Clinical Study Protocol

NCT Number: NCT02955355

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

Study Number: 161505

Document Version and Date: Amendment 4.0, 11 January 2022

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

PROTOCOL: 161505

TITLE:	Long-Term Tolerability and Safety of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
SHORT TITLE:	Long-Term Tolerability and Safety of HYQVIA/HyQvia in CIDP
STUDY PHASE:	IIIb
DRUG:	Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia)
IND NUMBER:	014381
EUDRACT NUMBER:	2016 000374 37
NCT NUMBER:	NCT02955355
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:	TBD
PROTOCOL HISTORY:	**Amendment 4: 2022 Jan 11** **Replaces:** Amendment 3: 2019 AUG 05 Amendment 2: 2018 NOV 14 Amendment 1: 2016 JUN 27 Original: 2016 JAN 20

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature: [redacted]	Date: 12-Jan-2022
[redacted], MD	

Investigator's Acknowledgement

I have read this protocol for Study 161505.

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

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:

- AE, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2
- Non-Medical Complaints, Section 12.4

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20; HYQVIA/HyQvia[i])
Name(s) of Active Ingredient(s)	Immune Globulin Infusion 10% (Human) for HYQVIA/HyQvia
CLINICAL CONDITION(S)/INDICATION(S) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	
PROTOCOL ID	161505
PROTOCOL TITLE	Long-Term Tolerability and Safety of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
Short Title	Long-Term Tolerability and Safety of HYQVIA/HyQvia in CIDP
STUDY PHASE	Phase IIIb
PLANNED STUDY PERIOD	
Initiation	2016 Q2/3
Primary Completion	Dependent on approval of HYQVIA/HyQvia in countries participating in study.
Study Completion	Dependent on approval of HYQVIA/HyQvia in countries participating in study.
Duration	Dependent on approval of HYQVIA/HyQvia in countries participating in study.
STUDY OBJECTIVES AND PURPOSE	
Study Purpose The purpose of this study is to assess the long-term safety, tolerability, and immunogenicity of the subcutaneous (SC) treatment with Immune Globulin Subcutaneous (IGSC) facilitated with rHuPH20 (HYQVIA/HyQvia) in subjects with CIDP who have completed Baxalta Clinical Study Protocol 161403 Epoch 1 without CIDP worsening.	
Primary Objective 1. To evaluate the long-term safety, tolerability, and immunogenicity of HYQVIA/HyQvia	
Exploratory Objective(s) 1. To assess the long-term effect of HYQVIA/HyQvia on clinical outcome measures, including prevention of relapse, change in functional ability, hand grip strength, and muscle strength 2. To assess the long-term effect of HYQVIA/HyQvia on quality of life, health utility, health resource utilization (HRU), treatment satisfaction, treatment preference, and subject global impression of change	

[i] HYQVIA and HyQvia are registered trademarks of Baxalta US Inc./Baxalta Innovations GmbH.

3. To evaluate improvement in functional impact on everyday tasks as measured by a pre-specified subscore of R-ODS	
STUDY DESIGN	
Study Type	Long-term Safety, Tolerability, Immunogenicity, Efficacy, Pharmacoeconomics
Control Type	No control
Study Indication Type	Treatment
Intervention Model	Single-group, non-randomized
Blinding/Masking	Open-label
Study Design	This study is a Phase IIIb, open-label, multicenter study to assess the long-term safety, tolerability, and immunogenicity of HYQVIA/HyQvia (IGI, 10% with rHuPH20 administered subcutaneously) for maintenance therapy to prevent relapse. This study is an extension of Baxalta Clinical Study 161403, a Phase III Efficacy, Safety, and Tolerability Study of HYQVIA/HyQvia and GAMMAGARD LIQUID/KIOVIG in CIDP. Enrollment into this study is open to subjects who have completed Study 161403 Epoch 1 without CIDP worsening and who have provided informed consent. Subjects must meet all eligibility criteria (see section '**SUBJECT SELECTION**') in order to participate in this Extension Study. As of December 3, 2021, a total of 121 subjects completed the pivotal study (161403), 77 of whom rolled over into the extension study (161505). There are 11 ongoing subjects in the pivotal study with potential to roll over into the extension study. Hence, it is estimated that a maximum of 88 subjects will be eligible for study participation. In this Extension Study, eligible subjects will receive HYQVIA/HyQvia in an open-label fashion until relapse or until predetermined study end for the specific country from which the subject is participating (see section '**Planned Duration of Subject Participation',** below). **<u>Dose of HYQVIA/HyQvia and Dosing Regimen:</u>** Subjects will continue to receive the same dose and dosing regimen of HYQVIA/HyQvia in the Extension Study as the subject's full dose received in Epoch 1 of the Phase III Study 161403. The study product components of HYQVIA/HyQvia will be administered sequentially. SC infusion of rHuPH20 solution at a dose of 80 U/g Immunoglobulin G (IgG) will be administered first, to be followed by SC infusion of IGI, 10% within 10 minutes of completion of the infusion of rHuPH20 solution.

Entry into Extension Study:

Enrollment into the Extension Study (signed informed consent) may take place immediately prior to or during the subject's study completion visit in Study 161403. The termination visit of Study 161403 is to serve as the baseline visit for the Extension Study. Therefore, informed consent for the Extension Study must be obtained on the day of or prior to conducting the end-of-treatment assessments in Study 161403 in order for those assessments to serve as the baseline assessments in the Extension Study. Subject's eligibility for entrance into the Extension Study must be determined prior to the first investigational product (IP) infusion in the Extension Study, which will occur at the next visit (the first treatment visit in the Extension Study). The first administration in the Extension Study will take place at the subject's next scheduled dosing (every 2, 3, or 4 weeks). The dose will be the same as that administered in Study 161403. The first infusion will be at the subject's full dose; there will be no ramp-up of dose.

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

Administration and Study Site Visits:

As some subjects were receiving placebo treatment and have not been exposed to HYQVIA/HyQvia while participating in Study 161403, all subjects will have at least the first 2 infusion visits in the Extension Study at the study site to facilitate safety monitoring.

Subjects from Study 161403:

The first 2 infusions in the Extension Study will be conducted at the investigator's site. Thereafter and per investigator's discretion, the SC infusions for subjects rolling over from Study 161403 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 and if product can be shipped from the pharmacy to the respective locations.

The ability of the subject (and/or caregiver) to perform infusion procedures independently is a prerequisite for self-administration in general. As needed, retraining and verification of the subject's (and/or caregiver's) proficiency in independently self-administering infusions will be provided and must be documented.

	Whilst HYQVIA/HyQvia infusions will occur at 2-, 3-, or 4-week intervals, at home or in clinic, Study Site Visits are only mandatory for the first and second dose and then every 12 weeks (±5 days) in the Extension Study. However, an unscheduled visit can occur at any time should the need arise.
Planned Duration of Subject Participation	Each subject will have the opportunity to receive HYQVIA/HyQvia until approval of HyQvia marketing authorization for the treatment of CIDP in either US or EU (whichever comes later) unless one of the following criteria is met: Early subject discontinuation from treatment or study due to CIDP worsening that, at the discretion of the investigator, would preclude further treatment with IP 1. Country-specific predetermined date, as may be mandated by regulations. 2. Sponsor's decision to early discontinue further participation of a subject in the study 3. Early study termination at the sponsor's discretion, for any reason 4. Upon unblinding of study 161403, subjects who did not have CIDP worsening while on placebo treatment during Epoch 1 should discuss options regarding continued participation in this long-term clinical trial with the investigator 5. Subject becomes pregnant during the study
Outcome Measures	
Primary Outcome Measures **Safety/Tolerability** 1. Number (percentage) of subjects experiencing any treatment-emergent serious and/or non- serious 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 non-serious adverse reactions (Ars) plus suspected ARs 4. Rate of AEs that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other factors as listed in Table 12-1, expressed as number of events per infusion and per subject-year 5. Number (percentage) of treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality 6. Number (percentage) of causally related SAEs and/or AEs associated with infusions 7. Number (percentage) of AEs temporally associated with infusions (defined as AEs occurring during or within 72 hours after completion of an infusion) 8. Number (percentage) of serious and/or non-serious ARs plus suspected ARs associated with infusions 9. Number (percentage) of infusions associated with 1 or more systemic AEs	

10. Number (percentage) of infusions associated with 1 or more local infusion site reactions
11. Number and proportion of infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs
12. Rates of systemic and local AEs, regardless of causality, expressed as number of events per infusion, per subject, and per subject-year
13. Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year
14. Rates of systemic and local ARs plus suspected ARs, expressed as number of events per infusion, per subject, and per subject-year
15. Number of subjects with AE(s) that led to discontinuation from study
16. Number and rate per infusion of moderate or severe AEs that may be a result of immune- mediated response to either immunoglobulin, rHuPH20, or other factors as defined in Table 12-1 (Section 12.7.10)
17. Number (percentage) of subjects experiencing treatment-emergent local infusion site reactions
18. Number (percentage) of subjects with treatment-emergent with local tolerability* events during the first 8 weeks of open-label Extension Study 161505 among subjects originally randomized to placebo (no ramp up), versus during the 8 week-ramp-up period for subjects originally randomized to HYQVIA in double-blind Study 161403. * Subjects for which infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.
19. Number (percentage) of subjects experiencing local infusion reactions, as a function of dosing interval, infusion rate per site, and infusion volume per site.
20. Number (percentage) of subjects whose anti-hyaluronidase antibody titers rise by ≥ 4 fold from the original baseline value from study 161403 using combined data from both studies (161403 and 161505).

Immunogenicity

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

Exploratory Outcomes

Efficacy

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

3. Time to relapse
4. Percentage of subjects with change in Rasch-built Overall Disability Scale (R-ODS) score by >4 points from baseline
5. Change in adjusted INCAT disability score from baseline
6. Percentage of subjects with change in hand grip strength score by >8 kPa from baseline
7. Change in Medical Research Council (MRC) sum score from baseline
8. Change from baseline in functional impact on everyday tasks as measured by R-ODS sub-components

Subject Reported Outcomes and Health Economics

1. Short Form-36 (SF-36) scores and changes from baseline over various time periods
2. EuroQoL (Quality of Life)-5 Dimensions (EQ-5D-3L) scores and changes from baseline over various time periods
3. HRU, including days off school/work, unscheduled physician visits, hospitalization, and emergency room visits, plus the total number of acute physician visits (office and emergency room due to CIDP exacerbation, any CIDP-related issue, any cause), over various time periods
4. Treatment satisfaction
5. Treatment preference
6. Subject global impression of change

Other

1. Trough serum IgG levels

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION

Active Product	**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 **Dosage form**: Injection, solution **Mode of Administration**: One to 3 infusion sites per infusion day are allowed. The infusion rate of rHuPH20 may be started at the previous infusion rate tolerated in the 161403 study. Infusion rates may be increased as tolerated by the subject and at the discretion of the investigator. **2. IGI, 10%** **Dose**: Same monthly equivalent dose as the individual subject's IgG treatment in Study 161403. **Dosing Frequency**: Every 2, 3, or 4 weeks **Dosage form**: Injection, solution

	Mode of Administration: SC infusion, to be administered via a peristaltic infusion pump with programmable infusion rates and infusion volumes at 1 to 3 infusion sites per infusion day, with step-wise increases in infusion rate. IGI 10% solution may be administered at 1, 2, or 3 infusion sites. The recommended site(s) for the infusion of HYQVIA/HyQvia are the middle to upper abdomen and thighs. For the initial 2 infusions, it may be delivered at an infusion rate of 10 to 240 mL/h per infusion site for subjects ≥40 kg and 5 to 80 mL/h per infusion site for subjects <40 kg, as tolerated by the subject and/or at the discretion of the investigator. For subsequent administrations, infusion rate may be increased as tolerated by the subject and at the discretion of the investigator. Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US and CANADA 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 for each pump is provided in the Investigator Site Infusion Manual. Prior to subjects being allowed to infuse at these higher infusion rates in the home setting, this should first be conducted under medical supervision in the clinic setting. At high infusion rates, above 750 mL/h (if trifurcated needle set for 3 infusion sites is used), 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. One to 3 sites can be used at the discretion of the investigator and subject based on tolerability and total IgG dose volume for the individual subject. IGI, 10% solution may be administered at 1 or 2 infusion sites with a maximum infusion volume of up to 600 mL per infusion site for subjects weighing ≥40 kg. If using 3 infusion sites, the maximum is 400 mL/site since on any given infusion day, the maximum infusion volume should not exceed 1200 mL for subjects weighing ≥40 kg. IGI 10% solution may be administered at 1 or 2 infusion sites with a maximum infusion volume of up to 300 mL per infusion site for subjects <40 kg, as tolerated. If using 3 infusion sites, the maximum is 200 mL/site since on any given infusion day, the maximum infusion volume should not exceed 600 mL for subjects weighing <40 kg.

	If a subject's IgG dose per kg of body weight on a given day exceeds 1.3 g/kg/day or exceeds the SC maximum infusion volume the subject can tolerate, not to exceed 1200 mL/day, the HYQVIA/HyQvia dose may be administered over multiple days as divided doses with 48 to 72 hours recommended between doses (eg, Day 1 and Day 3 of a given infusion cycle, but left to the investigator's discretion) to allow absorption of infusion fluid at infusion site(s). Note: The volume (mL) of infusion solution to be administered will be calculated using the subject's body weight measured at baseline. Adjustment based on body weight changes during the course of the study is not planned, however it may be done if deemed medically necessary by the investigator (eg, clinically significant body weight change). After baseline, for study visits where the subject's body weight is measured (see Table 21-1, 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. At a few selected study sites, subjects may be asked to permit still photographs of the infusion sites, which will be used for educational and demonstration purposes, both within and external to the study. Only the infusion site will be photographed, and no identifying features will be included. The site staff will be instructed on how to collect the still photographs. Subjects who agree will sign a separate consent.
SUBJECT SELECTION	
Targeted Accrual	Maximum 88 subjects
Number of Groups/ Arms/Cohorts	1
Inclusion Criteria Subjects who meet **ALL** of the following criteria are eligible for this study: 1. Has completed Epoch 1 of Study 161403 without CIDP worsening. 2. If female of childbearing potential, the subject must have a negative pregnancy test at baseline and agree to employ adequate birth control measures (eg, birth control pills/patches, intrauterine device [IUD], or diaphragm or condom [for male partner] with spermicidal jelly or foam) throughout the course of the study.	

Exclusion Criteria

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

1. Subject has a serious medical condition such that in the opinion of the investigator the subject's safety or medical care would be impacted by participation in this Extension Study.
2. New medical condition that developed during participation in Study 161403 that in the judgment of the investigator could increase risk to the subject or interfere with the evaluation of investigational medicinal product and/or conduct of the study.
3. Subject is scheduled to participate in another, non-Baxalta clinical study involving an IP or investigational device during the course of this study.
4. The subject is nursing or intends to begin nursing during the course of the study.
5. 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 Study 161403) involving an IP or investigational device during the course of this study.
6. The subject is a family member or employee of the investigator.

STATISTICAL ANALYSIS

Sample Size Calculation

Not applicable

Planned Statistical Analysis

Data will be analyzed descriptively .

Analysis Populations

Safety Set: The Safety (SAF) analysis set will be defined as all subjects who are enrolled in the Extension Study and received at least one dose of study medication. This will be the primary analysis set for all safety analyses. Descriptive analyses based on the Safety Set that are to be presented by treatment that a subject received during Study 161403 Epoch 1.

Safety Analysis

Descriptive statistics will be performed for all safety and tolerability outcome measures that are described in the section Primary Outcome Measures.

Immunogenicity

The number and percentage of subjects who meet each of the following criteria will be summarized: (1) subjects who have binding and/or neutralizing antibodies to rHuPH20, (2) subjects who have rHuPH20 antibody titers that decline toward normal (titer <160) during continuous exposure to rHuPH20, (3) subjects who have a >10,000 titer of binding antibodies to rHuPH20 neutralizing antibodies and cross reactivity with Hyal-1,2 and 4. All immunogenicity analyses will be performed on the SAF analysis set.

Exploratory Efficacy

Exploratory efficacy analyses will be presented for the SAF analysis set. Subject relapse rates will be characterized by 6-month and cumulative relapse rates at the end of each consecutive 6-month study period and at the end of the study, as well as a Kaplan-Meier estimate of the median time to relapse. Point estimates and appropriate two-tailed, 95% confidence intervals will be provided.

Scores and changes from baseline in R-ODS, adjusted INCAT disability, hand grip strength, and MRC sum will be summarized by visit, using basic descriptive statistics. Baseline will be defined as the score at the study completion (end-of- SC treatment) visit in Study 161403.

Trough Serum IgG Levels

Trough plasma concentrations of IgG will be summarized and based on the SAF set, using the sample size, mean, SD, median, minimum, maximum, geometric mean, and SD of the geometric mean.

Subject-Reported Outcomes and Health Economics

The SF-36 section scores, EQ-5D-3L visual analog scale (VAS) scores, Treatment Satisfaction (TSQM-9) scores, and their respective changes from baseline will be summarized by visit using descriptive statistics for continuous data. The EQ-5D-3L item scores, Treatment Preference results, and Patient Global Impressionof Change (PGIC) scores will be summarized by the number and percentage of subjects who gave each possible response.

Health Resource Utilization (HRU) (such as days off school/work, unscheduled physician visits, hospitalization and emergency room visits, number of acute physician visits (office and emergency room visits due to CIDP exacerbation, any CIDP-related issue, any cause) over various time periods (pre-SC to End of Extension Study, baseline Extension Study to End of Extension Study) will be summarized by the number and percentage of subjects who experienced each type of event, with descriptive statistics for the number of events of each type.

Data will be analyzed descriptively.

Interim Analysis

An interim analysis is planned to be performed based on an interim data cut-off to occur within 30 days after the last subject in study 161403 had its last visit in Epoch 1. The data are planned to be included in future regulatory submissions. Outcome measures to be analyzed will include, but may not be limited to:

- Number of subjects with a relapse (defined as a worsening of functional disability defined as an increase of ≥1 adjusted INCAT disability scores in 2 consecutive timepoints, relative to baseline)
- Time to relapse
- Change in R-ODS score from baseline
- Change in adjusted INCAT disability score from baseline
- Change in hand grip strength score from baseline
- Change in MRC sum score from baseline
- Cumulative treatment-emergent serious and non-serious AEs
- Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year
- Infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs, for both local and systemic AEs
- Anti-rHuPH20 binding and neutralizing antibody titers
- Any relevant information that may support safety evaluation

No corrections for multiplicity will be applied as this interim analysis is of a purely descriptive nature. In addition to the interim analysis, Study 161505 safety data available at time of data cut for Study 161403 interim safety analysis (details in study protocol) will be summarized, in order to assess the long-term safety of HYQVIA.

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Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AAN	American Academy of Neurology
ADA	Antibody detection assay
AE(s)	Adverse event(s)
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR(s)	Adverse reaction(s)
AST	Aspartate aminotransferase
B19V	Parvovirus B19
BMI	Body mass index
BUN	Blood urea nitrogen
C3	Complement component 3
C4	Complement component 4
CH50	50% hemolytic complement activity of serum
CHO	Chinese hamster ovary
CIC	Circulating immune complex
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CMAP	Compound motor action potential
CPK	Creatine phosphokinase
CRF(s)	Case report form(s)
CTA	Clinical Trial Agreement
CTFG	Clinical Trial Facilitation Group
DADS	Distal acquired demyelinating symmetric neuropathy
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
EC(s)	Ethics committee(s)
ECOG	Eastern Cooperative Oncology Group
ECRF/eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EFNS/PNS	European Federation of Neurological Societies/Peripheral Nerve Society

Abbreviation	Definition
EMA	European Medicines Agency
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
GGT	Gamma-glutamyl transferase
HAV	Hepatitis A virus
HbA1C	Hemoglobin A1C; also known as glycosylated or glycated hemoglobin
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
HEV	Hepatitis E virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
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
IP(s)	Investigational product(s)
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous
LDH	Lactate dehydrogenase
MADSAM	Multifocal acquired demyelinating sensory and motor neuropathy
MCS	Mental component summary score

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MMN	Multi-focal motor neuropathy
MRC	Medical Research Council
NMC	Non-medical complaint
PCS	Physical component summary score
PE	Plasma exchange
PGIC	Patient Global Impression of Change
PID	Primary immunodeficiency disease
RBC	Red blood cell
rHuPH20	Recombinant human hyaluronidase
R-ODS	Rasch-built Overall Disability Scale
RSI	Reference Safety Information
SAE(s)	Serious adverse event(s)
SAER	Serious adverse event report
SAP	Statistical analysis plan
SC	Subcutaneous
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
TRALI	Transfusion related acute lung injury
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 multi-focal motor neuropathy (MMN) (Hahn et al., 2013). Clinical studies in neurological indications have also shown significant results with intravenous (IV) immunoglobulin (IGIV) preparations in the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Hughes et al., 2008, Léger et al., 2013).

CIDP is a 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 0.15-1.6/100,000 (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) (Note: 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 result in impaired dexterity in carrying out tasks 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) IGSC replacement therapy is considered to be effective, safe, and also highly appreciated by patients (Misbah et al., 2009, Nicolay et al., 2006) 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 AE 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-mediated neuropathies for IgG usage, that require immunomodulatory doses up to 5 times higher than immune replacement doses.

One clinical study with HYQVIA/HyQvia in CIDP is currently ongoing: Study 161403, a Phase III Efficacy, Safety, and Tolerability Study of HYQVIA/HyQvia and GAMMAGARD LIQUID/KIOVIG. It is a Phase III multicenter, double-blind, placebo controlled study.

This clinical study is being performed to investigate the long-term tolerability and safety of rHuPH20-facilitated IGSC therapy in subjects with CIDP, who have completed Baxalta Clinical Study 161403 Epoch 1 without CIDP worsening.

6.1 Description of Investigational Product

6.1.1 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. Further information is provided in the Investigator's Brochure (IB) for IGI, 10% with rHuPH20.

6.1.1.1 Recombinant Human Hyaluronidase

rHuPH20 (molecular weight of ~61 kDa) is produced from genetically engineered Chinese Hamster Ovary (CHO) cells containing a deoxyribonucleic acid (DNA) plasmid encoding for a soluble fragment of human hyaluronidase PH20. rHuPH20 is a soluble recombinant form of human hyaluronidase that modifies the permeability of connective tissue through the hydrolysis of hyaluronan. rHuPH20 acts locally and transiently within the SC space to increase the tissue dispersion and absorption of other injected drugs and fluids. rHuPH20 is locally catabolized. In SC tissue, rHuPH20 has a half-life of less than 30 minutes, and in the systemic circulation a half-life of less than 5 minutes (Halozyme data on file). Hyaluronan is a gel-like polysaccharide that limits the movement of fluids and other molecules in the SC tissue. It is degraded by naturally occurring hyaluronidase and has a very fast turnover (half-life of approximately 0.5 days) in SC tissue.

The addition of rHuPH20 accelerates the depolymerization of hyaluronan, resulting in a decreased resistance to fluid flow and a transient increase in permeability of the local SC tissue. The interstitial matrix and normal permeability of the SC tissue is restored within 24 to 48 hours due to the naturally occurring rapid regeneration of hyaluronan in the body.

rHuPH20 drug product is supplied as a sterile, clear, colorless, ready-for-use solution in the label strength of 160 U/mL, containing the additional excipients sodium chloride, sodium phosphate, albumin human, ethylenediaminetetraacetic acid (EDTA) disodium, calcium chloride, and sodium hydroxide and/or hydrochloric acid added for pH adjustment. rHuPH20 solution contains 0.1% human albumin with an approximate pH of 7.4 and osmolality of 290 to 350 mOsm. rHuPH20 solution is preservative-free. rHuPH20 solution provides for high margins of safety with respect to viruses, due to comprehensive virus testing at the Master Cell Bank, Working Cell Bank and bulk harvest stage, effective virus reduction during the purification process, and the use of pharmaceutical grade human albumin as an excipient with no other materials of human or animal origin involved in the manufacturing process.

6.1.1.2 Immune Globulin Infusion 10% (Human)

The manufacturing process of IGI, 10% is in compliance with the US 21 Code of Federal Regulations and Recommendations and Guidelines published by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA). IGI, 10% is manufactured from human plasma by employing a modified Cohn-Oncley cold alcohol fractionation process, as well as cation and anion exchange chromatography. Screening against potentially infectious agents (such as hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], and parvovirus B19 [B19V]) begins with the donor selection process and continues throughout plasma collection and preparation. To further improve the margin of safety, three validated, dedicated, independent, and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent treatment, nanofiltration, and incubation at a low pH and elevated temperature in the final formulation.

The finished medicinal product, IGI, 10%, is a purified, functionally intact IgG solution formulated with 0.25 M glycine (for a stabilizing effect) at 10% weight/volume (w/v) protein concentration and a pH of 4.6 to 5.1. The preparation is an isotonic solution containing approximately 100 mg of protein per mL, of which at least 98% is IgG with an IgG subclass distribution representative of native human plasma. The product contains no preservatives.

6.1.2 Dose Justification

The IgG dosing regimen for HYQVIA/HyQvia will be the same as in Study 161403.

6.2 Clinical Condition/Indication

For maintenance therapy of CIDP to prevent neuromuscular disability and impairment.

6.3 Population To Be Studied

This study will enroll subjects who have completed Study 161403 Epoch 1 without CIDP worsening and who have agreed to enter this Extension Study. It is estimated that a maximum of 88 subjects will be eligible for enrollment into the study.

6.4 Findings from Nonclinical and Clinical Studies

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

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

6.5.1 HYQVIA/HyQvia

The clinical development program for HYQVIA/HyQvia has demonstrated that IGI, 10% administered via SC treatment with rHuPH20 is efficacious and safe in PID. The safety, tolerability, efficacy, and bioavailability of HYQVIA/HyQvia were investigated in one pivotal Phase III study (160603) and an Extension Study (160902) in subjects with PID. One supportive clinical study (160602) in subjects with PID using GAMMAGARD LIQUID/KIOVIG (IGI, 10%) administered subcutaneously was also conducted. Further information is provided in the IB for IGI, 10% with rHuPH20 as well as Prescribing Information for HYQVIA and the 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. Study 160603 compared the efficacy, pharmacokinetics, safety, and tolerability of IGIV, 10% and IGI, 10% administered subcutaneously following rHuPH20 solution. Study 160902, an extension to study 160603, assessed the long-term tolerability and safety of IGI, 10% following administration of rHuPH20 solution.

Eighteen percent (15 of 83) of subjects with PID receiving IGI, 10% with rHuPH20 in Baxter Study 160603 and Study 160902 developed non-neutralizing antibodies to rHuPH20. The clinical significance of these antibodies is not known. The clinical data from Baxter Study 160603 and Study 160902 have shown no temporal association between ARs and the presence of anti-rHuPH20 antibodies, and there was no increase in incidence or severity of ARs in subjects who developed anti-rHuPH20 antibodies. In all subjects, antibody titers decreased despite continued treatment. There is a theoretical potential risk for such antibodies to cross react with human hyaluronidase, which is known to be expressed in the adult male testes, epididymis, and sperm. It is unknown whether these antibodies may interfere with fertilization and fetal development in humans. Treatment-emergent antibodies against rHuPH20 (binding and neutralizing antibodies) will be monitored during this clinical study (See Section 12.7.10 for details).

Pregnancy, Breast Feeding, Fertility

IGSC products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy or on the fetus and the neonate are to be expected. Development and reproductive toxicology studies have been conducted with rHuPH20 in mice and rabbits. No adverse effects on pregnancy and fetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to rHuPH20 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 currently unknown.

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens that have a mucosal portal of entry.

For subjects in the European Union (EU): The safety of HyQvia for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant or breastfeeding women.

For subjects in US: HyQvia should be given to a pregnant or nursing woman only if clearly indicated.

There are currently no clinical safety data for HyQvia on fertility available. Clinical experience with immunoglobulins suggests that no harmful effects of IGI 10% on fertility are to be expected. Animal studies do not indicate direct or indirect harmful effects of rHuPH20 with respect to reproductive potential at the doses used for facilitating administration of IGI 10%.

Subjects who become pregnant during the study should be withdrawn from the study.

See Section 6.5.2 for the known risks associated with IGI, 10%.

6.5.2 GAMMAGARD LIQUID/KIOVIG

GAMMAGARD LIQUID/KIOVIG will not be used as an investigational drug in this study. However, GAMMAGARD LIQUID/KIOVIG—also known as IGI, 10%—is the immunoglobulin product in HYQVIA/HyQvia. Information on this product is therefore also presented:

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 IGI, 10% for further information, as well as the Prescribing Information for GAMMAGARD LIQUID and the SmPC for KIOVIG.

Serious ARs (defined as serious adverse events [SAEs] occurring during or within 72 hours of infusion or any casually related SAE occurring within the study period) that 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 subjects were:

- PID, IV administration: headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, pharyngolaryngeal 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, hyper viscosity, 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, 10% treatment include anaphylactic or severe systemic hypersensitivity reactions to IG, and immunoglobulin A (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 IGI, 10%.

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 Clinical Trial Regulation EU No. 536/2014 and 2005/28/EC, the Declaration of Helsinki, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

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

7.3 Exploratory Objectives

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

8. STUDY DESIGN

8.1 Brief Summary

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

8.2 Overall Study Design

The overall study design is illustrated in Figure 21-1. 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.

Enrollment into this study is open to subjects who have completed Study 161403 Epoch 1 without CIDP worsening and who have provided informed consent.

Subjects must meet all eligibility criteria (see Section 9) in order to participate in this Extension study. It is estimated that a maximum of 88 subjects will be eligible for study participation.

In this Extension Study, eligible subjects will receive HYQVIA/HyQvia in an open-label fashion until relapse or until predetermined study end for the specific country from which the subject is participating as described in Section 8.3.

Dose of HYQVIA/HyQvia and Dosing Regimen:

Subjects will continue to receive the same dose and dosing regimen of HYQVIA/HyQvia in the Extension Study as the subject's full dose received in Epoch 1 of the Phase III pivotal study (Study 161403).

Entry into Extension Study:

Enrollment into the Extension Study (signed informed consent) may take place prior to or during the subject's study completion visit in Study 161403. The termination visit of Study 161403 is to serve as the baseline visit for the Extension Study. Therefore, the informed consent for the Extension Study must be obtained on the day of or prior to conducting the end-of-treatment assessments in Study 161403 in order for those assessments to serve as the baseline assessments in the Extension Study.

Subject's eligibility for entrance into the Extension Study must be determined prior to the first investigational product (IP) infusion in the Extension Study, which will occur at the next visit (the first treatment visit in the Extension Study). The first administration in the Extension Study will take place at the subject's next scheduled dosing (every 2, 3, or 4 weeks). The dose will be the same as that administered in Study 161403. The first infusion will be at the subject's full dose; there will be no ramp-up of dose.

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

Administration and Study Site Visits:

As some subjects were receiving placebo treatment and have not been exposed to HYQVIA/HyQvia while participating in the 161403 protocol, all subjects will have at least the first 2 infusion visits in this Extension Study at the study site to facilitate safety monitoring.

Subjects from Study 161403:

The first 2 infusions in the Extension Study will be conducted at the investigator's site. Thereafter and per investigator's discretion, the SC infusions for subjects rolling over from Study 161403 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 and if product can be shipped from the pharmacy to the respective locations.

The ability of the subject (and/or caregiver) to independently perform infusion procedures is a prerequisite for self-administration. As needed, retraining and verification of the subject's (and/or caregiver's) proficiency in independently self-administering infusions will be provided and must be documented.

Whilst HYQVIA/HyQvia infusions will occur at 2-, 3-, or 4-week intervals, at home or in clinic, Study Site Visits are only mandatory at 1 week after the first and second dose and then every 12 weeks (±5 days) in the Extension Study. However, an unscheduled visit can occur at any time should the need arise.

8.3 Duration of Study Period(s) and Subject Participation

Each subject will have the opportunity to receive HYQVIA/HyQvia until approval of HyQvia marketing authorization for the treatment of CIDP in either US or EU (whichever comes later) unless 1 of the following criteria is met:

2. Early subject discontinuation from treatment or study due to CIDP worsening that at the discretion of the investigator would preclude further treatment with IP.
3. Country-specific predetermined date, as may be mandated by regulations.
4. Sponsor's decision to early discontinue further participation of a subject in the study.
5. Early study termination at the sponsor's discretion, for any reason.
6. Upon unblinding of study 161403, subjects who did not have CIDP worsening while on placebo treatment during Epoch 1 should discuss options regarding continued participation in this long-term clinical trial with the investigator.
7. Subject becomes pregnant during the study.

8.4 Outcome Measures

8.4.1 Primary Outcome Measures

8.4.1.1 Safety/Tolerability

The primary outcome measure is safety/tolerability (each of these analyzed over time period, eg, first year, second year, third year, etc.) and immunogenicity.

1. Number (percentage) of subjects experiencing any treatment-emergent SAEs and/or AEs, regardless of causality.
2. Number (percentage) of subjects experiencing causally related SAEs and/or AEs.
3. Number (percentage) of subjects with serious and/or non-serious ARs plus suspected ARs.
4. Rate of AEs that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other factors as listed in Table 12-1, expressed as number of events per infusion and per subject-year.
5. Number (percentage) of treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality
6. Number (percentage) of causally related SAEs and/or AEs associated with infusions

7. Number (percentage) of AEs temporally associated with infusions (defined as AEs occurring during or within 72 hours after completion of an infusion)
8. Number (percentage) of serious and/or non-serious ARs plus suspected ARs associated with infusions
9. Number (percentage) of infusions associated with 1 or more systemic AEs.
10. Number (percentage) of infusions associated with 1 or more local infusion site reactions.
11. Number and proportion of infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.
12. Rates of systemic and local AEs, regardless of causality, expressed as number of events per infusion, per subject, and per subject-year.
13. Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year.
14. Rates of systemic and local ARs plus suspected ARs, expressed as number of events per infusion, per subject, and per subject-year.
15. Number of subjects with an AE(s) that led to discontinuation from study.
16. Number and rate per infusion of moderate or severe AEs that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other factors as defined in Table 12-1 (Section 12.7.11).
17. Number (percentage) of subjects experiencing treatment-emergent local infusion site reactions. All local infusion site treatment-emergent AEs are to be reported as adverse reactions.
18. Number (percentage) of subjects with treatment-emergent with local tolerability* events during the first 8 weeks of open-label Extension study 161505 among subjects originally randomized to placebo (no ramp up), versus during the 8 week-ramp-up period for subjects originally randomized to active HYQVIA in double-blind Study 161403.

    * Subjects for which infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.

19. Number (percentage) of subjects with local infusion reactions, as a function of dosing interval, infusion rate per site, and infusion volume per site.

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

8.4.1.2 Immunogenicity

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

8.4.2 Exploratory Outcomes Measure

8.4.2.1 Exploratory Efficacy-Type Outcomes Measures

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

8.4.2.2 Subject-Reported Outcomes and Health Economics

1. Short Form-36 (SF-36) scores and changes from baseline over various time periods.
2. EuroQoL (Quality of Life)-5 Dimensions (EQ-5D-3L) scores and changes from baseline over various time periods.
3. HRU, including days off school/work, unscheduled physician visits, hospitalization, and emergency room visits, plus the total number of acute physician visits (office and emergency room due to CIDP exacerbation, any CIDP-related issue, any cause), over various time periods.
4. Treatment satisfaction.
5. Treatment preference.
6. Subject global impression of change.

8.4.2.3 Other

1. Trough serum IgG levels

8.5 Randomization and Blinding

This is a non-randomized, open-label, active treatment clinical study. No comparator is planned.

8.6 Study Stopping Rules

There will be no specific stopping rules for this study; however, the study may be terminated by the sponsor at any time. The safety of the subjects in this study shall be monitored by an external, independent Data Monitoring Committee (DMC) (see Section 17.4).

8.7 Investigational Product(s)

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°C to 8°C or 36°F to 46°F). Do not freeze the product. Do not use if expiration date is exceeded.

8.7.1.2 IGI, 10%

Dosage Form: Injection, solution.

Packaging: IGI, 10% will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials. IGI, 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% will be labeled according to regulatory requirements for clinical studies.

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

8.7.2 Preparation and Storage of Pooled Products

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

The vials of rHuPH20 must be stored under refrigerated conditions (2°C to 8°C or 36°F 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% for administration are to 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 hours from the time of preparation. When administration of pooled products will begin more than 3 hours from preparation, they must be kept at 2°C to 8°C (36°F 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 hours 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 or by home infusion (as per country regulations) and immediately following preparation and after reaching room temperature.

All solutions for infusion must be administered room temperature.

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

8.7.3 Administration

Mode of administration:

rHuPH20 solution and IGI, 10% solution will be administered subcutaneously in a sequential order, with IGI, 10% infusion being initiated within approximately 10 minutes of completing the infusion of the rHuPH20 solution. 1, 2, or 3 infusion sites may be used.

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, to infuse both study drugs.

rHuPH20: One to 3 infusion sites per infusion day are allowed. The infusion rate of rHuPH20 may be started at the previous infusion rate tolerated in the 161403 study. Infusion rates may be increased as tolerated by the subject and at the discretion of the investigator.

IGI, 10% solution: SC infusion, to be administered via a peristaltic infusion pump with programmable infusion rates and infusion volumes in 1 to 3 infusion sites per infusion day, with step-wise increases in infusion rate. IGI 10% solution may be administered at 1, 2, or 3 infusion sites. The recommended site(s) for the infusion of HYQVIA/HyQvia are the middle to upper abdomen and thighs.

For the initial 2 infusions, it may be delivered at an infusion rate of 10 to 240 mL/h per infusion site for subjects ≥40 kg and 5 to 80 mL/h per infusion site for subjects <40 kg, as tolerated by the subject and/or at the discretion of the investigator.

Due to a manufacturer (CME America) recall on the Body Guard 323 pump and pump tubing, a replacement pump (for US and CANADA 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 with each pump is provided in the Investigator Site Infusion Manual.

Prior to subjects being allowed to infuse at these higher infusion rates than specified in Infusion Manual in the home setting, this should first be conducted under medical supervision in the clinic setting. At high infusion rates above 750 mL/h (if trifurcated needle set for 3 infusion sites is used), 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. These rates should not be exceeded unless the investigator determines that higher infusion rates could be attempted and as long as the higher infusion rates are attempted under medical supervision in the clinic setting, prior to allowing their use in the home setting.

Site of administration: Bifurcated and trifurcated needle sets are to be used for 2 and 3 infusions, respectively. The recommended site(s) for the infusion of HYQVIA/HyQvia are the middle to upper abdomen and the thighs.

Volume of infusion per site: IGI 10% solution may be administered at 1, 2, or 3 infusion sites with a maximum infusion volume of up to 300 mL per infusion site for subjects weighing <40 kg, as tolerated. 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. One to 3 sites can be used at the discretion of the investigator and subject based on tolerability and total IgG dose volume for the individual subject. 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 a recommended 48 to 72 h apart (eg, Day 1 and Day 3 of a given infusion cycle, but left to the investigator's discretion) to allow the infused fluid to be absorbed.

Note: The volume (mL) of infusion solution to be administered will be calculated using the subject's body weight measured at baseline. Adjustment based on body weight changes during the course of the study is not planned, however it may be done if deemed medically necessary by the investigator (eg, clinically significant body weight change).

After baseline, for study visits where the subject's body weight is measured (see Table 21-2, 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.

At a few selected study sites, subjects may be asked to permit still photographs of the infusion sites, which will be used for educational and demonstration purposes, both within and external to the study. Only the infusion site will be photographed, and no identifying features will be included. The Site Staff will be instructed how to collect the still photographs. Subjects who agree will sign a separate consent.

8.7.4 Description of Treatment

Treatment: HYQVIA/HyQvia with rHuPH20

Treatment Period: Until relapse or discontinuation as described in Section 9.3.

Dose: Subjects will continue to receive the same dose and dosing regimen of HYQVIA/HyQvia in the Extension Study as the subject's full dose received in Epoch 1 of the Phase III pivotal study (Study 161403). All attempts should be made to maintain the original infusion schedule for subjects. If a subject receives a dose out of window, the dose will still be given prior to the next infusion, if possible. Subjects should return to the original planned visit schedule even if an infusion was given out of window.

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

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 or home, as applicable per study design). Records will be maintained that include 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 and the Infusion Data worksheet) 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 from (CRF).

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. Has completed Epoch 1 of Study 161403 without CIDP worsening.
2. If female of childbearing potential, the subject must have a negative pregnancy test at baseline and agree to employ adequate birth control measures (eg, birth control pills/patches, intrauterine device, or diaphragm or condom [for male partner] with spermicidal jelly or foam) throughout the course of the study.

9.2 Exclusion Criteria

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

1. Subject has a serious medical condition such that the subject's safety or medical care would be impacted by participation in this Extension Study
2. New medical condition that developed during participation in Study 161403 that, in the judgment of the investigator, could increase risk to the subject or interfere with the evaluation of investigational medicinal product (IMP) and/or conduct of the study
3. Subject is scheduled to participate in another non-Baxalta clinical study involving an IP or investigational device during the course of this study
4. The subject is nursing or intends to begin nursing during the course of the study
5. 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 Study 161403) involving an IP or investigational device during the course of this study
6. The subject is a family member or employee of the investigator

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 End of Study 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 also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and the infant up to 2 years post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome. (See also Section 12.1.2)
- The subject begins nursing. IP exposure will be discontinued. The investigator will record a narrative description of the course of the infant's development.
- The subject does not comply with the protocol (per the investigator's discretion).
- The subject develops severe hypersensitivity reactions related to IP administration.
- The subject uses prohibited medications (see Section 10.5) during the course of this study.
- The subject participates in another clinical study involving an IP or device during the course of this study.

Each subject will have the opportunity to receive HYQVIA/HyQvia until approval of HyQvia marketing authorization in either US or EU (whichever comes later) unless 1 of the following criteria is met:

- Early subject discontinuation from treatment or study due to CIDP worsening that at the discretion of the investigator would preclude further treatment with IP
- Country-specific predetermined date, as may be mandated by regulations.
- Sponsor's decision to early discontinue further participation of a subject in the study
- Early study termination at the sponsor's discretion, for any reason
- Upon unblinding of study 161403, subjects who did not have CIDP worsening while on placebo treatment during Epoch 1 should discuss options regarding continued participation in this long-term clinical trial with the investigator.
- Subject becomes pregnant during the study.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the informed consent form [ICF] 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 SIC: protocol identifier (eg, 161505) to be provided by the sponsor, 3-digit study site number (eg, 002) to be provided by the sponsor, and 3-digit subject number (eg, 003) reflecting the order of providing informed consent (ie, signing the ICF). For example, the third subject who signed an ICF at study site 002 will be identified as Subject 161505-002003. 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 a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome.

The overall study design is illustrated in Figure 21-1. Details on the procedures to be performed at each study visit, including screening (baseline), 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 at the screening/baseline period.

In order to be eligible to participate in this extension study, subjects must have completed Epoch 1 of Study 161403 without CIDP worsening.

For subjects enrolling from Study 161403 Epoch 1, enrollment into the Extension Study (signed informed consent) may take place prior to or during the subject's study completion visit in Study 161403. Since the Study 161403 termination visit is to serve as the baseline visit for the Extension Study, the informed consent for the Extension Study

must be obtained on the day of or prior to conducting the end-of-treatment assessments in Study 161403 in order for those assessments to serve as the baseline assessments in the Extension Study.

Subject's eligibility for entrance into the Extension Study must be determined prior to the first IP infusion in the Extension Study, which will occur at the next visit (the first treatment visit in the Extension Study).

For all subjects, the following procedures will also be performed at baseline:

- Medical history
- Vital signs as well as weight
- Physical exam
- INCAT disability score
- R-ODS
- Hand grip strength
- MRC sum score
- SF-36
- EQ-5D-3L
- HRU
- Treatment satisfaction
- Treatment preference
- AEs
- Laboratory assessments as outlined in Table 21-2
- Hemoglobin A1C (HbA1C) assessment if required
- Concomitant medications

At least the first 2 infusions should be performed at the site under supervision of the investigator/designee for the assessment if the subject is ready for independent infusions. Subsequent infusions may be self-administered at home or other suitable location. Details are provided in Section 8.2. Infusions that coincide with post-baseline study visits may be performed at the site; however, such infusions should be self-administered.

10.3.1.1 Rescreening

Not applicable.

10.3.2 Treatment Period

During the treatment phase of this extension study, subjects will receive HYQVIA/HyQvia in an open-label fashion until approval of HyQvia marketing authorization for the treatment of CIDP in either US or EU (whichever comes later) unless one of the criteria in Section 9.3 is met. For detailed procedures and assessments, see Table 21-1 and Table 21-2.

10.3.2.1 SC Infusion Visits (Including Home Infusions)

Packaging, labeling, and storage of IPs are described in Section 8.7.1, and preparation and storage of pooled IP solutions are 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.

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.

Subjects will continue to receive the same dose and dosing regimen of HYQVIA/HyQvia in the Extension Study as the subject's full dose received in Epoch 1 of the Phase III pivotal study (Study 161403).

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

The first administration in the Extension Study will take place at the subject's next scheduled dosing (every 2, 3, or 4 weeks). The dose will be the same as that administered in Study 161403. The first infusion will be at the subject's full dose; there will be no ramp-up of dose.

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

For each SC infusion on each infusion day, the following infusion-related information will be recorded on the Infusion Data worksheet and in the subject's electronic diary (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%)
- 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%)
- Actual volume infused (mL) (total of rHuPH20 solution plus the IGI, 10%)
- Number of infusion sites
- Maximum infusion rate tolerated
- Length of SC needle used (mm)
- Whether a healthcare professional (eg, 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 (24 to 72 hours + 1 business day) to monitor for changes in a subject's functional status (according to the same criteria used in Study 161403) and to document AEs, concomitant medications, and non-drug therapies, which may have occurred within this period 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).

10.3.2.2 Unscheduled Visit for Relapse Assessment

Subjects who relapse (defined as an increase in adjusted INCAT disability score by ≥1 point relative to the baseline score of this extension study on 2 consecutive INCAT assessments) will be discontinued from the extension study.

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.

10.3.3 Study Completion/Early Termination Visit

Subjects may end their active participation in the SC treatment period in 1 of 2 ways. For a detailed schedule of study procedures and assessments, see Section 21.2.

1. Subjects may be requested to complete treatment in the study, which may be as soon as the subject participating country gets market authorization for the treatment of CIDP in either US or EU (whichever comes later). Study completion assessments are to be conducted on the day of the final infusion. This will mark the subjects' completion of the study.
2. A subject may withdraw their participation in the study or be discontinued from the study prior to completing treatment. 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 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:

- Systemic corticosteroids at doses >10 mg/prednisolone/day or its equivalent are not permitted throughout the course of the study if given for worsening of CIDP.
- Low-dose systemic corticosteroids (≤10 mg prednisolone/day or its equivalent) are permitted; however, the dosage should remain stable unless a change is deemed medically necessary.
  - In the event a change in low-dose systemic corticosteroid dose or the addition of a low-dose systemic corticosteroid is necessary during the study, it must be approved by the Medical Monitor prior to the addition/change being made, whenever possible. It must be determined whether continuing in the study may pose increased risk to the subject due to the condition requiring treatment and/or whether the condition may impede the subject's participation in the study or confound the results of the study.
- Non-systemic corticosteroids (eg, 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 during the course of the study is not permitted.

PE has been shown to provide short-term clinical benefits in improving neurological disability in CIDP. Thus, use of PE 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:

Other IgG products

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 is receiving IgG therapy. Annual influenza vaccines are permitted.

10.5.2 Pre-Medications for Infusion Administration

For subjects who are prone to infusion-related AEs, if the same type of mild-to-moderate, non-serious AE(s) expected to be related to infusion (eg, 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, nonsteroidal anti-inflammatory drugs (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 (eg, 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 will be provided to each subject at baseline to record the following information throughout the study: Occurrence of signs/symptoms indicative of AEs
- Use of concomitant medications and non-drug therapies
- Infusion records (see Section 10.3.1 and Section 10.3.2.1)
- 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.
- R-ODS
- Infusion-related information (see Section 10.3.2.1)

Subjects, caregivers, and/or subjects' legally authorized representatives 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 data 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 subject-reported data. An Infusion Data 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 third party eDiary vendor data will be imported via a validated transfer to Data Management and incorporated via SAS into the final SAS data transfers.

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 to the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (eg, death), 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). 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 study so that the investigator/designee can further assess and document that the subject (and/or caregiver) is 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. 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 30 August 2021, and the EMA Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic, Version 3 (28 April 2020).

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 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. Due to COVID-19-related factors, delayed or missing infusions could put a study subject at risk of developing CIDP worsening (as defined by ≥1-point increase in adjusted INCAT score). The allowable period for treatment COVID-19 related treatment lapse is set 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. 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.
4. The study site staff may administer the IP and/or collect labs at home, as necessary when COVID-19 is at risk at the hospital setting. All 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.
5. 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.
6. 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.

7. 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.
8. 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.
9. 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 (eg, no upper limb problems and walking not affected) and 10 is severely incapacitated (eg, inability to move either arm for any purposeful movement and restricted to wheelchair, unable to stand and walk a few steps withhelp).

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 a 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 MRC to that subject. For detailed administration timepoints, 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 composed 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 using a translated version, as applicable. It is recommended that the subject completes the assessment using the same translated version throughout the course of their participation in the study. For detailed administration timepoints, see Section 21.2 Schedule of Study Procedures and Assessments.

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.

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 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 the 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 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.

In accordance with ICH E9, 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:

- Outcome is fatal/results in death (including fetal death)
- 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
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- 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, hepatitis E virus (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; however, 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 (i.e., including active comparators) that is both serious and unexpected (SUSAR).

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 reporting of SUSARs is described in Section 12.1.2.3.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** 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/or 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 hours following the end of IP infusion, or
- an AE for which causality assessment is missing or indeterminate.

12.1.1.6 Pre-existing Diseases

Pre-existing diseases that are present before entry in to 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 non-serious events experienced after the first IP exposure are not reportable on the AE CRF, unless otherwise specified; nor will they be included in the analysis of AEs:

- 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).
- Infusion site swelling following SC infusion of IGI, 10% 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.
- Pre-existing 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 AEs 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 12.1.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- 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 a 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 AEs 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 administration of IP will be reported on a Pregnancy Report Form. Attempts will be made to follow the subject through completion of the pregnancy and the infant up to 2 years post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

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:

- 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)

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- 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
- 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 hours 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.

12.1.2.3 Safety Reporting

The sponsor will ensure that all relevant information about 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, the European Clinical Trial Directive [2005/28/EC], and Clinical Trial Regulation EU No. 536/2014). The sponsor will comply with applicable laws/ requirements for reporting SUSARs and all other SAEs to the ECs and investigators.

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:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- 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 EC(s) and relevant competent authority(s) 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 non-serious 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:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction, 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 baseline, 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 baseline throughout the study, will be recorded on the appropriate CRF(s).

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

12.6 Physical Examinations

At baseline and other study visits (as described in Table 21-1), 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 baseline, 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 pre-existing 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 (Hct), 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 absolute neutrophil count (ANC), and absolute lymphocyte count.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine, amylase, lipase, aldolase, and glucose.

Samples for hematology and clinical chemistry assessments will be collected in the appropriate matrix as specified in the laboratory manual. With the exception of baseline and early termination visits, samples for hematology and clinical chemistry collected during the 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.

12.7.2 Hemolytic Panel

The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coomb's) test (antibody elution to be performed if direct Coomb's test is positive), reticulocyte count, and urine hemosiderin. The Hgb result obtained from the baseline visit will serve as the baseline Hgb value for the duration of the current study. For subsequent tests in the current protocol, 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 hours; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia.

Hemolytic tests will be performed at the central laboratory or other laboratories as appropriate (eg, antibody elution in the event of positive direct Coomb's 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)

Hemoglobin A1C (HbA1C) measurements will be performed only in subjects diagnosed with diabetes mellitus. During the study, HbA1C will be measured at baseline, first treatment visit, at Weeks 48 and 96, and as deemed medically necessary and at the end- of-treatment visit of each treatment period (or during the 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

Serum iron, ferritin, and total iron binding capacity (TIBC) will be monitored every 12 months and at the end- of-treatment visit. 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 Viral Serology Tests

The need for HIV and Hepatitis serology should be determined by the PI based upon clinical assessment and interval medical history. Serum samples may be collected for viral serology testing for HAV antibody, hepatitis B surface antigen (HBsAg), HCV antibody, and HIV-1/HIV-2 antibody. Additional tests, such as hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and/or nucleic acid tests, may be performed as considered necessary by the PI.

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.

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.

See Section 21.3 for detailed sample collection timepoints.

12.7.6 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. Urinalysis should be completed before the first IP dose is given.

12.7.7 Pregnancy Test

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

12.7.8 Assessment of Laboratory Values

12.7.8.1 Toxicity Grading Scale

The Common Toxicity Criteria of the Eastern Cooperative Oncology Group (ECOG) (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 (U.S.Department of Health and Human Services et al., 2008).

Laboratory parameters not listed in Table 21-3 will not be graded. However, clinical significance of those abnormal laboratory values will be assessed as described in Section 12.7.8.2.

12.7.8.2 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the appropriate eCRF/laboratory form. For each abnormal laboratory value, the investigator will determine whether the laboratory value (except hyaluronidase antibody values) is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value 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 pre-existing 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.

12.7.9 Trough Serum IgG

Following baseline assessment, trough serum IgG samples must be collected on the day of the **site-administered (see Table 21-1)** 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) just prior to the start of the infusion.

Blood samples are to be collected and processed according to the 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 (back-up) sample.

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

12.7.10 Anti-rHuPH20 Antibodies

The potential for immune response to rHuPH20 will be monitored in all subjects who have received rHuPH20 administration. Serum samples for the detection of anti-rHuPH20 binding and neutralizing antibodies will be collected at baseline, Weeks 12, 24, 36, 48, 60, 72, 84, and 96, and every 12 weeks, and at the Study Completion/Termination Visit.

Blood samples for the detection of anti-rHuPH20 binding neutralizing antibodies will be collected and processed according to the 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 (back-up) sample. All subjects will be monitored for the formation of anti-rHuPH20 antibodies using validated anti-rHuPH20 antibody detection assay (ADA) (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. Samples with rHuPH20-binding antibody titers >10,000 titer will be tested for cross reactivity with Hyal-1, 2 and 4.

12.7.11 Immunogenicity Panel

At baseline (Week 0 predose) of the pivotal Phase III Study 161403, samples had to 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 extension study, subjects who have (a) 2 consecutive anti-rHuPH20 antibody titers of ≥1:160 that are elevated from the subject's baseline titers, and (b) a moderate or severe AE that 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 That May be a Result of Immune-Mediated Response to Either Immunoglobulin, rHuPH20, or Other Factors

Allergic reactions • Urticaria • New-onset bronchospasm • Oedema of tongue, lips, face (angioedema) • Anaphylaxis • Stevens-Johnson syndrome • Erythema multiforme • Toxic epidermal necrolysis
Immune complex mediated reactions – Local • Induration/nodule at the site of administration that persists for more than 48 hours • Excessive inflammation at the site of administration - severe redness, heat, swelling, and/or pain • Tissue necrosis/ulceration at the site of administration • Dystrophic or fibrotic changes at the site of administration • Pigmented skin changes at the site of drug administration
Immune complex mediated reactions – Systemic • Arthritis • Vasculitis (purpuric rash) • Glomerulonephritis - hematuria, red cell casts in urine, progressive renal dysfunction

Table 12-2
Immunogenicity Panel

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

12.7.11.1 Guidance on Reporting and Assessing rHuPH20 antibody test results

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 AEs.

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

For AEs occurring upon or after subsequent SC 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 AE to one or the other component during this period.

12.7.12 Back-up Samples and Biobanking

Back-up samples should be taken and stored appropriately for repeat or additional analysis, if necessary. These samples may be used short-term for re-testing, further evaluation of an AE, or follow-up of other test results. The following samples are planned:

- Serum IgG samples (back-up aliquots)
- Anti-rHuPH20 binding antibody samples (back-up aliquots)
- Anti-rHuPH20 neutralizing antibody samples (back-up aliquots)

Baseline and end-of-trial serum/plasma back-up samples will be stored for possible testing of pathogens for no more than 2 years after the final study report has been completed.

Other back-up samples that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test, investigation of an AE or suspected seroconversion). Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and subsequently the samples will be destroyed. The need for HIV and hepatitis serology should be determined by the PI based upon clinical assessment and interval medical history. For detailed sampling timepoints, see Table 21-2.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/minute), pulse rate (beats/minute), 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 baseline, periodically at each infusion visit, and at study completion/early termination visit (See Section 21.2 Schedule of Study Procedures and Assessments detailed collection timepoints).

For the initial 2 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 an 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) will be obtained from the baseline visit in Study 161403. Weight (lb or kg), as well as body mass index (BMI), will be collected at baseline of Study 161505. Subsequently, body weight will be re-measured every 24 weeks and in the event of clinically significant change in body weight (see Section 21.2 for detailed measurement timepoints). All body weight 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 Short Form-36 Health Survey

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 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.

13.2 EuroQoL (Quality of Life)-5 Dimensions (EQ-5D-3L)

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-3L 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 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. HRU 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 electronic diary on an ongoing 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.

13.4 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.

13.5 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.

13.6 Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) scale is a single item recorded at study completion/termination 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.

14. STATISTICS

Detailed statistical analysis methods will be described in the statistical analysis plan (SAP).

14.1 Sample Size and Power Calculations

Not applicable. This study is an extension to Study 161403. As indicated in Section 7.1, the purpose of this study is to assess the long-term safety, tolerability, and immunogenicity of HYQVIA in subjects with CIDP who have completed Study 161403 Epoch 1 without CIDP worsening. Enrollment in Study 161505 is open to subjects who have completed Study 161403 Epoch 1 without CIDP worsening and who have provided informed consent. [redacted]

14.2 Datasets and Analysis Cohorts

Safety Set: The Safety (SAF) analysis set will include all subjects who are enrolled in the Extension Study and received at least one dose of study medication. This will be the primary analysis set for all safety analyses. Descriptive analyses based on the Safety Set that are to be presented by treatment received during Study 161403 Epoch 1.

14.3 Handling of Missing, Unused, and Spurious Data

Missing or incomplete AE start/stop dates, relationship to study medication, severity, and seriousness will be imputed. Missing or partial AE start dates will be imputed for the purpose of determining treatment emergence. If an AE start date is completely missing, the AE will be considered treatment-emergent in the extension study. If a partial AE start date is supplied, then the later of (1) the first infusion date in the Extension Study or (2) the earliest date that is consistent with the available data will be used as an imputed start date for determining treatment emergence. If an AE has a missing causality assessment, the relationship of the AE to treatment will be counted as “related”. If an AE has a missing severity assessment, the severity will be imputed as “unknown”, except that if the subject also had a severe AE categorized under the same preferred term, then the AE of unknown severity will be imputed as a severe AE. Events of unknown seriousness will be tabulated as SAEs; however, every effort will be made to avoid data lock with events for which a determination of seriousness remains missing. The Medical Monitoring Plan presents details of how this effort will be executed.

If an infusion record is completely missing, or the planned infusion date cannot be determined from the recorded data, then the infusion will be imputed as "Not done". Otherwise, any infusion that has some amount of recorded data will be assumed to have been completed, unless the available data indicate otherwise. If the infusion dose level is missing, it will be imputed as unchanged from the previous infusion. If an infusion start date and/or time is missing or incomplete, a date and time of infusion will be imputed.

Missing antibody data will be imputed as "No new development of antibodies". No specific values will be imputed for quantitative summaries.

Missing INCAT assessments that pertain to determination of relapse status will be imputed as "No relapse".

Missing Ig trough levels will not be imputed for any quantitative analysis.

Missing or incomplete start and stop dates for prior/concomitant medications and non-drug therapies will be imputed to support determination of prior and concomitant medication status.

Missing or incomplete assessment dates (or date-times if needed to support calculations) will be imputed for time to event analyses.

The SAP will provide more detailed imputation rules for the handling of missing and incomplete dates and times of assessments and events.

Clinical laboratory values that contain non-numeric values due to assay results that were above or below the limit of quantitation will be imputed at the upper or lower limit of the assay, respectively, if needed for any analysis.

Data will not be imputed in any quantitative summaries by timepoint or visit. Both scheduled and unscheduled assessments will be used in all event-based analyses (relapse, occurrence of AEs, etc.). Unscheduled visit data will not be used in any "by-visit" descriptive summaries.

Data such as (but not limited to) laboratory tests that were not specified for collection in the protocol will be reviewed on a case-by-case basis for handling decisions during the study. Full documentation of data related to subject safety will be the primary consideration in establishing how such data will be handled.

Data points that appear to be spurious (eg, outliers, values incompatible with life) will be queried and either corrected or explained, if possible. Outliers will not be excluded from, or identified in, any analysis unless otherwise specified. Any data points that are specified for exclusion will be documented in table footnotes or cross-referenced to an appropriate listing.

14.4 Methods of Analysis

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

Continuous measures will be summarized using the number of subjects in the sample (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical outcomes will be summarized using the number and percentage of subjects. Event rates will be estimated in several different ways, depending on the outcome measure, as explained in the remainder of this section. All collected data will be listed or provided in Clinical Data Interchange Standards Consortium (CDISC)-compliant datasets.

14.4.1 Primary Outcome Measure

14.4.1.1 Safety/Tolerability

Clinically important treatment-emergent abnormalities in vital signs, laboratory assessments, and physical examination results will be reported as AEs. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 (Sep 2015) and reported by body system (ie, MedDRA system organ class), preferred term, and treatment received in the previous study (Study 161403).

All analyses of AEs will be performed using data from the SAF analysis set. All TEAEs, SAEs, ARs/suspected ARs, AEs that could be related to possible immune-mediated responses to one or more study medication components, AEs that are temporally related to infusion, and other subsets of AEs will be reported using (1) the number and percentage of subjects who experienced a particular type of event at any time during the study, (2) the number and rate of reports of a specified type of event per subject-year of time at risk, and/or (3) the number and rate of reports of a specified type of event per infusion.

Any ongoing TEAE that occurred during Study 161403 will be reported in the continuation study as medical history. If this specific ongoing AE becomes worse after the first infusion in the continuation study, this AE will be reported as a new TEAE.

All AEs that occur after the last infusion in Study 161403 and before the first infusion in the continuation study will be reported as a new TEAE and analyzed based on the treatment in the Study 161403.

Note 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.

The purpose of examining all TEAEs without regard to causality is to identify any potential new signals that may arise. The following summaries of all TEAEs are planned:

1. The number and percentage of subjects who had any TEAE, any serious TEAE, any TEAE leading to early withdrawal, any TEAE with onset during and within 72 hours after infusion, any moderate or severe TEAE, any localized TEAE, any moderate or severe localized TEAE, or any TEAE leading to death will be summarized in a single table.
2. The number and percentage of subjects who had a TEAE, serious TEAE, TEAE leading to early withdrawal, TEAE that occurred in >5% of subjects, or TEAE that occurred during or within 72 hours after infusion will be summarized overall and by treatment, MedDRA system organ class, and preferred term in a separate table for each specified group of events.
3. The total number of reports, and event rates expressed as number of events (reports) per infusion, per subject, and per subject-year of time at risk, will be summarized overall and by treatment, MedDRA system organ class, and preferred term in separate tables for all TEAEs, serious TEAEs, and TEAEs that occurred during and within 72 hours after infusion.
4. The number and percentage of subjects with TEAEs will be summarized in descending order of overall frequency.
5. The number and percentage of subjects with TEAEs will be summarized overall and by treatment, MedDRA system organ class, preferred term, and maximum severity.
6. The number of reports of TEAEs that occurred during and within 72 hours after infusion will be summarized overall and by treatment, MedDRA system organ class, preferred term, and severity.
7. The number and percentage of subjects with treatment-emergent local infusion site reactions and number of reports of reactions will be summarized overall and by treatment. Note: All local infusion site treatment-emergent AEs are to be reported as adverse reactions.

8. The number and percentage of subjects with local infusion reactions, as a function of dosing interval, infusion rate per site, and infusion volume per site, will be summarized overall and by treatment.
9. The number and percentage of subjects whose anti-hyaluronidase antibody titers rise by ≥ 4 fold from the original baseline value from Study 161403 using combined data from both studies (161403 and 161505) will be summarized, and such rises will be correlated with TEAEs using descriptive statistics.

The purpose of examining ARs/suspected ARs is to obtain a clear picture of AEs that are recognized as causally related to the study medication. The following summaries of ARs and suspected ARs are planned:

1. The number and percentage of subjects who had any AR/suspected AR, any serious AR/suspected AR, an AR/suspected AR leading to early withdrawal, an AR/suspected AR with onset during or within 72 hours after infusion, any moderate or severe AR/suspected AR, any localized AR/suspected AR, any moderate or severe localized AR/suspected AR, or any AR/suspected AR leading to death will be summarized overall and by treatment in a single table.
2. The number and percentage of subjects who had an AR/suspected AR, serious AR/suspected ARs, AR/suspected AR leading to early withdrawal, AR/suspected AR that occurred in >5% of subjects, or AR/suspected AR that occurred during or within 72 hours after infusion will be summarized overall and by treatment, MedDRA system organ class, and preferred term in separate tables for each specified group of events.
3. The total number of reports of ARs/suspected ARs, and the event rates expressed as number of events (reports) per infusion, per subject, and per subject-year of time at risk, will be summarized overall and by treatment, MedDRA system organ class, and preferred term in separate tables for all ARs/suspected ARs, serious ARs/suspected ARs, and ARs/suspected ARs that occurred during and within 72 hours after infusion.
4. The number and percentage of subjects with ARs/suspected ARs will be summarized overall and by treatment and preferred term, in descending order of overall frequency.
5. The number and percentage of subjects with ARs/suspected ARs will be summarized overall and by treatment, MedDRA system organ class, preferred term, and maximum severity.

The number of reports of ARs/suspected ARs that occurred during and within 72 hours after infusion will be summarized overall and by treatment, MedDRA system organ class, preferred term, and severity. A single table that includes all temporally associated TEAEs (regardless of causality) and all AEs that are causally related but not temporally associated will be generated to support the product insert. The table will include the number and percentage of subjects, and the number of reports, for each relevant type of event.

14.4.1.2 Tolerability

The number and percentage of infusions in which the infusion rate is reduced and/or the infusion is interrupted or stopped due to intolerability and/or AEs will be reported for all AEs and both local and systemic AEs.

In addition, the local tolerability* during the first 8 weeks of open-label study 161505 among subjects originally randomized to placebo (no ramp-up), versus during the 8 week-ramp-up period for subjects originally randomized to active HYQVIA in double-blind study 161403 will be summarized.

*In terms of number and percentage of subjects for which infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.

Note: AE implies TEAE.

14.4.1.3 Immunogenicity

The development and course of immunogenicity will be described by the number and percentage of subjects who meet each of the following criteria: (1) subjects who have binding and/or neutralizing antibodies to rHuPH20, (2) subjects who have rHuPH20 antibody titers that decline toward normal (<160) during continuous exposure to rHuPH20, (3) subjects who have a >10,000 titer of binding antibodies to rHuPH20: neutralizing antibodies and cross reactivity with Hyal-1,2 and 4. All immunogenicity analyses will be performed on the SAF analysis set.

14.4.2 Exploratory Outcome Measures

14.4.2.1 Exploratory Efficacy

Exploratory efficacy analyses will be presented for the SAF analysis set.
Subject relapse rates will be characterized by 6-month and cumulative relapse rates at the end of each consecutive 6-month study period and at the end of the study, as well as a Kaplan-Meier estimate of the median time to relapse. Point estimates and appropriate two-tailed, 95% confidence intervals will be provided.

Subject relapse is defined as a worsening of functional disability, as indicated by an increase of ≥1 adjusted INCAT disability scores in 2 consecutive timepoints relative to baseline score of this extension study.

Scores and changes from baseline in R-ODS, adjusted INCAT disability, hand grip strength, a pre-specified subset of R-ODS, and MRC sum will be summarized by visit, using basic descriptive statistics. The percentage of subjects whose R-ODS scores change from baseline by ≥4 points, and the percentage of subjects whose hand grip strength score changes from baseline by ≥8 kPa, will also be reported. Baseline will be defined as the score at the study completion (end-of-SC treatment) visit in Study 161403.

14.4.2.2 Subject-Reported Outcomes and Health Economics

The SF-36 section scores, the EQ-5D-3L, Visual Analog Scale (VAS) scores, Treatment Satisfaction (TSQM-9) scores, and their respective changes from baseline will be summarized by visit using descriptive statistics for continuous data.

The EQ-5D-3L item scores, Treatment Preference results, and PGIC scores will be summarized by the number and percentage of subjects who gave each possible response.

Information collected on the HRU form includes days off school/work, unscheduled physician visits, hospitalization, and emergency room visits. These events plus the total number of acute physician visits (office and emergency room visits due to CIDP exacerbation, any CIDP-related issue, any cause) will be summarized over various time periods (pre-SC to end of Extension Study, baseline Extension Study to end of Extension Study). The number and percentage of subjects who experienced each of these types of events during the Extension Study will be reported. Descriptive statistics for the number of events of each type will be presented for subjects who experienced each event.

14.4.2.3 Trough Serum IgG Levels

Trough plasma concentrations of IgG will be summarized and based on the SAF set, using the sample size, mean, SD, median, minimum, maximum, geometric mean, and SD of the geometric mean.

14.5 Planned Interim Analysis of the Study

An interim analysis is planned to be performed based on an interim data cut-off to occur within 30 days after the last subject in study 161403 had its last visit in Epoch 1. The data are planned to be included in future regulatory submissions. Data to be analyzed descriptively will include but may not be limited to:

- Number of subjects with a relapse
- Time to relapse
- Percentage of subjects with change in R-ODS score by ≥4 points from baseline
- Change in adjusted INCAT disability score from baseline
- Percentage of subjects with change in hand grip strength score by >8 kPa from baseline
- Change in MRC sum score from baseline
- Cumulative treatment-emergent serious and non-serious AEs
- Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year
- Infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs, for both local and systemic AEs
- Anti-rHuPH20 binding and neutralizing antibody titers
- Any relevant information that may support safety evaluation

No corrections for multiplicity will be applied as this interim analysis is of a purely descriptive nature. In addition to the interim analysis, Study 161505 safety data available at time of data freeze for Study 161403 interim safety analysis (details in study protocol) will be analyzed descriptively, in order to assess the long-term safety of HYQVIA.

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 Clinical Trial Agreement. 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. Sub-investigators 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) 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

Inter-laboratory standardization methods will be described in the data management plan as needed. A standardization program will be implemented to provide standardized training to raters and to monitor inter-rater reliability as part of the 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 patients participate in this study, the protocol, ICF, any promotional material/advertisements, and any other written information 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(s), 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(s) approval.

17.3 Informed Consent

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

All patients and/or their legally authorized representative must sign an ICF before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable (see Section 17.2). The ICF 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 or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the ICF, subjects or their legally authorized representative(s) 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 ICF, after approval by the applicable EC and regulatory authorities will be provided by the investigator to the subjects who consented to participate in the study.

17.4 Data Monitoring Committee

This study will be monitored by an external, independent 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, all of whom who are not participating in this study. The DMC may recommend to stop the study if it finds toxicities or if treatment is proven to be not beneficial.

The DMC will be responsible for reviewing the data obtained in the study, including (but not necessarily limited to) 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 study.

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

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 ICFs, correspondence with the EC and the study monitor/sponsor, baseline 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 national and local 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.

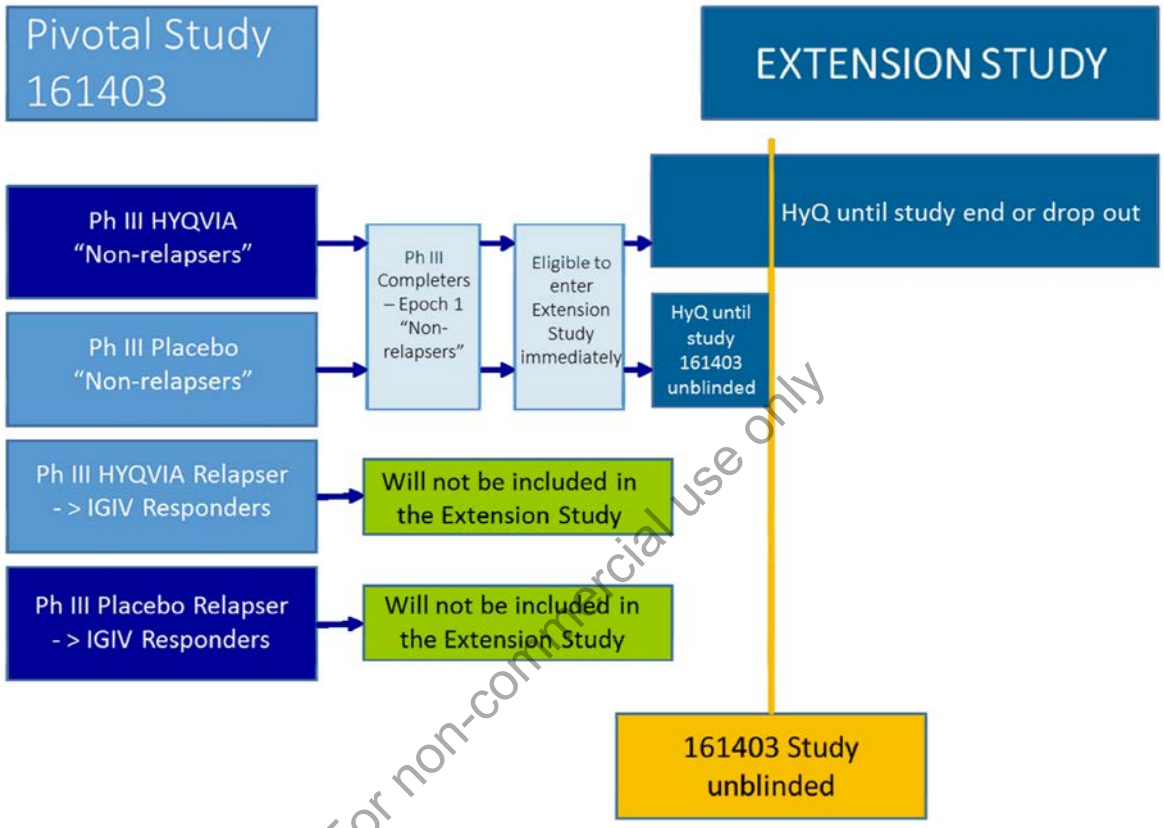
20. PUBLICATION POLICY

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

21. SUPPLEMENTS

21.1 Study Flow Chart

Figure 21-1
Study Flow Chart for Study 161505



21.2 Schedule of Study Procedures and Assessments

Table 21-1
Schedule of Study Procedures and Assessments

Procedures/ Assessments	Termination Visit Study 161403/ Baseline Visit in Extension Study[a]	First Treatment Visit in Extension Study	Interval Study Visits									Study Completion/ Termination Visit	Unscheduled Visit
Week	**-4, -3, -2**	**0**	**+4, +3, +2[b]**	**12**	**24**	**36**	**48**	**60[c]**	**72[c]**	**84[c]**	**96 and every 12 Wks[c]**	**Country Dependent**	**Any**
Informed Consent[d]	X												
Eligibility Criteria	X												
Medical History	X												
Body Weight	X	Every 24 weeks and in the event of clinically significant change in body weight											
Infusion[e]	Every 2, 3, or 4 weeks[f]												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X		X	X	X	X	X	X	X	X	X	X
INCAT Disability Score	X			X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X	X
Hand Grip Strength	X			X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X	X
MRC Sum Score	X			X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X	X
R-ODS	X			X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X	X
SF-36	X				X		X		X		Every other visit (ie, every 24 weeks)	X	

Table 21-1
Schedule of Study Procedures and Assessments

Procedures/ Assessments	Termination Visit Study 161403/ Baseline Visit in Extension Study[a]	First Treatment Visit in Extension Study	Interval Study Visits									Study Completion/ Termination Visit	Unscheduled Visit
Week	**-4, -3, -2**	**0**	**+4, +3, +2[b]**	**12**	**24**	**36**	**48**	**60[c]**	**72[c]**	**84[c]**	**96 and every 12 Wks[c]**	**Country Dependent**	**Any**
EQ-5D	X				X		X		X		Every other visit (ie, every 24 weeks)	X	
HRU	X	X	X	X	X	X	X	X	X	X	X	X	
Treatment Satisfaction	X				X		X		X		Every other visit (ie, every 24 weeks)	X	
Treatment Preference	X				X		X		X		Every other visit (ie, every 24 weeks)	X	
PGIC												X	
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-Infusion Telephone Follow-up[j]	Every 2, 3, or 4 weeks (24 to 72 hours + 1 business day after each infusion visit)												
Laboratory Assessment[g]	X	X[a]	X	X	X	X	X	X	X	X	X	X	X[h]
HbA1C[i]	X	X					X				X	X	
Concomitant Medications[j]	X	X	X	X	X	X	X	X	X	X	X	X	X

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Abbreviations: EQ-5D=EuroQoL (Quality of Life)-5 Dimensions; HbA1C=hemoglobin A1C; HRU=Health Resource Utilization; INCAT=Inflammatory Neuropathy Cause and Treatment disability scale; MRC=Medical Research Council; PGIC=Patient Global Impression of Change scale; R-ODS=Rasch-built Overall Disability Scale; SF-36=Short Form-36 health survey.

[a] To occur in conjunction with Termination Visit in Study 161403 except for Urinalysis. This test requires an additional sampling since it is not part of the Termination Visit in Study 161403. If another assessment is not available at a termination visit, it will be performed at the first infusion visit.

[b] ±5 days.

[c] Study visits should occur approximately 4 times per year (approximately every 12 weeks±5 days) but do not need to coincide with an infusion.

[d] Occurs at prior to baseline. If assessments at End of Study Visit in Study 161403 are to be used as baseline for the Extension Study, then informed consent must be obtained on the day of or prior to conducting the end-of-treatment assessments in Study 161403.

[e] The first 2 infusions will be conducted at the investigator's site. Subsequent infusions may be self-administered at an infusion center or other suitable location. For details, see Section 8.2. Infusions that coincide with post-baseline study visits may be performed at the site; however, such infusions should be self-administered.

[f] Subjects will continue to receive HYQVIA/HyQvia infusions every 2, or 3, or 4 weeks (±3 days) following the schedule of their previous study. All attempts should be made to maintain the original infusion schedule for subjects. If a subject receives a dose out of window, the dose will still be given prior to the next infusion, if possible. Subjects should return to the original planned visit schedule if an infusion was given out of window.

[g] For laboratory assessments, see Section 21.3 below.

[h] As required

[i] During the study, HbA1C will be measured for subjects with diabetes mellitus at baseline, first treatment visit, at Weeks 48 and 96 and as deemed medically necessary.

[j] 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 this period 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).

[k] To be performed prior to the start of the infusion

21.3 Clinical Laboratory Assessments

Table 21-2
Clinical Laboratory Assessments

Assessments	Termination Visit Study 161403/ Baseline Visit in Extension Study[a]	First Infusion Visit	Interval/Study Visits									Study Completion/ Termination Visit	Unscheduled Visit
Week	**-4, -3, -2**	**0**	**+4, +3, +2**	**12**	**24**	**36**	**48**	**60[b]**	**72[b]**	**84[b]**	**96 and every 12 wks[b]**	**Country Dependent**	**Any**
Hematology[c]	X		X	X	X	X	X	X	X	X	X	X	X[d]
Clinical Chemistry[e]	X		X	X	X	X	X	X	X	X	X	X	X[d]
Serum iron, ferritin, and TIBC	X						X				X	X	X[d]
Urinalysis[f]	X		X		X		X		X		X	X	X[d]
Pregnancy Test–Urine	X				X		X		X		X	X	X[d]
Viral Pathogen Serology	X[d]											X[d]	X[d]
Serum IgG[g]	X			X	X	X	X	X	X	X	X	X	X[d]
Binding Antibodies to rHuPH20[h]	X			X	X	X	X	X	X	X	X	X	X[d]
Neutralizing Antibodies to rHuPH20[i]	X			X	X	X	X	X	X	X	X	X	X[d]
Hemolysis Panel[j]			X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[d,k]

Continued on Next Page

Continued

Abbreviations: Hgb=hemoglobin; IgG=immunoglobulin G; IP=Investigational Product; rHuPH20=recombinant human hyaluronidase; TIBC=total iron binding capacity.

[a] To occur in conjunction with termination visit in Study 161403 except for urinalysis. This test requires an additional sampling since it is not part of the termination visit in Study 161403. If another assessment is not available at a termination visit, it will be performed at the first infusion visit.

[b] Study visits should occur approximately 4 times per year (approximately every 12 weeks ±5 days) but do not need to coincide with an infusion.

[C] Hematology assessments: complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [ie, white blood cell count]) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. In addition, absolute neutrophil counts and lymphocyte counts will be determined.

[d] As optional: The need for HIV and Hepatitis serology should be determined by the PI based upon:
- Clinical assessment and interval medical history.

[e] Clinical chemistry assessments: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, creatine phosphokinase, gamma-glutamyl-transferase, amylase, lipase, aldolase, lactate dehydrogenase, and glucose.

[f] Urinalysis assessments: protein, glucose, blood, bilirubin, urobilinogen, specific gravity, pH, color, ketones, nitrite, leukocyte esterase, and microscopic analysis.

[g] To be collected before the administration of Investigational Product (IP) at that visit (if IP administration is scheduled), for trough levels.

[h] In some subjects with high anti-rHuPH20 antibodies and who consent to participate, additional assessments for further evaluation of safety may be performed.

[i] In the event of an antibody titer of 1:160 or greater.

[j] Hemolysis Panel: The hemolytic anemia panel will consist of hemoglobin (Hgb), lactate dehydrogenase, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coomb's) test (antibody elution to be performed if direct Coomb's test is positive), reticulocyte count, as well as urine hemosiderin. The hemolytic anemia panel be conducted only in the event of a drop in Hgb of 1 g/dL or more compared to baseline value.

[k] The Hgb result obtained from the baseline visit in the Extension Study will serve as the baseline Hgb value for the duration of the Extension Study. In the event of a drop in Hgb of 1 g/dL or more compared to previous Hgb, every effort is to be made to perform a hemolytic panel within 72 hours. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia.

21.4 Toxicity Grading Scale for Laboratory Values

Table 21-3
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

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Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; N/A=not applicable; ULN=upper limit of normal; WBC=white blood cell; 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 (U.S.Department of Health and Human Services et al., 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 uses 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 rHuPH20 in mice and rabbits. No adverse effects on pregnancy were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to rHuPH20 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 Facility Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15) (Clinical Trial Facilitation Group (CTFG), 2014), birth control methods that 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[ii]
- Intrauterine device (IUD) [ii]
- Intrauterine hormone-releasing system (IUS)[ii]

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

- Bilateral tubal occlusion[ii]
- Vasectomized partner(s)[ii]
- 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

In this section, major changes from the previous version of the protocol, dated 2019 AUG 05, are described and their rationale is given.

1. Protocol Title Page, Protocol Signature Page

Description of Change: Sponsor entity and sponsor information changed

Purpose of Change: Administrative update of sponsor information.

2. Section 2

Description of Changes: Serious Adverse Event Reporting description changed.

Purpose of Change: Administrative error in the protocol template update.

3. Synopsis, Section 6.3, Section 8.2

Description of Change: target accrual updated to 88 throughout the protocol.

Purpose of Change: The pivotal trial (study 161403) was closed to recruitment on August 17, 2021. As of December 3, 2021, a total of 121 subjects completed the pivotal study and 77 of them rolled over into the extension study (161505). There are 11 ongoing subjects in the pivotal study with potential to roll over into the extension study. Hence, a maximum of 88 subjects are expected to be enrolled into the extension study

4. Synopsis, Section 7.3, Section 8.4.2.1, Section 14.4.2.1

Description of Change: Addition of exploratory objective: To evaluate improvement in functional impact on everyday tasks as measured by a pre-specified subscore of R-ODS

Purpose of Change: to provide a more patientcentric assessment of treatment benefit.

5. Synopsis, Section 8.4.1.1

Description of Change: Safety/ Tolerability outcome measures description changed

Purpose of Change: The wording of the safety/tolerability outcome measures was changed to align with safety/tolerability outcome measures in 161403 study protocol.

6. Synopsis, Section 8.4.2.1

Description of Change: clarification of definition of CIDP worsening defined as ≥8 kPa decrease in the mean hand grip strength in the 'most affected hand' instead of 'one hand'

Purpose of Change: to align with the changes in the 161403 study protocol.

7. Synopsis, Section 8.7.3

Description of Change: Change that the Site will be instructed how to collect the still photographs.

Purpose of the change: To avoid having a third party to collect the still photographs. The site staff will take the still photographs.

8. Synopsis, Section 8.7.3

Description of Change: Mode of Administration description wording changed to clarify type of pump used for the study and infusion parameter are referenced in the study Site Infusion Manual.

Purpose of Change: The addition of the Q Core pump was necessary due to the US recall of the BodyGuard 323 pump.

9. Synopsis, Section 14

Description of Change:

- Added additional information as to maximum enrollment based on actual accrual and relapse rate in study 161403.
- Clarify throughout the section that analyses will be presented by actual treatment received in Study 161403 Epoch 1 and overall, where applicable.
- Removed "subgroup" from "treatment subgroup" to align with 161403 study protocol.
- Update the planned interim analysis timing.
- Clarify that no correction for multiplicity will be applied as this interim analysis is of purely descriptive nature.

Purpose of Change:

Maximum enrollment updated to reflect actual accrual and relapse rate in study 161403. Addition of analyses will be presented by actual treatment received in study 161403 and overall to provide clarification. Update planned interim analysis timing to support regulatory submission.

10. Synopsis, Section 14.5

Description of change: Timing of planned interim data cut-off was changed to occur within 30 days after the last subject in study 161403 had its last visit in Epoch 1 instead of six months of database lock of 161403.

Purpose of change: The sponsor will submit available data from this study with the planned regulatory submission of the final results of the 161403 pivotal study.

11. 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.

12. Sections 13.2 and 14.4.2

Description of Changes: EQ-5D was replaced by EQ-5D-3L.

Purpose of Change: To clarify that EQ-5D-3L version of EQ-5D has been used in the study for data capture and analysis.

13. Table 21-1

Description of Change: footnotes and description h, i, j, k changed

Purpose of Change: Correction of misalignment in prior amendment 3, 2019 Aug 05, addition of footnote k in alignment with 161403 study protocol.

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22. SUMMARY OF CHANGES

Protocol 161505: Amendment 3: 2019 AUG 05

Replaces: Amendment 2: 2018 NOV 14

In this section, major changes from the previous version of the protocol, dated 2018 NOV 14, are described and their rationale is given.

1. Throughout the document
   Description of Change: Minor grammatical and/or administrative changes that do not substantively affect the study conduct or subject safety have been made; also, references have been updated.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Synopsis, Section 8.4.1.1, Section 14.4.1.1, Section 14.4.1.2
   Description of Change: Addition of Outcome Measure in Primary Outcome Measures under Safety/Tolerability. Included local infusion site reactions to be reported as AEs.
   Purpose for Change: To address the feedback received from FDA on 19 Jun 2019.

3. Synopsis, Section 8.4.2.3, Section 14.4.2.3
   Description of Change: Addition of "Other" Outcome Measure in Exploratory Outcome Measures - measurement of serum trough IgG levels.
   Purpose for Change: It was inadvertently not included in the previous versions and added in this version to maintain consistency with study 161403.

4. Synopsis, Section 9.3
   Description of Change: Addition of "pregnancy" to list of reasons why subject would not receive HYQVIA/HyQvia until approval
   Purpose for Change: It was inadvertently not included in the previous versions and added in this version to maintain consistency with study 161403.

5. Sections 12.1.2, 14.4.1
   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.
   Purpose of Change: To maintain consistency with study 161403.

6. Section 10.3.1, 12.7.3, Table 21-1, footnote ‘h’.
   Description of Change: Hemoglobin A1C (HbA1C) measurements will be performed only in subjects diagnosed with diabetes mellitus.
   Purpose of Change: To reflect administrative updates; to improve the readability and/or clarity of the protocol.

7. Section 14.5
   Description of Change: An interim analysis is planned to be performed 6 months after unblinding of Study 161403 (unblinding of Epoch 1) and the data are planned to be included in future regulatory registrations.
   Purpose of Change: To address the feedback received from FDA on 19 Jun 2019.

22. SUMMARY OF CHANGES

Protocol 161505: Amendment 2: 2018 NOV 14

Replaces: Amendment 1: 2016 JUN 27

In this section, major changes from the previous version of the protocol, dated 2016 JUN 27, are described and their rationale is given.

1. **Throughout the document**
   Description of Change: Minor grammatical, operational, and/or administrative changes that do not substantively affect the study conduct or subject safety have been made, which are not individually listed.
   Purpose for Change: To reflect administrative updates; to improve the readability and/or clarity of the protocol. Other minor changes have been made to align with the current protocol template and for consistency with applicable revised text in the recent Study 161403 Amendment 3 (31 January 2018), and to reflect updates to expected enrollment.

2. **Throughout the document**
   Description of Change: All references to Study 161601 have been deleted, which are not individually listed in this Summary of Changes.
   Purpose for Change: Study 161601 is no longer a source for this extension study.

3. **Throughout the document**
   Description of Change: All references to the "HYQVIA/HyQvia Pregnancy Registry" have been deleted.
   Purpose for Change: This registry has been closed; pregnancies will continue to be handled and reported using the standard safety reporting processes.

4. **Synopsis, (PLANNED STUDY PERIOD)**
   Description of Change: Correction made to the following text:

Primary Completion	Dependent on approval of HYQVIA/HyQvia in countries participating in study. This is expected to be no later than end of 2021.
Study Completion	Dependent on approval of HYQVIA/HyQvia in countries participating in study. This is expected to be no later than end of 2021.
Duration	Dependent on approval of HYQVIA/HyQvia in countries participating in study; total study duration (first subject in to last subject out): 5.5 years maximum (2.5 years maximum treatment per subject, or up to 3 years if mandated by regulations)

corrected to:

Primary Completion	Dependent on approval of HYQVIA/HyQvia in countries participating in study. ~~This is expected to be no later than end of 2021.~~
Study Completion	Dependent on approval of HYQVIA/HyQvia in countries participating in study. ~~This is expected to be no later than end of 2021.~~
Duration	Dependent on approval of HYQVIA/HyQvia in countries participating in study~~. ; total study duration (first subject in to last subject out): 5.5 years maximum (2.5 years maximum treatment per subject, or up to 3 years if mandated by regulations)~~

Purpose for Change: The expected duration of the study has been revised upwards.

5. **Synopsis, (Planned Duration of Subject Participation);**
Section 8.3 (Duration of Study Periods and Subject Participation);
Section 9.3 (Withdrawal and Discontinuation);
Section 10.3.2 (Treatment Period)
Description of Change: Correction made to the following text:

Planned Duration of Subject Participation	Each subject will have the opportunity to receive HYQVIA/HyQvia for a maximum of 2.5 years unless one of the following criteria is met: 1. Early subject discontinuation from treatment or study due to CIDP worsening that, at the discretion of the investigator, would preclude further treatment with IP 2. Country-specific predetermined date, as may be mandated by regulations. This can be earlier than 2.5 years or later (up to 3 years) (eg, United Kingdom [UK], Israel) 3. Sponsor's decision to early discontinue further participation of a subject in the study 4. Early study termination at the sponsor's discretion, for any reason 5. Early discontinuation for subjects who did not have CIDP worsening while on placebo treatment during Epoch 1 in Study 161403 will be offered HYQVIA/HyQvia following unblinding of Study 161403 treatment allocation 6. Subject becomes pregnant during the study

corrected to:

Planned Duration of Subject Participation	Each subject will have the opportunity to receive HYQVIA/HyQvia **until approval of HyQvia marketing authorization for the treatment of CIDP in either US or EU (whichever comes later)** ~~for a maximum of 2.5 years~~ unless one of the following criteria is met: 1. Early subject discontinuation from treatment or study due to CIDP worsening that, at the discretion of the investigator, would preclude further treatment with IP 2. Country-specific predetermined date, as may be mandated by regulations**.** ~~This can be earlier than 2.5 years or later (up to 3 years) (eg, United Kingdom [UK], Israel)~~ 3. Sponsor's decision to early discontinue further participation of a subject in the study 4. Early study termination at the sponsor's discretion, for any reason 5. **Upon unblinding of study 161403, subjects who did not have CIDP worsening while on placebo treatment during Epoch 1 should discuss options regarding continued participation in this long-term clinical trial with the investigator** 6. Subject becomes pregnant during the study

Purpose for Change: Correction and clarification. The expected duration of the study was revised upwards. Point number 5 was re-worded to clarify the conduct of the study.

6. **Synopsis, (INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION)**

Description of Change: Revised text as follows:

"Mode of Administration: SC infusion, to be administered via a peristaltic infusion pump with programmable infusion rates and infusion volumes at 1 to 3 infusion sites per infusion day, with step-wise increases in infusion rate. IGI 10% solution may be administered at 1, 2, or 3 infusion sites. **The recommended site(s) for the infusion of HYQVIA/HyQvia are the middle to upper abdomen and thighs.**

…

For t~~T~~he initial 2 infusions, ~~are given~~ **it may be delivered** at an infusion rate of 10 to 240 mL/h per infusion site for subjects ≥40 kg and 5 to 80 mL/h per infusion site for subjects <40 kg, as tolerated by the subject and/**or** at the discretion of the investigator.

…

Prior to subjects being allowed to infuse at these higher infusion rates in the home setting, this should first be conducted under medical supervision in the clinic setting.

…

~~The recommended site(s) for the infusion of HYQVIA/HyQvia are the middle to upper abdomen and thighs. These rates should not be exceeded unless the investigator determines that higher infusion rates could be attempted as long as the higher infusion rates are attempted under medical supervision in the clinic setting, prior to allowing their use in the home setting.~~

One to 3 sites can be used at the discretion of the investigator and subject based on tolerability and total IgG dose volume for the individual subject.

IGI, 10% solution may be administered at 1 or 2 infusion sites with a maximum infusion volume of up to 600 mL per infusion site for subjects weighing ≥40 kg. If using 3 infusion sites, the maximum is 400 mL/site since on any given infusion day, the maximum infusion volume should not exceed 1200 mL for subjects weighing ≥40 kg.

IGI 10% solution may be administered at 1 or 2 infusion sites with a maximum infusion volume of up to 300 mL per infusion site for subjects <40 kg, as tolerated. If using 3 infusion sites, the maximum is 200 mL/site since on any given infusion day, the maximum infusion volume should not exceed 600 mL for subjects weighing <40 kg.

If a subject's IgG dose per kg of body weight on a given day exceeds 1.3 g/kg/day or exceeds the SC maximum infusion volume the subject can tolerate, not to exceed 1200 mL/day, the HYQVIA/HyQvia dose may be administered over multiple days as divided doses with 48 to 72 hours recommended between doses (eg, Day 1 and Day 3 of a given infusion cycle, but left to the investigator's discretion) to allow absorption of infusion fluid at infusion site(s).

~~IGI, 10% solution may be administered at 1, 2, or 3 infusion sites with a maximum infusion volume of up to 300 mL per infusion site for subjects weighing <40 kg, as tolerated. 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. One to 3 sites can be used at the discretion of the investigator and subject based on tolerability and total IgG dose volume for the individual subject. 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.~~"

Purpose for Change: For consistency within the protocol body and to align with pivotal Study 161403.

7. **Synopsis, Section 8.4.2 (Exploratory Outcome Measures)**
Description of Change: Pharmacokinetic and administration-related outcomes deleted.
Purpose for Change: Not applicable to this study.

8. **Synopsis, Section 8.7.3 (Administration)**
Description of Change:
Revised rHuPH20 administration text to clarify that the initial infusion rate is to carry over from Study 161403. Added text to clarify that the recommended intervals between divided doses were optional and that this was to be left to the investigator's discretion. Revised text to align between synopsis and body.

9. **Synopsis, Section 8.7.3 (Administration)**
Revised text:
rHuPH20:
One to 3 infusion sites per infusion day are allowed. ~~The initial 2 SC infusions are given at an~~ **The** infusion rate of ~~60 to 120 mL/h per infusion site (or a total of 120 to 240 mL/h, or a total of 180 to 360 mL/h over 2 and 3 sites, respectively). Bifurcated and trifurcated needle sets are to~~ **rHuPH20 may** be ~~used for 2 and 3 infusion sites, respectively. For subsequent administrations~~**started at the previous** infusion rate **tolerated in the 161403 study. Infusion rates** may be increased as tolerated by the subject and at the discretion of the investigator, but not to exceed 300 mL/h per infusion site (or not to exceed a total of 600 mL/h or ~~of~~ 900 mL/h over 2 and 3 sites, respectively). SC infusion of IGI, 10% solution will begin within 10 minutes of completion of SC infusion of rHuPH20 solution.
IGI, 10% solution: SC infusion, to be administered via a peristaltic infusion pump with programmable infusion rates and infusion volumes at 1 to 3 infusion sites per infusion day, with step-wise increases in infusion rate. **IGI 10% solution may be administered at 1, 2, or 3 infusion sites. The recommended site(s) for the infusion of HYQVIA/HyQvia are the middle to upper abdomen and thighs.**
~~The~~**For the** initial 2 infusions~~are given at~~, **it may be delivere**d an infusion rate of 10 to 240 mL/h per infusion site for subjects ≥40 kg and 5 to 80 mL/h per infusion site for subjects <40 kg, as tolerated by the subject and/**or** at the discretion of the investigator.
For subsequent administrations, infusion rate may be increased as tolerated by the subject and at the discretion of the investigator up to 300 mL/h per infusion site (or up to a total of 600 mL/h over 2 sites if bifurcated needle set is used, or up to a total of 900 mL/h over 3 sites if trifurcated needle set is used) for subjects ≥40 kg.

For subjects weighing <40 kg, infusion rates of up to 160 mL/h per infusion site (or up to a total of 320 and 480 mL/h over 2 and 3 sites if bifurcated and trifurcated need set is, respectively). **Prior to subjects being allowed to infuse at these higher infusion rates in the home setting, this should first be conducted under medical supervision in the clinic setting.** At high infusion rates above 750 mL/h (if trifurcated needle set for 3 infusion sites is used), 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.

Site of administration: ~~Bifurcated and trifurcated needle sets are to be used for 2 and 3 infusions, respectively. The recommended site(s) for the infusion of HYQVIA/HyQvia are the right and left middle to upper abdomen and the right and left thighs.~~ These rates should not be exceeded unless the investigator determines that higher infusion rates could be attempted and ~~so~~**as** long as the higher infusion rates are attempted under medical supervision in the clinic setting, prior to allowing their use in the home setting.

Site of administration: **Bifurcated and trifurcated needle sets are to be used for 2 and 3 infusions, respectively. The recommended site(s) for the infusion of HYQVIA/HyQvia are the middle to upper abdomen and the thighs.**

Volume of infusion per site: IGI~~,~~ 10% solution may be administered at 1, 2, or 3 infusion sites with a maximum infusion volume of up to ~~600 mL for subjects weighing ≥40 kg or up to~~ 300 mL per infusion site for subjects weighing <40 kg, as tolerated. . 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. One to 3 sites can be used at the discretion of the investigator and subject based on tolerability and total IgG dose volume for the individual subject. ~~If a subject's IgG dose per~~**Should the total infusion volume that is to be administered exceed either 1200 mL for subjects ≥40** kg ~~of body weight on a given day exceeds 1.3 g/kg/day,~~ or ~~exceeds the SC~~ **600 mL for subjects <40kg, or exceed the** maximum infusion volume ~~the~~**a** subject can tolerate ~~not to exceed 1200 mL/~~**on a given infusion** day, **then** the ~~HYQVIA/HyQvia~~**total** dose may be administered over multiple days as divided doses ~~with~~**a recommended** 48 to 72 ~~hours between doses~~**h apart** (eg, Day 1 and Day 3 of a given infusion cycle**, but left to the investigator's discretion**) to allow ~~absorption of infusion~~ **the infused** fluid ~~at infusion site(s).~~**to be absorbed.**

Note: The volume (mL) of infusion solution to be administered will be calculated using the subject's body weight measured at baseline. Adjustment based on body weight changes during the course of the study is not planned, however it may be done if deemed medically necessary by the investigator (eg, clinically significant

body weight change). After baseline, for study visits where the subject's body weight is measured (see Table 21 2, 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.

At a few selected study sites, subjects may be asked to permit still photographs of the infusion sites, which will be used for educational and demonstration purposes, both within and external to the study. Only the infusion site will be photographed, and no identifying features will be included. A third party company will manage the collection of still photographs. Subjects who agree will sign a separate consent.

Purpose for Change: Information for sites.

10. **Synopsis, Section 13.5 (Treatment Preference)**

Description of Change: Deleted:

~~At a few selected study sites, subjects will be asked to utilize two new approved devices to facilitate an easier administration process for the delivery of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia). The subject or Caregiver will be required to demonstrate a new self proficiency checklist to assure the understanding of how to utilize the new devices. The subject will be asked to perform a an extra patient satisfaction, and treatment preference survey prior to starting the use of the new devices and then at final termination visit as currently planned. Subjects who agree will sign a separate consent.~~ (synopsis)

~~An additional treatment preference questionnaire will be requested for a select number of subjects prior to the use of two new approved devices to facilitate an easier administration process for the delivery of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia).~~

(Section 13.5)

Purpose for Change: No longer relevant to this study.

11. **Synopsis, Section 14.5 (Planned Final Analysis of the Study)**

Description of Change: Added: **In addition to the interim analysis, Study 161505 safety data available at time of data cut for Study 161403 interim safety analysis (details in study protocol) will be summarized, in order to assess the long-term safety of HYQVIA.**

Deleted: ~~Data from the analyses will be used to monitor the safety and tolerability of the IP in the study and to update the scientific community on the progress of the study at the scientific meetings.~~

Purpose for Change: Not relevant to this study.

12. **Section 6 (BACKGROUND INFORMATION)**
Description of Change: Revised text as follows "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.[15,16]"
Purpose for Change: Correction.

13. **Section 6.1.1.1 (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.

14. **Section 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, April 1996~~ **ICH GCP R2, November 2016**), Title 21 of the US Code of Federal Regulations, the EU Clinical Trial Regulation EU No. 536/2014 and 2005/28/EC, **the Declaration of Helsinki,** and applicable national and local regulatory requirements.
Purpose for Change: Updated regulatory statute.

15. **Section 8.8 (Source Data),**
Section 10.3.2.1 (SC Infusion Visits [Including Home Infusions]), and
Section 10.6 (Subject Diary and Patient Reported Outcomes)
Description of Change: added new text "Infusion Data worksheet"
Purpose for Change: Clarification for sites.

16. **Section 10.3 (Screening and Study Visits)**
Description of Change: Deleted: "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."
Purpose for Change: Clarification for sites.

17. **Section 10.3.2 (Treatment Period)**
Description of Change: Added text "For detailed procedures and assessments, see Table 21 1 and Table 21 2."
Purpose for Change: Clarification for sites.

18. **Section 10.3.3 (Study Completion/Early Termination Visit)**
Description of Change: Revised text:
1. Subjects may **be requested to** complete **treatment in the study, may be as soon as the subject participating country gets market authorization for the treatment of CIDP in either US or EU (whichever comes later).** ~~a maximum of 2.5 years of treatment (or up to 3 years if mandated by regulations).~~ Study completion assessments are to be conducted on the day of the final infusion. This will mark the subjects' completion of the study.
2. A subject may withdraw their participation in the study or be discontinued from the study prior to completing treatment ~~for 2.5 years (or up to 3 years if mandated by regulations)~~. These subjects will be asked to undergo an early termination visit at the study site prior to discontinuation from the study.
Purpose for Change: Revised study duration upwards.

19. **Section 10.5.1 (Immunizations)**
Description of Change: Added text clarifying that seasonal influenza vaccines are permitted during the study.
Purpose for Change: Clarification for sites.

20. **Section 10.6 (Subject Diary and Patient Reported Outcomes):**
Description of Change: added: **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.**
…
…. **for patient reported data. An Infusion Data worksheet will serve as an additional source document.**
Purpose for Change: Clarification for sites.

21. **Section 12.1.2.3 (Safety Reporting):**
Description of Change: revised text "The sponsor will ensure that all relevant information about 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~~**2005/28/EC**]**, and Clinical Trial Regulation EU No. 536/2014**). The sponsor will comply with applicable laws/requirements for reporting SUSARs and all other SAEs to the ECs and investigators."
Purpose for Change: Updated regulatory statutes.

22. **Section 12.7.5 (Viral Serology Tests – new section)**
Added text:
Viral Serology Tests
The need for HIV and Hepatitis serology should be determined by the PI based upon clinical assessment and interval medical history. Serum samples may be collected for viral serology testing for HAV antibody, hepatitis B surface antigen (HBsAg), HCV antibody, and HIV-1/HIV-2 antibody. Additional tests, such as hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and/or nucleic acid tests, may be performed as considered necessary by the PI. 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.
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.
See Section 21.3 for detailed sample collection timepoints.
Purpose for Change: Guidance for sites.

23. **Section 12.7.8 Trough Serum IgG**
Description of Change: "Following baseline assessment, trough serum IgG samples must be collected on the day of the **site-administered (see Table 21-1)** 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) just prior to the start of the infusion."
Purpose for Change: To clarify that trough serum IgG will only be taken before infusions done at sites (and not at home or other infusions).

24. **Section ADDED:**
12.7.10.1 Guidance on Reporting and Assessing rHuPH20 (hyaluronidase) antibody test results
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 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 AEs occurring upon or after subsequent SC 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.
Purpose for Change: Text was added to clarify that neutralizing antibodies do not have to be reported as AEs.

25. **Section 12.7.11 (Back-up Samples and Biobanking)**
Description of Change: Added text "The need for HIV and hepatitis serology should be determined by the PI based upon clinical assessment and interval medical history."
Purpose for Change: Clarification for sites.

26. **Section 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.

27. **Section 14.1 (Sample Size and Power Calculations)**
Description of Change: The following text was revised: **Not applicable. This study is an extension to Study 161403. As indicated in Section 7.1, the purpose of this study is to assess the long-term safety, tolerability, and immunogenicity of HYQVIA in subjects with CIDP who have completed Study 161403 Epoch 1 without CIDP worsening. Enrollment in Study 161505 is open to subjects who have completed Study 161403 Epoch 1 without CIDP worsening and who have provided informed consent. The planned enrollment is 174 subjects, of whom approximately 148 subjects were assumed will complete the study; therefore, a maximum of 148 subjects are expected to enroll in the extension**.
~~The purpose of this non-comparative study is to collect long-term data on safety, tolerability, and immunogenicity from subjects who completed Study 161403 Epoch 1 without CIDP worsening. An estimated maximum of 149 subjects are expected to qualify for enrollment in this study, based on the planned enrollment and anticipated discontinuation rate in Study 161403. The study is not statistically powered.~~
Purpose for Change: Clarification.

28. **Section 8.6 (Study Stopping Rules),**
Section 17.4 (Data Monitoring Committee)
Description of Change: Description of the Internal Safety Review Board (ISRB) was deleted and replaced with new text describing the Data Monitoring Committee (DMC).
Purpose for Change: Administrative change.

29. **Sections 21.2 (Schedule of Study Procedures and Assessments) and**
Section 21.3 (Clinical Laboratory Assessments)
Description of Change: Added table row and text to table footnotes specifying that an extra urinalysis sample may be needed. Added footnote to clarify timing of telephone follow-ups. Modified footnote text to clarify that the need for HIV and hepatitis serology should be determined by the PI based upon clinical assessment and interval medical history.
Purpose for Change: Clarification.

22. SUMMARY OF CHANGES

Protocol 161505: **Amendment 1:** 2016 JUN 27

Replaces: Original: 2016 JAN 20

In this section, changes from the previous version of the protocol, dated 2016 JAN 20, are described and their rationale is given.

1. Throughout the document
   Description of Change: Minor grammatical and/or administrative changes that do not substantively affect the study conduct or subject safety have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. 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. Most of Section 12.1.2.3 was deleted. Section 12.3 was updated from eCRF reporting to SAE Report Form reporting.
   Purpose for Change: The EDC system cannot pull all information on to the form which is required for Baxalta GDS. EDC should be re-programmed. Most of the text in Section 12.1.2.3 was no longer needed as it describes processes for electronic SAE reporting. Section 12.3 updates were made to reflect the changes from eCRF reporting of SAEs to paper reporting.

3. Throughout the document
   Description of Change: The study protocol has been amended to incorporate subjects who participated in Study 161601, a Phase II Safety, Tolerability and Immunogenicity Study of HYQVIA/HyQvia in CIDP. Relevant text was changed to maintain consistency throughout the document with additional text added to indicate that subjects may have participated in Study 161601 or Study 161403.
   Purpose for Change: To specify that eligible subjects may also be recruited from Study 161601.

4. Throughout the document
   Description of Change: The maximum treatment duration was clarified to extend up to 3 years if mandated by regulations.
   Purpose of Change: To comply with regulations for trial duration in certain countries (eg, United Kingdom, Israel).

5. Synopsis, Section 8.2 Overall Study Design
   Description of Change: Text was added to clarify the location(s) for infusion for subjects entering from Study 161403 and Study 161601, including study site infusion center, subject's home, other suitable locations, and the conditions for these options.
   Purpose for Change: To clarify the possible locations for subjects and specify the differences for subjects enrolled from Study 161403 and Study 161601 to receive the study infusion.

6. Synopsis, Section 8.2 Overall Study Design, Section 8.3 Duration of Study Periods and Subject Participation, Section 9.3 Withdrawal and Discontinuation
   Description of Change: The following criterion was deleted: "Study termination upon commercial availability of HYQVIA/HyQvia in the subject's country (or decision is made to not seek market authorization in that country)" and additional details specifying other reasons for extension of study participation. Related text in Section 8.2 was updated to reflect the changes in Section 8.3.
   Purpose for Change: This reason for subject discontinuation is no longer applicable.

7. Synopsis, Section 8.7.3 Administration
   Description of Change: Text was added to clarify the determination of infusion rate based on subject weight, and to specify the differences for administration with single, bifurcated, or trifurcated SC needle sets.
   Purpose for Change: To clarify infusion rate for each subject based on body weight and address how to proceed following an occlusion alarm; and how the volume is distributed over multiple sites.

8. Synopsis, Section 6.3 Population to be Studied, Section 8.2 Overall Study Design, Section 14.1 Sample Size and Power Calculations
   Description of Change: The number of potential subjects was increased from 124 to 149.
   Purpose of Change: To acknowledge the potential to accrue 149 subjects.

9. Section 5 List of Abbreviations, Section 15 Direct Access to Source Data/Documents, Quality Control and Quality Assurance, Section 17 Ethics, Section 18 Data Handling and Record Keeping, Section 19 Financing and Insurance, Section 20 Publication Policy
   Description of Change: An abbreviation for the term Clinical Trial Agreement (CTA) was added, and the text was updated accordingly.
   Purpose for Change: Updates to align with new template text.

10. Section 6 Background Information
    Description of Change: A description of Study 161403 was added.
    Purpose for Change: To update the background information to include an additional parent study for Study 161505.

11. Section 6.5.2 GAMMAGARD LIQUID/KIOVIG
    Description of Change: The following text was added "GAMMAGARD LIQUID/KIOVIG will not be used as an investigational drug in this study. However, GAMMAGARD LIQUID/KIOVIG—also known as IGI, 10%—is the immunoglobulin product in HYQVIA/HyQvia. Information on this product is therefore also presented:"
    Purpose for Change: To add clarification as both drugs are used in some of the parent studies.

12. Section 8.2 Overall Study Design
    Description of Change: The word "relapse" was clarified to "study end", and the phrase "predetermined study end for the specific country in which the subject is participating" was clarified to "premature termination for any reason described in Section 8.3."
    Purpose for Change: To provide a complete list of study termination criteria.

13. 16.1 Investigator's Responsibility, Section 16.3 Monitoring, 16.4 Auditing, 17.3 Informed Consent, 18.3 Document and Data Retention
    Description of Change: The phrase "national and local" was added to define the regulatory requirements.
    Purpose for Change: To comply with updated template text.

14. Section 8.7.2 Preparation and Storage of Pooled Products
    Description of Change: The following text was added "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. Synopsis, Section 8.7.3 Administration
    Description of Change: Recommendations were modified to include a trifurcated SC needle set.
    Purpose for Change: To add the option to administer the investigational product simultaneously at 3 body sites using a trifurcated needle set.

16. Section 10.1 Informed Consent and Enrollment, Section 10.2 Subject Identification Code, Section 10.3 Screening and Study Visits, 12.5 Medical, Medication, and Non-Drug Therapy History
    Description of Change: Language was modified to clarify that each individual providing informed consent is considered a subject.
    Purpose for Change: To comply with updated template text.

17. Throughout the document, Section 10.3.1 Screening and Baseline Period
    Description of Change: The screening period or visit is referred to as "baseline" throughout the document for consistency, and the statement "which may last up to 4 weeks" has been deleted.
    Purpose of Change: To clarify screening procedures for the Extension Study.

18. Section 10.5 Medications and Non-Drug Therapies
    Description of Change: "Other medications that are not permitted during the course of the study" was clarified to include "Other IgG products" only.
    Purpose of Change: To clarify that the only IgG product a subjects may take is the investigational product.

19. Section 10.6 Subject Diary and Patient Reported Outcomes
    Description of Change: A bullet point was added for "Infusion-related information (see Section 10.3.2.1)", and additional information was added on how the diary data would be imported and validated.
    Purpose for Change: To add additional outcomes listed in Section 10.3.2.1 not considered "Infusion records", and to add clarification on the data transfer.

20. 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.

21. Section 12.1.1.1 Serious Adverse Event
    Description of Change: "Uncomplicated pregnancies" were clarified to refer to only those following maternal exposure to the investigational product.
    Purpose for Change: To clarify that uncomplicated pregnancies following paternal exposure to the investigational product are not considered AEs.

22. Section 12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)
    Description of Change: Standard template language was added to define SUSARs.
    Purpose for Change: To define SUSARs per Baxalta protocol template requirements.

23. Section 12.7.8 Trough Serum IgG
    Description of Change: The following language was deleted "The baseline trough serum IgG sample will be collected prior to the last SC infusion during the Study Completion (end of SC treatment) Visit in the 161403 study."
    Purpose for Change: To clarify when baseline trough serum IgG samples will be collected regardless of parent study participation by each subject.

24. Section 12.7.11 Backup Samples/Biobanking
    Description of Change: The following language was added: "Baseline and end-of-trial serum/plasma backup samples will be stored for possible testing of pathogens for no more than 2 years after the final study report has been completed. Other backup samples that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test, investigation of an AE or suspected seroconversion). Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and subsequently the samples will be destroyed."
    Purpose for Change: Updated based on regulatory feedback.

25. Section 16.6 Laboratory and Reader Standardization
    Description of Change: The following phrase was added "Inter-laboratory standardization methods will be described in the data management plan as needed."
    Purpose for Change: To allow for use of the appropriate standardization methods as needed.

26. Section 17.4 Data Monitoring Committee
    Description of Change: Language was added to indicate that individuals on the internal safety review board may not be actively recruiting subjects and that the board may recommend stopping the study based on safety signals or medical concerns or if the treatment is proven to be not beneficial.
    Purpose for Change: To clarify the roles of individuals on the internal safety review board.

27. Figures and Tables
    Description of Change: Titles were edited for brevity and clarity.
    Purpose for Change: To improve understandability.

28. Section 12.7.9 Anti-rHuPH20 Antibodies, Section 12.7.10 Immunogenicity Panel, Section 21.1 Study Flow Chart, Section 21.1 Schedule of Study Procedures and Assessments, Section 21.3 Clinical Laboratory Assessments
    Description of Change: Study visit numbers were updated according to addition of subjects from Study 161601.
    Purpose for Change: To accurately reflect at which weeks study visits would occur.

29. Synopsis, Section 14.4 Method of Analysis, Section 14.5 Planned Interim Analysis of the Study
    Description of Change: The planned statistical analysis was updated. Subgroup analysis was removed and changed to single group analysis.
    Purpose for Change: Decision on subgroup analysis will be determined in the SAP.

30. Section 14.4.2.1 Exploratory Efficacy
    Description of Change: The phrase "Kaplan Meier" was deleted.
    Purpose for Change: Biostatistics team members re-evaluated the most appropriate study testing.

31. Synopsis, 8.7.3 Administration
    Description of Change: The maximum infusion volume was define as 1200 mL/d.
    Purpose for Change: To clarify the maximum infusion volume of the investigational product.

32. Table 21.2 Schedule of Study Procedures and Assessments, Table 21.2 Schedule of Study Procedures and Assessments
    Description of Change: Cells were merged on the row marked "Infusion". Two footnotes were added to clarify that infusions will be administered according to the schedule of each subject's previous study (every 2, 3, or 4 weeks), and to specify the visit windows.
    Reason for Change: To improve clarity of the table.

33. Section 8.7.4 Description of Treatment, Table 21.1 Schedule of Study Procedures and Assessments
    Description of Change: The following sentences were added "All attempts should be made to maintain the original infusion schedule for subjects. If a subjects receives a dose out of window, the dose will still be given prior to the next infusion, if possible. Patients should return to the original planned visit schedule even if an infusion was given out of window."
    Reason for Change: To clarify that each subject should be kept on the same infusion schedule as in the parent study.

34. Table 21.1 Schedule of Study Procedures and Assessments
    Description of Change: Footnote a was added to the column marked "First Treatment Visit in Extension Study" and row marked "Laboratory Assessment".
    Purpose for Change: To improve clarity.

35. Table 21.2 Clinical Laboratory Assessments
    Description of Change: The following sentence was added to footnote j: "The hemolytic anemia panel be conducted only in the event of a drop in Hgb of 1 g/dL or more compared to baseline value."
    Purpose for Change: To clarify that the hemolytic panel will be conducted only if there is a decrease in hemoglobin.

36. Section 10.2 Subject Identification Code
    Description of Change: The study site and subject numbers were clarified to be 3-digit numbers.
    Purpose for Change: To clarify the subject identification code that will be used by this study to conform to other related studies.