or 3 infusion sites per infusion day

Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US only) will be the Q Core – Sapphire pump.

The Body Guard 323 pump and pump tubing will continue to be used in EU/ROW. Details on the infusion parameters will be noted in the Investigator Site Infusion Manual.

The rHuPH20 solution and IGI, 10%/0.25% albumin placebo solution will be administered in a sequential order, with IGI, 10%/0.25% albumin placebo infusion being initiated within approximately 10 minutes of completing the infusion of the rHuPH20 solution.

It is recommended to use a 24G thin-walled, single, bifurcated, or trifurcated SC needle set labeled for high flow and a peristaltic infusion pump with variable rate programming capability for both rHuPH20 and IGI, 10% /placebo solution.

IGI, 10%/placebo solution:

IGI,10/Placebo solution is administered second, within 10 minutes of the rHuPH20 being completed.

Table 8-1. Recommended SC Infusion Rates for IGI, 10% (or Placebo) for Subjects <40kg BW

	Infusion Rate Per Infusion Site (mL/h)		
	First 2 Infusions	**Next 2 Infusions**	**All Subsequent Infusions**
First 5 – 15 min	5	10	Infusion rates may be adjusted and an abbreviated infusion rate ramp-up scheme may be employed at the investigator's discretion and based on subject's tolerability level, but not to exceed 160 mL/h per infusion site For details of using Bifurcated and Trifucated infusion sets and infusion rates recommended see the Investigator Site Infusion Manual
Next 5 - 15 min	10	20	
Next 5 - 15 min	20	40	
Next 5 - 15 min	40	80	
Remainder of infusion	80	160	

Abbreviation: BW = Body weight; SC=Subcutaneous

Table 8-2. Recommended SC Infusion Rates for IGI, 10% (or Placebo) for Subjects ≥40kg BW

	Infusion Rate Per Infusion Site (mL/h)		
	First 2 Infusions	**Next 2 Infusions**	**All Subsequent Infusions**
First 5 – 15 min	10	10	Infusion rates may be adjusted and an abbreviated infusion rate ramp-up scheme may be employed at the investigator's discretion and based on subject's tolerability level, but not to exceed 300 mL/h per infusion site. For details of using Bifurcated and Trifucated infusion sets and infusion rates recommended see the Investigator Site Infusion Manual
Next 5 - 15 min	30	30	
Next 5 - 15 min	60	120	
Next 5 - 15 min	120	240	
Remainder of infusion	240	300	

Abbreviation: BW = Body weight; SC=Subcutaneous

Site of administration: The recommended site(s) for SC infusion are the right and left middle to upper abdomen and the right and left thighs, at the subject's preference. If 2 infusion sites are used concurrently, the 2 or 3 infusion sites should be on opposite sides of the middle to upper abdomen at least 10 cm apart or on opposite thighs. Avoid bony prominences, visible blood vessels, scars, and areas that are inflamed or infected. For large IgG doses (or matching infusion volume for subjects in the placebo group), the entire dose may be administered over multiple days as divided doses at least 48 to 72 h apart for tenderness, erythema, or swelling that may result from the previous infusion to subside.

Volume of infusion per site: IGI, 10% or 0.25% albumin placebo solution may be administered at 1, 2, or 3 infusions sites with a maximum infusion volume of 600 mL for subjects weighing ≥40 kg or up to 300 mL for subjects weighing <40 kg (or as tolerated) at each infusion site. On a given infusion day, the maximum infusion volume should not exceed 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg. Should the total infusion volume that is to be administered exceed either 1200 mL for subjects ≥40 kg or 600 mL for subjects <40kg, or exceed the maximum infusion volume a subject can tolerate on a given infusion day, then the total dose may be administered over multiple days as divided doses 48 to 72 h apart (eg, Day 1 and Day 3 of a given infusion cycle) to allow the infused fluid to be absorbed.

8.7.3.2 Epoch 2

Subjects will receive GAMMAGARD LIQUID/KIOVIG (all subjects with the exception of those at US sites) or GAMUNEX®-C (subjects at US sites only).

Mode of administration: IV infusion

Rate of administration: GAMMAGARD LIQUID/KIOVIG will be administered intravenously with a step-wise increase in infusion rate regulated using a peristaltic infusion pump with programmable infusion rates and infusion volumes.

Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US only) will be the Q Core – Sapphire pump.

IV infusion (to be administered via a peristalic variable rate infusion pump).

The Body Guard 323 pump and pump tubing will continue to be used in EU/ROW. Details on the infusion parameters will be noted in the Investigator Site Infusion Manual. The recommended starting infusion rate is 0.5 mL/kg BW/h, which may be gradually increased up to 5.4 mL/kg BW/h as tolerated by the subject. Induction dose (2 g/kg BW) is to be administered over 2 to 5 consecutive days. Maintenance infusions at the same monthly equivalent dose as the individual subject's pre-randomized IGIV doses are to be administered over 2 to 5 consecutive days, every 3 weeks.

It is recommended that, for the initial 2 infusions, IGIV 10% should be infused at starting infusion rate of 0.5 mL/kg BW/h. The infusion rate may be gradually increased up to 5.4 mL/kg BW/h, at the discretion of the investigator and if tolerated by the subject. For all subsequent infusions, the starting infusion rate and the increases in the infusion rate may be determined by the investigator or in accordance with institutional standardized infusion rate protocols. The maximum infusion rate should not exceed 5.4 mL/kg BW/h at any time. In the EU, the maximum infusion rate for Body Guard 323 pump is 500 mL/hr.

GAMUNEX®-C will be administered in accordance with the GAMUNEX®-C Prescribing Information and based on the subject's pre-study IGIV treatment history, including initial and maximum tolerated rate(s) of administration.

8.7.4 Description of Treatment

8.7.4.1 Epoch 1

Treatment: Either HYQVIA/HyQvia or placebo (0.25% human albumin in LR solution) with rHuPH20, based on treatment assignment

Treatment Period: 6 months, or until relapse

Dose:

- **rHuPH20** solution**:** 80 U rHuPH20/g IgG, or 80 U rHuPH20/10 mL of the 0.25% albumin placebo solution. If the IGI, 10%/0.25% albumin placebo solution is given at a single site, the entire dose of recombinant rHuPH20 should be given at the site. When using bifurcated or trifurcated needle set, IGI, 10%/placebo is to be divided between 2 or 3 sites, respectively. Additionally, rHuPH20 dose should be divided between 2 or 3 sites by maintaining the ratio of 80 U rHuPH20 per 10 mL of IGI 10% or placebo (0.25% human albumin in LR solution).
- **IGI, 10% or placebo**: Same as the subject's pre-randomization monthly equivalent IgG dose for subjects receiving IGI, 10%, or at matching infusion volume for subjects in the placebo group. No conversion factor will be applied when switching from pre-randomization IGIV to IGI, 10% or 0.25% albumin placebo with rHuPH20 treatment; that is, the monthly IgG dose of IGI, 10% (or matching infusion volume for subjects in the placebo group) will be the same as the subject's pre-randomization monthly dose of IGIV.

Dosing frequency: Every 2, 3, or 4 weeks, except during the ramp-up period. See Table 8-3 below for dosing schedule during the ramp-up period.

1. Subjects on pre-randomization IGIV treatment schedule every 2, 3, or 4 weeks will continue to receive HYQVIA/HyQvia or 0.25% albumin placebo with rHuPH20 administration at the same dosing frequency during the study. Adjustment to dosing interval is not allowed, except due to intolerability.
2. Adjustment to the dosing frequency as the subject transitions from pre-randomization IGIV to SC IGI, 10% or 0.25% albumin placebo will only be allowed in the following cases:
    a. For subjects with pre-randomization IGIV dosing every 5 or 6 weeks, the dosing interval in the study will be converted to 2, 3, or 4 weeks while maintaining the same monthly equivalent IgG dose (or matching infusion volumes for subjects in the placebo group). The choice of 2-, 3-, or 4-week interval will be at the discretion of the investigator and based on the subject's tolerability.

b. For subjects with an IgG dose (or matching infusion volume for subjects in the placebo group) that exceeds the SC maximum infusion volume that a given subject can tolerate, HYQVIA/HyQvia or 0.25% albumin placebo with rHuPH20 may be administered at a 2-, 3-, or 4-week dosing interval at the discretion of the investigator and as tolerated by the subject while maintaining the same monthly equivalent dose.

Ramp-up Schedule: During the transition from pre-randomization IV to SC dosing, a dose ramp-up schedule to gradually increase the SC infusion volume will be employed until the subject's full dose is reached (see Table 8-3). The first SC administration (1-week dose) will take place 2 weeks (±3 days) following the subject's last pre-randomization IGIV administration, regardless of the pre-randomization IGIV dosing interval.

Table 8-3. SC Dosing Ramp-Up Schedule During the Transition from IV to SC Dosing

Dosing Schedule	Study Visits												
	S / BL Period (up to 8 Wks)	SC Treatment Period (6 Months)											
	Pre-SC BL	W1[a] (2 Wks After Pre-SC BL)	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Q2W	Last full IGIV dose	1-W	1-W	2-W (full dose) and every 2 weeks thereafter									
Q3W		1-W	1-W	2-W	--	3-W (full dose) and every 3 weeks thereafter							
Q4W		1-W	1-W	2-W	--	3-W	--	--	4-W (full dose) and every 4 weeks thereafter				

Abbreviations: S = Screening; BL = Baseline; Pre-SC BL = Pre-subcutaneous treatment baseline visit; wks = weeks; W = Week; 1-W = 1-week dose; 2-W = 2-week dose; 3-W = 3-week dose; 4-W = 4-week dose; --: No infusion will be administered for the particular week as marked.

[a] W1 indicates when the first administration of HYQVIA/HyQvia or 0.25% albumin placebo with rHuPH20 is given. The first SC administration will take place 2 weeks (±3 days) following the subject's last pre-randomization IGIV administration.
As an example, a monthly dose of 1.6 g/kg (equivalent to 0.4 g/kg per week) would be administered according to the following SC ramp-up regimens (as applicable):
0.8 g/kg BW Q2W: 0.4 g/kg BW during Week 1 and Week 2 visits, 0.8 g/kg BW (full dose) during Week 3 visit and every 2 weeks thereafter (Week 5, Week 7,…,Week 27).
1.2 g/kg BW Q3W: 0.4 g/kg BW during Week 1 and Week 2 visits, 0.8 g/kg BW during Week 3 visit, 1.2 g/kg BW (full dose) during Week 5 visit and every 3 weeks thereafter (Week 8, Week 11,…,Week 26).
1.6 g/kg BW Q4W: 0.4 g/kg BW during Week 1 and Week 2 visits, 0.8 g/kg BW during Week 3 visit, 1.2 g/kg BW during Week 5 visit, 1.6 g/kg BW (full dose) during Week 8 visit and every 4 weeks thereafter (Week 12, Week 16,…,Week 28).

8.7.4.2 Epoch 2

Treatment: GAMMAGARD LIQUID/KIOVIG (all subjects with the exception of those at US sites) or GAMUNEX®-C (subjects at US sites only)

Treatment period: 6 months

Dosing and dosing frequency:

GAMMAGARD LIQUID/KIOVIG:
The first IGIV dose will be 2 g/kg BW given as divided doses over 2 to 5 consecutive days (for GAMMAGARD LIQUID/KIOVIG), followed by maintenance infusions at the same monthly dose as the individual subject's pre-randomization IGIV doses are to be administered over 2 to 5 days (for GAMMAGARD LIQUID/KIOVIG) every 3 weeks.

GAMUNEX-C:
The recommended initial infusion rate is 2 mg/kg/min (0.02 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min) In the EU, the maximum infusion rate for the Body Guard 323 is 500 mL/hr; see GAMUNEX-C prescribing information. For patients judged to be at risk for renal dysfunction or thrombosis, this drug is recommended to be administered at the minimum infusion rate practicable. Induction dose (2 g/kg BW) is to be administered over 2 to 4 consecutive days, maintenance infusion of 1 g/kg (10 mL/kg) administered over 1 day or divided into 2 doses of 0.5 g/kg (5 mL/kg) given on 2 consecutive days, every 3 weeks

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, with a maximum dose of 100 g/1000 mL/day. There will be no adjustments to the dosing interval of every 3 weeks.

8.7.4.3 Weight-Based Determination of Infusion Volume

In both Epoch 1 and Epoch 2, the volume (mL) of infusion solution to be administered will be calculated using the subject's BW measured at screening. Adjustment based on BW changes during the course of the study is not planned, however may be done if deemed medically necessary by the investigator (eg, clinically significant BW change). After screening, for study visits where the subject's BW is measured, (see Section 21.2 Schedule of Study Procedures and Assessments for detailed timepoints), it is to be measured on site using the same scale/instrument throughout the study for that individual subject.

8.7.5 Investigational Product Accountability

The investigator/designee (or the central pharmacy, as applicable) will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator/designee (or the central pharmacy, as applicable) will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (eg, infusion center; home, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator/designee (or the central pharmacy, as applicable) will provide documentation in accordance with the sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study include but are not limited to: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries (including electronic diaries) or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the case report form (CRF). All data entered in to the CRF should be able to be verified by a corresponding source document.

For additional information on study documentation and CRFs, see Section 18.2.
The use of subject diaries is described in Section 10.6.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Males or females of age ≥18 years old at the time of screening.
2. Subject has a documented diagnosis of definite or probable CIDP (focal atypical CIDP and pure sensory atypical CIDP will be excluded), as confirmed by a neurologist specializing/experienced in neuromuscular diseases to be consistent with the EFNS/PNS 2010 criteria (European Federation of Neurological Societies, 2010). Fulfillment of electrodiagnostic criteria must be confirmed by an independent qualified/experienced central reader.
3. Subject has responded to IgG treatment in the past (partial or complete resolution of neurological symptoms and deficits), and must currently be on stable doses of IGIV treatment within the dose range equivalent to a cumulative monthly dose of 0.4 to 2.4 g/kg BW (inclusive) administered intravenously for at least 12 weeks prior to screening. The dosing interval of IGIV treatment must be between 2 and 6 weeks (inclusive). Variations in the dosing interval of up to ±7 days or monthly dose amount of up to ±20% between subject's pre study IgG infusions are within acceptable limits
4. INCAT disability score between 0 and 7 (inclusive). Subjects with INCAT scores of 0, 1 (whether from upper or lower extremities), or 2 (if at least 1 point is from an upper extremity) at screening and/or baseline will be required to have a history of significant disability as defined by an INCAT disability score of 2 (must be exclusively from the lower extremities) or greater documented in the medical record. Subjects will be eligible if one of the below eligibility criteria are met:
    a. Screening and Baseline INCAT disability score of between 3 and 7 inclusive. Screening and/or Baseline INCAT disability score of 2 (both points are from lower extremities)
    b. Screening and/or Baseline INCAT disability score of 2 (both points are not from lower extremities) AND has at least a score of 2 or greater documented in the medical record prior to screening. If a score was greater than 2 documented in the medical record prior to screening at least 2 points must be from lower extremities.
    c. Screening and/or Baseline INCAT disability score of 0 or 1 AND has at least a score of 2 or greater (both from lower extremities) documented in the medical record prior to screening, at least 2 points must be from lower extremities.

5. If female of childbearing potential, the subject must have a negative pregnancy test at screening and agree to employ a highly effective contraceptive measure (see Section 21.5 for more details) throughout the course of the study and for at least 30 days after the last administration of investigational product (IP).
6. Subject is willing and able to sign an Informed Consent Form (ICF).
7. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are NOT eligible for this study:

1. Subjects with focal atypical CIDP or pure sensory atypical CIDP.
2. Any neuropathy of other causes, including:
   a. Hereditary demyelinating neuropathies, such as hereditary sensory and motor neuropathy (HSMN) (Charcot-Marie-Tooth [CMT] disease), and hereditary sensory and autonomic neuropathies (HSANs)
   b. Neuropathies secondary to infections, disorders, or systemic diseases such as Borrelia burgdorferi infection (Lyme disease), diphtheria, systemic lupus erythematosus, POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, lymphoma, and amyloidosis.
   c. Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
   d. Multifocal motor neuropathy (MMN)
   e. Drug-, biologic-, chemotherapy-, or toxin-induced peripheral neuropathy
3. Immunoglobulin M (IgM) paraproteinemia, including IgM monoclonal gammopathy with high titer antibodies to myelin-associated glycoprotein
4. Presence of prominent sphincter disturbance.
5. Any central demyelinating disorders such as multiple sclerosis.
6. Any chronic or debilitating disease, or central nervous disorder that causes neurological symptoms or may interfere with assessment of CIDP or outcome measures, including (but not limited to) arthritis, stroke, Parkinson's disease, and diabetic peripheral neuropathy.
   (Subjects with clinically diagnosed diabetes mellitus who do not have diabetic peripheral neuropathy and who have adequate glycemic control with hemoglobin A1C [HbA1C] level of <7.5% at screening will be eligible for the study, provided the electrodiagnostic criteria are consistent with the diagnosis of a definite or probable CIDP consistent with the EFNS/PNS 2010 criteria and the subject agrees to maintain adequate glycemic control.)

7. Congestive heart failure (New York Heart Association [NYHA] class III/IV), unstable angina, unstable cardiac arrhythmias, or uncontrolled hypertension (defined as diastolic blood pressure >100 mmHg and/or systolic blood pressure >160 mmHg).
8. History of deep vein thrombosis or thromboembolic events (eg, cerebrovascular accident, pulmonary embolism) within 12 months prior to screening.
9. Condition(s) which could alter protein catabolism and/or IgG utilization (eg, protein-losing enteropathies, nephrotic syndrome).
10. Known history of chronic kidney disease, or glomerular filtration rate (GFR) of <60 mL/min/1.73m2 estimated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009) at the time of screening.
11. Subject with active malignancy requiring chemotherapy and/or radiotherapy, or history of malignancy with less than 2 years of complete remission prior to screening. Exceptions to this exclusion are: adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and stable prostate cancer not requiring treatment.
12. Clinically significant anemia that precludes repeated blood sampling during the study, or hemoglobin (Hgb) level of <10.0 g/dL at the time of screening.
13. Known history of hypersensitivity or ARs such as urticaria, breathing difficulty, severe hypotension, or anaphylaxis following administration of human blood products such as human IgG, albumin, or other blood components.
14. Known allergy to hyaluronidase of human (including recombinant human hyaluronidase) or animal origin such as bee or wasp venom.
15. Known history of, or immunoglobulin A (IgA) deficiency (<8 mg/dL) at the time of screening.
16. Abnormal laboratory values at screening meeting any one of the following criteria:
    a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 x upper limit of normal (ULN)
    b. Platelet count <100,000 cells/µL
    c. Absolute neutrophil count (ANC) <1000 cells/µL
17. Ongoing/active infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) Type 1/2 infection at the time of screening. (Subjects with immunity to hepatitis B from either active vaccination or from previous natural infection are eligible to participate in the study.)

18. The subject has received or is currently receiving treatment with immunomodulatory/immunosuppressive agents within 6 months prior to screening.
19. The subject has received or is currently receiving treatment with any corticosteroids dose within 8 weeks prior to screening, regardless of indication.
20. The subject has undergone plasma exchange (PE) within 3 months prior to screening.
21. The subject has any disorder or condition that in the investigator's judgment may impede the subject's participation in the study, pose increased risk to the subject, or confound the results of the study.
22. The subject is nursing or intends to begin nursing during the course of the study.
23. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment, or is scheduled to participate in another clinical study (with the exception of the HYQVIA/HyQvia extension study in CIDP) involving an IP or investigational device during the course of this study.
24. The subject is a family member or employee of the investigator.
25. Subjects with acquired or inherited thrombophilic disorders. These will include the specific types of acquired or inherited thrombophilic disorders that could put subjects at risk of develop thrombotic events. Examples include
    a. Hereditary Thrombophilias:
        i. Factor V Leiden mutation
        ii. Prothrombin 20210A mutation
        iii. Protein C deficiency
        iv. Protein S deficiency
        v. Antithrombin deficiency
    b. Acquired thrombophilias
        i. Antiphospholipid antibody syndrome
        ii. Activated protein C Resistance acquired
        iii. Homocystinemia

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the appropriate CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.7 and Section 21.2.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects may also be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject becomes pregnant. IP exposure will be discontinued. If the subject has been exposed to rHuPH20, attempts will be made to follow the subject through completion of the pregnancy and the infant up to 1 year postdelivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome. (See also Section 12.1.2)
2. The subject begins nursing. IP exposure will be discontinued. The investigator will record a narrative description of the course of the infant's development.
3. The subject frequently misses administration of IP (more than 2 consecutive infusions after reaching full dose).
4. The subject develops severe hypersensitivity reactions related to IP administration.
5. The subject uses prohibited medications (see Section 10.5) during the course of this study.
6. The subject participates in another clinical study involving an IP or device during the course of this study.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier (eg, 161403) to be provided by the sponsor, 2- or 3-digit number study site number (eg, 02) to be provided by the sponsor, and 3- or 4-digit subject number (eg, 0003) reflecting the order of providing informed consent. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 161403-020003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects who provided informed consent. The log will also serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End-of-Study CRF should be completed, and a new ICF, new SIC, and new CRF are required for that subject.

The overall study design is illustrated in Section 21.1 Study Flow Chart. Schematics for study assessments and visits are detailed in Section 21.2. Details on the procedures to be performed at each study visit, including screening, can be found in Section 21.2 Schedule of Study Procedures and Assessments and Section 21.3 Clinical Laboratory Assessments.

10.3.1 Screening and Baseline Period

A subject's eligibility will be determined during the screening/baseline period, which may last up to 8 weeks.

In order to be eligible to participate in this study, subjects must have a documented diagnosis of definite or probable CIDP in accordance with the EFNS/PNS 2010 criteria (European Federation of Neurological Societies, 2010). Subjects with focal atypical CIDP and pure sensory atypical CIDP will not be eligible. To fulfill the electrodiagnostic

criteria, nerve conduction studies will be performed on all subjects, which will be used for confirmation of CIDP diagnosis. The subject's previous electrodiagnostic records including those obtained at the time of diagnosis, if available, can be used for initial screening. If a previous evaluable nerve conduction report is available, an additional study at the time of screening is not mandatory **but highly recommended**. This is recommended because according to recent data it would be possible to determine whether the subject is going to need IgG for control of his disease or if the subject is in remission by reviewing these 2 separate tests.

Standardized procedures and selection of nerve segments for assessments are detailed in the nerve conduction manual. All nerve conduction study records will be reviewed by an independent central reader who specializes in neuromuscular diseases in order to confirm the diagnosis of definite or probable CIDP in accordance to the EFNS/PNS 2010 guideline on management of CIDP (European Federation of Neurological Societies, 2010). Nerve conduction records obtained at screening (if available) or pre-study (if not available at screening) will serve as the baseline for comparison to post-screening/baseline records to identify any new demyelinating findings during the course of the study.

Nerve conduction studies will be repeated during the end of Epoch 1 visit for those subjects who did not relapse following 6 months of SC treatment, or at the time of relapse (ie, during the pre-IV baseline visit prior to initiation of IGIV treatment for those entering into Epoch 2), or during early termination visit for those who will be discontinued from the study. For subjects who undergo Epoch 2, nerve conduction studies will be repeated during the end of Epoch 2 treatment visit for those subjects who responded to and completed 6 months of IGIV treatment, or during early termination visit for those who will be discontinued from the study due to relapse or other reasons. It is recommended that the same nerve segments will be assessed as those examined at the time of CIDP diagnosis and/or during screening nerve conduction studies.

All eligible subjects must be on a stable dosing regimen of IGIV treatment at a monthly equivalent dose of 0.4 to 2.4 g/kg BW with a dosing interval between 2 and 6 weeks for at least 12 weeks prior to screening. Subjects with changes to IGIV prescribed dosing regimen (dose or dosing interval) related to unstable CIDP disease conditions or changes to other CIDP-related immunomodulatory/immunosuppressive agents within 8 weeks of screening are not allowed to enter into the study. These subjects may be rescreened when their CIDP conditions and IGIV dosing regimen remain stable for at least 3 months. The subject's monthly equivalent IGIV dose will be calculated based on the subject's pre-study IGIV dosing records within 12 weeks prior to screening.

Variations in the dosing interval of up to ±7 days or monthly dose amount of up to ±20% between subject's pre-study IgG infusions are within acceptable limits.

A subjects' medical history pertaining to CIDP will include time of first CIDP symptoms and time since CIDP diagnosis, as available. Use of any IgG products, PE, steroids, and/or immunomodulatory/immunosuppressive agents for up to 6 months prior to screening will be recorded (including product, dose, dosing frequency, route of administration, treatment start and stop dates) on the medication and non-drug therapy CRF(s). Other medical, medication and/or non-drug therapy history will also be recorded (see Section 12.5).

Diabetes mellitus is a common comorbidity in CIDP patient population. Some patients may develop diabetic peripheral neuropathy, which may be associated with similar clinical presentation and demyelinating abnormalities as CIDP and thus may confound assessment of disease activities and study outcome measures. Thus, CIDP subjects who also have diabetic peripheral neuropathy will not be eligible to participate in this study. CIDP subjects with clinically diagnosed diabetes mellitus who do not have diabetic peripheral neuropathy at screening will be allowed, provided that the subject has adequate glycemic control as verified by HbA1C test result of <7.5% at the time of screening and agrees to maintain adequate glycemic control throughout the course of the study. Glycemic control will be monitored (only in those subjects with clinically diagnosed diabetes mellitus) throughout the course of the study (see Section 12.7.3 for more details).

A 12-lead electrocardiogram (ECG) will be performed at screening for the determination of eligibility (e.g., exclusion of clinically significant cardiac abnormalities, such as unstable cardiac arrhythmias, and detection of other clinically significant cardiac abnormalities that may indicate an underlying condition that may impede the subject's participation in the study, pose increased risk to the subject, or confound the results of the study).

Screening blood pressure measurements may be repeated in the event of exclusionary values obtained during initial measurement, in order to verify eligibility. The following screening laboratory tests may be repeated once at least 1 week apart in the event of abnormal laboratory values or suspected erroneous values: serum creatinine (for the determination of GFR), Hgb, AST, ALT, platelet count, and absolute neutrophil count.

During the screening/baseline period, subjects will continue to receive their own IGIV treatment and adhere to the same dose and dosing frequency as prescribed by their physician prior their entry into this study (referred to as "pre-randomization" IGIV infusions) for the duration of the screening/baseline period. Adjustments to the subject's IGIV dose and/or dosing frequency during screening/baseline period are not allowed. The following information will be recorded for subject's pre-randomization IGIV infusions that occur after enrollment, but prior to randomization:

- Date and time of infusion, product name
- Dose administered
- Dosing interval
- AE(s)
- Concomitant medications and/or non-drug therapies

The INCAT disability scale assessment will be performed during screening and the pre-SC treatment baseline visit to assess the subject's level of functional abilities. The screening INCAT should be conducted as soon as possible for initial determination of whether a subject's INCAT disability score falls within the inclusionary range of 0 to 7 (inclusive) (see additional description in Section 9.1). However, the final determination of eligibility for the INCAT inclusion criterion will take the pre-SC treatment baseline INCAT disability score into consideration. The baseline INCAT disability score must also be within the range of 0 to 7 (inclusive) (see additional description in Section 9.1). Additionally, as only subjects whose CIDP condition remains stable on IGIV treatment will be enrolled into the study, any clinically significant changes in the subject's functional ability (eg, 1 or more point worsening on the adjusted INCAT disability score) between screening and baseline assessments should be reviewed and the subject's final eligibility determination will made in consultation with the Medical Monitor.

10.3.1.1 Rescreening

Subjects may be rescreened only once. Subjects who have failed screening based on the following reasons may be rescreened, after the cause underlying the initial screen failure has been resolved:

1. Subjects whose ineligibility is associated with a time period specified in the Inclusion Criteria (see Section 9.1) or Exclusion Criteria (see Section 9.2)
    - Inclusion criterion #3: Changes to IGIV dose and/or dosing interval within 12 weeks prior to screening.

- Exclusion criterion #18/19: the subject has received or is currently receiving treatment with any corticosteroids dose within 8 weeks prior to screening, regardless of indication, or any immunomodulatory/immunosuppressive agents within 6 months prior to screening.
- Exclusion criterion #20: Recently treated with previous PE within 3 months prior to screening.
- Exclusion criterion #23: Recent participation in another clinical study involving an IP or investigational device within 30 days prior to enrollment

2. Subjects with screening laboratory abnormalities meeting exclusion criterion #16.
3. Subjects who have been erroneously determined to be ineligible to participate in this study.
4. Subjects with other reasons for initial screen failure may be rescreened at the discretion of the investigator.

All subjects must sign a new ICF prior to rescreening procedures. Subjects who are rescreened will be assigned a new SIC and new CRFs are required for that subject.

The following screening procedures will be performed at rescreening:

- Demographics
- Medical, medication and non-drug therapy history
- Vital signs as well as height, weight, and body mass index (BMI)
- Physical exam
- Screening laboratory assessments
- INCAT disability score
- R-ODS
- Hand grip strength
- MRC sum score

When completing a rescreen, the following procedure(s) do not need to be performed if they were already conducted during the initial screening, unless a reason exists to repeat the procedure(s) (eg, there is an erroneous result from the initial screening or a medical condition necessitates a repeat):

- 12-lead ECG
- Electrodiagnostic test

10.3.2 Randomization

Randomization is to take place after a subject has completed all the screening procedures and, at a minimum, baseline INCAT assessments, and met all eligibility criteria, but before the first SC administration in Epoch 1.

10.3.3 Epoch 1: SC Treatment Period

During the SC treatment phase of this study, subjects will receive either HYQVIA/HyQvia or 0.25% albumin placebo with rHuPH20 in a double-blind fashion for a period of 6 months or until relapse.

10.3.3.1 SC Infusion Visits

Packaging, labeling, and storage of IPs are described in Section 8.7.1 and preparation and storage of pooled IP solutions is described in Section 8.7.2. Route and rate of administration are described in Section 8.7.3. Description of treatment, including treatment period, doses and dosage frequency, are detailed in Section 8.7.4.1.

The number of infusion visits during the SC treatment period will vary across subjects, depending on whether their infusion cycles are every 2, 3, or 4 weeks.

The first SC administration of HYQVIA/HyQvia or 0.25% albumin placebo with rHuPH20 will take place 2 weeks (±3 days) following the last pre-randomization IGIV administration. To gradually increase the SC infusion volume, a dose ramp-up schedule will be utilized until the subject's full dose is reached (see Table 8-3).

The SC infusions during the ramp-up period and, at a minimum, the first full-dose infusion will be administered under direct supervision at the study site or infusion center to monitor for safety and tolerability. In addition, this will allow for the determination of the infusion rate and infusion volume per infusion site that can be tolerated by the subject. At the investigator's discretion, the remainder of the SC infusions may then take place at the study site, infusion center, or at the subject's home or other suitable location, as acceptable per local regulations and standard practices of the study site.

HYQVIA/HyQvia or 0.25% albumin placebo with rHuPH20 will be administered by an appropriately trained healthcare professional (eg, infusion nurse), self-administered by the subject, and/or, as applicable, by a caregiver who may assist the subject with self-administration. The ability of the subject (and/or caregiver) to perform infusion procedures independently is a prerequisite for self-administration. Training will be provided to the subject (and/or caregiver) by the investigator/designee.

The investigator/designee must assess and be satisfied that the subject (and/or caregiver) is/are capable of independently performing self-infusion procedures per the infusion manual and will adhere to the IP administration schedule. Training of the subject (and/or caregiver), as well as the investigator/designee's evaluation of the subject's (and/or caregiver's) proficiency in independently self-administering the treatment, must be documented. The subject (and/or caregiver) may be asked to return to the study site during the SC treatment period so that the investigator/designee can further assess and document that the subject (and/or caregiver) continues to be capable of independently performing self-infusion procedures. The infusions may be carried out by the subject (and/or caregiver) in the presence of a healthcare professional. The healthcare professional may intervene only if necessary. Such intervention and the reason for intervention will be documented.

For each SC infusion on each infusion day, the following infusion related information will be recorded in the subject's DIARYpro (manuals containing detailed instructions will be provided to the sites and subjects):

- Date of the infusion
- Location of the infusion (eg, study site/infusion center, home)
- Start and stop times of the infusion for rHuPH20 solution and the pooled study product (IGI, 10%/0.25% albumin placebo solution)
- Any unplanned infusion rate change(s), infusion interruption(s), and/or discontinuation(s), as well as reason(s) for the event(s).
  - If an infusion is interrupted and restarted after an interruption, the time the infusion is interrupted, restarted, and ends, as well as the rate of infusion upon restart, will be recorded.
- Planned infusion volume (mL)
  (total of rHuPH20 solution plus the IGI, 10%/0.25% albumin placebo solution)
- Actual volume infused (mL)
  (total of rHuPH20 solution plus the IGI, 10%/0.25% albumin placebo solution)
- Number of infusion sites
- Maximum infusion rate tolerated
- Length of SC needle used (mm)
- Whether a healthcare professional (e.g., infusion nurse) was present during the infusion
- The individual who administered the infusion (subject, caregiver, or nurse)

- Any infusion-related interventions performed by the healthcare professional (eg, infusion nurse) and reason(s) for intervention
- Any AE(s) that occur during or after the infusion
- Use of any medications or non-drug therapies to treat AE(s)
- Any changes to the subject's concomitant medications or non-drug therapies

Telephone follow-up will be conducted by the investigator/designee following each infusion visit (after 24 h but within 72 h + 1 business day) to monitor for changes in a subject's functional status and to document AEs, concomitant medications, and non-drug therapies, which may have occurred within 72 h after the completion of an infusion (or after the completion of the last day of dosing for an infusion that was administered over multiple consecutive days).

10.3.3.2 SC Treatment Interim Visit

Subjects will be asked to return to the study site for interim assessments during the following week:

- Every 2 weeks dosing schedule: Week 15 (+/- 1 infusion visit)
- Every 3 weeks dosing schedule: Week 14 (+/- 1 infusion visit)
- Every 4 weeks dosing schedule: Week 16 (+/- 1 infusion visit)

The interim visit assessments must be completed prior to the SC infusion on the day of infusion (preferred) or within 3 days prior to the infusion visit due to scheduling availability. Details on the procedures and assessments to be performed at the interim visit can be found in Section 21.2 and Section 21.3.

10.3.3.3 Unscheduled Visit for Relapse Assessment

Subjects who relapse (defined as an increase in adjusted INCAT disability score by ≥1 point relative to the pre-SC treatment baseline score, on 2 consecutive INCAT assessments) will be offered open-label IGIV treatment in Epoch 2.

At any time during the SC treatment period, unscheduled visit(s) to the study site will be allowed for subjects who experience CIDP worsening to perform INCAT, R-ODS, hand grip strength, and MRC sum score assessments. For subjects whose adjusted INCAT disability score has increased by ≥1 point compared to the pre-SC treatment baseline score, INCAT, R-ODS, hand grip strength, and MRC sum score assessments will be repeated at the pre-IV treatment baseline visit for those subjects who will enter into Epoch 2 or at the early termination visit for those who choose not to enter into Epoch 2 and will be discontinued early from the study.

10.3.3.4 End-of-SC Treatment Period

Subjects may end their active participation in the SC treatment period in one of three ways. For a detailed schedule of procedures and assessments, see Section 21.2.

1. Subjects may complete the entire 6-month SC treatment period without relapse. These subjects will be asked to undergo an End-of-Epoch 1 visit at the study site. End of SC treatment assessments are to be conducted on the day of the final infusion in the SC treatment period. This will mark the subjects' completion of the study.
    - Subjects may opt to participate in an open-label extension study for the evaluation of long-term safety, tolerability, immunogenicity, and efficacy of HYQVIA/HyQvia in CIDP. Subjects who are interested will be asked to provide informed consent for the extension study prior to conducting any of the End-of-SC Treatment Period (study completion) procedures.
2. A subject may withdraw their participation in the study or be discontinued from the study prior to completing the entire 6-month SC treatment period, or a subject may relapse and choose not to enter into Epoch 2 for IV treatment. These subjects will be asked to undergo an early termination visit at the study site prior to discontinuation from the study.
3. Subjects may experience relapse of their CIDP as determined by 2 consecutive INCAT assessments performed at the site. These subjects will be offered IGIV treatment in Epoch 2. Subjects who will be going on to receive IV treatment will undergo an end-of-SC treatment/pre-IV treatment baseline assessment visit at the study site. (In these cases, an early termination visit for the SC treatment period is not applicable and does not need to be conducted). These pre-IV treatment baseline assessments must be completed prior to the first IV treatment.

10.3.4 Epoch 2: IV Treatment Period

10.3.4.1 Baseline

Open-label treatment with IGIV will be provided for subjects who meet the definition of relapse during the SC treatment period as determined by 2 consecutive INCAT assessments performed at the site. An INCAT assessment will be performed at the time the subject is being evaluated for relapse, and again just prior to initiation of IGIV treatment. Subjects will be asked to complete a pre-IV treatment baseline assessment visit at the study site. These assessments will also serve as the end-of-SC treatment assessments. Details on the procedures and assessments to be performed at the pre-IV treatment baseline visit can be found in Section 21.2 and Section 21.3. Pre-IV treatment baseline assessments must be completed prior to initiation of treatment with IGIV.

The pre-IV treatment baseline INCAT assessment will be used 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. IGIV treatment will be initiated only after CIDP relapse is confirmed.

10.3.4.2 IV Infusion Visits

Packaging, labeling and storage of IPs are described in Section 8.7.1 and preparation and storage of pooled IP solutions is described in Section 8.7.2. Route and rate of administration are described in Section 8.7.3. Description of treatment, including treatment period, doses and dosage frequency, are detailed in Section 8.7.4.

In Epoch 2, subjects will receive IV infusions of GAMMAGARD LIQUID/KIOVIG (all subjects with the exception of those at US sites) or GAMUNEX®-C (US only) every 3 weeks (±3 days) for a total of 6 months. Following the completion of the pre-IV treatment baseline assessments including INCAT disability scale and other clinical outcome measures, subject may receive the first IGIV infusion as soon as practically feasible.

All IV treatment infusions will be performed at the study site/infusion center. In addition, subjects will undergo follow-up assessments at the study site every 3 weeks (ie, every infusion visit) until their study completion or early withdrawal/discontinuation.

For each IV infusion, the following infusion-related information will be recorded in the subject's DIARYpro (manuals containing detailed instructions will be provided to the sites and subjects):

- Date, start and end time of the infusion on each day of infusion
- Planned and actual infusion volume on each of infusion day
- Maximum tolerated infusion rate
- Any changes in infusion rates (with the exception of pre-programmed infusion rate changes/ramp-up), interruption(s) and/or discontinuation of an infusion
- Any unplanned infusion rate change(s), infusion interruption(s), and/or discontinuation, as well as reason(s) for the event(s)
  - ➢ If an infusion is interrupted and restarted after an interruption, the time the infusion is interrupted, restarted, and ends, as well as the rate of infusion upon restart, will be recorded.
- Any AE(s) that occur during or after infusion

- Use of any medications or non-drug therapies to treat AE(s)
- Any changes to the subject's concomitant medications or non-drug therapies

Telephone follow-up will be conducted by the investigator/designee following each infusion visit (after 24 h but within 72 h + 1 business day) to monitor for changes in a subject's functional status and to document AEs, concomitant medications, and non-drug therapies, which may have occurred within 72 h after the completion of an infusion (or after the completion of the last day of dosing for an infusion that was administered over multiple consecutive days).

10.3.4.3 IV Treatment Interim Visit

Interim assessments are to be conducted during Week 13 (+/- 1 infusion visit) during the IV treatment period. Details on the procedures and assessments to be performed at the interim visit can be found in Section 21.2 and Section 21.3.

10.3.4.4 End of IV Treatment Period

Subjects may end their active participation in the IV treatment period, and thus the study, in one of two ways. For a detailed schedule of procedures and assessments, see Section 21.2 and Section 21.3.

1. Subjects may complete the entire 6-month IV treatment period. These subjects will be asked to undergo an End-of-Epoch 2 visit at the study site. End of IV treatment assessments are to be conducted pre-infusion on the day of the final infusion in the IV treatment period. This will mark the subjects' completion of the study.
2. A subject may withdraw their participation in their study or be discontinued from the study prior to completing the entire 6-month IV treatment period. These subjects will be asked to undergo an early termination visit at the study site prior to discontinuation from the study.

10.4 Management of Infusion-Related AEs

It is the investigator's responsibility to monitor the safety and well-being of the subject and to assure that all post-randomization infusions are conducted in the prescribed and timely manner throughout the study, regardless of the location of administration. Subjects and caregivers will be provided with information about the typical signs and symptoms of possible AEs, and when the subject/caregiver should immediately call the investigator or go to the emergency room/department for immediate treatment.

The occurrence of certain AEs, such as headache, chills, or body aches, may be reduced by slowing the infusion rate.

Any suspicion of allergic, hypersensitivity, or anaphylactic reaction(s) requires immediate discontinuation of the infusion and administration of appropriate medical treatment in accordance with the local standard of care.

Any rate reductions, interruptions or discontinuation of an infusion and, if applicable, any medications and/or non-drug therapies used to treat AE(s), must be recorded in the appropriate CRF(s). The use of any pre-medication(s) must be recorded in the appropriate CRF(s). See Section 10.5.2 for further information about pre-medication prior to SC and IV infusions in this study.

10.5 Medications and Non-Drug Therapies

Steroids are commonly used in clinical practice as one of the first line therapies for the treatment of CIDP. The use of steroids, however, may confound the interpretation and analysis of the efficacy outcome measures in this study. Therefore, the guidelines listed below concerning the use of steroids in this study are to be followed:

1. Subject who have received or is currently receiving treatment with any corticosteroids dose within 8 weeks prior to screening, regardless of indication are not permitted.
2. Non-systemic corticosteroids (e .g, topical, ophthalmic, or inhaled glucocorticoids) are allowed at any time before screening and during the course of the study.

Immunomodulatory/immunosuppressive agents (such as azathioprine and methotrexate) have been reported to be beneficial and may be considered for use as an add-on therapy in clinical practice when the response to corticosteroids, IGIV, or PE is inadequate (European Federation of Neurological Societies, 2010). However, clinical efficacy of these agents remains to be proven. Nevertheless, to avoid confounding effects on the interpretation of the efficacy outcome measures in this study, the use of immunomodulatory/immunosuppressive agents within 6 months before screening (for corticosteroids: within 8 weeks prior to screening, for details see Section 9.2 Exclusion Criteria) and during the course of the study is not permitted.

Plasma exchange has been shown to provide short-term clinical benefits in improving neurological disability in CIDP. Thus, use of PE within 3 months before screening and during the course of the study is not permitted to avoid confounding effect on the interpretation of the efficacy outcome measures in this study.

Other medications that are **not** permitted during the course of the study include the following:

1. Other IgG products

- With the exception of the subject's IGIV treatment during the screening/baseline period; however, following randomization, use of the subject's pre-randomization IGIV will no longer be permitted

2. Hyperimmune serum

For questions about medications and non-drug therapies that are not listed, please consult the Medical Monitor.

10.5.1 Immunizations

Passive transfer of antibodies (such as via IgG treatment) may transiently impair the immune responses to live attenuated virus vaccines, such as mumps, rubella, and varicella for up to 6 months and for 1 year or more to measles (rubeola). Subjects should be instructed that when they are receiving vaccinations that they are to inform the immunizing healthcare professional of this potential interaction between IgG treatment and vaccinations, and that the subject may have recently been exposed to IgG therapy due to blinded study product in Epoch 1. Subjects being treated in Epoch 2 should also inform the healthcare professional that the subject is receiving IGIV treatment.

10.5.2 Pre-Medications for Infusion Administration

Subjects who are prone to AEs occurring in conjunction with infusions of IGIV products are often pre-medicated with antipyretics (e.g., acetaminophen), non-steroidal anti-inflammatory drugs [NSAIDs], antihistamines, and/or corticosteroids. In this study, pre-medications to prophylactically treat infusion-related AEs should be avoided, if possible, for both SC and IV infusions. Reactions experienced by subjects with pre-study IGIV treatment do not automatically necessitate the use of pre-medication(s) for SC infusions and/or IV infusions in this study. In addition, reactions that occurred with SC infusions (Epoch 1) do not necessitate automatic pre-medication for IV infusions (Epoch 2).

For subjects who are prone to infusion-related AEs, if the same type of mild-to-moderate, nonserious AE(s) expected to be related to infusion (e.g., headache, chills, fever, flushing, malaise) occur(s) during or after 2 or more infusions, the subject may be pre-medicated for subsequent infusion(s) at the discretion of the investigator in accordance with the standard of care at the investigative site. Subjects may be pre-medicated with acetaminophen, NSAIDs, antihistamines and/or topical corticosteroids.
If any of these agents do not adequately prevent the infusion-related AE(s), consult with the Medical Monitor.

Topical anesthetics (eg, Emla) may be used if the needle insertion was intolerable in prior infusions. Subjects who have a history of using topical anesthetics (e.g., Emla) for IV infusions may also use these topical anesthetics for SC infusions.

The use of any pre-medications should be recorded in the appropriate CRF(s).

10.6 Subject Diary and Patient Reported Outcomes

An electronic subject diary (DIARYpro) will be provided to each subject at screening to record the following information throughout the study:

1. Occurrence of signs/symptoms indicative of AEs
2. Use of concomitant medications and non-drug therapies
3. Infusion records (see Section 10.3.1, Section 10.3.3.1, and Section 10.3.4.2)
4. HRU (such as days off school/work, unscheduled physician visits [including urgent care visits to see healthcare providers], hospitalizations, and emergency room visits). HRU does not include visits and days off from work/school for study related outpatient procedures and assessments.
5. R-ODS

Subjects and caregivers will be trained on use of the diary. In cases where the subject or the caregiver are not self-administering therapy, site staff will have an option in the diary to enter the infusion data only. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator/designee will review the diary for completeness and request missing information periodically and in a timely manner. Untoward medical events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

Subject entries in the diary will serve as source records for patient reported data.
An Infusion Data Collection worksheet will serve as an additional source document.
During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator/designee will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be imported via a validated transfer to Data Management.

10.7 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE, discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, eg, technical problems, death). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Section 21.2 Schedule of Study Procedures and Assessments and Section 21.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.8 Procedures for Monitoring Subject Compliance

For study procedures that are to be performed under the direct supervision of the investigator/healthcare professional (eg, infusion nurse) at the study site or infusion center, no separate procedures will be used to monitor subject compliance.

Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee, must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions. A healthcare professional (eg, infusion nurse) may be present to observe the subject's self-administration. The subject (and/or caregiver) may be asked to return to the study site during the SC treatment period so that the investigator/designee can further assess and document that the subject (and/or caregiver) is still capable of continuing to independently perform self-infusion procedures.

10.9 Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 Related Factor

This amendment aims to ensure subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by the COVID-19 pandemic. Amendment 6 provides flexibility to study participants to opt for home healthcare (HHC) solutions as permitted by local regulations. This guidance takes references from the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 03 June 2020, and the EMA Guidance on the Management of Clinical Trials During the COVID 19 (Coronavirus) Pandemic, Version 3 (28 April 2020).

The unpredictable clinical trial landscape due to the COVID-19 outbreak poses a risk to the conduct of the trial. Quarantines, site closures, travel limitations and site personnel or trial participants infected with COVID-19 have resulted in slowed recruitment and potential protocol deviations, with significant delays in achieving the planned recruitment target anticipated.

In the current COVID-19 environment, the requirement for a confirmatory INCAT for diagnosis of CIDP relapse poses a risk to the patient's safety as it requires an additional visit to the study site. Site closures, travel restrictions, and scheduling conflicts with the INCAT raters further pose a risk. As a result, Amendment 6 includes a sensitivity analysis where relapse is 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. The rationale for the proposed change includes: 1) Inability to perform a second INCAT could result in misclassification of subject who have experienced clinically significant CIDP

worsening consistent with a relapse as no relapse. Hence, the requirement for confirmatory INCAT poses a risk to the integrity of the study; 2) INCAT is not sensitive to small fluctuations in clinical symptoms; it captures only significant deterioration. For that reason, clinical worsening severe enough to be captured by the INCAT score is not expected to rapidly reverse without an alternative treatment. The clinical implication of this is that repeated INCAT assessments within a small time window would reveal similar results; 3) Prior studies of CIDP that used INCAT required only one assessment for end point ascertainment (Lancet Neurol 2008 ;7 :136-144; Lancet Neurol. 2018;17(8):689; Neurol Neuroimmunol Neuroinflamm 2019;6:e590; Lancet Neurol 2018;17: 35–46). The proposed change in the amendment is expected to make the results of ADVANCE-1 comparable with the literature.

As the COVID-19 pandemic outbreak may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case by case basis following consultation with the medical monitor, with patient safety as the priority.

Procedural changes in amendment-6 due to COVID-19 may include the following:

1. The subject (or subject's legal representative on behalf of the subject) may withdraw from the study. All attempts will be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason will be recorded. If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related adverse event), this will be specified as the reason for subject withdrawal in the eCRF. This approach may apply to screening and randomization failures as well.
2. The protocol amendment #5 dated 10 May 2019 specifies that the investigator and the sponsor have the discretion to discontinue any subject from the study if the subject frequently misses administration of IP (more than 2 consecutive infusions after reaching full dose). Missing two consecutive infusions could result in a lapse in treatment for up to 12 weeks depending on the assigned dosing regimen. Such a long lapse due to COVID-19-related factors could put a study subject at risk of developing CIDP worsening (as defined by ≥1-point increase in adjusted INCAT score). The sponsor will reduce the allowable period for treatment lapse to 14 days to allow the study subjects to timely switch to alternative treatments (such as steroids) that can be more easily administered at home settings. In the case where a subject is stable as of 14 days past the scheduled infusion date, an additional 7 days may be allowed on a case-by-case basis by the Takeda medical monitor (totaling up to 21-day lapse).

3. Subjects who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the trial may be rescreened once if the Takeda medical monitor agrees.
4. Alternative study drug delivery to trial participants may be necessary to avoid unnecessary patient visits to sites while providing needed study drug. Additional study drug may be dispensed during a scheduled study visit or study drug may be shipped directly from investigational sites to participants' residences by a contracted logistics provider or distributor in compliance with national laws or temporary national emergency measures and Takeda processes.
5. The study site staff may administer the IP and/or collect labs at home, as necessary when COVID is at risk at the hospital setting. IP infusions during the ramp-up period will be performed at the clinic. All other infusion visits may be conducted at the clinic or by home healthcare visits to extend flexibility to patients during the COVID-19 public health emergency. Study drug may be administered by a trained health care professional as part of home nursing or home health care. Infusion training, infusion material, personal protective equipment, lab kits and tools to collect the lab samples will be provided to the subject and the health care professional. Home healthcare visits conducted by the study staff will be documented in the study records and eCRF.
6. For home healthcare visits managed by the study site, collection of clinical laboratory samples may be performed by a delegated qualified health care professional who can visit the trial participant's residence.
7. Unscheduled remote visits via virtual communications (eg, TeleHealth application) may be performed as a safety check on subject well-being, as deemed necessary. Safety and efficacy assessments may be conducted by phone (e.g., collection of AEs and monitoring), video conferencing (Telehealth or Telemedicine, physician), or site staff visiting the subject's residence. All efficacy assessments including the INCAT assessment will be performed by appropriately certified or trained staff (as applicable). Local visits and telemedicine must comply with national and local laws and regulations. The type of alternative visit must be recorded on the eCRF.
8. In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by applicable local regulations and permitted by the IRB/IEC.

9. Subjects who are anxious to travel to the study due to COVID-19 may be offered free transportation to the study site at off-hospital hours to conduct infusion visits in a safe and isolated section of the clinic. Transfer of study participants to investigational sites away from risk zones or closer to their home may be permitted.
10. Missing visits, missing data, alternative visits, and deviations from the protocol-specified procedures (e.g., not collecting a protocol-specified specimen, such as post dose bloodwork) will be recorded as related to COVID-19.

11. ASSESSMENT OF EFFICACY

11.1 The Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale

The INCAT 10-points disability scale (Hughes et al., 2001) is the most widely used assessment tool to measure the functional activity level of patients with CIDP. The INCAT disability scale consists of upper and lower extremity components, with a maximum of 5 points for the upper extremities (arm disability) and a maximum of 5 points for the lower extremities (leg disability), which are summed for an overall INCAT disability score ranging from 0 to 10 points, where 0 is normal (e.g., no upper limb problems and walking not affected) and 10 is severely incapacitated (e.g., inability to move either arm for any purposeful movement and restricted to wheelchair, unable to stand and walk a few steps with help). The INCAT disability score is considered to be an effective and responsive tool to assess clinical response to treatment in CIDP (Hughes et al., 2008, Merkies et al., 2010). An adjusted INCAT disability score is the same as the INCAT disability score, with the only exception in the exclusion of changes from 0 (normal) to 1 (minor symptoms) (or vice versa) in upper limb function since this reflects only a symptomatic change and is not considered to be clinically meaningful change of functional ability (Hughes et al., 2008). A ≥1-point change in the adjusted INCAT disability score is considered to be a clinically significant response to treatment, and has been used as the primary efficacy outcome measure in a number of clinical trials in CIDP, including the pivotal trials for other IGIV products (Hughes et al., 2008, Léger et al., 2013).

The INCAT disability scale will be administered at the study site by the investigator/designee using a validated translated version, as applicable. It is recommended that the investigator/designee complete the assessment using the same translated version throughout the course of their participation in the study.

In order to reduce the possibility of bias, investigators/designees who perform INCAT assessments must not have access to information regarding any AE(s) experienced by the particular subject they are evaluating. The investigator/designee who administers the INCAT to a particular subject should remain constant throughout the study for that particular subject and should be the same individual that administers the Hand Grip Strength assessment and MRC to that subject. For detail, see Section 21.2 Schedule of Study Procedures and Assessments.

11.2 Rasch-Built Overall Disability Scale (R-ODS)

The R-ODS is a patient self-reported, linearly-weighted overall disability scale that was specifically designed to capture activity and social participation limitations in patients with immune-mediated peripheral neuropathies including CIDP (van Nes et al., 2011). The R-ODS is comprised of 24 items for which subjects are asked to rate their functioning (ie, no difficulty, some difficulty, or could not do) related to a variety of everyday tasks at the moment of completion. The R-ODS has a high internal/external validity, acceptable reliability scores, and high discriminant validity. In a recent publication, the R-ODS was reported to be a more responsive scale in capturing clinically meaningful changes over time in newly diagnosed or relapsing patients with Guillain Barré Syndrome (GBS) and CIDP, compared with the widely used ordinal-based INCAT (Draak et al., 2014).

The R-ODS will be directly recorded in the subject's electronic diary (DIARYpro) using a translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of their participation in the study. To further measure patient centric benefit of HyQvia in CIDP an alternative scoring algorithm will be applied to evaluate benefit of functional impact on everyday tasks. Specifics of the alternative scoring (in addition to the full score) will be pre-specified in the SAP, along with psychometric evidence supporting the alternative scoring algorithm, based on data from the current trial.

For detailed administration timepoints, see Section 21.2. DIARYpro will be dispensed to the subjects at screening. R-ODS data collected during screening will not be used for analysis.

11.3 Hand Grip Strength

Grip strength, a measure of a subject's distal strength and upper limb function, is commonly used in clinical practice to monitor the subject's clinical and functional status, as well as response to treatment (Merkies et al., 2000). Hand grip strength measurement using devices such as a hand dynamometer is of particular relevance in subjects with peripheral neuropathies in which distal weakness predominates.

In this study, hand grip strength will be assessed as a measure of motor function using the Vigorimeter (Martin, Tuttlingen, Germany), an instrument that is commonly used in patients with immune-mediated neuropathies. The instrument has good validity, reliability, and responsiveness, and has been shown to capture both meaningful improvement and deterioration earlier than the INCAT disability scale.

Recently the Vigorimeter was proposed as one of the cardinal assessment tools in addition to the R-ODS (Vanhoutte et al., 2013a, Vanhoutte et al., 2013b). Hand grip strength will be administered at the study site by the investigator/designee. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments.

11.4 Medical Research Council (MRC) Sum Score

The MRC sum score will serve as a measure of muscle strength (Kleyweg et al., 1991). To obtain an MRC sum score, the following muscles on each side of the body are examined and the strength of each muscle is rated according to the MRC scale: deltoids, biceps, wrist extensors, iliopsoas, quadriceps, and anterior tibialis. The MRC scale ranges from 0 to 5, where:

- 0 = no visible contraction;
- 1 = visible contraction without movement of the limb;
- 2 = movement of the limb but not against gravity;
- 3 = movement against gravity over (almost) the full range;
- 4 = movement against gravity and resistance; and,
- 5 = normal.

All scores from both left and right side of the body are summed to obtain the MRC sum score. The MRC sum score ranges from 0 (paralysis) to 60 (normal strength).

The MRC scale will be administered at the study site by the investigator/designee. The investigator/designee who performs the MRC scale evaluation for a particular subject should remain constant throughout the study for that particular subject and should be the same individual that administers the INCAT and Hand Grip strength assessment to that subject. In order to reduce the possibility of bias, investigators/designees who perform MRC scale assessments must not have access to information regarding any AE(s) experienced by the particular subject they are evaluating. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

12.1.1.1 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

1. Outcome is fatal/results in death (including fetal death)
2. Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
4. Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
5. Is a congenital anomaly/birth defect
6. Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

- Reviewed and confirmed seroconversion for HIV, HAV, HBV, HCV, HEV, or B19V
- Thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accidents [eg, stroke, transient ischemic event])
- Hemolytic anemia

Uncomplicated pregnancies, following maternal exposure to IP are not considered as an (S)AE. Any pregnancy that occurs after maternal administration of medicinal product will be reported on a Pregnancy Report Form and 1 year postdelivery, if feasible. Any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, a SAE should be submitted to regulatory agencies expeditiously.

The sponsor will ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening, as well as all other serious unexpected ARs, are reported to regulatory authorities within the timeframes mandated by the applicable regulations (eg ICH Guideline E2A and the European Clinical Trial Directive (2001/20/EC). The sponsor will comply with applicable laws/requirements for reporting SUSARs and all other SAEs to the ECs and investigators.

12.1.1.3 Nonserious Adverse Event

A nonserious AE is an AE that does not meet the criteria of an SAE.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the IB and prescribing information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

12.1.1.5 Adverse Reactions Plus Suspected Adverse Reactions

An AR plus suspected AR is any AE that meets any of the following criteria:

- An AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or
- An AE that begins during infusion of IP or within 72 h following the end of IP infusion, or
- An AE for which causality assessment is missing or indeterminate.

12.1.1.6 Preexisting Diseases

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

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following nonserious events experienced after the first IP exposure are not reportable, unless otherwise specified; on the AE CRF nor will they be included in the analysis of AEs:

1. CIDP relapse or worsening reflective of disease progression and meeting ≥1 point increase in the adjusted INCAT disability score will be collected and recorded on the appropriate CRF(s).

2. Infusion site swelling following SC infusion of IGI, 10% or 0.25% albumin placebo solution that is reported by subjects will be captured and reported as adverse events. Infusion of a large quantity of fluid into the SC space would be expected to cause some degree of swelling (except the US sites, as per FDA request, infusion-site swelling will be reported as AEs).
3. Preexisting conditions related to hospitalizations and elective surgeries planned prior to study entry are not considered SAEs or AEs provided they are documented in the subject's medical records.

All other AE from the first IP exposure until study completion/discontinuation date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

1. Seriousness as defined in Section 12.1.1.1
2. Severity as defined in Section 12.1.2.1
3. Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. Follow-up information will be recorded in the appropriate CRF(s) as applicable, unless the database has already locked. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing, underdosing, abuse, and withdrawal) that result in adverse events meeting criteria for SAEs, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after maternal administration of IP will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year postdelivery, if feasible. Any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

If an investigator becomes aware of an SAE occurring in a subject within 30 days after study completion, the SAE must be reported on the provided SAE Report Form within 24 h after awareness; no additional reporting on CRFs is necessary. Thereafter, AEs of any nature are to be reported using standard forms such as the Council for International Organizations of Medical Sciences (CIOMS) form or MedWatch form, etc.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

1. Mild
    - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
    - The AE resolves spontaneously or may require minimal therapeutic intervention.
2. Moderate
    - The AE produces limited impairment of function and may require therapeutic intervention.
    - The AE produces no sequela/sequelae.
3. Severe
    - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
    - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

1. Not related (both circumstances must be met)
    - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
    - Is not associated with the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
2. Unlikely related (either 1 or both circumstances are met)
    - Has little or no temporal relationship to the IP
    - A more likely alternative etiology exists
3. Possibly related (both circumstances must be met)
    - Follows a reasonable temporal relationship to the administration of IP
    - An alternative etiology is equally or less likely compared to the potential relationship to the IP
4. Probably related (both circumstances must be met)
    - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
        - Reappearance of a similar reaction upon re-administration (positive rechallenge)
        - Positive results in a drug sensitivity test (skin test, etc.)
        - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
    - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 72 h after completion of IP administration, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

1. Immediate change in study design or study procedures
2. Temporary or permanent halt of a given clinical trial or trials
3. Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees and relevant competent authorities are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each serious untoward medical occurrence experienced before the first IP exposure (ie, from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF and on the SAE Report Form. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each nonserious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE**. NMCs include but are not limited to the following:

1. A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
1. Missing components
2. Damage to the product or unit carton
3. A mislabeled product (eg, potential counterfeiting/tampering)
4. A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

Medical history related to CIDP (such as time of first symptoms and time since diagnosis, as available), as well as medication history (eg, use of steroid and/or immunomodulatory/immunosuppressive agents) and/or non-drug therapies (eg, PE) related to the treatment of CIDP from 6 months (or 3 months for PE) prior to screening throughout the study, will be recorded on the appropriate CRF(s).

All other medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Table 21-1, Table 21-2, and Table 21-3, and Table 21-4), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.6), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

For detailed sampling timepoints, see Section 21.3 Clinical Laboratory Assessments.

12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of Hgb, hematocrit, erythrocytes (ie, RBC count), and leukocytes (ie, white blood cell [WBC] count) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts, as well as ANC, and absolute lymphocyte account. Measurements for Hgb and hematocrit will be performed at different time points according to Section 21.3 (Table 21-5, Table 21-6, Table 21-7, and Table 21-8). Epoch 2 E2W3 is required for those subjects taking Gamunex-C.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, AST total bilirubin, direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine, and glucose. At any time when the LDH test result is 2x ULN or greater, LDH isoenzymes panel will be performed.

Samples for hematology and clinical chemistry assessments will be collected in the appropriate matrix as specified in the laboratory manual. With the exception of screening and early termination visits, samples for hematology and clinical chemistry collected during treatment period must be collected prior to IP administration.
At any time during the study, unscheduled hematology and/or clinical chemistry test(s) may be performed as part of AE/safety investigation or may be repeated once in the event of abnormalities in test results due to errors.

Hematology and clinical chemistry assessments will be performed at the central laboratory following standardized assay procedures.

12.7.1.1 Glomerular Filtration Rate

For eligibility determination (exclusion criterion #10), serum creatinine obtained as part of the clinical chemistry panel will be used for the estimation of GFR according to the CKD-EPI creatinine equation (2009), as follows (Levey et al., 2009):

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where Scr is serum creatinine (mg/dL)

$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

12.7.2 Hemolytic Panel

The first hemolytic panel will be measured at Epoch 1 Week 1 (E1W1). The Hgb result obtained from the E1W1 will serve as the baseline Hgb value for the duration of the study. In case of absence of E1W1 result for any reason screening Hgb result serve as the baseline Hgb value. Hemoglobin and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of ≥1 g/dL compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 hours. If it is not feasible to do so, the hemolytic panel must be performed as soon as possible but at the next scheduled visit, at latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia. Any LDH test result of 2x ULN or greater will trigger analysis of the sample for LDH isoenzymes.

It is not necessary to repeat the hemolytic panel if the drop of ≥ 1 g/dL Hgb remains constant 72 hours after the first full dose of the IP or after an unscheduled visit blood draw, unless it drops further. It is recommended that the investigator uses good medical judgement in assessing subjects with an unexplained decrease in serum Hgb as other medical conditions beside hemolysis can cause this, and therefore may require additional investigations.

The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin.

Hemolytic tests will be performed at the central laboratory or other laboratories as appropriate (eg, antibody elution in the event of positive direct Coombs test). Complete hematology and clinical chemistry assessments may be performed in order to obtain laboratory results required for a hemolytic panel.

12.7.3 Hemoglobin A1C (HbA1C)

HbA1C measurements will be performed only in subjects with clinically diagnosed diabetes mellitus at screening to support eligibility determination. During the study, HbA1C will be measured at baseline, during the interim visit, and at the end of treatment visit of each treatment period (or during early termination visit in subjects who discontinue early on the study) to monitor glycemic control in these subjects.

12.7.4 Serum Iron, Ferritin, and Total Iron Binding Capacity (TIBC)

During each of the treatment periods, serum iron, ferritin, and TIBC will be monitored. At any time during the study, the iron panel may be performed as part of AE/safety evaluation. Serum iron, ferritin, and TIBC tests will be performed at the central laboratory.

12.7.5 Serum IgA

Serum IgA level will be measured for the determination of eligibility. Serum IgA measurement will be performed at the central laboratory using an assay with a lower quantification limit of 8 mg/dL.

12.7.6 Viral Serology Tests

Serum samples will be collected for viral serology testing for HAV antibody, hepatitis B surface antigen (HBsAg), HCV antibody, and HIV-1/HIV-2 antibody. Additional tests, such as hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and/or nucleic acid tests, may be performed as necessary to confirm eligibility determination. Subjects with immunity to hepatitis B from active vaccination are those with negative HBsAg, positive hepatitis B surface antibody [HBsAb], and negative HBcAb. Subjects with past infection are defined as those with negative HBsAg, positive HBsAb, and positive HBcAb. All viral testing will be performed at the central laboratory at screening for eligibility determination (exclusion criterion #17).

Unscheduled serology testing may be performed in the event of suspected hepatitis/HIV infection. Any seroconversion result for HBV, HCV, or HIV shall be re-tested and additional tests for investigation may be conducted, in particular in the event of absence of clear alternative etiology.

In addition, the serum retention samples collected at baseline (Epoch 1 Week 1 predose), periodically following initiation of treatment, and at the end of each treatment period/early termination visit will be stored and may be used for possible testing of pathogens identified in the future. See Section 21.3 for detailed sample collection timepoints.

12.7.7 Urine Tests

Urinalysis will include color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination. Urinalysis tests will be conducted at the central laboratory.

12.7.8 Pregnancy Test

For female subjects of childbearing potential, urine pregnancy test will be performed, unless a serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

12.7.9 Assessment of Laboratory Values

12.7.9.1 Toxicity Grading Scale

The Common Toxicity Criteria of the Eastern Cooperative Oncology Group, 2006, published by Oken et al., 1982, will be used to grade the following laboratory values:

- ALP, ALT, AST, BUN, Hgb, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and WBC.
  Grading for LDH will use the same thresholds as defined for ALT and AST.
- Sodium and potassium will be graded using the thresholds taken from the World Health Organization (WHO) toxicity grading system (World Health Organization, 2003).

The laboratory parameters and the corresponding grading scale are provided in Section 21.4.
The toxicity scale is defined as: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening (Food and Drug Administration, 2008).

Laboratory parameters not listed in Table 21-9 will not be graded. However, clinical significance of those abnormal laboratory values will be assessed as described in Section 12.7.9.2.

12.7.9.2 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the appropriate CRF/laboratory form. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the laboratory value (except hyaluronidase antibody values) constitutes a new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.6), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie, because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.7.10 Trough Serum IgG

The screening/baseline trough serum IgG sample will be collected prior to the last pre-randomization IGIV dosing during the screening/baseline period. If due to scheduling difficulties, blood sampling at other pre-randomization IGIV infusions will be allowed. However, serum IgG samples must be collected prior to start of the pre-randomization IGIV infusion (or prior to the first day of IGIV infusion if the IGIV dose is divided over multiple days in an infusion cycle).

During Epoch 1 and Epoch 2 (as applicable), trough serum IgG samples must be collected on the day of the IP administration (or on the first day of IP infusion if the IP dose is to be administered as divided doses over multiple days in an infusion cycle) prior to the start of the infusion.

Blood samples are to be collected and processed according to directions provided in the laboratory manual. Each serum sample will be split into duplicate aliquots of approximately equal volume; one of which will serve as a retention (backup) sample. Serum IgG trough levels must also be collected on each subject on or after day 120 or at the time of CIDP symptom relapse.

Total IgG level in serum will be determined using a validated nephelometric assay method at a specialty laboratory.

12.7.11 Anti-rHuPH20 Antibodies

The potential for immune response to rHuPH20 will be monitored in all subjects (regardless of treatment assignment to the active or placebo treatment group) who have received rHuPH20 administration in Epoch 1. Serum samples for the detection of anti-rHuPH20 binding and neutralizing antibodies will be collected at baseline (Epoch 1 Week 1 prior to IP administration), during early time course (ie, at 2, 4, and 7 to 8 weeks since start of treatment), during the Epoch 1 interim visit (ie, at 13 to 15 weeks since start of treatment; the precise week of sample collection depends on the subject's dosing frequency and scheduling), and at the end-of-SC treatment visit (ie, 25 to 27 weeks since start of treatment; the precise week of sample collection depends on the subject's dosing frequency and scheduling)/early termination visit. In the event that no safety concerns are observed, the early sampling time points (i.e., at 2, 4, and 7 to 8 weeks since treatment initiation) may be waived or modified upon recommendation by the DMC and notification by the sponsor or sponsor's representative. See Section 21.3.

During Epoch 2, serum samples will be collected for continued monitoring for the detection of anti-rHuPH20 binding and neutralizing antibodies during the pre-IV baseline visit, Epoch 2 interim visit, and at the end of Epoch 2 treatment/early termination visit.

Blood samples for the detection of anti-rHuPH20 binding neutralizing antibodies will be collected and processed according to directions provided in the laboratory manual. At each collection timepoint, serum samples will be collected into separate tubes labeled for binding antibodies and neutralizing antibodies. Each will then be split into duplicate aliquots of approximately equal volume; one of which will serve as a retention (backup) sample. All subjects will be monitored for the formation of anti-rHuPH20 antibodies using validated anti-rHuPH20 antibody detection (ADA) assay (also known as the Screening and Confirmatory Binding Assay). Samples with antibody titers ≥1:160 will be analyzed for the presence of neutralizing antibodies using a validated assay based on neutralization of rHuPH20 activity.

12.7.12 Immunogenicity Panel

At baseline (Week 1 predose), samples will be collected for the following tests to be conducted: 50% hemolytic complement activity of serum (CH50), serum complement component 3 (C3), serum complement component 4 (C4), C1q binding assay, and circulating immune complex (CIC) Raji cell assay.

At any time during the course of the study, subjects who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications (see Table 12-1) will be asked to return to the study site as soon as possible to undergo an additional panel of testing outlined in Table 12-2.

Table 12-1. List of Conditions/Symptoms Which May be a Result of Immune-Mediated Response to Either Immunoglobulin, rHuPH20, or Other Concomitant Medications

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 h • 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 hematuria, red cell casts in urine, progressive renal dysfunction

Table 12-2. Immunogenicity Panel

1.	Repeat test for anti-rHuPH20 binding antibody titers
5.	Test (or repeat test, as applicable) for the presence of neutralizing anti rHuPH20 antibodies
6.	Assessment of cross reactivity to human HYAL1, HYAL2, and HYAL4 only for subjects whose anti-rHuPH20 binding antibody titer exceeds 1:10,000
7.	Hematology panel with manual differential (see Section 12.7.1)
8.	Clinical chemistry panel (see Section 12.7.1)
9.	CH50
10.	Serum C3
11.	Serum C4
12.	C1q binding assay
13.	CIC Raji cell assay
14.	Blood draw for additional testing as necessary

Blood samples are to be collected and processed according to the directions provided in the laboratory manual. The tests should be performed at the central laboratory and/or specialty laboratories as appropriate.

12.7.12.1 Guidance on Reporting and Assessing rHuPH20 (hyaluronidase) antibody test results

Epoch 1: Hyaluronidase is administered as Investigational Medicinal Product (IMP) in Epoch 1. All hyaluronidase antibody test results (titers, and binding or neutralizing) will be assessed for clinical significance by the investigator in the electronic data capture (EDC) database but are not to be reported as adverse events.

For adverse events occurring during the subcutaneous infusion of hyaluronidase the investigator and sponsor will independently assess relatedness, also taking into account quantitative and qualitative test results for hyaluronidase antibodies.

For adverse events occurring upon or after subsequent subcutaneous infusion of the immunoglobulin component an assessment of causality is confounded by the presence of the consecutively administered IMPs. The overlap is transient due to the short half-life of hyaluronidase of about 30 minutes in the SC space. The investigator and sponsor will independently evaluate the relatedness of an adverse event to one or the other component during this period.

Epoch 2: No hyaluronidase is administered during Epoch 2. All hyaluronidase antibody test results (titers, and binding or neutralizing) will be assessed for clinical significance by the investigator in the EDC database but are not to be reported as adverse events.

For adverse events occurring in Epoch 2 the investigator and sponsor will independently assess relatedness, also taking into account the cumulative quantitative and qualitative test results for hyaluronidase antibodies.

12.7.13 Backup Samples/Biobanking

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and resting systolic and diastolic blood pressure (mmHg). Blood pressure will be measured when subjects are in the supine/sitting position. Vital signs will be measured at screening, periodically throughout each treatment period, and at study completion/early termination visit (See Section 21.2 Schedule of Study Procedures and Assessments detailed collection timepoints).

For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken only in the event of an AE that occurs during an infusion and when a healthcare professional (eg, infusion nurse) is present to take the measurements. In these cases, vital signs will be taken at the onset of AE (or as soon as the AE is reported) and within 60 minutes of completion of an infusion. Additional vital signs may be taken as deemed medically necessary to monitor the AE. Subjects/caregivers will be instructed that if a healthcare professional is not present at an infusion and the subject experiences an AE necessitating stopping of the infusion, the subject/caregiver should immediately contact the investigator or go to the emergency room/department.

Body height (in or cm) and weight (lb or kg), as well as BMI will be collected at screening. Subsequently, BW will be re-measured during each treatment period (see Section 21.2 for detailed measurement timepoints). All BW measurements are to be taken at the study site using the same scale/instrument throughout the study for that individual subject. Subject's self-reported weights will not be used at any time during the course of the study.

Vital sign values are to be recorded on the appropriate CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1) and record the medical diagnosis (preferably), symptom, or sign on the AE CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

13. OTHER ASSESSMENTS

13.1 Electrodiagnostic studies (EMG)

Electrodiagnostic (EDX) studies that were conducted prior to initiation of SC (Epoch-1) treatment (baseline EDX study) will be used to ensure that subjects meet EFNS/PNS diagnostic criteria (van den Bergh et al, 2010) for inclusion into Epoch-1. In addition, EDX studies will be repeated prior to initiation (baseline EDX study) and at the completion (exit EDX study) of Epoch-1 and Epoch-2 to provide additional information regarding disease activity while on therapy. For purposes of comparison, the same nerve segments will be evaluated at the exit and baseline studies. EDX studies will be performed according to standard practice, using supramaximal percutaneous nerve stimulation to determine compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes. At a minimum, two limbs and four motor nerves (median , ulnar, peroneal, tibial nerves) per limb will be examined (please see the Nerve Conduction Study Manual for details). EDX studies will be reviewed by an evaluator at the Central Reading Site (Cornell University). The results of the evaluation and whether the subject meets inclusion criteria, will be reported back to the study site within two business days of submission. For each subject, the EDX studies will be analyzed for total number and specific types of demyelinating abnormalities (DA) in each study, resolution of original DA seen in screening EDX and new DA in exit EDX. Demyelinating abnormalities will be determined following EFNS/PNS criteria and include:

- Prolonged distal motor latency
- Partial motor conduction block
- Probable partial motor conduction block
- Temporal dispersion
- Prolonged distal CMAP duration
- Conduction velocity slowing
- Prolonged F-wave minimal latency

All EDX assessments will be done blinded to the treatment assignment by a central lab located at the Cornell University. For further information regarding EDX testing, please refer to the Nerve Conduction Studies Manual.

13.2 Short Form-36 Health Survey (SF-36)

Quality of life measures are useful in assessing the relative burden of disease as well as the degree to which treatment has made a difference in the well-being of an individual. The Short Form (SF)-36 health survey will be utilized to assess changes in HRQOL and functional health (Ware et al., 2000). The SF-36 health survey is a standardized, validated instrument designed to be self-administered by subjects aged 14 years and older and is composed of items grouped into 8 domains. The domains reflected in the physical component summary score (PCS) are physical functioning, role-physical, bodily pain, and general health. The domains captured in the mental component summary score (MCS) include social functioning, role-emotional, vitality, and mental health.

The SF-36 health survey will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments.

13.3 EQ-5D

The EQ-5D is a validated, self-administered assessment of overall health designed by (The EuroQol Group, 1990). It is a descriptive system of HRQOL states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Subjects are asked to describe their health state that day by choosing 1 of 3 responses that reflect the levels of severity for each of the 5 dimensions: no problems, some or moderate problems, or extreme problems. The EQ-5D also includes a standard vertical 20-cm visual analogue scale (similar to a thermometer) for recording a subject's rating of their current HRQOL state.

The EQ-5D will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments.

13.4 Health Resource Utilization

The HRU items will assess subjects' utilization of health services such as days off from school/work, unscheduled physician visits (including urgent care visits to see healthcare providers), hospitalizations, and emergency room visits. Health Resource Utilization does not include visits and days off from school/work for study related outpatient procedures and assessments.

The HRU items will be directly recorded in the subject's DIARYpro on an on-going basis during the study. If a translated version is used, it is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments. DIARYpro will be dispensed to the subjects at screening. HRU data collected during screening will not be used for analysis.

13.5 Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a 9-item, validated, self-administered instrument to assess patients' satisfaction with medication. The 3 domains assessed are effectiveness, convenience, and global satisfaction.

The TSQM-9 will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments.

13.6 Treatment Preference

The treatment preference questionnaire is a self-administered, non-validated scale assessing patient preference for various attributes of IgG therapy, such as ease of administration, frequency and duration of administration, and convenience.

The treatment preference questionnaire will be administered at the study site using a translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments.

13.7 Patient Global Impression of Change

The PGIC scale is a single item that evaluates the subject's perspective on whether or not they have improved since the beginning of treatment. The PGIC is used as an 'anchor' in the determination of clinically meaningful change. Subjects rate their perception of improvement or deterioration since the beginning of treatment on a 7-point scale ranging from "very much worse" to "very much improved".

The PGIC scale will be completed using a translated version, as applicable. It is recommended that the subject complete the item using the same translated version throughout the course of the study. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments.

14. STATISTICS

This statistical analysis section provides:

- Sample size estimation (along with the underlying assumptions) and the planned SAP for HYQVIA/HyQvia during the placebo-controlled, randomized, SC treatment period.
- Sample size estimation (along with the underlying assumptions) and the planned SAP for GAMMAGARD LIQUID/KIOVIG during the open-label IV period.

Detailed statistical analysis methods will be described in the SAP.

14.1 Epoch 1: SC Treatment Period

14.1.1 Sample Size and Power Calculations

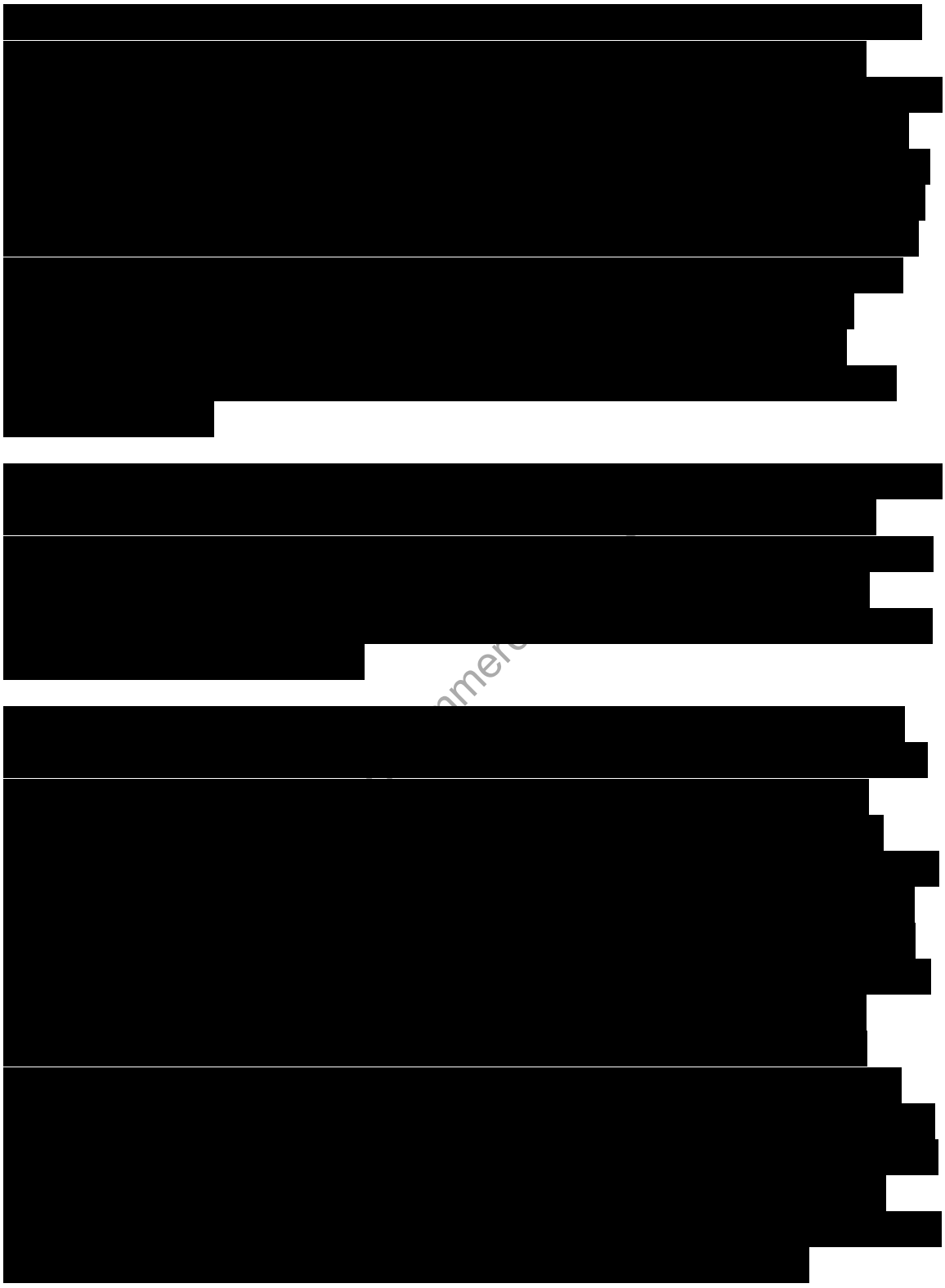
14.1.1.1 Summary

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).

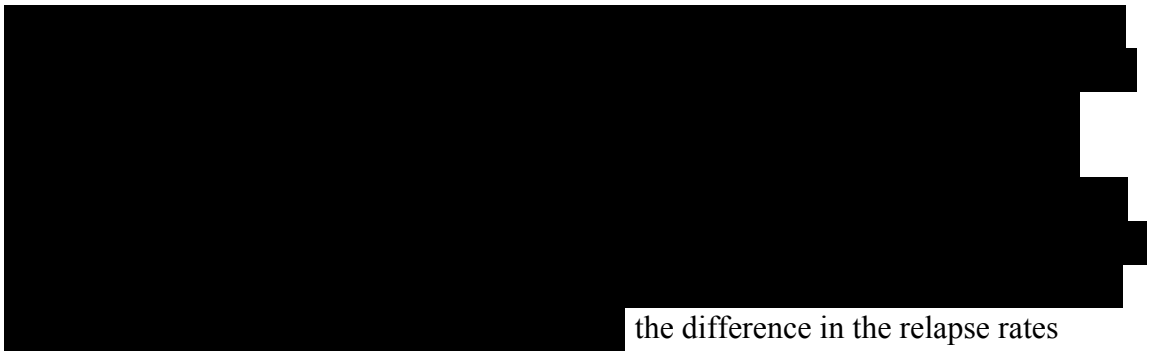
Based on additional information provided by more recent scientific literature, the original sample size assumptions are no longer considered to be relevant and a larger treatment difference in relapse rates of 29% is now expected compared with the originally assumed 18% difference. Whilst the assumed 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.

As discussed in 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]



14.1.1.3 Power calculation



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.

14.1.1.4 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.

14.1.2 Datasets and Analysis Cohorts

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.

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.

A Per-Protocol (PP) analysis set will include all randomized subjects who received any double-blind study medication, and had no major 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. Such protocol deviations will be determined prior to Epoch 1 data lock and treatment unblinding.

14.1.3 Handling of Missing, Unused, and Spurious Data

Rules for handling missing data will be described in the SAP.

14.1.4 Methods of Analysis

14.1.4.1 Primary Outcome Measure

A relapse is defined as worsening of functional disability by ≥1 point (increase) relative to pre-SC treatment baseline in 2 consecutive adjusted INCAT disability scores.

The null hypothesis is that relapse rates are not different between the HYQVIA/HyQvia and placebo with rHuPH20 treatment groups. The primary efficacy outcome measure is the Epoch 1 relapse rate in the MITT analysis set. The primary analysis is a comparison of relapse rates in the two treatment groups, using a continuity-corrected chi-square test conducted at the 5% level of statistical significance, with missing outcomes imputed as no relapse. The estimated relapse rates will be presented for each planned treatment group, along with the 95% CI computed using the Wilson score method.

Sensitivity analyses will include comparisons of the relapse rates in (1) the MITT analysis Set with missing imputed as a relapse, (2) an MITT Observed Cases analysis (missing outcomes excluded), (3) the PP Set with missing 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. Justification for this sensitivity analysis in the context of the Covid-19 pandemic is given in Section 10.9. These sensitivity analyses will use similar statistical methods to the primary analysis.

14.1.4.2 Secondary Outcome Measures

14.1.4.2.1 Efficacy

Clinical worsening of CIDP, defined as one or more of the following: subject relapse; ≥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, will be analyzed using the same methods as the primary endpoint.

Time to relapse, defined as time from the date of the first SC administration of HYQVIA/HyQvia or placebo with rHuPH20 to the date of relapse, will be compared between treatment groups using the Wilcoxon survival test. Additionally, the survival function will be estimated using the Kaplan-Meier curve. The analysis will be performed using data from the MITT analysis set with the planned Epoch 1 treatment.

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. The last non-missing change in Epoch 1 will be used from subjects who discontinued early. If an analysis of overall discontinuation rates shows a differential dropout rate between treatments that is significant at the 5% level, then a repeated-measures analysis of the change in ADL (R-ODS) will be used to investigate the robustness of results of the ANCOVA with last observation carried forward (LOCF) imputation in the MITT analysis set. The repeated-measure analysis will employ a restricted maximum likelihood (REML)-based, mixed-model repeated measure (MMRM) model which contains fixed terms for treatment group and planned timepoint, with baseline R-ODS as a covariate and subject as a random factor; additional details will be provided in the SAP. These analyses will be performed in the MITT population.

14.1.4.2.2 Safety

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and reported by body system, preferred term, and treatment group. Clinically significant, treatment-emergent changes in physical exams, vital signs, ECGs, and clinical laboratory measurements will be recorded as AEs; therefore, safety analyses will be primarily based on analysis of AEs, including ARs plus suspected ARs. Safety endpoints will be summarized descriptively in the Epoch 1 Safety Set using actual treatment.

Treatment-emergent AEs (TEAEs), serious TEAEs, and other AE-related outcome measures will be described by the number and percentage of subjects in each treatment group who experienced a particular type of event. Additionally, event rates will be expressed as number of events (reports) per infusion, per subject, and per subject-year. Both systemic event and events that are localized to the infusion site(s) will be examined. The relationship of AEs to infusions will be described further in terms of the number and proportion of infusions that were associated with an AE, and the number and proportion of infusions that were not completed as planned (interrupted, discontinued) due to an AE.

In addition, the incidence (number of percentage of subjects) of local infusion site reactions will be provided by geographic region (US, non-US) and overall. Infusion site swelling following SC infusion of IGI, 10% or 0.25% albumin placebo solution that is reported by subjects will be captured and reported as adverse events.

The first occurrence of any TEAE and the first occurrence of any treatment-emergent SAE will be analyzed using a Cox PH model to obtain an overall hazard ratio (HR) for treatment, adjusted for time in study (ie, duration of treatment). Separate HR's for the relationship of AEs with treatment will be computed for subjects who had total treatment durations of 0 to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, and 13 to 26 weeks at the time of the data cut-off.

These analyses will address the potential impact of any imbalance in AE rates due to differential dropout rates in Epoch 1 between HYQVIA/HyQvia and placebo with rHuPH20, and will characterize the relationship of AEs to treatment, overall and over time. Point estimates and CIs will be reported.

Similar analyses will be performed for ARs plus suspected ARs.

Summaries of subject deaths during study (if any) and of AEs leading to discontinuation will be provided.

For the purpose of summaries and listings the durations of AEs will be calculated as follows: (stop day – start day) + 1 day, which yields the number of days on which the AE was present.

For each body system and overall, the number and proportion of subjects that experienced an AE will be presented by treatment group.

For laboratory measurements, data will be summarized by treatment group and time point. Summaries of continuous measurements will include sample size, mean, standard deviation (SD), minimum, and maximum. For categorical measurements, the proportion of observations in each category will be presented.

Subjects are defined as having elevated rHuPH20 antibody titers if they have two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers. If at least 5 subjects in each treatment group have elevated titers, then an exploratory 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.

In addition, an exploratory analysis of <u>*any*</u> treatment emergent *abnormal titer or rises above* baseline in anti-rHuPH20 antibody titer will be performed to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs.

14.1.4.3 Tertiary Outcome Measures

Treatment satisfaction, treatment preference, PGIC, HRU (such as days off school/work, unscheduled physician visits, hospitalization, and emergency room visits) and changes from pre-IV treatment baseline in adjusted INCAT disability scores, hand grip strength scores, MRC sum scores, SF-36 scores and EQ-5D scores will be summarized in the MITT analysis set, by planned treatment group, using descriptive statistics (sample size, mean, SD, median, minimum, maximum) for continuous measures or the number and percentage of subjects for categorical measures.

R-ODS will also be evaluated as described in the secondary outcome measures above using a targeted subscale measuring impact on ability to complete everyday tasks. In addition, a separate psychometric statistical plan (PSAP) will be finalized prior to Epoch 1 data lock to confirm the targeted subscale is fit-for-purpose and the subset scoring's validity and reliability.

EDX studies will be obtained prior to initiation (baseline EDX study) and at the completion of the trial (exit EDX study). Repeat EDX studies are expected to reveal resolution of previously identified demyelinating abnormalities (DA) or occurrence of new DA that reflects ongoing disease activity. The total number of DA at Epoch-1 baseline and Epoch-1 exit, as well as their change, and the number of new DA in exit EDX will be summarized using descriptive statistics (sample size, mean, SD, median, minimum, maximum) for continuous measures or the number and percentage of subjects for categorical measures. The minimum data requirement is the availability of bilateral tibial, peroneal, median and ulnar measurements at both baseline and exit studies in every subject. Only subjects with complete baseline and exit EDX (i.e. with all 56 measurements) will be included into the analyses.

Trough plasma concentrations of IgG will be summarized for the Safety set, by actual treatment, using the sample size, mean, SD, median, minimum, maximum, geometric mean, and SD of the geometric mean.

In addition, potential correlation 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.

14.2 Epoch 2: IV Treatment Period

14.2.1 Sample Size and Power Calculations

14.2.1.1 Upper Limit of Response Rate from Historical Control

In Epoch 2 (the IV treatment period), the study 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%.

14.2.1.2 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 14.1.1).

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.

14.2.2 Datasets and Analysis Cohorts

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.

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.

14.2.3 Handling of Missing, Unused, and Spurious Data

Rules for handling missing data will be described in the SAP.

14.2.4 Methods of Analysis

14.2.4.1 Primary Outcome Measure

The primary outcome measure in Epoch 2 is the response rate. 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.

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.

14.2.4.2 Secondary Outcome Measures

14.2.4.2.1 Clinical Improvement of CIDP

Clinically meaningful improvement of CIDP, defined as one or more of the following: subject response (defined as a decrease of ≥1 point in the adjusted INCAT disability score at 2 consecutive time points); ≥8 kPa increase in the hand grip strength in the more affected hand; ≥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, will be presented using descriptive statistics.

14.2.4.2.2 Time to Response

The median time to response will be presented for the GAMMAGARD LIQUID/KIOVIG Placebo Relapse analysis set. Additionally, INCAT will be summarized by time point. Summary statistics will include sample size, mean, standard deviation, minimum, and maximum.

As a supportive analysis, these analyses will be repeated on the Full Placebo Relapse analysis set.

14.2.4.2.3 Safety

Epoch 2 safety set, including SAEs, TEAEs, ARs plus suspected ARs, deaths, and discontinuations due to AE will be analyzed using methods similar to Epoch 1. Analyses will be performed in the Epoch 2 Safety Set using the actual treatment. Safety endpoints will be summarized descriptively by IGIV treatment (ie, GAMMAGARD LIQUID/KIOVIG and GAMUNEX®-C separately).

For the purpose of summaries and listings the durations of AEs will be calculated as follows: (stop day – start day) + 1 day, which yields the number of days on which the AE was present.

For each body system and overall, the number and proportion of subjects that experienced an AE will be presented by IGIV treatment (ie, GAMMAGARD LIQUID/KIOVIG and GAMUNEX®-C separately).

Laboratory measurements will be summarized by time point and IGIV treatment (ie, GAMMAGARD LIQUID/KIOVIG and GAMUNEX®-C separately). Summaries of continuous measurements will include sample size, mean, SD, minimum, and maximum. For categorical measurements, the proportion of observations in each category will be presented.

14.2.4.3 Tertiary Outcome Measures

Responder rates for the E1:HYQVIA/HyQvia Relapse – E2:IGIV analysis set and the E1:HYQVIA/HyQvia Relapse – E2:GGL/KIOVIG analysis set will be summarized by sample size and proportion. As the expected sample size for the Full HYQVIA/HyQvia Relapse analysis set is only 5, no CIs will be constructed.

All other tertiary outcome measures will be summarized descriptively.

14.3 Planned Interim Analyses of the Study

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.

14.3.1 Interim Safety Analysis

An interim safety analysis will be 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 will be independently reviewed by the DMC, and the Interim Safety Analysis Report along with the DMC recommendation will be used to update regulatory authorities.

The interim safety analysis will include a minimum of 30 subjects who have been 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.

Safety data to be reviewed at the interim safety analysis will include, but may not be limited to:

- Cumulative treatment-emergent serious and nonserious AEs
- Cumulative ARs plus suspected ARs
- Anti-rHuPH20 binding and neutralizing antibody titers
- Clinically significant abnormal clinical laboratory test results
- Any relevant information that may support safety evaluation

Safety data will be summarized descriptively by Epoch 1 treatment (actual) for the Epoch 1 Safety set. If more than 5 subjects have relapsed prior to the cut-off date for the Interim Safety Analysis, then safety data will also be presented for the Epoch 2 Safety set.

The first occurrence of any TEAE and the first occurrence of any treatment-emergent SAE will be analyzed using a Cox Proportional Hazard model to obtain an overall HR for treatment, adjusted for time in study (ie, duration of treatment).

Separate HR's for the relationship of AEs with treatment will be computed for subjects who had total treatment durations of 0 to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, and 13 to 26 weeks at the time of the data cut-off. These analyses will address the potential impact of any imbalance in AE rates due to differential dropout rates in Epoch 1 between HYQVIA/HyQvia and placebo with rHuPH20, and will characterize the relationship of AEs to treatment, overall and over time. Point estimates and CIs will be reported.

Subjects are defined as having elevated rHuPH20 antibody titers if they have two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers. If at least 5 subjects in each treatment group have elevated titers, then an exploratory 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.

In addition, an exploratory analysis of *any* treatment emergent *abnormal titer or rises above* baseline in anti-rHuPH20 antibody titer will be performed to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs.

In addition, the 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 **OR** who experience CIDP worsening (defined as ≥8 kPa decrease in the hand grip strength in the more affected hand) **OR** ≥4 points decrease in R-ODS relative to the pre-SC treatment baseline score (at the time of withdrawal from the SC treatment period) will be evaluated.

14.3.2 Formal Interim Analysis (Epoch 1 Final Analysis)

Formal Interim 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.

- No multiplicity adjustment for the control of Type 1 error (false positive conclusion) will be made, as the analysis of Epoch 1 data will include all Epoch 1 data for all subjects who have completed participation in Epoch 1.
- The study SAP will be finalized and approved prior to Epoch 1 data lock and treatment unblinding.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Subinvestigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

16.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

16.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

16.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

16.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

16.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta and Takeda Development Center Americas) will also ensure the responsible EC and relevant competent authority is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

16.6 Laboratory and Reader Standardization

A central reader will be used to confirm CIDP diagnosis for eligibility determination based on review of electrodiagnostic records and other relevant medical records in accordance with EFNS/PNS 2010 guideline. Electrodiagnostic test if repeated during screening will be conducted in accordance with standardized procedures.

A standardization program will be implemented to provide standardized training to raters and to monitor inter-rater reliability as part of clinical quality assurance program. Clinical assessments (eg, INCAT, hand grip strength, MRC sum score) will be conducted in accordance with standardized procedures.

All required training and certification for specified study assessments will be documented in a training plan that will include the responsibilities of the sponsor/designee and the process of certification for the specified study assessments.

Laboratory assessments will be performed at a central laboratory using standardized procedures. Measurements of trough serum IgG levels and anti-rHuPH20 antibodies will be performed at the respective specialty laboratories.

17. ETHICS

17.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

17.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

17.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 17.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure.

The informed consent will be updated, if necessary. This new information and/or revised informed consent form, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see Section 17.3).

17.4 Data Monitoring Committee

This study will be monitored by an independent, external DMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the fields of immune-mediated neuropathy clinical care and research, IG/antibody therapy, and/or clinical immunogenicity assessments of therapeutic proteins, as well as an unblinded statistician; all of whom who are not participating in this study. The DMC may recommend to stop the trial if it finds toxicities or if treatment is proven to be not beneficial.

The DMC will be responsible for monitoring the data obtained in the study, including (but not necessarily limited to) periodic review of SAEs, AEs, clinically significant abnormal laboratory test results, anti-rHuPH20 antibody data, and any relevant information that may have an impact on the safety of the participants or the ethics of the trial. In addition, the DMC will be responsible for reviewing interim safety analysis. If no significant trends of treatment-emergent hemolytic anemia or safety concerns related to potential immune response to rHuPH20 are detected, the initial frequent clinical laboratory assessment and/or anti-rHuPH20 antibody sampling schedule may be waived/modified upon recommendation by the DMC and notification by the sponsor/sponsor's representative. Based on data reviews, the DMC will make a recommendation to continue the study as is, temporarily suspend the study, or terminate the study.

The membership, responsibilities, interactions, and operations of the DMC will be detailed in the DMC Charter.

17.5 Description of Ethical Considerations Relating to the Trial

The need for a placebo-controlled study, with reference to articles 16 and 7 of the Declaration of Helsinki is discussed below. This Section 17.5 is intended to fulfill the requirements as laid down in article 22 of the Declaration of Helsinki.

Article 16 states "In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects."

The study design follows the current clinical practice as set forward in the current EFNS/PNS guidelines (European Federation of Neurological Societies, 2010), to periodically evaluate the need for continuous IgG therapy and to provide IGIV as an effective treatment of those subjects who relapse during the periodic evaluation (see below under **risks of serious or irreversible harm**). We consider the addition of a treatment option and the prospect of self-infusion, and therefore empowerment of the patient, besides the availability of immediate rescue treatment, justifies the risks and burden to the research subjects.

Article 7 states "Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights."

Our protocol is not different from the medical practice as promoted by the current EFNS/PNS guidelines, as stated above.

According to the Declaration of Helsinki article 33, conducting a placebo-controlled trial is possible if:

- Compelling methodological reasons exist
- The patient will not be subject to additional risks of serious or irreversible harm
- No proven intervention exists

This placebo-controlled study is designed in accordance with the current version of the Declaration of Helsinki:

- **Compelling methodological reasons exist**

The safety and efficacy of intravenous immunoglobulin G (IGIV) treatment in CIDP is considered a proven intervention, however HyQvia (a rHuPH20-facilitated subcutaneous immunoglobulin G [IGSC]) is a new product that is administered subcutaneously (rather than intravenously) resulting in a unique PK, bioavailability and safety profile. The safety, tolerability, and efficacy of HyQvia as a treatment option for CIDP have yet to be demonstrated.

During protocol development, a non-inferiority, active-comparator, double-masked- (for masking both IGIV and IGSC) design has been considered due to concerns about the ethics of including a placebo group when an effective IGIV treatment is available. Sample size for the active-comparator study design was estimated according to the US FDA Guidance for Industry: Non-Inferiority Clinical Trials (U.S. Department of Health and Human Services et al., 2010). An active-control relapse rate of 14% was

assumed, based on data from the ICE study (Hughes et al., 2008). Non-inferiority margins calculated using the preferred 95%-95% rule and the 90%-95% alternative rule were 1.15 and 1.37, respectively.

Using the 95% to 95% rule and non-inferiority margin of 1.15, it was determined that a sample size of 4,286 subjects per treatment arm would be required to show non-inferiority using a 1-tailed, 97.5% CI. Preservation of up to 80% of the control effect would increase this sample size to 107,144 per treatment arm.

Using the 90% to 95% rule and non-inferiority margin of 1.37, it was determined that a sample size of 705 subjects per treatment arm would be required to show non-inferiority using a 1-tailed, 97.5% CI. Preservation of up to 80% of the control effect would increase this sample size to 26,786 subjects per group.

In both cases, these required calculated sample sizes will be increased for relapse rates lower than 14%. On the other hand, a non-inferiority margin greater than 1.37, which would result in lower sample size, is not clinically acceptable.

CIDP is a rare disease with a worldwide prevalence ranging from 1.9 to 8.9/100,000 with an annual incidence of 0.15 to 1.6/100,000 (Iijima et al., 2008, Laughlin et al., 2009, Lunn et al., 1999, McLeod et al., 1999, Mygland and Monstad, 2001). A sample size of 705 per treatment arm (ie, total of 1,410 randomized subjects in a study) or greater is not feasible to recruit in this patient population.

Another drawback of an active-comparator, non-inferiority study is that it requires the use of a double-masked-design for masking since currently only intravenous immunoglobulin products are approved for the treatment of CIDP (therefore, the active comparator to HyQvia which is a SC administration must be IGIV). To protect the blind, the double-masked-design will involve simultaneous intravenous and subcutaneous infusions, which means doubling an already large infusion volume due to large IgG doses typically required to treat CIDP patients. To illustrate, the mean monthly dose of IgG in CIDP is 1.3 g/kg BW, which is equivalent to approximately 1000 mL of IgG 10% solution for an 80-kg patient. Some CIDP patients may require monthly doses as high as 2.4 g/kg BW (ie, approximately 2000 mL). Double-masked-design means administering twice the infusion volumes (equivalent to 2000 to 4000 mL). Such high volumes subject the patients to undue safety risks including fluid overload, edema and potentially congestive heart failure. Additionally, total infusion administration time will markedly increase, adding unnecessary burden to the patients participating in the study.

Therefore, it is concluded that an active-comparator, non-inferiority design for a study in CIDP is not feasible. As an alternative, it is proposed to keep the current placebo-controlled design, with close monitoring for early detection for signs of relapse and provision of IGIV rescue therapy immediately without delay. The study protocol has been reviewed and discussed with the independent DMC comprised of 2 physicians/clinical researchers who are recognized experts in the CIDP and an independent biostatistician. The DMC agreed that the placebo-controlled study as designed that includes relapse risk mitigation measures and management are acceptable and ethical.

- **The patient will not be subject to additional risks of serious or irreversible harm**

The progression of CIDP occurs over a long period of time. Bouchard et al. in a review of 100 CIDP patients found that in long-standing disease the cumulative loss of axons correlates with a poor prognosis (Bouchard et al., 1999).

With newer therapies for CIDP (IGIV), the prognosis of CIDP has been improved. In an institutional-based evaluation (Hahn et al., 2005), 88% of patients returned to normal or had only minor non-disabling symptoms remaining (modified Rankin score of 0 or 1); 64% of these patients had discontinued all medication and were in full remission for 5.7 years. Many of these patients required aggressive therapy during the early stage of the disease, often with combination of several therapeutic modalities (including prednisone, PE and IGIV). It is concluded that even severe relapse can be treated adequately with excellent response and recovery. In the proposed study, subjects with modest relapse will be immediately rescued.

The EFNS/PNS guidelines (European Federation of Neurological Societies, 2010) for the management of CIDP encourage physicians to periodically reduce a subject's treatment dose and/or dosing frequency (even to the point of temporarily discontinuing the subject's treatment) to assess the patient's need for continued therapy:

> "If a patient becomes stable on a regimen of intermittent IVIg, the dose (or, perhaps, frequency) of IVIg should be reduced periodically to establish the need for ongoing therapy because patients may need less IVIg than they receive or in fact none at all."

The proposed (161403) study design including a placebo arm (in essence, withdrawing IGIV therapy) is consistent with the EFNS/PNS recommendation to evaluate the need for continuous therapy and to provide IGIV as an effective treatment of those subjects who relapse.

Treatment withdrawal or use of placebo control has been commonly employed in recent or ongoing clinical studies of IGIV treatment in CIDP. In a previous study (ICE study of Gamunex-C) (Hughes et al., 2008), subjects were exposed to placebo twice during the trial. There were no reports of permanent disability or axonal injury. Likewise, in a recent study (PRIMA study of Privigen) (Léger et al., 2013), subjects who had been receiving IGIV were also mandated to withdraw their IGIV treatment for up to 10 weeks until disease deterioration (≥1 adjusted INCAT disability score) occurred before subjects were allowed to be enrolled in the study to receive IGIV study drug (Privigen). In a currently ongoing CIDP study (PATH study of Hizentra; NCT01545076; EudraCT Number 2011-003448-28) being conducted in multiple EU countries, all subjects are at least once exposed to drug withdrawal with half of the subjects (randomized to placebo group) being exposed to drug withdrawal for a second time. In the current proposed 161403 study, subjects will not be required to withdraw their IGIV treatment at study entry. In fact, subjects will be required to continue on their own IGIV therapy during screening and baseline period until randomization. At randomization, half of the participants will be exposed to placebo (ie, subjected to IG treatment cessation) until CIDP worsening defined as ≥1 point increases in the adjusted INCAT disability score, which is the same criteria as that used in the other CIDP clinical trials mentioned above.

In the proposed clinical trial, the sponsor is taking multiple mitigation steps to assure the prevention of serious or irreversible harm, safety of the patients and to prevent axonal/permanent injury. The following are the measures to mitigate the above risk:

1. During the proposed 161403 study, the subject's CIDP disease condition will be closely and frequently monitored. Subjects will be provided with a DIARYpro to report their level of activities of daily living on a weekly basis by filling out a 24item questionnaire (R-ODS). R-ODS has been demonstrated to have a significantly higher responsiveness compared to the INCAT disability scale, and is recommended to be the primary instrument for the assessment of the subject's activity and functional levels (Vanhoutte et al., 2013a). Subject's self-reported R-ODS scores can be readily accessible for frequent review by the investigator. Any clinical signs of CIDP worsening would be readily captured, thus reducing the possibility of untreated relapse and/or delay in treatment of relapse.
2. Additionally, subjects will be instructed to contact the study site/investigator in the event of suspected CIDP worsening ("feeling worse"). At any time, unscheduled visit to the study site will be arranged as soon as possible to evaluate if the CIDP worsening meets the definition of relapse by INCAT assessments. Subjects with confirmed CIDP relapse in Epoch 1 will be offered IGIV rescue immediately without any mandatory waiting period, thus minimizing the possibility of causing axonal injury/permanent damage.

3. Patients whose disease progresses by ≥1 adjusted INCAT disability score will be rescued with IGIV at a dose of 2 gram/kg BW. This definition of disease progression (by ≥1 adjusted INCAT disability score) correlates with a very modest clinical progression. The protocol-specified IGIV treatment (an induction dose of 2 g/kg BW followed by maintenance infusions every 3 weeks) is consistent with the recommended treatment guidelines (EFNS/PNS 2010 (European Federation of Neurological Societies, 2010)) and has been established to be effective in large clinical trials for more than 1 IGIV products (eg, ICE study (Hughes et al., 2008) and PRIMA study (Léger et al., 2013)). The maintenance IGIV dose to be used in rescuing the subjects who relapsed during Epoch 1 is the same as the subject's pre-study IGIV maintenance treatment which has been shown to be effective in maintaining the disease in remission. Additionally, recognizing subjects at times may need a higher IGIV dose following CIDP relapse, the protocol allows IGIV dose adjustments (increases) in order to restore the subject's functional ability to baseline level. These measures will assure that subjects participating in the study would not suffer additional axonal injury or permanent disability.
4. The proposed study will have a DMC, composed of independent neurologists with expertise in the field of peripheral neuropathy. The Board will review all safety data, as well as data assessing response to rescue therapy of a relapse, in a fully unblinded fashion. The Board will alert the sponsor in case of a safety signal and will recommend actions to be taken that may include termination of the study.

18. DATA HANDLING AND RECORD KEEPING

18.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

18.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 18.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

18.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

19. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

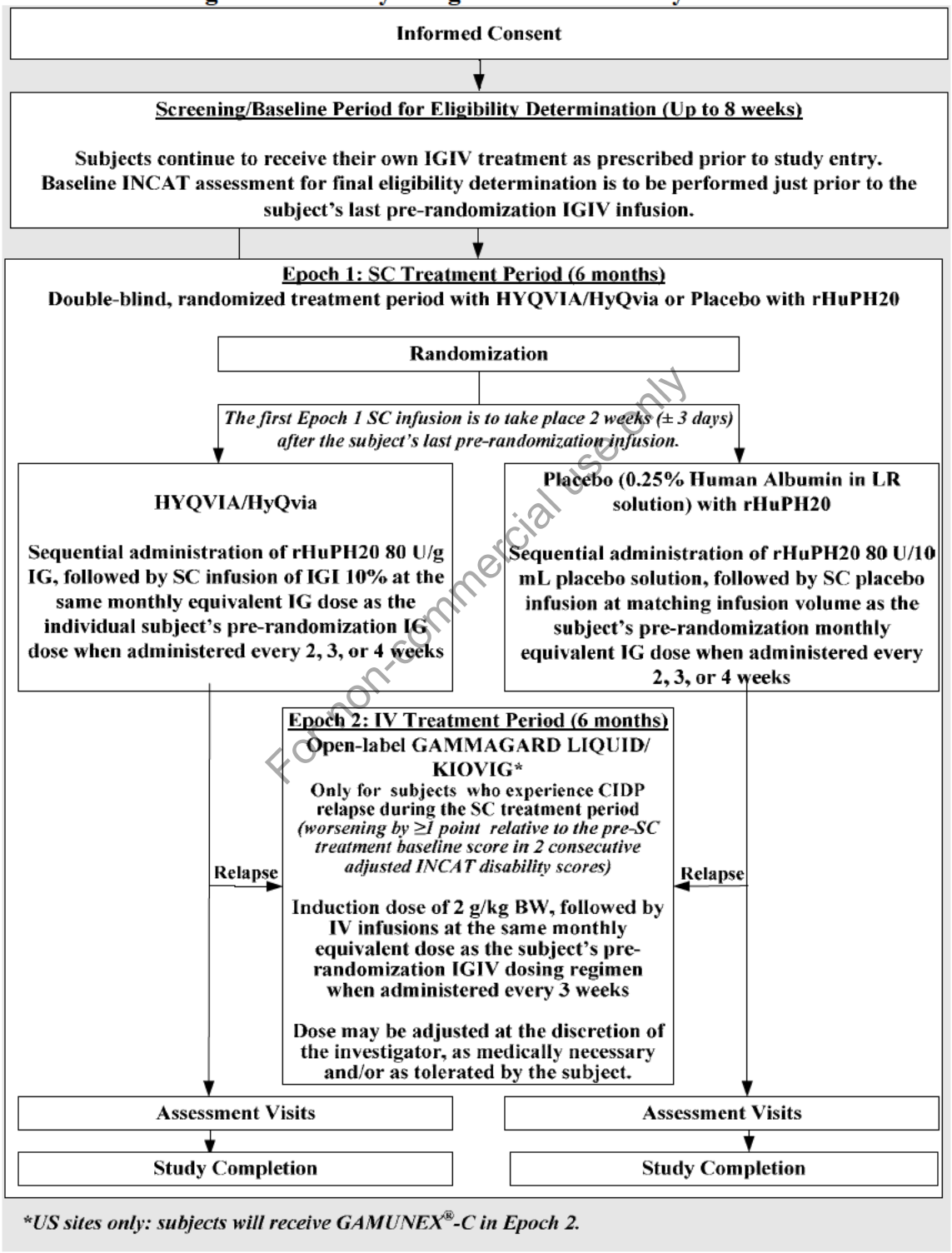
20. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

21. SUPPLEMENTS

21.1 Study Flow Chart

Figure 21-1. Study Design for Clinical Study 161403



**US sites only: subjects will receive GAMUNEX®-C in Epoch 2.*

21.2 Schedule of Study Procedures and Assessments

Table 21-1. Schedule of Study Procedures and Assessments: SC Treatment Period (Epoch 1) – Every 2 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL[a] (Up to 8 Weeks)		SC Treatment Period[b] (6 Months)																	U[c]	ET[d]
Study Visits	S	Pre-SC BL	Ramp-Up		SC Infusions Every 2 Weeks (±3 Days)																
			E1 W1[e]	E1 W2[e]	E1 W3	E1 W3 +72 hrs	E1 W4[f]	E1 W5[v]	E1 W7	E1 W9	E1 W11	E1 W13	E1W15/ E1Int[g]	E1 W17	E1 W19	E1 W21	E1 W23	E1 W25	E1W27/ EOE1T		
Informed Consent[h]	X																				
Eligibility Determination	X	X																			
Demographics	X																				
Medical, Medication, and Non-Drug Therapy History	X																				
Body Height	X																				
Body Weight	X												X[g]						X		
Body mass index	X												X[g]								
Vital Signs[i]	X		X[j]	X[j]	X[j]			X[j]	X[j]	X[j]	X[j]	X[j]	X[g,j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]		X
Physical Exam	X		X[k]										X[g,k]						X[k]		X
12-Lead ECG	X																		X		X
Electrodiagnostic Test/ Nerve Conduction Studies	X[l]																		X[k]		X
Screening and Safety Labs[m]	X		X[k]		X[k]	X[n]	X	X[k]					X[g,k]						X[k]		X
INCAT Disability Score	X	X[k,o]						X[k]		X[k]		X[k]	X[g,k]		X[k]		X[k]		X[k]	X	X
Hand Grip Strength		X[k]											X[g,k]						X[k]	X	X
MRC sum score[p]		X[k]											X[g,k]						X[k]	X	X

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Study Period	Screening/ Pre-SC BL[a] (Up to 8 Weeks)		SC Treatment Period[b] (6 Months)																U[c]	ET[d]
Study Visits	S	Pre-SC BL	Ramp-Up		SC Infusions Every 2 Weeks (±3 Days)															
			E1 W1[e]	E1 W2[e]	E1 W3	E1 W3 +72 hrs	E1 W4[f]	E1 W5[v]	E1 W7	E1 W9	E1 W11	E1 W13	E1W15/ E1Int[g]	E1 W17	E1 W19	E1 W21	E1 W23	E1 W25	E1W27/ EOE1T	
R-ODS		X[k]	←									X[q]						→	X	X
SF-36		X																	X	X
EQ-5D		X																	X	X
HRU[r]		←										X						→		
Treatment Satisfaction		X																	X	X
Treatment Preference		X																	X	X
PGIC																			X	X
Subject's pre-randomization IgG Treatment	← X	→																		
Randomization		X[s]																		
IP Administration			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Infusion self-administration proficiency checklist[t]			←									X						→		
Post-Infusion Telephone Follow-up[u]			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Serum IgG[m]		X[k]	X[k]										X[g,k]						X[k]		X
Anti-rHuPH20 Antibodies[m]			X[k]		X[k]			X[k]		X[k]			X[g,k]						X[k]		X

Table 21-1. Schedule of Study Procedures and Assessments: SC Treatment Period (Epoch 1) – Every 2 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL[a] (Up to 8 Weeks)		SC Treatment Period[b] (6 Months)																	U[c]	ET[d]
Study Visits	S	Pre-SC BL	Ramp-Up		SC Infusions Every 2 Weeks (±3 Days)																
			E1 W1[e]	E1 W2[e]	E1 W3	E1 W3 +72 hrs	E1 W4[f]	E1 W5[v]	E1 W7	E1 W9	E1 W11	E1 W13	E1W15/ E1Int[g]	E1 W17	E1 W19	E1 W21	E1 W23	E1 W25	E1W27/ EOE1T		
Plasma/Serum Retention Samples[m]			X[k]		X[k]			X[k]		X[k]			X[g,k]						X[k]		X
Adverse Events	←											X								→	
Concomitant Medications and Non-Drug Therapies	←											X								→	

Abbreviations: AE = adverse event; CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy; E1W = Epoch 1 week number; E1Int = Epoch 1 interim visit; ECG = Electrocardiogram; EOE1T = End-of-Epoch 1 treatment visit; EQ-5D = EuroQoL (Quality of Life)-5 Dimensions Questionnaire; ET = Early termination visit; IgG = Immunoglobulin G; IGIV = Intravenous immunoglobulin G; INCAT = Inflammatory Neuropathy Cause and Treatment; h = hours; HRU = Health resource utilization; MRC = Medical Research Council; PGIC = Patient global impression of change scale; IP = Investigational product; Pre-SC BL = Pre-subcutaneous treatment baseline visit; rHuPH20 = Recombinant human hyaluronidase R-ODS = Rasch-built Overall Disability Scale; S=Screening; SC = Subcutaneous; SF-36 = Short Form-36 Survey; U = Unscheduled visit for relapse assessment.

[a] The Pre-SC treatment baseline visit is to take place on the day of the subject's last pre-randomization IGIV infusion, which is to be administered at the study site. The first SC administration of HYQVIA/HyQvia or placebo with rHuPH20 will take place 2 weeks (±3 days) following the last pre-randomization IGIV administration regardless of the subject's pre-randomization IGIV dosing interval. For the rest of the SC period, SC administrations are calculated from Week 1 and not the Pre-SC BL Visit.

[b] During the SC treatment period, subjects who relapse (defined as an increase in adjusted INCAT disability score by ≥1 point relative to the pre-SC treatment baseline score, on 2 consecutive INCAT assessments) will be offered open-label IGIV treatment. Subjects who will receive IV treatment will undergo an end-of-SC treatment/pre-IV treatment baseline assessment visit (instead of the ET visit). For the schedule of study procedures and assessments during the IV treatment period, see Table 21-4. For any deviation from allowable study visit windows (±2 or ±3 day windows), subjects would be required to be brought back to the original planned visit date of the next visit in order to ensure subject safety. All other assessment or procedure visits, which do not have a visit window or a reference note in the protocol, should follow visit windows of ±3 days. There will be no visit window allowed in the ramp up period after Visit 1 (Week 1).

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[c] 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.

[d] The early termination visit is to be conducted for subjects who are being prematurely discontinued from the SC treatment period and will not undergo IV treatment period.

[e] The Week 1 infusion visit takes place 2 weeks (±3 days) after the subject's last pre-randomization IGIV administration (Pre-SC BL visit). Week 1 should be calculated from the last day of dosing for an infusion dose that is to be administered over multiple days. For the rest of the SC period, the reference to calculate the visit is Week 1 and not the Pre-SC BL Visit (Exception: Week 3+72 h, Week 4 (please see note f) and Week 5 that are calculated from Week 3 due to safety assessments in the protocol). During the ramp-up period, treatment will be given as a 1-week equivalent dose during the Week 1 and Week 2 infusion visits. The full (2-week) dose will be administered beginning at Week 3.

[f] To be collected 7 (±2) days (ie, 5 – 9 days) after the Week 3 infusion, the subject's first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[g] Subjects on a dosing schedule of every 2 weeks will be asked to return to the study site for interim assessments of the assessments that are to be conducted on the day of infusion (±3 days) during Week 15.

[h] Written informed consent must be obtained prior to any study procedures including screening.

[i] Vital signs include pulse rate, resting systolic and diastolic blood pressure, body temperature, and respiratory rate. Vital signs are to be taken at baseline (prior to infusion during E1W1 visit), during the initial 3 SC infusion visits, the interim visit, and at the end-of-SC treatment visit.

[j] For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken only in the event of an AE that occurs during an infusion and when a healthcare professional (eg, infusion nurse) is present to take the measurements. See further details in Section 12.8.

[k] To be performed prior to the start of the infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days).

[l] If available, subjects' previous nerve conduction study records consistent with electrodiagnostic criteria for Definite or Probable CIDP per EFNS/PNS 2010 guideline on management of CIDP may be used during initial screening for eligibility assessment. An additional study at the time of screening is not mandatory but highly recommended. Subjects' nerve conduction study record(s) must be reviewed by an independent central reader to confirm and document the diagnosis of CIDP based on electrodiagnostic criteria.

[m] For detailed sampling timepoints, see Table 21-5. Whenever there is an overlap of a safety visit and an infusion visit, the safety laboratory assessments should be performed first prior to the IP infusion.

[n] To be collected at 72 (±24) h (ie, 48 – 96 hrs) after the Week 3 infusion, the subject's first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[o] The baseline INCAT disability score will be used to confirm subject eligibility for the inclusion criterion of an INCAT disability score between 0 and 7 (inclusive) (ie, Inclusion Criterion #4), at which time the final determination of eligibility will be made.

[p] The MRC sum score is obtained by examining the following muscles on each side of the body: deltoids, biceps, wrist extensors, iliopsoas, quadriceps, and anterior tibialis, and rating the strength of each muscle according to the MRC scale. All scores from muscles on both left and right side of the body are summed to obtain the MRC sum score.

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[q] Beginning with the E1W1 visit, the R-ODS will be completed at least once weekly. If R-ODS assessment coincides with an infusion visit, the R-ODS is to be performed prior to the start of the infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days). eDiary (DIARYpro) will be dispensed to the subjects at screening. R-ODS data collected during screening will not be used for analysis.

[r] The health resource utilization (HRU) questionnaire includes days off school/work, unscheduled physician visits, hospitalization, and emergency room visits. Beginning with the Pre-SC BL visit, HRU items will be recorded on an ongoing basis during the study. Note: The data entered by subjects for HRU during screening in the DIARYpro will not be used for analysis.

[s] Randomization can occur between the last day of IGIV and Week 1 assessments (once last IGIV is fully administered and eligbility is confirmed).

[t] SC infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse), self-administered by the subject, and/or, as applicable, by a caregiver who may assist the subject with self-administration. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at home or other suitable locations. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The subject (and/or caregiver) may be asked to return to the study site during the SC treatment period so that the investigator/designee can further assess and document that the subject (and/or caregiver) continues to be capable of independently performing self-infusion procedures.

[u] Telephone follow-up will be conducted by the investigator/designee following each infusion visit (after 24h but within 72 h + 1 business day) to monitor for changes in a subject's functional status and to document AEs, concomitant medications, and non-drug therapies, which may have occurred within 72 h after the completion of an infusion (or after the completion of the last day of dosing for an infusion that was administered over multiple consecutive days).

[v] A minimum of a 3 day interval is required between E1W4 and E1W5 visits.

Table 21-2. Schedule of Study Procedures and Assessments: SC Treatment Period (Epoch 1) – Every 3 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL[a] (Up to 8 Weeks)		SC Treatment Period[b] (6 Months)														U[c]	ET[d]
Study Visits	S	Pre-SC BL	Ramp-Up			SC Infusions Every 3 Weeks (±3 Days)												
			E1 W1[e]	E1 W2[e]	E1 W3[e]	E1 W5	E1 W5 +72 hrs	E1 W6[f]	E1 W7[v]	E1 W8	E1 W11	E1W14/ E1Int[g]	E1 W17	E1 W20	E1 W23	E1W26 /EOE1T		
Informed Consent[h]	X																	
Eligibility Determination	X	X																
Demographics	X																	
Medical, Medication, and Non-Drug Therapy History	X																	
Body Height	X																	
Body Weight	X											X[g]				X		
Body mass index	X											X[g]						
Vital Signs[i]	X		X[j]	X[j]	X[j]	X[j]				X[j]	X[j]	X[g,j]	X[j]	X[j]	X[j]	X[j]		X
Physical Exam	X		X[k]									X[g,k]				X[k]		X
12-Lead ECG	X															X		X
Electrodiagnostic Test/Nerve Conduction Studies	X[l]															X[k]		X
Screening and Safety Labs[m]	X		X[k]		X[k]	X[k]	X[n]	X	X			X[g,k]				X[k]		X
INCAT Disability Score	X	X[k,o]				X[k]				X[k]	X[k]	X[g,k]	X[k]	X[k]	X[k]	X[k]	X	X
Hand Grip Strength		X[k]										X[g,k]				X[k]	X	X
MRC sum score[p]		X[k]										X[g,k]				X[k]	X	X
R-ODS		X[k]	←							X[q]						→	X	X
SF-36		X														X		X
EQ-5D		X														X		X
HRU[r]		←								X						→		
Treatment Satisfaction		X														X		X

Table 21-2. Schedule of Study Procedures and Assessments: SC Treatment Period (Epoch 1) – Every 3 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL[a] (Up to 8 Weeks)		SC Treatment Period[b] (6 Months)														U[c]	ET[d]
Study Visits	S	Pre-SC BL	Ramp-Up			SC Infusions Every 3 Weeks (±3 Days)												
			E1 W1[e]	E1 W2[e]	E1 W3[e]	E1 W5	E1 W5 +72 hrs	E1 W6[f]	E1 W7[v]	E1 W8	E1 W11	E1W14/ E1Int[g]	E1 W17	E1 W20	E1 W23	E1W26 /EOE1T		
Treatment Preference		X														X		X
PGIC																X		X
Subject's pre-randomization IgG Treatment	←X→																	
Randomization		X[s]																
IP Administration			X	X	X	X				X	X	X	X	X	X	X		
Infusion self-administration proficiency checklist[t]			←X→															
Post-Infusion Telephone Follow-up[u]			X	X	X	X				X	X	X	X	X	X	X		
Serum IgG[m]		X[k]	X[k]									X[g,k]				X[k]		X
Anti-rHuPH20 Antibodies[m]			X[k]		X[k]	X[k]				X[k]		X[g,k]				X[k]		X
Plasma/Serum Retention Samples[m]			X		X[k]	X[k]				X[k]		X[g,k]				X		X
Adverse Events	←X→																	
Concomitant Medications and Non-Drug Therapies	←X→																	

Abbreviations: E1W = Epoch 1 week number; E1Int = Epoch 1 interim visit; ECG = Electrocardiogram; EOE1T = End-of-Epoch 1 treatment visit; EQ-5D = EuroQoL (Quality of Life)-5 Dimensions Questionnaire; ET = Early termination visit; HRU = Health resource utilization; IgG = Immunoglobulin G; IGIV = Intravenous immunoglobulin G; INCAT = Inflammatory Neuropathy Cause and Treatment; IP = Investigational product; MRC = Medical Research Council; PGIC = Patient global impression of change scale; Pre-SC BL = Pre-subcutaneous treatment baseline visit; rHuPH20 = Recombinant human hyaluronidase; R-ODS = Rasch-built Overall Disability Scale; S = Screening; SC = Subcutaneous; SF-36 = Short Form-36 Survey; U = Unscheduled visit for relapse assessment

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[a] The Pre-SC treatment baseline visit is to take place on the day of the subject's last pre-randomization IGIV infusion, which is to be administered at the study site. The first SC administration of HYQVIA/HyQvia or placebo with rHuPH20 will take place 2 weeks (±3 days) following the last pre-randomization IGIV administration regardless of the subject's pre-randomization IGIV dosing interval. For the rest of the SC period, SC administrations are calculated from Week 1 and not the Pre-SC BL Visit

[b] During the SC treatment period, subjects who relapse (defined as an increase in adjusted INCAT disability score by ≥1 point relative to the pre-SC treatment baseline score, on 2 consecutive INCAT assessments) will be offered open-label IGIV treatment. Subjects who will receive IV treatment will undergo an end-of-SC treatment/pre-IV treatment baseline assessment visit (instead of the ET visit). For the schedule of study procedures and assessments during the IV treatment period, see Table 21-4. For any deviation from allowable study visit windows (±2 or ±3 day windows), subjects would be required to be brought back to the original planned visit date of the next visit in order to ensure subject safety. All other assessment or procedure visits, which do not have a visit window or a reference note in the protocol, should follow visit windows of ±3 days. There will be no visit window allowed in the ramp-up period after Visit 1 (Week 1).

[c] 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 the 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.

[d] The early termination visit is to be conducted for subjects who are being prematurely discontinued from the SC treatment period and will not undergo IV treatment period.

[e] The Week 1 infusion visit takes place 2 weeks (±3 days) after the subject's last pre-randomization IGIV administration (Pre-SC BL visit). Week 1 should be calculated from the last day of dosing for an infusion dose that is to be administered over multiple days. For the rest of the SC period, the reference to calculate the visit is Week 1 and not the Pre-SC BL Visit (Exception: Week 5+72 h, Week 6 (please see note f) and Week 7 that are calculated from Week 5 due to safety assessments in the protocol). During the ramp-up period, treatment will be given as 1-week equivalent dose during the Week 1 and Week 2 infusion visits, and then a 2-week equivalent dose during Week 3. The full (3-week) dose will be administered beginning at Week 5.

[f] To be collected 7 (±2) days (ie, 5 – 9 days) after the Week 5 infusion, the subject's first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[g] Subjects on a dosing schedule of every 3 weeks will be asked to return to the study site for interim assessments of the assessments that are to be conducted on the day of infusion (±3 days) during Week 14.

[h] Written informed consent must be obtained prior to any study procedures including screening.

[i] Vital signs include pulse rate, resting systolic and diastolic blood pressure, body temperature, and respiratory rate. Vital signs are to be taken at baseline (prior to infusion during E1W1 visit), during the initial 3 SC infusion visits, the interim visit, and at the end-of-SC treatment visit.

[j] For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken only in the event of an AE that occurs during an infusion and when a healthcare professional (eg, infusion nurse) is present to take the measurements. See further details in Section 12.8.

[k] To be performed prior to the start of the infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days).

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[l] If available, subjects' previous nerve conduction study records consistent with electrodiagnostic criteria for Definite or Probable CIDP per EFNS/PNS 2010 guideline on management of CIDP may be used during initial screening for eligibility assessment. An additional study at the time of screening is not mandatory but highly recommended. Subjects' nerve conduction study record(s) must be reviewed by an independent central reader to confirm and document the diagnosis of CIDP based on electrodiagnostic criteria.

[m] For detailed sampling timepoints, see Table 21-5. Whenever there is an overlap of a safety visit and an infusion visit, the safety laboratory assessments should be performed first prior to the IP infusion.

[n] To be collected 72 (±24) h (ie, 48 – 96 h) after the Week 5 infusion, the subject's first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[o] The baseline INCAT disability score will be used to confirm subject eligibility for the inclusion criterion of an INCAT disability score between 0 and 7 (inclusive) (ie, Inclusion Criterion #4), at which time the final determination of eligibility will be made.

[p] The MRC sum score is obtained by examining the following muscles on each side of the body: deltoids, biceps, wrist extensors, iliopsoas, quadriceps, and anterior tibialis, and rating the strength of each muscle according to the MRC scale. All scores from muscles on both left and right side of the body are summed to obtain the MRC sum score.

[q] Beginning with the Epoch 1 Week 1 (E1W1) visit, the R-ODS will be completed at least once weekly. If R-ODS assessment coincides with an infusion visit, the R-ODS is to be performed prior to the start of the infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days). eDiary (DIARYpro) will be dispensed to the subjects at screening; R-ODS data collected during screening will not be used for analysis.

[r] The health resource utilization (HRU) questionnaire includes days off school/work, unscheduled physician visits, hospitalization, and emergency room visits. Beginning with the Pre-SC BL visit, HRU items will be recorded on an ongoing basis during the study. Note: The data entered by subjects for HRU during screening in the DIARYpro will not be used for analysis.

[s] Randomization can occur between the last day of IGIV and Week 1 assessments (once last IGIV is fully administered and eligbility is confirmed).

[t] SC infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse), self-administered by the subject, and/or, as applicable, by a caregiver who may assist the subject with self-administration. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at home or other suitable locations. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The subject (and/or caregiver) may be asked to return to the study site during the SC treatment period so that the investigator/designee can further assess and document that the subject (and/or caregiver) continues to be capable of independently performing self-infusion procedures.

[u] Telephone follow-up will be conducted by the investigator/designee following each infusion visit (after 24 h but within 72 h + 1 business day) to monitor for changes in a subject's functional status and to document AEs, concomitant medications, and non-drug therapies, which may have occurred within 72 h after the completion of an infusion (or after the completion of the last day of dosing for an infusion that was administered over multiple consecutive days).

[v] A minimum of a 3 day interval is required between E1W6 and E1W7 visits.

Table 21-3. Schedule of Study Procedures and Assessments: SC Treatment Period (Epoch 1) – Every 4 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL[a] (Up to 8 Weeks)		SC Treatment Period[b] (6 Months)													U[c]	ET[d]
Study Visits	S	Pre-SC BL	Ramp-Up				SC Infusions Every 4 Weeks (±3 Days)										
			E1 W1[e]	E1 W2[e]	E1 W3[e]	E1 W5[e]	E1 W8	E1 W8 +72 hrs	E1 W9[f]	E1 W10[v]	E1 W12	E1W16/ E1Int[g]	E1 W20	E1 W24	E1W28/ EOE1T		
Informed Consent[h]	X																
Eligibility Determination	X	X															
Demographics	X																
Medical, Medication, and Non-Drug Therapy History	X																
Body Height	X																
Body Weight	X											X[g]			X		
Body mass index	X											X[g]					
Vital Signs[i]	X		X[j]	X[j]	X[j]	X[j]	X[j]				X[j]	X[g,j]	X[j]	X[j]	X[j]		X
Physical Exam	X		X[k]									X[g,k]			X[k]		X
12-Lead ECG	X														X		X
Electrodiagnostic Test/Nerve Conduction Studies	X[l]														X[k]		X
Screening and Safety Labs[m]	X		X[k]		X[k]		X[k]	X[n]	X	X		X[g,k]			X[k]		X
INCAT Disability Score	X	X[k,o]				X[k]	X[k]				X[k]	X[g,k]	X[k]	X[k]	X[k]	X	X
Hand Grip Strength		X[k]										X[g,k]			X[k]	X	X
MRC sum score[p]		X[k]										X[g,k]			X[k]	X	X
R-ODS		X[k]	←							X[q]					→	X	X
SF-36		X													X		X
EQ-5D		X													X		X
HRU[r]		←								X					→		

Table 21-3. Schedule of Study Procedures and Assessments: SC Treatment Period (Epoch 1) – Every 4 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL[a] (Up to 8 Weeks)		SC Treatment Period[b] (6 Months)													U[c]	ET[d]
Study Visits	S	Pre-SC BL	Ramp-Up				SC Infusions Every 4 Weeks (±3 Days)										
			E1 W1[e]	E1 W2[e]	E1 W3[e]	E1 W5[e]	E1 W8	E1 W8 +72 hrs	E1 W9[f]	E1 W10[v]	E1 W12	E1W16/ E1Int[g]	E1 W20	E1 W24	E1W28/ EOE1T		
Treatment Satisfaction		X													X		X
Treatment Preference		X													X		X
PGIC															X		X
Subject's pre-randomization IgG Treatment	← X →																
Randomization		X[s]															
IP Administration			X	X	X	X	X				X	X	X	X	X		
Infusion self-assessment proficiency checklist[t]			←							X					→		
Post-Infusion Telephone Follow-up[u]			X	X	X	X	X				X	X	X	X	X		
Serum IgG[m]		X[k]	X[k]									X[g,k]			X[k]		X
Anti-rHuPH20 Antibodies[m]			X[k]		X[k]	X[k]	X[k]					X[g,k]			X[k]		X
Plasma/Serum Retention Samples[m]			X[k]		X[k]	X[k]	X[k]					X[g,k]			X[k]		X
Adverse Events	←									X					→		
Concomitant Medications and Non-Drug Therapies	←									X					→		

Abbreviations: E1Int = Epoch 1 interim visit; E1W = Epoch 1 week number; ECG = Electrocardiogram; EOE1T = End-of-Epoch 1 visit; ET = Early termination visit; EQ-5D = EuroQoL (Quality of Life)-5 Dimensions Questionnaire; HRU = Health resource utilization; IgG = Immunoglobulin G; INCAT = Inflammatory Neuropathy Cause and Treatment; IP = Investigational product; MRC = Medical Research Council; PGIC = Patient global impression of change scale; Pre-SC BL = Pre-subcutaneous treatment baseline visit; rHuPH20 = Recombinant human hyaluronidase R-ODS = Rasch-built Overall Disability Scale; S = Screening; SC = Subcutaneous; SF-36 = Short Form-36 Survey; U = Unscheduled visit for relapse assessment.

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[a] The Pre-SC treatment baseline visit is to take place on the day of the subject's last pre-randomization IGIV infusion, which is to be administered at the study site. The first SC administration of HYQVIA/HyQvia or placebo with rHuPH20 will take place 2 weeks (±3 days) following the last pre-randomization IGIV administration regardless of the subject's pre-randomization IGIV dosing interval. For the rest of the SC period, SC administrations are calculated from Week 1 and not the Pre-SC BL Visit.

[b] During the SC treatment period, subjects who relapse (defined as an increase in adjusted INCAT disability score by ≥1 point) will be offered open-label IGIV treatment. Subjects who will receive IV treatment will undergo an end-of-SC treatment/pre-IV treatment baseline assessment visit (instead of the ET visit). For the schedule of study procedures and assessments during the IV treatment period, see Table 21-4. For any deviation from allowable study visit windows (±2 or ±3 day windows), subjects would be required to be brought back to the original planned visit date of the next visit in order to ensure subject safety. All other assessment or procedure visits, which do not have a visit window or a reference note in the protocol, should follow visit windows of ±3 days. There will be no visit window allowed in the ramp-up period after Visit 1 (Week 1).

c. 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.

[d] The early termination visit is to be conducted for subjects who are being prematurely discontinued from the SC treatment period and will not undergo IV treatment period.

[e] The Week 1 infusion visit takes place 2 weeks (±3 days) after the subject's last pre-randomization IGIV administration (Pre-SC BL visit). Week 1 should be calculated from the last day of dosing for an infusion dose that is to be administered over multiple days. For the rest of the SC period, the reference to calculate the visit is Week 1 and not the Pre-SC BL Visit (Exception: Week 8+72 h, Week 9 (please see note f) and Week 10 that are calculated from Week 8 due to safety assessments in the protocol). During the ramp-up period, treatment will be given as 1-week equivalent dose during the Week 1 and Week 2 infusion visits, followed by a 2-week equivalent dose during Week 3, and then a 3-week equivalent dose during Week 5. The full (4-week) dose will be administered beginning at Week 8.

[f] To be collected 7 (±2) days (ie, 5 – 9 days) after the Week 8 infusion, the subject's first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[g] Subjects on a dosing schedule of every 4 weeks will be asked to return to the study site for interim assessments of the assessments that are to be conducted on the day of infusion (± 3 days) during Week 16.

[h] Written informed consent must be obtained prior to any study procedures including screening.

[i] Vital signs include pulse rate, resting systolic and diastolic blood pressure, body temperature, and respiratory rate. Vital signs are to be taken at baseline (prior to infusion during E1W1 visit), during the initial 3 SC infusion visits, the interim visit, and at the end-of-SC treatment visit.

[j] For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken only in the event of an AE that occurs during an infusion and when a healthcare professional (eg, infusion nurse) is present to take the measurements. See further details in Section 12.8.

[k] To be performed prior to the start of the infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days).

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[l] If available, subjects' previous nerve conduction study records consistent with electrodiagnostic criteria for Definite or Probable CIDP per EFNS/PNS 2010 guideline on management of CIDP may be used during initial screening for eligibility assessment. An additional study at the time of screening is not mandatory but highly recommended. Subjects' nerve conduction study record(s) must be reviewed by an independent central reader to confirm and document the diagnosis of CIDP based on electrodiagnostic criteria.

[m] For detailed sampling timepoints, see Table 21-5. Whenever there is an overlap of a safety visit and an infusion visit, the safety laboratory assessments should be performed first prior to the IP infusion.

[n] To be collected 72 (±24) h (ie, 48 – 96 h) after the Week 8 infusion, the subject's first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[o] The baseline INCAT disability score will be used to confirm subject eligibility for the inclusion criterion of an INCAT disability score between 0 and 7 (inclusive) (ie, Inclusion Criterion #4), at which time the final determination of eligibility will be made.

[p] The MRC sum score is obtained by examining the following muscles on each side of the body: deltoids, biceps, wrist extensors, iliopsoas, quadriceps, and anterior tibialis, and rating the strength of each muscle according to the MRC scale. All scores from muscles on both left and right side of the body are summed to obtain the MRC sum score.

[q] Beginning with the Epoch 1 Week 1 (E1W1) visit, the R-ODS will be completed at least once weekly. If R-ODS assessment coincides with an infusion visit, the R-ODS is to be performed prior to the start of the infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days). eDiary (DIARYpro) will be dispensed to the subjects at screening. R-ODS data collected during screening will not be used for analysis.

[r] The health resource utilization (HRU) questionnaire includes days off school/work, unscheduled physician visits, hospitalization, and emergency room visits. Beginning with the Pre-SC BL visit, HRU items will be recorded on an ongoing basis during the study. Note: The data entered by subjects for HRU during screening in the DIARYpro will not be used for analysis.

[s] Randomization can occur between the last day of IGIV and Week 1 assessments (once last IGIV is fully administered and eligbility is confirmed).

[t] SC infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse), self-administered by the subject, and/or, as applicable, by a caregiver who may assist the subject with self-administration. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at home or other suitable locations. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The subject (and/or caregiver) may be asked to return to the study site during the SC treatment period so that the investigator/designee can further assess and document that the subject (and/or caregiver) continues to be capable of independently performing self-infusion procedures.

[u] Telephone follow-up will be conducted by the investigator/designee following each infusion visit (after 24 h but within 72 h + 1 business day) to monitor for changes in a subject's functional status and to document AEs, concomitant medications, and non-drug therapies, which may have occurred within 72 h after the completion of an infusion (or after the completion of the last day of dosing for an infusion that was administered over multiple consecutive days).

[v] A minimum of a 3 day interval is required between E1W9 and E1W10 visits.

Table 21-4. Schedule of Study Procedures and Assessments: IV Treatment Period (Epoch 2) – Every 3 Weeks Dosing Regimen

Study Period	IV Treatment Period (6 Months) IV Infusions Every 3 Weeks (±3 Days)										U[c]	ET
Study Visits	**Pre-IV BL/ E2W1[a]**	**E2W3**	**E2W4**	**E2W7**	**E2W10**	**E2W13/ E2Int[b]**	**E2W16**	**E2W19**	**E2W22**	**E2W25/ EOE2T**		
Body weight	X					X[b]				X		
Vital Signs[d]	X		X	X	X	X	X	X	X	X		X
Physical Exam	X									X		X
12-Lead ECG	X									X		X
Nerve Conduction Studies	X[e]									X[e]		X
Safety Labs[f]	X[e]	X				X[b,e]				X[e]		X
INCAT Disability Score[g]	X[e,h]		X[e]	X[e]	X[e]	X[b,e]	X[e]	X[e]	X[e]	X[e]	X	X
Hand Grip Strength	X[e]		X[e]	X[e]	X[e]	X[b,e]	X[e]	X[e]	X[e]	X[e]	X	X
MRC sum score[i]	X[e]		X[e]	X[e]	X[e]	X[b,e]	X[e]	X[e]	X[e]	X[e]	X	X
R-ODS[e]	← X[j] →										X	X
SF-36	X									X		X
EQ-5D	X									X		X
HRU[k]		← X →										
Treatment Satisfaction	X									X		X
Treatment Preference	X									X		X
PGIC	X									X		X
IP Administration[l]	X[l]		X	X	X	X	X	X	X	X		
Post-Infusion Telephone Follow-up[m]	X		X	X	X	X	X	X	X	X		
Serum IgG[e]	X					X[b]				X		X
Anti-rHuPH20 Antibodies[e]	X					X[b]				X		X
Plasma/Serum Retention Samples[e]	X					X[b]				X		X
Adverse Events		← X →										

Table 21-4. Schedule of Study Procedures and Assessments: IV Treatment Period (Epoch 2) – Every 3 Weeks Dosing Regimen

Study Period	IV Treatment Period (6 Months) IV Infusions Every 3 Weeks (±3 Days)										U[c]	ET
Study Visits	**Pre-IV BL/ E2W1[a]**	**E2W3**	**E2W4**	**E2W7**	**E2W10**	**E2W13/ E2Int[b]**	**E2W16**	**E2W19**	**E2W22**	**E2W25/ EOE2T**		
Concomitant Medications and Non-Drug Therapies		← X →										

Abbreviations: IV = Intravenous; Pre-IV BL = Pre-intravenous treatment baseline visit; E2W = Epoch 2 week number; E2Int = Epoch 2 interim visit; EOE2T = End-of-Epoch 2 treatment visit; U = Unscheduled visit for relapse assessment ; ET = Early termination visit; ECG = Electrocardiogram; INCAT = Inflammatory Neuropathy Cause and Treatment; MRC = Medical Research Council; R-ODS = Rasch-built Overall Disability Scale; SF-36 = Short Form-36 Survey; EQ-5D = EuroQoL (Quality of Life)-5 Dimensions Questionnaire; HRU = Health Resource Utilization; PGIC = Patient global impression of change scale; IP = Investigational product; IgG = Immunoglobulin G; rHuPH20 = Recombinant human hyaluronidase.

[a] For subjects who meet the definition of relapse during the SC treatment period and are to receive IGIV treatment, the pre-IV treatment baseline assessments will also serve as the end-of-SC treatment assessments.

[b] Interim assessments are to be conducted on the day of infusion (or within 3 days prior to the day of infusion will be acceptable) during Week 13 (±1 infusion visit, ie, Week 10. Week 13, Week 16).

[c] At any time during the IV treatment period, unscheduled visit(s) for INCAT assessments will be allowed for subjects who experience CIDP worsening, in order to determine whether the worsening meets the definition of relapse (ie, worsening in functional disability by ≥1 point relative to the pre-SC treatment baseline in 2 consecutive adjusted INCAT disability scores). Subjects who relapse during Epoch 2, will have a close-out visit and terminate participation in the study, in order to have the opportunity to receive other/additional treatment

[d] Vital signs include pulse rate, resting systolic and diastolic blood pressure, body temperature, and respiratory rate. Vital signs are to be monitored and recorded on each day of infusion (at any time prior to infusion, prior to each infusion rate change, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion).

[e] To be performed prior to infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days).

[f] For detailed sampling timepoints, see Table 21-8.

[g] In case the first INCAT evaluation indicating relapse (during Epoch 1) occurs during a study visit and not at an unscheduled visit, and the second (confirmatory) INCAT evaluation (Pre-IV BL Epoch 2) is performed on the same day, and in addition the Investigator's preference is to administer the rescue medication (E2W1) also on the same day—repetition of same laboratory assessments should be avoided, except for Serum IgG, which must be collected at the time of relapse (eg, combining E1W15 at 2 weekly dose regimen, E1W14 at 3 weekly dose regimen, or E1W16 at 4 weekly dose regimen together with Pre-IV BL Epoch 2 and E2W1 all on the same day). In this case laboratory assessments of Epoch 1 study visit are the same as the ones in E2W1 before IP. These laboratory assessments should then be performed only once for subject's safety regarding blood volume taken.

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[h] 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 met relapse criteria (ie, an increase in adjusted INCAT disability score by ≥1 point relative to the pre-SC treatment baseline score, on 2 consecutive INCAT assessments). The pre-IV treatment baseline INCAT disability score will be used 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.

[i] The MRC sum score is obtained by examining the following muscles on each side of the body: deltoids, biceps, wrist extensors, iliopsoas, quadriceps, and anterior tibialis, and rating the strength of each muscle according to the MRC scale. All scores from muscles on both left and right side of the body are summed to obtain the MRC sum score.

[j] The R-ODS will be completed at least once weekly. If R-ODS assessment coincides with an infusion visit, the R-ODS is to be performed prior to the start of the infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days).

[k] The HRU questionnaire includes days off school/work, unscheduled physician visits, hospitalization, and emergency room visits. HRU items will be recorded on an ongoing basis during the study.

[l] GAMMAGARD Liquid/KIOVIG or GAMUNEX-C (for US sites only), can be given as a rescue medication on Epoch 2, after the second INCAT evaluation, as early as the same day and no later than 7 days, at the discretion of the Investigator When administration of the rescue medication (E2W1) does not occur on same day as second (confirmatory) INCAT evaluation (Pre-IV BL Epoch 2), then Table 21-4 all study procedures and assessments should be performed at 'Pre-IV BL' Epoch 2 day and Table 21-8, all clinical laboratory assessments should be performed (before infusion) at 'E2W1' visit day.

[m] Telephone follow-up will be conducted by the investigator/designee following each infusion visit (after 24 h but within 72 h + 1 business day) to monitor for changes in a subject's functional status and to document AEs, concomitant medications, and non-drug therapies, which may have occurred within 72 h after the completion of an infusion (or after the completion of the last day of dosing for an infusion that was administered over multiple consecutive days).

21.3 Clinical Laboratory Assessments

Table 21-5. Clinical Laboratory Assessments: SC Treatment Period (Epoch 1) – Every 2 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL (Up to 8 Weeks)		SC Treatment Period[a] (6 Months)																	ET[c]
Study Visits	S	Pre-SC BL	Ramp-Up		SC Infusions Every 2 Weeks (±3 Days)															
			E1 W1[d]	E1 W2	E1 W3[d]	E1 W3 +72 hrs	E1 W4[e]	E1 W5[d]	E1 W7	E1 W9[d]	E1 W11	E1 W13	E1W15/ E1Int[b,d]	E1 W17	E1 W19	E1 W21	E1 W23	E1 W25	E1W27/ EOE1T[d]	
Hematology Panel[f]	X		X		X	X[g]	X	X					X						X	X
Clinical Chemistry Panel[h]	X		X										X						X	X
HbA1C[i]	X		X										X						X	X
Blood type			X																	
Serum iron, ferritin, and TIBC			X																X	X
Hemolytic Panel[j]			X	← X (as applicable) →																
Serum Immunoglobulin A	X																			
HAV Antibody, HBsAg, HCV Antibody, and HIV-1/HIV-2 Antibody	X																			
Serum IgG[k]		X[l]	X										X						X	X
Anti-rHuPH20 Antibodies – Binding Antibodies			X		X			X		X			X						X	X
Anti-rHuPH20 Antibodies – Neutralizing Antibodies			X		X			X		X			X						X	X
CH50, serum C3, serum C4, C1q binding assay, and CIC Raji cell assay			X																	
Immunogenicity Panel[m]				← X (as applicable) →																

Table 21-5. Clinical Laboratory Assessments: SC Treatment Period (Epoch 1) – Every 2 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL (Up to 8 Weeks)		SC Treatment Period[a] (6 Months)																ET[c]
Study Visits	S	Pre-SC BL	Ramp-Up		SC Infusions Every 2 Weeks (±3 Days)														
			E1 W1[d]	E1 W2	E1 W3[d]	E1 W3 +72 hrs	E1 W4[e]	E1 W5[d]	E1 W7	E1 W9[d]	E1 W11	E1 W13	E1W15/ E1Int[b,d]	E1 W17	E1 W19	E1 W21	E1 W23	E1 W25	E1W27/ EOE1T[d]	
Plasma and Serum Retention Samples			X		X[i]			X		X			X						X	X
Urinalysis[n]	X																			
Pregnancy Test[o]	X																		X	X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CIC = Circulating immune complex; CPK = creatine phosphokinase; E1Int = Epoch 1 interim visit; E1W = Epoch 1 week number; EOE1T = End-of-Epoch 1 treatment visit; ET = Early termination visit; GGT = gamma-glutamyl-transferase; HAV = Hepatitis A virus; HbA1C = Hemoglobin A1C; HBsAg = Hepatitis B surface antigen; HcT = hematocrit, Hgb = hemoglobin; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; IgG = Immunoglobulin G; IP = investigational product; IV = intravenous; LDH = lactate dehydrogenase; Pre-SC BL = Pre-subcutaneous treatment baseline visit; RBC = red blood cell; rHuPH20 = Recombinant human hyaluronidase; S = Screening; SC = Subcutaneous; TIBC = Total iron binding capacity; ULN = upper limit of normal; WBC = white blood cell.

[a] During the SC treatment period, subjects who relapse (defined as an increase in adjusted INCAT disability score by ≥1 point relative to the pre-SC treatment baseline score, on 2 consecutive INCAT assessments) will be offered open-label IGIV treatment. For the schedule of study procedures and assessments during the IV treatment period, see Table 21-4. For any deviation from allowable study visit windows (±2 or ±3 day windows), subjects would be required to be brought back to the original planned visit date of the next visit in order to ensure subject safety. All other assessment or procedure visits, which do not have a visit window or a reference note in the protocol, should follow visit windows of ±3 days. There will be no visit window allowed in the ramp-up period after Visit 1 (Week 1).

[b] The interim visit is to take place on the day of infusion (or within 3 days prior to infusion will be acceptable due to scheduling availability) during Week 15 (±1 infusion visit).

[c] The early termination visit is to be conducted for subjects who are being prematurely discontinued from the SC treatment period and will not undergo IV treatment.

[d] Samples must be collected prior to IP administration (ie, prior to initiation of rHuPH20 administration) on the day of infusion (or prior to IP administration on the first day of dosing for an infusion dose that is to be administered over multiple days).

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[e] To be collected 7 (±2) days (ie, 5 – 9 days) after the Week 3 infusion, the first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[f] The hematology panel will consist of complete blood count (Hgb, Hct, erythrocytes [ie, RBC] count), leukocytes [ie, WBC] count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), ANC, absolute lymphocyte count, and platelet count, a reticulocyte count to the hemolytic panel to be run in the event of a 1 g/dL or more drop in Hgb from baseline.

[g] In addition to the predose sample (see footnote d), sample for hematology is also to be collected 72 (±24) h (ie, 48 to 96 h) after the first full-dose infusion (Week 3) of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[h] The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, ALP, GGT, LDH, CPK, BUN, creatinine, and glucose. At any time when the LDH test result is 2× ULN or greater, LDH isoenzymes panel will be performed.

[i] For subjects with clinically diagnosed diabetes mellitus only.

[j] The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin. The lab results obtained predose during the E1W1 visit will serve as the baseline values. In case of absence of E1W1 result for any reason screening Hgb result serve as the baseline Hgb value. Hgb and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of 1 g/dL or more compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 h; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at the latest . At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia.

[k] Prior to start of infusion (as applicable).

[l] To be collected prior to the start of the subject's last pre-randomization IGIV infusion.

[m] At any time during the course of the study. For those subjects who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications (see Table 12-1). will be asked to return to the study site as soon as possible to undergo an additional panel of testing outlined in Table 12-2.

[n] Urinalysis includes color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

[o] For female subjects of childbearing potential only. Urine pregnancy test will be performed, unless serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

Table 21-6. Clinical Laboratory Assessments: SC Treatment Period (Epoch 1) – Every 3 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL (Up to 8 Weeks)		SC Treatment Period[a] (6 Months)														ET[c]
			Ramp-Up			SC Infusions Every 3 Weeks (±3 Days)											
Study Visits	**S**	**Pre-SC BL**	**E1 W1[d]**	**E1 W2**	**E1 W3[d]**	**E1 W5[d]**	**E1W5 +72 hrs**	**E1 W6[e]**	**E1 W7**	**E1 W8[d]**	**E1 W11**	**E1 W14/ E1Int[b,d]**	**E1 W17**	**E1 W20**	**E1 W23**	**E1 W26/ EOE1T[d]**	
Hematology Panel[f]	**X**		X		X	X	X[g]	X	X			X				X	X
Clinical Chemistry Panel[h]	X		X									X				X	X
HbA1C[i]	X		X									X				X	X
Blood Type			X														
Serum iron, ferritin, and TIBC			X													X	X
Hemolytic Panel[j]			X	←								X (as applicable)				→	
Serum Immunoglobulin A	X																
HAV Antibody, HBsAg, HCV Antibody, and HIV-1/HIV-2 Antibody	X																
Serum IgG		X[k]	X									X				X	X
Anti-rHuPH20 Antibodies – Binding Antibodies			X		X	X				X		X				X	X
Anti-rHuPH20 Antibodies – Neutralizing Antibodies			X		X	X				X		X				X	X
CH50, serum C3, serum C4, C1q binding assay, and CIC Raji cell assay			X														
Immunogenicity Panel[l]				←								X (as applicable)				→	
Plasma/Serum Retention Samples			X		X	X				X		X				X	X

Table 21-6. Clinical Laboratory Assessments: SC Treatment Period (Epoch 1) – Every 3 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL (Up to 8 Weeks)		SC Treatment Period[a] (6 Months)														ET[c]
			Ramp-Up			SC Infusions Every 3 Weeks (±3 Days)											
Study Visits	**S**	**Pre-SC BL**	**E1 W1[d]**	**E1 W2**	**E1 W3[d]**	**E1 W5[d]**	**E1W5 +72 hrs**	**E1 W6[e]**	**E1 W7**	**E1 W8[d]**	**E1 W11**	**E1 W14/ E1Int[b,d]**	**E1 W17**	**E1 W20**	**E1 W23**	**E1 W26/ EOE1T[d]**	
Urinalysis[m]	X																
Pregnancy Test[n]	X															X	X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CIC = Circulating immune complex; CPK = creatine phosphokinase; E1Int = Epoch 1 interim visit; E1W = Epoch 1 week number; GGT = gamma-glutamyl transferase; HAV = Hepatitis A virus; HBsAg = Hepatitis B surface antigen; Hct = hematocrit; HCV = Hepatitis C virus; Hgb = hemoglobin; HIV = Human immunodeficiency virus; EOE1T = End-of-Epoch 1 treatment visit; ET = Early termination visit; HbA1C = Hemoglobin A1C; IgG = Immunoglobulin G; LDH = lactate dehydrogenase; Pre-SC BL = Pre-subcutaneous treatment baseline visit; RBC = red blood cell; rHuPH20 = Recombinant human hyaluronidase; S = Screening; SC = Subcutaneous; TIBC = Total iron binding capacity; ULN = upper limit of normal; WBC = white blood cell.

[a] During the SC treatment period, subjects who relapse (defined as an increase in adjusted INCAT disability score by ≥1 point relative to the pre-SC treatment baseline score, on 2 consecutive INCAT assessments) will be offered open-label IGIV treatment. For the schedule of study procedures and assessments during the IV treatment period, see Table 21-4. For any deviation from allowable study visit windows (±2 or ±3 day windows), subjects would be required to be brought back to the original planned visit date of the next visit in order to ensure subject safety. All other assessment or procedure visits, which do not have a visit window or a reference note in the protocol, should follow visit windows of ±3 days. There will be no visit window allowed in the Ramp-up period after Visit 1 (Week 1).

[b] The interim visit is to take place on the day of infusion (or within 3 days prior to infusion will be acceptable due to scheduling availability) during Week 14 (±1 infusion visit).

[c] The early termination visit is to be conducted for subjects who are being prematurely discontinued from the SC treatment period and will not undergo IV treatment.

[d] Samples must be collected prior to IP administration (ie, prior to initiation of rHuPH20 administration) on the day of infusion (or prior to IP administration on the first day of dosing for an infusion dose that is to be administered over multiple days).

[e] To be collected 7 (±2) days (ie, 5 – 9 days) after the subject's Week 5 infusion, the first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

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[f] The hematology panel will consist of complete blood count (Hgb, Hct, erythrocytes [ie, RBC count]), leukocytes [ie, WBC count] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), ANC, absolute lymphocyte count, and platelet count, a reticulocyte count to the hemolytic panel to be run in the event of a 1 g/dL or more drop in hemoglobin from baseline.

[g] In addition to the predose sample (see footnote d), sample for hematology is also to be collected 72 (±24) h (ie, 48 – 96 h) after the subject's Week 5 infusion, the first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[h] The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, ALP, GGT, LDH, CPK, BUN, creatinine, and glucose. At any time when the LDH test result is 2× ULN or greater, LDH isoenzymes panel will be performed.

[i] For subjects with clinically diagnosed diabetes mellitus only.

[j] The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin. The lab results obtained predose during the Epoch 1 Week 1 (E1W1) visit will serve as the baseline values. In case of absence of E1W1 result for any reason screening Hgb result serve as the baseline Hgb value. Hgb and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of ≥1 g/dL compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 h; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at the latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia.

[k] To be collected prior to the subject's last pre-randomization IGIV infusion.

[l] At any time during the course of the study. For those subjects who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications (see Table 12-1) will be asked to return to the study site as soon as possible to undergo an additional panel of testing outlined in Table 12-2.

[m] Urinalysis includes color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

[n] For female subjects of childbearing potential only. Urine pregnancy test will be performed, unless serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

Table 21-7. Clinical Laboratory Assessments: SC Treatment Period (Epoch 1) – Every 4 Weeks Dosing Regimen

Study Period	Screening/ Pre-SC BL (Up to 8 Weeks)		SC Treatment Period[a] (6 Months)													ET[c]
Study Visits	S	Pre-SC BL	Ramp-Up				SC Infusions Every 4 Weeks (±3 Days)									
			E1 W1[d]	E1 W2	E1 W3[d]	E1 W5[d]	E1 W8[d]	E1 W8 +72 hrs	E1 W9[e]	E1 W10	E1 W12	E1W16/ E1Int[b,d]	E1 W20	E1 W24	E1W28/ EOE1T[d]	
Hematology Panel[f]	X		X		X		X	X[g]	X	X		X			X	X
Clinical Chemistry Panel[h]	X		X									X			X	X
HbA1C[i]	X		X									X			X	X
Blood Type			X													
Serum iron, ferritin, and TIBC			X												X	X
Hemolytic Panel[j]			X	← X (as applicable) →												
Serum Immunoglobulin A	X															
HAV Antibody, HBsAg, HCV Antibody, and HIV-1/HIV-2 Antibody	X															
Serum IgG		X[k]	X									X			X	X
Anti-rHuPH20 Antibodies – Binding Antibodies			X		X	X	X					X			X	X
Anti-rHuPH20 Antibodies – Neutralizing Antibodies			X		X	X	X					X			X	X
CH50, serum C3, serum C4, C1q binding assay, and CIC Raji cell assay			X													
Immunogenicity Panel[l]				← X (as applicable) →												
Plasma/Serum Retention Samples			X		X	X	X					X			X	X
Urinalysis[m]	X															
Pregnancy Test[n]	X														X	X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CIC = Circulating immune complex; CPK = creatine phosphokinase; E1Int = Epoch 1 interim visit; E1W = Epoch 1 week number; EOE1T = End-of-Epoch 1 treatment visit; ET = Early termination visit; GGT = gamma-glutamyl transferase; HAV = Hepatitis A virus; HbA1C = Hemoglobin A1C; HbsAg = Hepatitis B surface antigen; Hct = hematocrit; HCV = Hepatitis C virus; Hgb = hemoglobin; HIV = Human immunodeficiency virus; IgG = Immunoglobulin G; Pre-SC BL = Pre-subcutaneous treatment baseline visit; RBC = red blood cell; rHuPH20 = Recombinant human hyaluronidase; S = Screening; SC = Subcutaneous; TIBC = Total iron binding capacity; ULN = upper limit of normal; WBC = white blood cell.

[a] During the SC treatment period, subjects who relapse (defined as an increase in adjusted INCAT disability score by ≥1 point) will be offered open-label IGIV treatment. For the schedule of study procedures and assessments during the IV treatment period, see Table 21-4. For any deviation from allowable study visit windows (±2 or ±3 day windows), subjects would be required to be brought back to the original planned visit date of the next visit in order to ensure subject safety. All other assessment or procedure visits, which do not have a visit window or a reference note in the protocol, should follow visit windows of ±3 days. There will be no visit window allowed in the ramp-up period after Visit 1 (Week 1).

[b] The interim visit is to take place on the day of infusion (or within 3 days prior to infusion will be acceptable due to scheduling availability) during Week 16 (±1 infusion visit).

[c] The early termination visit is to be conducted for subjects who are being prematurely discontinued from the SC treatment period and will not undergo IV treatment.

[d] Samples must be collected prior to IP administration (ie, prior to initiation of rHuPH20 administration) on the day of infusion (or prior to IP administration on the first day of dosing for an infusion dose that is to be administered over multiple days).

[e] To be collected 7 (±2) days (ie, 5 – 9 days) after the subject's Week 8 infusion visit, the first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[f] The hematology panel will consist of complete blood count (Hgb, Hct, erythrocytes [ie, RBC count]), leukocytes [ie, WBC count] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), ANC, absolute lymphocyte count, and platelet count, a reticulocyte count to the hemolytic panel to be run in the event of a 1 g/dL or more drop in hemoglobin from baseline.

[g] In addition to the predose sample (see footnote d), sample for hematology is also to be collected 72 (±24) h (ie, 48 – 96 h) after the subject's Week 8 infusion, the first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20).

[h] The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, ALP, GGT LDH, CPK, BUN, creatinine, and glucose. At any time when the LDH test result is 2× ULN or greater, LDH isoenzymes panel will be performed.

[i] For subjects with clinically diagnosed diabetes mellitus only.

[j] The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin. The lab results obtained predose during the Epoch 1 Week 1 (E1W1) visit will serve as the baseline values. In case of absence of E1W1 result for any reason screening Hgb result serve as the baseline Hgb value. Hgb and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of ≥ 1 g/dL compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 h; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at the latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia.

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[k] To be collected prior to the subject's last pre-randomization IGIV infusion.

[l] At any time during the course of the study. For those subjects who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications (see Table 12-1) will be asked to return to the study site as soon as possible to undergo an additional panel of testing outlined in Table 12-2.

[m] Urinalysis includes color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

[n] For female subjects of childbearing potential only. Urine pregnancy test will be performed, unless serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

Table 21-8. Clinical Laboratory Assessments – IV Treatment Period (Epoch 2)

Study Period	IV Treatment Period (6 Months) IV Infusions Every 3 Weeks (±3 Days)										ET[c]
Study Visits	**Pre-IV BL/ E2W1[a,d]**	**E2W3[d]**	**E2W4**	**E2W7**	**E2W10**	**E2W13/ E2Int[b,d]**	**E2W16**	**E2W19**	**E2W22**	**E2W25/ EOE2T[d]**	
Hematology Panel[e]	X	X				**X**				X	X
Clinical Chemistry Panel[f]	X					X				X	X
HbA1C[g]	X					X				X	X
Serum iron, ferritin, and TIBC										X	X
Hemolytic Panel[h]	← X (as applicable) →										
Serum IgG	X					X				X	X
Anti-rHuPH20 Antibodies – Binding Antibodies	X					X				X	X
Anti-rHuPH20 Antibodies – Neutralizing Antibodies	X					X				X	X
Immunogenicity Panel[i]	← X (as applicable) →										
Plasma/Serum Retention Samples	X					X				X	X
Pregnancy Test[j]										X	X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CIC = Circulating immune complex; CPK = creatine phosphokinase; E2Int = Epoch 2 interim visit; EOE2T = End-of-Epoch 2 treatment visit; ET = Early termination visit; E2W= Epoch 2 week number; GGT = gamma-glutamyl transferase; HbA1C = Hemoglobin A1C; Hct = hematocrit; IgG = Immunoglobulin G; IV = Intravenous; LDH = lactate dehydrogenase; Pre-IV BL = Pre-intravenous treatment baseline visit; RBC = red blood cell; rHuPH20 = Recombinant human hyaluronidase; TIBC = Total iron binding capacity; ULN = upper limit of normal; WBC = white blood cell.

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[a] For subjects who meet the definition of relapse during the SC treatment period and are to receive IV treatment, the pre-IV treatment baseline assessments will also serve as the end-of-SC treatment assessments. The pre-IV treatment baseline assessments can be conducted on the same day of the first IGIV 10% infusion; however, all samples must be collected prior to infusion (or prior to the first day of dosing for an infusion that is to be administered over multiple consecutive days).
In case the first INCAT evaluation indicating relapse (during Epoch 1) occurs during a study visit and not at an unscheduled visit, and the second (confirmatory) INCAT evaluation (Pre-IV BL Epoch 2) is performed on the same day, and in addition the Investigator's preference is to administer the rescue medication (E2W1) also on the same day—repetition of same lab assessments should be avoided (eg, combining E1W15 at 2 weekly dose regimen, E1W14 at 3 weekly dose regimen, or E1W16 at 4 weekly dose regimen together with Pre-IV BL Epoch 2 and E2W1 all on the same day). In this case laboratory assessments of Epoch 1 study visit are the same as the ones in E2W1 before IP. These laboratory assessments should then be performed only once for subject's safety regarding blood volume taken.
When administration of the rescue medication (E2W1) does not occur on same day as second (confirmatory) INCAT evaluation (Pre-IV BL Epoch 2), then Table 21-4 all study procedures and assessments should be performed at 'Pre-IV BL' Epoch 2 day and Table 21-8, all clinical laboratory assessments should be performed (before infusion) at 'E2W1' visit day.

[b] The Epoch 2 interim visit is to take place during Week 13 (±1 infusion visit).

[c] The early termination (ET) visit is to be conducted for subjects who are being prematurely discontinued from the IV treatment period.

[d] Samples must be collected prior to infusion. Samples must be collected prior to infusion on the day of infusion (or prior to infusion on the first day of dosing for an infusion dose that is to be administered over multiple days).

[e] The hematology panel will consist of complete blood count (Hgb, Hct, erythrocytes [ie, RBC count]), leukocytes [ie, WBC count] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), ANC, absolute lymphocyte count, and platelet count.

[f] The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, ALP, GGT, LDH, CPK, BUN, creatinine, and glucose. At any time when the LDH test result is 2× ULN or greater, LDH isoenzymes panel will be performed.

[g] For subjects with clinically diagnosed diabetes mellitus only.

[h] The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (antibody elution to be performed if direct Coombs test is positive), reticulocyte count, as well as urine hemosiderin. The lab results obtained from the Epoch 1 Week 1 (E1W1) will serve as the baseline values. In case of absence of E1W1 result for any reason screening Hgb result serve as the baseline Hgb value. Hgb and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of 1 ≥ g/dL compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 h; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible, but at the next scheduled visit, at the latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia. Epoch 2 E2W3 is required for those subjects taking Gamanx-C.

[i] At any time during the course of the study. For those subjects who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications (see Table 12-1) will be asked to return to the study site as soon as possible to undergo an additional panel of testing outlined in Table 12-2.

[j] For female subjects of childbearing potential only. Urine pregnancy test will be performed, unless serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

21.4 Toxicity Grading Scale for Laboratory Values

Table 21-9. Grading of Laboratory Parameters

Analyte	Direction	WNL is Grade 0	No Grade 1	Units	Grade 0[a]		Grade 1[a]		Grade 2[a]		Grade 3[a]		Grade 4[a]		Source
					Low	High	Low	High	Low	High	Low	High	Low	High	
ALP	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
ALT	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
AST	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
LDH	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	N/A
BUN	Increase	NO	NO	ULN	0.0	1.4	1.5	2.5	2.6	5.0	5.1	10	10.1	.	ECOG
Hemoglobin	Decrease	YES	NO	g/dL	.	.	.	10.0	8.0	9.9	6.5	7.9	0.0	6.4	ECOG
Lymphocytes	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Neutrophils	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Platelet Count	Decrease	YES	NO	x10^3/uL	.	.	.	75.0	50.0	74.9	25	49.9	0.0	24.9	ECOG
Potassium	Decrease	NO	NO	mmol/L	3.5	.	3.0	3.4	2.5	2.9	2.0	2.4	0.0	1.9	WHO
Potassium	Increase	NO	NO	mmol/L	0.0	5.5	5.6	6.0	6.1	6.5	6.6	7.0	7.1	.	WHO
Serum Creatinine	Increase	YES	NO	ULN	.	.	.	1.4	1.5	3.0	3.1	6.0	6.1	.	ECOG
Sodium	Decrease	NO	NO	mmol/L	136	.	130	135	123	129	116	122	0.0	115	WHO
Sodium	Increase	NO	NO	mmol/L	0.0	145	146	150	151	157	158	165	166	.	WHO
Serum Total Bilirubin	Increase	YES	YES	ULN	.	.	.	.	.	1.4	1.5	3.0	3.1	.	ECOG
WBC	Decrease	NO	NO	x10^3/uL	4.0	.	3.0	3.9	2.0	2.9	1.0	1.9	0.0	0.9	ECOG

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; BUN = blood urea nitrogen; ULN = upper limit of normal; ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization; WNL = within normal limits.

[a] The toxicity scale is defined as: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening (Food and Drug Administration, 2008). Grading scale criteria taken from ECOG (Eastern Cooperative Oncology Group, 2006) and WHO (World Health Organization, 2003) guidelines, with the exception of LDH that use the same thresholds as defined for ALT and AST.

21.5 Contraceptive Methods for Female Subjects of Childbearing Potential

No clinical studies have been conducted with GAMMAGARD LIQUID/KIOVIG or HYQVIA/HyQvia in pregnant women.

Animal reproduction studies have not been conducted with GAMMAGARD LIQUID/KIOVIG (IGI 10%) and IGI 10% component of HYQVIA/HyQvia. It is also not known whether IGI 10% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, clinical experience with immunoglobulins suggests that no harmful effects of IGI 10% on fertility are to be expected.

Development and reproductive toxicology studies have been conducted with recombinant human hyaluronidase in mice and rabbits. No adverse effects on pregnancy were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to recombinant human hyaluronidase were transferred to offspring in utero. The effects of antibodies to the rHuPH20 component of HYQVIA on the human embryo or on human fetal development are unknown.

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration of IP. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15) (Heads of Medicines Agencies and Clinical Trial Facilitation Group (CTFG), 2014), birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[viii]
- Intrauterine device (IUD)[viii]

[viii] Contraception methods that are considered to have low user dependency.

- Intrauterine hormone-releasing system (IUS)[viii]
- Bilateral tubal occlusion[viii]
- Vasectomised partner(s)[viii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

22. SUMMARY OF CHANGES

Protocol 161403: Amendment 6 2021 MAY 20

Replaces: Amendment 5: 2019 MAY 10

In this section, changes other than grammatical, formatting and/or administrative changes from the previous version of the protocol (dated 2019 MAY 10) are described and their rationales are given.

1. Synopsis, Section 8.3
   Description of Change: Maximum overall duration of the study was changed from 68 months to 72 months and enrollment period was changed from 61 months to 64 months.
   Purpose of Change: To reflect changes made in response to sponsor decision for ending the study enrollment.

2. Synopsis, Sections 7.2.3, 13
   Description of Change: The following tertiary objectives were added for Epoch 1:
   - To evaluate improvement in functional impact on everyday tasks as measured by a pre-specificed subscore of R-ODS
   - To assess the effect of HYQVIA/HyQvia on the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.
   Purpose of Change: to better assess treatment benefit in patients.

3. Synopsis, Section 7.3.3
   Description of Change: The following tertiary objective was added for Epoch 2:
   - To assess the effect of GAMMAGARD LIQUID/KIOVIG on the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.
   Purpose of Change: To better assess treatment effects.

4. Synopsis [study design], Sections 8.6, 14.1.1, 14.2.1.2
   Description of Change: Details related to stopping randomization on Epoch 1.
   Purpose of Change: Randomization to Epoch 1 will be stopped by the sponsor prior to achieving the original planned total of 174 randomized subjects. Sample size assumptions revised based on more recent scientific literature.

5. Synopsis [study design (Epoch 1: SC Treatment Period)]
   Description of Change: Addition of text added to collect trough serum IgG levels and additional patient reported outcome (PRO) measures.
   Purpose of Change: Updates.

6. Synopsis [study design (Epoch 1: SC Treatment Period)], Section 8
   Description of Change: Details related to IP administration at site, infusion related data to be recorded and subject/caregiver's training were added.
   Purpose of Change: Updates.

7. Synopsis, Section 8.4.1.3.1
   Description of Change: Following tertiary outcome measures were added for Epoch 1:
   - Change from pre-SC treatment baseline in functional impact on everyday tasks as measured by R-ODS sub-components
   - Change from pre-screen baseline in the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.

   Purpose of Change: Better assess treatment benefits for patients.

8. Synopsis, Section 8.4.2.3.1
   Description of Change: Following tertiary outcome measure was added for Epoch 2:
   - Change from pre-IV baseline in the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies.

   Purpose of Change: Better assess treatment effects.

9. Synopsis (Mode of administration), Section 8.7.3
   Description of Change: Details related to the mode of administration of rHuPH20, IGI, 10% and placebo treatment were revised to specify the use of peristalic pump. Duration to be maintained between rHuPH20 and 0.25% albumin placebo infusions was specified. Region specific details related to the use of peristalic pump were added. Reference to Site Infusion Manual was added to check recommended infusion rates.
   Purpose of Change: Change made due to the pump recall in the US of the body guard.

10. Synopsis, Section 8.7.3.2, Section 8.7.4.2
    Description of Change: Specifications of infusion pump (ie peristalic variable rate infusion pump) to be used for IV infusion of GAMMAGARD LIQUID/KIOVIG/ GAMUNEX®-C in Epoch 2 were added. Maximum infusion rate for Body Guard pump was specified.
    Purpose of Change: Change made due to the pump recall in the US of the body guard.

11. Synopsis, Section 8
    Description of Change: Details related to the mode of administration of placebo treatment (0.25% human albumin in LR solution and rHuPH20) were revised to specify the use of peristalic infusion pump, region specific details related to the peristalic pump and duration between rHuPH20 and 0.25% albumin placebo solution infusions.
    Purpose of Change: Change made due to the pump recall in the US of the body guard. Synopsis (Statistical Analysis)

12. Synopsis (planned statistical analysis), Section 14.1.4.3
    Description of Change: Details related to statistical analysis of R-ODS score and demyelinating abnormalities based on electrodiagnostic studies (tertiary outcome measures) were added.
    Purpose of Change: To document additional endpoints.

13. Synopsis
    Description of Change: The following footnote was removed:
    At high infusion rates above 750 mL/h, the pump occlusion alarm may be activated due to high back pressure, stopping the pump. If this occurs, then reduce the infusion rate to allow proper pump function.
    Purpose of Change: Update.

14. Section 5. List of Abbreviations.
    Description of Change: New abbreviations added.
    Purpose of Change: Updates.

15. Section 6
    Description of Change: Literature references describing therapeutic efficacy and safety of IGSC treatment and impact of COVID-19 pandemic on ongoing drug-development efforts were added.
    Purpose of Change: To reflect changes made in response to the COVID-19 pandemic.

16. Section 8.5.2 Unblinding
    Description of Change: Language updated to reflect updated study procedure.
    Purpose of Change: Update.

17. Sections 8.6, 8.6.1 Study Stopping Rules
    Description of Change: Language updated to reflect new stopping rule changes.
    Purpose of Change: Stopping the study due to the impact caused by COVID-19 pandemic.

18. Section 8.6.2 Trial Integrity
    Description of Change: This is a new section added to the amendment # 6.
    Purpose of Change: To clarify that despite study stopping before achieving originally planned total number of subjects, trial integrity is maintained.

19. Section 10.9
    Description of Change: Added a new section 'Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 Related Factor' to address possible impact of COVID-19 pandemic on operational details such as site visits for subjects/study staff, IP administration at home, laboratory sample collection at home, remote visits via virtual communication etc.
    Purpose of Change: to reflect changes made in response to the COVID-19 pandemic.

20. Section 11.2
    Description of Change: Specified that an alternative scoring algorithm would be applied to R-ODS (in addition to the full score) to measure the patient centric benefit of HyQvia.
    Purpose of Change: introduce patient-centric endpoint.

21. Section 13.1
    Description of Change: Added a new section to describe Electrodiagnostic studies
    Purpose of Change: introduce new endpoint to further assess treatment effect.

22. Section 14.1.3
    Description of Change: Clarified that rules for handling missing data will be described in the SAP.
    Purpose of Change: Update.

23. Synopsis (Analysis of Primary Outcome Measure), Section 14.1.4.1
    Description of Change: Added a sensitivity analysis with alternative relapse definition due to expected missed confirmation visits during Covid-19 pandemic.
    Purpose of change: Update

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Protocol amendment #6: 161403-protocol-amend-6-2021may20
Amendment to amendment #5: 2019 MAY 10; 23 items

1. Synopsis, Section 8.3 Description of Change: Maximum overall duration of the study was changed from 68 months to 72 months and enrollment period was changed from 61 months to 64 months. Purpose of Change: To reflect changes made in response to sponsor decision for ending the study enrollment.

2. Synopsis, Sections 7.2.3, 13 Description of Change: The following tertiary objectives were added for Epoch 1: - To evaluate improvement in functional impact on everyday tasks as measured by a pre-specificed subscore of R-ODS - To assess the effect of HYQVIA/HyQvia on the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies. Purpose of Change: to better assess treatment benefit in patients.

3. Synopsis, Section 7.3.3 Description of Change: The following tertiary objective was added for Epoch 2: - To assess the effect of GAMMAGARD LIQUID/KIOVIG on the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies. Purpose of Change: To better assess treatment effects.

4. Synopsis [study design], Sections 8.6, 14.1.1, 14.2.1.2 Description of Change: Details related to stopping randomization on Epoch 1. Purpose of Change: Randomization to Epoch 1 will be stopped by the sponsor prior to achieving the original planned total of 174 randomized subjects. Sample size assumptions revised based on more recent scientific literature.

5. Synopsis [study design (Epoch 1: SC Treatment Period)] Description of Change: Addition of text added to collect trough serum IgG levels and additional patient reported outcome (PRO) measures. Purpose of Change: Updates.

6. Synopsis [study design (Epoch 1: SC Treatment Period)], Section 8 Description of Change: Details related to IP administration at site, infusion related data to be recorded and subject/caregiver's training were added. Purpose of Change: Updates.

7. Synopsis, Section 8.4.1.3.1 Description of Change: Following tertiary outcome measures were added for Epoch 1: - Change from pre-SC treatment baseline in functional impact on everyday tasks as measured by R-ODS sub-components - Change from pre-screen baseline in the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies. Purpose of Change: Better assess treatment benefits for patients.

8. Synopsis, Section 8.4.2.3.1 Description of Change: Following tertiary outcome measure was added for Epoch 2: - Change from pre-IV baseline in the total number or appearance of new demyelinating abnormalities on electrodiagnostic studies. Purpose of Change: Better assess treatment effects.

9. Synopsis (Mode of administration), Section 8.7.3 Description of Change: Details related to the mode of administration of rHuPH20, IGI, 10% and placebo treatment were revised to specify the use of peristalic pump. Duration to be maintained between rHuPH20 and 0.25% albumin placebo infusions was specified. Region specific details related to the use of peristalic pump were added. Reference to Site Infusion Manual was added to check recommended infusion rates. Purpose of Change: Change made due to the pump recall in the US of the body guard. Synopsis, Section 8.7.3.2, Section 8.7.4.2 Description of Change: Specifications of infusion pump (ie peristalic variable rate infusion pump) to be used for IV infusion of GAMMAGARD LIQUID/KIOVIG/ GAMUNEX®-C in Epoch 2 were added. Maximum infusion rate for Body Guard pump was specified. Purpose of Change: Change made due to the pump recall in the US of the body guard.

11. Synopsis, Section 8 Description of Change: Details related to the mode of administration of placebo treatment (0.25% human albumin in LR solution and rHuPH20) were revised to specify the use of peristalic infusion pump, region specific details related to the peristalic pump and duration between rHuPH20 and 0.25% albumin placebo solution infusions. Purpose of Change: Change made due to the pump recall in the US of the body guard. Synopsis (Statistical Analysis)

12. Synopsis (planned statistical analysis), Section 14.1.4.3 Description of Change: Details related to statistical analysis of R-ODS score and demyelinating abnormalities based on electrodiagnostic studies (tertiary outcome measures) were added. Purpose of Change: To document additional endpoints.

13. Synopsis Description of Change: The following footnote was removed: At high infusion rates above 750 mL/h, the pump occlusion alarm may be activated due to high back pressure, stopping the pump. If this occurs, then reduce the infusion rate to allow proper pump function. Purpose of Change: Update.

14. Section 5. List of Abbreviations. Description of Change: New abbreviations added. Purpose of Change: Updates.

15. Section 6 Description of Change: Literature references describing therapeutic efficacy and safety of IGSC treatment and impact of COVID-19 pandemic on ongoing drug development efforts were added. Purpose of Change: To reflect changes made in response to the COVID-19 pandemic.

16. Section 8.5.2 Unblinding Description of Change: Language updated to reflect updated study procedure. Purpose of Change: Update.

17. Sections 8.6, 8.6.1 Study Stopping Rules Description of Change: Language updated to reflect new stopping rule changes. Purpose of Change: Stopping the study due to the impact caused by COVID-19 pandemic.

18. Section 8.6.2 Trial Integrity Description of Change: This is a new section added to the amendment # 6. Purpose of Change: To clarify that despite study stopping before achieving originally planned total number of subjects, trial integrity is maintained.

19. Section 10.9 Description of Change: Added a new section 'Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 Related Factor' to address possible impact of COVID-19 pandemic on operational details such as site visits for subjects/study staff, IP administration at home, laboratory sample collection at home, remote visits via virtual communication etc. Purpose of Change: to reflect changes made in response to the COVID-19 pandemic.

20. Section 11.2 Description of Change: Specified that an alternative scoring algorithm would be applied to R-ODS (in addition to the full score) to measure the patient centric benefit of HyQvia. Purpose of Change: introduce patient-centric endpoint.

21. Section 13.1 Description of Change: Added a new section to describe Electrodiagnostic studies Purpose of Change: introduce new endpoint to further assess treatment effect.

22. Section 14.1.3 Description of Change: Clarified that rules for handling missing data will be described in the SAP. Purpose of Change: Update.

23. Synopsis (Analysis of Primary Outcome Measure), Section 14.1.4.1 Description of Change: Added a sensitivity analysis with alternative relapse definition due to expected missed confirmation visits during Covid-19 pandemic. Purpose of change: Update

Protocol amendment #5: 161403-protocol-amend-5-2019may10
Amendment to amendment #4: 2019 FEB 13; 12 items

1. Synopsis and throughout the document Description of Change: References to the electronic diary were changed to DIARYpro after an initial explanation. Purpose of Change: For clarity.

2. Synopsis, Section 9.2, Section 10.3.1, Section 10.5 Description of Change: Exclusion criterion 19 was adapted to preclude use of any corticosteroids within 8 weeks prior to screening, regardless of indication. [redacted]

3. Synopsis, Section 14.3.2 Description of Change: The following outcome measure was added: In addition, potential correlation 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. [redacted]

4. Synopsis, Section 14.1.4 Description of Change: The following outcome measure was added: In addition, potential correlation between serum IgG trough levels on or after day 120 or at the time of CIDP symptom relapse and relapse status (relapse, no relapse) will be assessed as an exploratory analysis. This change was also reflected in Section 12.7.10. [redacted]

5. List of Abbreviations Description of Change: DIARYpro was added, and eDiary was added. Purpose of Change: For increased clarity and better readability of the protocol.

6. Section 6.6 Description of Change: It was clarified that the study will be conducted in accordance with EU Directives (2001/20/EC; 2005/28/EC). Purpose of Change: To correct the guideline currently in place.

7. Section 8.8 Description of Change: All data entered in to the CRF should be able to be verified by a corresponding source document. Purpose of Change: Clarification requested by sites.

8. Section 11.1, Section 11.4 Description of Change: It was clarified in the text that the same individual should administer the Hand Grip test as who administers the INCAT and the MRC, for consistency. Purpose of Change: To improve intructions to the Investigators.

9. Synopsis, Section 12.1.2 Description of Change: It was added that: Infusion site swelling following SC infusion of IGI, 10% or 0.25% albumin placebo solution that is reported by subjects will be captured and reported as adverse events. [redacted]

10. Section 14.1.4.2.2 Description of Change: Following text language has been included: In addition, the incidence (number of percentage of subjects) of local infusion site reactions will be provided by geographic region (US, non-US) and overall. Infusion site swelling following SC infusion of IGI, 10% or 0.25% albumin placebo solution that is reported by subjects will be captured and reported as adverse events. [redacted]

11. Section 21.2 Description of Change: Xs were removed from Body Mass Index collections at three time points: E1W26ET/E1W27ET/E1W28ET visits. Purpose of Change: To correct a previous error in the protocol.

12. Section 21.2, Section 21.3 Description of Change: The footnote “g” was corrected per Protocol Amendment 4 (2019 FEB 13). Purpose of Change: This change was inadvertently not noted in the Summary of Changes in Protocol Amendment 4.

Protocol amendment #4: 161403-protocol-amend-4-2019feb13
Amendment to amendment #3: 161403-protocol-amend-3-2018jan31 (17 items)

1. Synopsis, Section 8.3 Description of Change: Overall duration of the study has been extended to 68 months and enrollment period has been extended to 61 months. Purpose of Change: To accomplish subject recruitment.

2. Synopsis Description of Change: Reference to GAMUNEX® -C Prescribing Instruction (for storage condition) has been included in the Synopsis. Purpose of Change: To provide clarity on the storage condition of GAMUNEX® -C for US sites who might be using GAMUNEX® -C in Epoch 2.

3. Synopsis, Section 8.7.4.2 Description of Change: The mode of administration of GAMUNEX-C – this has been amended. Purpose of Change: To make it in line with the Prescribing Instruction.

4. List of Abbreviations Description of Change: Moved the abbreviation “IWRS” up to match the alphabetical order. Removed duplicate entry of the abbreviation “Lactate Ringers”. Removed “CFR” from the list as it was used only once in the document. Additionally, usage of definitions or abbreviations is updated throughout the document. Purpose of Change: For better readability of the protocol.

5. Inclusion criteria Description of Change: The cross-reference to section 21.4 has been updated to correct section 21.5, in inclusion criterion#5. Purpose of Change: The cross-reference to section 21.4 in inclusion criterion #5 was incorrect in Protocol amendment # 3.

6. Synopsis, Section 9.2 Exclusion Criteria Description of Change: The phrase “multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)” has been removed from the hereditary demyelinating neuropathies in Exclusion criterion# 2a, and included as a separate exclusion criterion#2c. Purpose of Change: To improve intructions to the Investigators for clearer directions on eligibility.

7. Synopsis, Section 9.2 Exclusion Criteria Description of Change: An exclusion criterion for “thrombophilic disorders” has been added as exclusion criterion#25, in the synopsis and section 9.2 of the protocol. Purpose of Change: To improve intructions to the Investigator for clearer directions on eligibility.

8. Section 8.5.2 Unblinding Description of Change: Following text language has been included “Access to unblinding data during study conduct will be controlled to ensure that the scientific integrity and regulatory utility of the study are appropriately maintained and protected. Unblinding for Epoch 1 Final Analysis:At the completion of Epoch 1, all Epoch 1 data will be locked, treatment assignment will be unblinded, and all data will be analyzed as preplanned in the study Statis tical Analysis Plan (SAP). The analysis, described in Section 14.3.1 of this protocol, will be considered the final analysis of Epoch 1 data. Unblinding for Interim Safety Analysis: For the interim safety analysis described in Section 14.3.2, treatment assignment will be unblinded and all data will be analyzed as preplanned in the study SAP; similarly for any other interim analysis. Unblinding for Other Purposes during Study Conduct:Treatment assignment is not to be revealed before the study is completed/terminated, except for purposes of the Epoch 1 final analysis and the interim safety analysis, as noted above, and in emergency cases when unblinding is necessary for the clinical management of an SAE. In such events, the investigator may unblind via the integrated web

response system (IWRS) at any time (ie, 24 hours per day, 7 days per week) to obtain the treatment assignment. Details of unblinding procedures will be provided to study sites." Purpose of Change:Addition of unblinding language from the Amendment 2 (dated 2016 APR 22), and provide additional information.

9. Section 8.7.1.3 Placebo solution Description of Change: Storage temperature of Lactated Ringers solution has been included. Purpose of Change: To improve the clarity and readability of the protocol.

10. Section 8.7.3.1 Epoch 1 Description of Change: Language was updated to include "for both rHuPH20 and IGI,10% /placebo solution". Purpose of change: To improve clarity in the protocol.

11. Section 8.7.4.1 Epoch 1 Description of Change: Minor corrections were made, such as the spelling of "albumin" was corrected, and "rHu" was added before PH20 for clarity. Purpose of Change: To improve clarity in the protocol.

12. Section 6.5.1, Section 9.3, Section 12.1.1.1, Section 12.1.2 Description of Change:Language pertaining to pregnancy has been removed, and also the followup period was updated to 1 year postdelivery instead of 2 years postdelivery. Additional clarification added in section 12.1.1.1. Purpose of Change: Enrollment to Pregnancy registry has been closed.

13. Section 12.7.1 Hematology and Clinical Chemistry Description of Change: the following text was removed: "In the event that no safety concerns are raised, Two weeks following the first infusion, at the time of the first full dose, approximately 72 h, and 7 and 14 days following the first full dose in Epoch 1 and E2W3 in Epoch 2 sampling time points may be waived or modified upon recommendation by the DMC and notification by the sponsor/sponsor's representative". New text added: "Epoch 2 E2W3 is required for those subjects taking Gamunex-C". [redacted]

14. Section 12.7.2 Hemolytic Panel Description of Change: Following paragraph has been moved up to the beginning of the Hemolytic panel. "The first hemolytic panel will be measured at Epoch 1 Week 1 (E1W1). The Hgb result obtained from the E1W1 will serve as the baseline Hgb value for the duration of the study. In case of absence of E1W1 result for any reason screening Hgb result serve as the baseline Hgb value.Hemoglobin and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests, if there is a reduction in Hgb of ≥ 1 g/dL compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 hours.; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible but at the next scheduled visit, at latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia. Any LDH test result of 2 × ULN or greater will trigger analysis of the sample for LDH isoenzymes." Purpose of Change: to improve the clarity and readability of the protocol.

15. Section 12.7.2 Hemolytic Panel Description of Change: Following paragraph has been added to this section. "It is not necessary to repeat the hemolytic panel if the drop of ≥1 g/dL Hgb remains constant 72 hours after the first full dose of investigational product or after an unscheduled visit blood draw, unless it drops further. It is recommended that the investigator uses good medical judgement in assessing subjects with an unexplained decrease in serum Hgb as other medical conditions beside hemolysis can cause this, and therefore may require additional investigations." Purpose of Change: To improve the clarity of the protocol and and reflect the same instructions provided to sites in previous, 'memos' to sites.

16. Section 21 Schedule of Assessments Description of Change: Footnotes for R-ODS and HRU in Table 21-1 through Table 21-3 were updated to state “The data entered by subjects for HRU during screening in the DIARYpro will not be used for analysis”. Additionally, the relevant texts for R-ODS and HRU has been updated throughout the document to reflect the same clarification. Purpose of Change: To improve the assessments and clarity of the protocol.

17. Section 21 Schedule of Assessments Description of Change: INCAT disability score frequency of assessment was changed to approximately every 4 weeks in the Schedule of Study Procedures and Assessments Tables 21-1, Table 21-2 and Table 21-3. Corresponding footnote in each of the tables was also updated accordingly to reflect the change. [redacted]

Protocol amendment #3: 161403-protocol-amend-3-2018jan31
Amendment to amendment #2: 161403-protocol-amend-2-2016Apr22 (68 items)

1. Throughout the document Description of Change: Minor editorial/grammatical and/or administrative changes that do not substantively affect the study conduct or patient safety have been made. Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Section 1 Study Personnel Description of Change: Authorized representative was updated. Purpose for Change: Change in personnel.

3. Synopsis, 8.3 Duration of Study Periods and Subject Participation Description of Change: New estimates of study completion and duration were added. Purpose for Change: Updated the estimates to be in line with the extended enrollment period.

4. Synopsis, 6.3 Population To Be Studied, 8.1 Brief Summary, 9.1 Inclusion Criteria, 10.3.1 Screening and Baseline Period, 10.3.1.1 Rescreening Description of Change: The description of the stable dosing regimen of IGIV therapy was updated from 3 months to 12 weeks. Purpose for Change: For consistency in reporting times in weeks and for greater accuracy.

5. Synopsis; 9.1 Inclusion Criteria Description of Change: Removed the time limit on INCAT scores and replaced it with documentation in medical records. Purpose for Change: The exclusion of individuals whose last INCAT score was documented 24 months prior is arbitrary and excludes potential study participants who might otherwise qualify as long as they meet the other inclusion/exclusion criteria.

6. Synopsis; 9.1 Inclusion Criteria, 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: Definition of stability was added to the inclusion criteria. Purpose for Change: This was added to make the definition of stability more easily available for the Investigator.

7. Synopsis, 9.1 Inclusion Criteria Description of Change: Detail of INCAT scoring was added to Inclusion 4. Purpose for Change: To improve instructions to the Investigator for clearer directions on eligibility.

8. Synopsis, 9.2 Exclusion Criteria Description of Change: “MADSAM” was added to the list of hereditary demyelinating neuropathies. Purpose for Change: Added for clarity for the investigators.

9. Synopsis; 14.3 Planned Interim Safety Analysis of the Study Description of Change: In addition to the previously planned interim safety analysis, a formal IA of all Epoch 1 data was added. Details for this additional IA were added. Purpose for Change: The previous IA described was for safety, the additional IA is for submission purposes.

10. Synopsis Description of Change: Minor edits were made to the safety outcome measures 8, and 9 to align with the protocol body. Purpose for Change: To align with the protocol body text.

11. Synopsis; 8.4.1.2.2 Safety, 8.4.2.2.1 Safety Description of Change: A note was added to safety outcome measures "Note: Adverse events in this section refer to treatment-emergent AEs, if not specified." Purpose for Change: To clarify the type of AEs that will be evaluated.

12. Synopsis, 8.7.4.2 Epoch 2 Description of Change: Maintenance infusions were specified for GAMMAGARD LIQUID/KIOVIG and GAMUNEX® -C. A maximum dose was also added. Purpose for Change: The mode of administration section for GAMMAGARD LIQUID/KIOVIG and GAMUNEX® -C was updated to more clearly state the timing of the maintenance infusions. The maximum dose was added to ensure the safety of the subjects and align with clinical practice.

13. Synopsis Description of Change: The timing for subsequent doses for GAMMAGARD was updated from 1 to 2 days, to 2 to 5 days. Purpose for Change: To be more accurate to how investigators will dose.

14. Synopsis, 8.7.4.2 Epoch 2 Description of Change: The clause "every 3 weeks" was added to the mode of administration section on GAMMAGARD LIQUID/KIOVIG. Purpose for Change: To emphasize that this was a fixed dose schedule.

15. Synopsis, 14.1.2 Datasets and Analysis Cohorts Description of Change: The definition of PP analysis set was updated. Purpose for Change: For consistency within the company and between the final and interim analyses.

16. 6 Background Information Description of Change: A new reference was added to the sentence summarizing current publications on CIDP. Purpose for Change: A relevant recent publication was published and was felt useful to add.

17. 6.1.1.1.1 Recombinant Human Hyaluronidase (rHuPH20) Description of Change: Additional half-life information was added for rHuPH20. Purpose for Change: To support the additional text added on reporting and assessing antibody titer results.

18. 6.1.1.2 Placebo Control Description of Change: The following parenthetical was added after Lactated Ringer's solution "(also known as Ringer's Lactate or Hartmann's solution or Compound Sodium Lactate Solution for Infusion in some participating countries)". Purpose for Change: To clarify the possible names of the placebo control in various countries.

19. 6.2 Clinical Condition/Indication Description of Change: "Relapse of" was added to the clinical condition in Epoch 1. Purpose for Change: To align with the synopsis.

20. 6.5.2 GAMMAGARD LIQUID/KIOVIG Description of Change: The term pharyngolaryngeal pain was updated to laryngeal pain. Purpose for Change: To align with the current MedDRA preferred term.

21. 6.6 Compliance Statement Description of Change: "The Declaration of Helsinki (October 2013)" was removed. Purpose for Change: To align with the newest template language.

22. 8.2 Overall Study Design, Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: A reference point was added for Week 1. "Week 1 should be

calculated from the last day of dosing for an infusion dose that is to be administered over multiple days." Purpose for Change: To ensure consistency from all sites on determining Week 1.

23. 8.5.1 Blinding Description of Change: Specifications that Epoch 1 is blinded and Epoch 2 is open label were added, as well as a definition of completion was added for Epoch 1 subjects. Purpose for Change: To align with the changes in unblinding added into Section 8.5.2.

24. 8.5.2 Unblinding Description of Change: Language was updated from the standard unblinding language to describe that treatment assignments will be unblinded after Epoch 1. Purpose for Change: The study will be unblinded after the completion of Epoch 1.

25. 8.7.1.3 Placebo Solution Description of Change: Additional text was added describing the placebo packaging, including the coloration and dilution. Purpose for Change: Label language was slightly different between the US and Canada compared to the rest of world. This additional text was to help clarify for the sites based on these differences.

26. 10.3.1 Screening and Baseline Period Description of Change: "Product name" was added to the list of information captured for pre-randomization IGIV infusions. Purpose for Change: This information is pertinent for the safety group to assess and report on SAEs.

27. 10.3.1 Screening and Baseline Period Description of Change: Dosing interval was increased from 5 to 7 days. Purpose for Change: To allow for greater flexibility in the scheduling of subject visits. The change was not related to any safety or efficacy concerns.

28. 10.3.3.1 SC Infusion Visits, 10.3.4.2 IV Infusion Visits Description of Change: Clarification was added to the window around the telephone follow-up visits. Purpose for Change: To align with the table footnotes.

29. 10.6 Subject Diary and Patient Reported Outcomes Description of Change: Clarification was added that the diary will be the source records for patient-reported data. Purpose for Change: To add clarification for data management as there may be other sources for infusion data.

30. 10.6 Subject Diary and Patient Reported Outcomes Description of Change: The following sentence was removed "After a reconciliation against eCRF, the data will be imported into the study database." Purpose for Change: The study database will not be reconciled against the diary, information will be reviewed by the investigator at various visits.

31. 10.7 Subject Completion/Discontinuation Description of Change: Death was added as a reason for discontinuation. Purpose for Change: To clarify for the data management for field options in the eCRF.

32. 11.2 Rasch-Built Overall Disability Scale (R-ODS) Description of Change: Additional information on eDiaries at screening was added. Purpose for Change: To align with table footnotes.

33. 12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR) Description of Change: Added additional information on the requirements on reporting SUSARs. "The sponsor will ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or lifethreatening, as well as all other serious unexpected ARs, are reported to regulatory authorities within the timeframes mandated by the applicable regulations (eg, ICH Guideline E2A and the European Clinical Trial Directive (2001/20/EC). The sponsor will comply with applicable laws/requirements for reporting SUSARs and all other SAEs to the ECs and investigators." [redacted]

34. 12.1.2 Assessment of Adverse Events Description of Change: The qualifier of 30 days was added for SAE reporting after study completion using the SAE Report Form. Additional text was added regarding the use of CIOMS forms or MedWatch forms after the 30 days from study completion. Purpose for Change: Clarification was added to the timing of SAE reporting.

35. 12.7.1 Hematology and Clinical Chemistry, Table 21-1, Table 21-2, Table 21-3, Table 21-4, Table 21-5, Table 21-6, Table 21-7, and Table 21-8 Description of Change: A window was added for Hgb and hematocrit, and specifications for when a reticulocyte count would be performed was added to the body text and removed from the tables (21-1, 21-2, 21-3, 21-3, 21-4, 21-5, 21-6, 21-7) and added to table 21-8. Purpose for Change: Text was moved from the tables to the text body for clarity.

36. 12.7.9.2 Assessment of Abnormal Laboratory Values Description of Change: Specification was added that investigators did not need to indicate if hyaluronidase antibody values constituted an AE. Purpose for Change: To align with the new text in Section 12.7.12.1, Guidance on Reporting and Assessing rHuPH20 (hyaluronidase) antibody test results.

37. 12.7.10 Trough Serum IgG Description of Change: Removed “within 60 minutes” from the sentence regarding when the IgG sample must be collected. Purpose for Change: The sample needs collected prior to infusion but does not necessarily need to be collected within 60 minutes.

38. 12.7.12.1 Guidance on Reporting and Assessing rHuPH20 (hyaluronidase) antibody test results Description of Change: Guidance was added to the protocol on reporting and assessing antibody test results. Purpose for Change: Text was added to clarify that neutralizing antibodies do not have to be reported as AEs.

39. 12.8 Vital Signs Description of Change: The following clause was removed “subject’s electronic diary (as applicable)”. Purpose for Change: Vital signs are not collected in the electronic diary.

40. 16.6 Laboratory and Reader Standardization Description of Change: R-ODS was removed. Purpose for Change: R-ODS is not a PRO so it does not need to be included in this list.

41. 21.2 Schematics for Study Visits and Assessments Figure 21-1, Figure 21-2 Description of Change: Figure 21-1 and Figure 21-2 were removed. References to these figures were removed throughout the protocol. Purpose for Change: To avoid redundancy and potential errors from updates.

42. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3, Table 21-4 Description of Change: The words “at least” were added to the footnote about when the R-ODS assessment will be completed. Purpose for Change: The R-ODS assessment might be completed more than once a week.

43. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: Additional information on eDiary dispensation and data collection was added to the footnote. Purpose for Change: To add clarity for the protocol.

44. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: The words “after 24 h but within 72 h + 1 business day” and “or after completion of the last day of dosing for an infusion that was administered over multiple consecutive days” were added to the footnote. Purpose for Change: Clarification was added to the window around the telephone follow-up visits.

45. 21.3 Schedule of Study Procedures and Assessments Table 21-3 Description of Change: The footnote “to be performed prior to infusion” was updated to “to be performed prior to the start of

the infusion (or prior to the first day of dosing for an infusion dose that is to be administered over multiple days)". Purpose for Change: To align with the other assessment tables.

46. 21.3 Schedule of Study Procedures and Assessments Table 21-3 Description of Change: The footnote pertaining to the interim assessment/visits during Week 16 was updated to match the footnote in Table 21-7. Purpose for Change: For consistency within the protocol.

47. 21.3 Schedule of Study Procedures and Assessments Table 21-4 Description of Change: "Prior to each infusion rate change" was added to the list of when vital signs need monitored and recorded. Purpose for Change: To align with nursing standard of care and to ensure safety of the subjects in the study.

48. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3, Table 21-5, Table 21-6, Table 21-7 Description of Change: An extra column was added for the +72 h blood sample, related to Week 3 (Table 21-1), Week 5 (Table 21-2), and Week 8 (Table 21-3). Purpose for Change: To increase visibility of the following footnote and those related to it on other tables "To be collected 72 (±24) h (ie, 48 – 96 h) after the Week 3 infusion, the subject's first full-dose infusion of IP (HYQVIA/HyQvia or placebo with rHuPH20)." This was to help call attention to the difference in timing for the safety labs at this visit."

49. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3, Table 21-4, Table 21-5, Table 21-6, Table 21-7, 12.7.1 Hematology and Clinical Chemistry Description of Change: The following footnote was removed from the tables "In the event that no safety concerns are raised, these sampling time points may be waived or modified upon recommendation by the DMC and notification by the sponsor/sponsor's representative." And the following text was updated in Section 12.7.1 instead "In the event that no safety concerns are raised, 2 weeks following the first infusion, at the time of the first full dose, approximately 72 h, and 7 and 14 days following the first full dose in Epoch 1 and E2W3 in Epoch 2 sampling time points may be waived or modified upon recommendation by the DMC and notification by the sponsor/sponsor's representative." [redacted]

50. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: A footnote was updated to include the following "For the rest of the SC period, the reference to calculate the visit is Week 1 and not the Pre-SC BL Visit". Purpose for Change: To add clarity for the Investigators.

51. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3, Table 21-5, Table 21-6, Table 21-7 Description of Change: A footnote was updated to include the following: "For any deviation from allowable study visit windows (±2 or ±3 day windows), subjects would be required to be brought back to the original planned visit date of the next visit in order to ensure subject safety. All other assessment or procedure visits, which do not have a visit window or a reference note in the protocol, should follow visit windows of ±3 days. There will be no visit window allowed in the ramp up period after Visit 1 (Week 1)." Purpose for Change: To add clarity for the Investigators.

52. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: A footnote was updated to include the following (parenthesis to show variation among tables): "Week 1 should be calculated from the last day of dosing for an infusion dose that is to be administered over multiple days. For the rest of the SC period, the reference to calculate the visit is Week 1 and not the Pre-SC BL Visit (Exception: Week 3 (Week 5, Week 8) +72 h, Week 4 (Week 6, Week 9) (please see note f) and Week 5 (Week 7) that are calculated from Week 3

(Week 5, Week 10) due to safety assessments in the protocol)." Purpose for Change: To add clarity for the Investigators.

53. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: A footnote was updated to include the following: "ie, Week 13, Week 15, or Week 17." Similar footnotes were added on additional tables. Purpose for Change: To add clarity to the visit window.

54. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: An extra row and footnote was added for randomization. "Randomization can occur between the last day of IGIV and Week 1 assessments (once last IGIV is fully administered and eligibility is confirmed)." Purpose for Change: To add clarity for the Investigators.

55. 21.3 Schedule of Study Procedures and Assessments Table 21-1, 21-2, Table 21-3 Description of Change: A footnote was added "A minimum of a 3-day interval is required between E1W4 and E1W5 (E1W6 and E1W7, E1W9 and E1W10 visits, depending on the Table)." Purpose for Change: To specify the timing and procedure when there is an overlap of visits.

56. 21.3 Schedule of Study Procedures and Assessments Table 21-1, Table 21-2, Table 21-3 Description of Change: A footnote was added Whenever there is an overlap of a safety visit and an infusion visit, the safety laboratory assessments should be performed first prior to the IP infusion". Purpose for Change: To specify the timing and procedure when there is an overlap of visits.

57. 21.3 Schedule of Study Procedures and Assessments Table 21-4 Description of Change: Vital signs were added to all visits in the treatment period in the table. Purpose for Change: To align with the footnote as well as ensure the data is obtained.

58. 21.3 Schedule of Study Procedures and Assessments Table 21-4 Description of Change: The following text was added to a footnote "ie, Week 10, Week 13, Week 16". Purpose for Change: To help specify the timing.

59. 21.3 Schedule of Study Procedures and Assessments Table 21-4 Description of Change: Two new footnotes were added and additional information was added to an existing footnote to clarify the procedure when INCAT evaluation indicates relapse and to add GAMMAGARD Liquid/KIOVIG instructions for rescue medication. Two new footnotes were added: "In case the first INCAT evaluation indicating relapse (during Epoch 1) occurs during a study visit and not at an unscheduled visit, and the second (confirmatory) INCAT evaluation (Pre-IV BL Epoch 2) is performed on the same day, and in addition the Investigator's preference is to administer the rescue medication (E2W1) also on the same day—repetition of same laboratory assessments should be avoided (eg, combining E1W15 at 2 weekly dose regimen, E1W14 at 3 weekly dose regimen, or E1W16 at 4 weekly dose regimen together with Pre-IV BL Epoch 2 and E2W1 all on the same day. In this case laboratory assessments of Epoch 1 study visit are the same as the ones in E2W1 before IP. These laboratory assessments should then be performed only once for subject's safety regarding blood volume taken." "GAMMAGARD Liquid/KIOVIG or GAMUNEX-C (for US sites only), can be given as a rescue medication on Epoch 2, after the second INCAT evaluation, as early as the same day and no later than 7 days, at the discretion of the Investigator When administration of the rescue medication (E2W1) does not occur on same day as second (confirmatory) INCAT evaluation (Pre-IV BL Epoch 2), then Table 21-4 all study procedures and assessments should be performed at 'Pre-IV BL' Epoch 2 day and Table 21-8, all clinical laboratory assessments should be performed (before infusion) at 'E2W1' visit day." Additional information on existing footnote: "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." Purpose for Change: To add clarity for the Investigators.

60. 21.3 Schedule of Study Procedures and Assessments Table 21-5 Description of Change: A footnote "prior to start of infusion (as applicable)" was added to the row of Serum IgG. Purpose for Change: To align with the protocol text.

61. 21.3 Schedule of Study Procedures and Assessments Table 21-5 Description of Change: A footnote was updated from "to be collected prior to the subjects" to "to be collected prior to the start of the subjects". Purpose for Change: To align with the protocol text.

62. 21.3 Schedule of Study Procedures and Assessments Table 21-6 Description of Change: A footnote was moved from E1W7 to E1W8. Purpose for Change: There is no infusion at E1W7.

63. 21.3 Schedule of Study Procedures and Assessments Table 21-7 Description of Change: E1W26 was changed to E1W28. Purpose for Change: To align with Table 21-3.

64. Schedule of Study Procedures and Assessments Table 21-7 Description of Change: A column was added for E1W12. Purpose for Change: To align with the other table of assessments.

65. 21.3 Schedule of Study Procedures and Assessments Table 21-8 Description of Change: Additional information was added to a footnote to clarify the procedure when INCAT evaluation indicates relapse, and to add GAMMAGARD Liquid/KIOVIG instructions for rescue medication. "In case the first INCAT evaluation indicating relapse (during Epoch 1) occurs during a study visit and not at an unscheduled visit, and the second (confirmatory) INCAT evaluation (Pre-IV BL Epoch 2) is performed on the same day, and in addition the Investigator's preference is to administer the rescue medication (E2W1) also on the same day—repetition of same lab assessments should be avoided (eg, combining E1W15 at 2 weekly dose regimen, E1W14 at 3 weekly dose regimen, or E1W16 at 4 weekly dose regimen together with Pre-IV BL Epoch 2 and E2W1 all on the same day). In this case laboratory assessments of Epoch 1 study visit are the same as the ones in E2W1 before IP. These laboratory assessments should then be performed only once for subject's safety regarding blood volume taken. When administration of the rescue medication (E2W1) does not occur on same day as second (confirmatory) INCAT evaluation (Pre-IV BL Epoch 2), then Table 21-4 all study procedures and assessments should be performed at 'Pre-IV BL' Epoch 2 day and Table 21-8, all clinical laboratory assessments should be performed (before infusion) at 'E2W1' visit day." Purpose for Change: To add clarity for the Investigators.

66. 21.4 Clinical Laboratory Assessments Table 21-5, Table 21-6, Table 21-7, Table 21-8 Description of Change: A clause was added indicating that subjects who met the criteria would have to return for additional testing: "…will be asked to return to the study site as soon as possible to undergo an additional panel of testing outlined in Table 12-2." Purpose for Change: Updated for to match the body of the protocol.

67. 21.4 Clinical Laboratory Assessments Table 21-5 Description of Change: A footnote was added to the serum IgG. Purpose for Change: To align with the protocol body text.

68. Investigator Acknowledgement Description of Change: A second Investigator acknowledgement form was added. Purpose for Change: An EU specific acknowledgement page was added per template.

Protocol amendment #2: 161403-protocol-amend-2-2016apr22
Amendment to amendment #1: 161403-protocol-amend-1-2015aug25 (22 items)

1. Throughout the document Description of Change: Minor editorial/grammatical and/or administrative changes that do not substantively affect the study conduct or patient safety have been made. Investigator acknowledgement page for coordinating investigator has been updated. Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Throughout the document Description of Change: A secondary outcome measure was added to Epoch 1 and 2 with additional tertiary outcome measures added to Epoch 2. Relevant text was changed to maintain consistency throughout the document with additional text added to describe the biostatistical analysis of the specified outcome measures. Purpose for Change: To gain additional relevant information regarding outcome measures of efficacy.

3. Throughout the document Description of Change: The following sentence was added: "any LDH test result of 2X ULN or greater will trigger analysis of the sample for LDH isoenzymes." Purpose for Change: To clarify when LDH isoenzyme testing should be performed.

4. Synopsis, Section 9.1 Inclusion criteria Description of Change: An additional inclusion criteria was added: "Subject is willing and able to sign an informed consent form (ICF)". Language regarding the subjects' legal representative was deleted from the protocol: "or the subjects' legally authorized representatives". [redacted]

5. Section 10.3.1 Screening and Baseline Period Description of Change: The following text was added: "The subject's previous electrodiagnostic records including those obtained at the time of diagnosis, if available, can be used for initial screening. If a previous evaluable nerve conduction report is available, an additional study at the time of screening is not mandatory but highly recommended. This is recommended because according to recent data it would be possible to determine whether the subject is going to need IgG for control of his disease or if the subject is in remission by reviewing these 2 separate tests." Purpose for Change: This text was added to clarify the use of previous of electrodiagnostic records during Screening.

6. Section 10.3.4.4 End of IV Treatment Period Description of Change: The following bullet point was deleted: "Subjects who responded to IGIV treatment throughout the 6 month treatment period and completed the End-of-Epoch 2 visit may opt to participate in an open-label extension study for the evaluation of long term safety, tolerability, immunogenicity, and efficacy of HYQVIA/HyQvia in CIDP. Subjects who are interested will be asked to provide informed consent for the extension study prior to conducting any of the End-of-IV Treatment Period (study completion) procedures." Purpose for Change: Only subjects who complete Epoch 1 may opt to participate in the open-label extension.

7. Section 11.3 Hand Grip Strength Description of Change: The description of the JAMAR® PLUS + Hand Dynamometer has been replaced by a description of the Vigorimeter. Purpose for Change: The specific instrument used to measure hand grip strength was changed from the JAMAR® PLUS + Hand Dynamometer to the Vigorimeter.

8. Section 17.5 Description of Ethical Considerations Relating to the Trial Description of Change: This is a new section added to the protocol that contains an explanation and discussion of the ethical rationale used for design of the trial. Purpose for Change: To clarify the ethical considerations of the trial.

9. Synopsis, Section 9.1 Inclusion Criteria Description of Change: Males or females of age ≥18 at the time of screening. Purpose for Change: CIDP is a disease which can be found in subjects >80 years, this change was made by recommendation by Canadian investigator.

10. Throughout the document Description of Change: Minimal monthly maintenance dose of IGIV was decreased from 0.5 to 0.4 g/kg. Purpose for Change: After discussing with European Union, Canada, and US investigators and key opinion leaders, 0.4 g/kg was recommended as the lowest minimal monthly maintenance dose.

11. Synopsis, Section 9.2 Exclusion Criteria, Section 10.3.1.1 Rescreening, 10.5 Medications and Non-Drug Therapies Description of Change: Allowance for steroid treatment if administered >3 months prior to screening and within 3 months of screening allowing for a single steroid dose or Methylprednisolone Dose Pack for the treatment of AE and non-CIDP indications. Purpose for Change: A wide consensus from investigators and key opinion leaders agreed that these changes would be beneficial for the subjects.

12. Section 8.2 Overall Study Design, Section 21.3 Schedule of Study Procedures and Assessments (Table 21-1) Description of Change: Unscheduled visits in Epoch 2 were added. Purpose for Change: At any time during treatment period, unscheduled visit(s) for INCAT assessment will be allowed for patients who experience CIDP worsening, in order to determine whether worsening meets the definition of relapse.

13. Section 2.0 Serious Adverse Event Reporting, Section 12.1.2.3 Safety Reporting, Section 12.3 Untoward Medical Occurrences Description of Change: All SAEs, including SUSARS, are to be reported on the Serious Adverse Event Report (SAER) Form and transmitted to the Sponsor within 24 hours after becoming aware of an event. Section 12.1.2.3 was deleted. Section 12.3 was updated from eCRF reporting to SAE Report Form reporting. Purpose of Change: The EDC system cannot pull all information on to the form which is required for Baxalta GDS. EDC should be re-programmed. Section 12.1.2.3 was no longer needed as it describes processes for electronic SAE reporting. Section 12.3 updates were to reflect the changes from eCRF reporting of SAEs to paper reporting.

14. Section 8.7.2 Preparation and Storage of Pooled Products Description of Change: In case IGI, 10% and 0.25% albumin placebo solutions for administration have to be prepared using aseptic techniques without controlled air environment (Laminar Flow hood) in accordance with USP guideline 797 or its equivalent per regional or institutional standard practices and within the Pharmacy Manual, the study drug must only be administered to study subjects at the study site and immediately following preparation and after reaching room temperature. Additionally, clarification was made to change specify the infusion will be administered at room temperature. Purpose of Change: This will allow unblinded staff (Nurse) to prepare the study drug, and ensure the infusions are stored and administered at the correct temperatures.

15. Section 17.4 Data Monitoring Committee Description of Change: The DMC may recommend to stop the trial if it finds toxicities or if treatment is proven to be not beneficial. Purpose of Change: Major or critical decisions should be in the hands of the Sponsor/Management. For the purpose of "reason" "stopping the study" is a very grave decision and should be assess by a larger group including the program innovation team and other experts.

16. Synopsis, Section 9.1 Inclusion Criteria Description of Change: "Partial or complete resolution of neurological symptoms and deficits" was added to inclusion criteria 3. Purpose of Change: To clarify reasons subjects might have received IgG treatment.

17. Section 9.3 Withdrawal and Discontinuation Description of Change: Language was added to the Pregnancy Registry to specify that the participation is based on whether it is available in the respective country. Purpose of Change: To add flexibility for countries that might not have the Pregnancy Registry.

18. Section 12.1.1 Definitions Description of Change: A definition of TEAE was added into the protocol. Purpose of Change: The Baxalta template was updated.

19. Section 12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR) Description of Change: A new section on SUSARs were added into the protocol. Purpose of Change: Baxalta protocol template text was updated to include this additional language and reporting requirements.

20. Section 12.7.13 Backup Samples/Biobanking Description of Change: The clause "for no more than 2 years after the final study report has been completed" was added to the storage of serum samples. [redacted]

21. Throughout the document Description of Change: Updated template text. Purpose of Change: Baxalta protocol template was recently updated. Minor textual changes made throughout the document.

22. Synopsis, Section 8.7.3 Administration, Section 8.7.4 Description of Treatment Description of Change: Mode of administration is divided into 2 parts, 1 for bifurcated needle set, and 1 for trifurcated needle set. Purpose of Change: To add an option to administer study drug simultaneously at 3 body sites using a trifurcated needle set.

Protocol amendment #1: 161403-protocol-amend-1-2015aug25
Amendment to Original: 161403-protocol-2015may27 (4 items)

1. Throughout the document Description of Change: Minor editorial/grammatical and/or administrative changes that do not substantively affect the study conduct or patient safety have been made. Investigator acknowledgement page for coordinating investigator has been inserted. Section 21.3 Schedule of Study Procedures and Assessments and Section 21.4 Clinical Laboratory Assessments have been updated to fix a few missing assessments that were inadvertently omitted. Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Section 6.6 Compliance Statement Description of Change: Added the text "the Declaration of Helsinki (October 2013)". Purpose for Change: To explicitly state that this study will be conducted in compliance with the latest version of the Declaration of Helsinki. In the original protocol, this was implicitly referred to through the cited regulations including ICH GCP E6 and the European Clinical Trial Directive 2001/20/EC.

3. Section 8.5.2 Unblinding Description of Change: The text was revised as follows: "Treatment assignment is not to be revealed before the study is completed/terminated, except in emergency cases when unblinding is necessary for the clinical management of an SAE. In such events, ~~every attempt must be made to contact and consult with the study's Medical Monitor before breaking the blind. T~~the investigator may unblind via the integrated web response system (IWRS) at any time (ie, 24 hours per day, 7 days per week) to obtain the treatment assignment. ~~However, the medical monitor will not be unblinded.~~ Details of unblinding procedures ~~and contact information for the study's medical monitor~~ will be provided to study sites~~and will be included in the Medical Monitoring Plan~~. The investigator must keep a log stating the date and time of breaking the code, reason for breaking the code, study product administered, subject identification number and randomization code, and site personnel who were unblinded." Purpose for Change: To reflect that

the responsibility to break the treatment code in emergency situations resides solely with the investigator.

4. Section 12.1.2.3 Safety Reporting Description of Change: The following paragraph has been added: “The sponsor will ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening, as well as all other serious unexpected ARs, are reported to regulatory authorities within the timeframes mandated by the applicable regulations (eg, ICH Guideline E2A and the European Clinical Trial Directive (2001/20/EC). The sponsor will comply with applicable laws/requirements for reporting SUSARs and all other SAEs to the ECs and investigators.” Purpose for Change: To explicitly stated that the sponsor’s responsibility to inform regulatory authorities, ethics committees, and investigators worldwide of any SUSARs and all other SAEs in a timely manner in accordance with applicable regulations such as the European Clinical Trial Directive (2001/20/EC).

Original protocol: 161403-protocol-2015may27