



IgPro20_3004

Multicenter, open-label extension study to investigate the long-term safety and efficacy of IgPro20 in maintenance treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) in subjects completing study IgPro20_3003

Statistical Analysis Plan

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
BMI	Body mass index
bpm	Beats per minute
bw	Body weight
CIDP	Chronic inflammatory demyelinating polyneuropathy
DRM	Data review meeting
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFNS	European Federation of Neurological Societies
EQ-5D	EuroQoL 5-Dimension Questionnaire
ER	Erroneous record
EU	European Union
GBS	Guillain-Barré Syndrome
HRQL	Health-related quality of life
Ig	Immunoglobulin
IgG	Immunoglobulin G
IgPro20	CSL Behring's 20% SCIG preparation (trade name: Hizentra [®])
INCAT	Inflammatory Neuropathy Cause and Treatment
ITP	Immune thrombocytopenic purpura
ITTS	Intention-to-treat set
IV	Intravenous
IVIG	Intravenous immunoglobulin
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of uncertain significance
mm	Millimeter
mmHg	Millimeters of mercury
MRC	Medical Research Council
PNS	Peripheral Nerve Society
PPS	Per protocol set
QoL	Quality of life
RCA	Range change abnormal
RCAH	Range change abnormal high
RCAL	Range change abnormal low
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SD	Standard deviation
SDS	Safety data set

SOC	System organ class
SRC	Safety review committee
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States of America
VAS	Visual analog scale
WHO	World Health Organization
WPAI-GH	Work Productivity and Activity Impairment Questionnaire for General Health

1 INTRODUCTION

The current study, IgPro20_3004, is an extension study to the pivotal study IgPro20_3003. Clinical studies have demonstrated the clinical efficacy and safety of using intravenous immunoglobulins (IVIGs) to treat CIDP (Kieseier et al., 2008; Eftimov et al., 2009; Hughes et al., 2008). Study IgPro20_3003 was conducted to provide evidence of subcutaneous immunoglobulin (SCIG) as an alternative treatment option for CIDP in demonstrating safety and efficacy of IgPro20 as maintenance therapy in subjects treated with IVIG and switched to SCIG.

The current extension study will provide further insight into the long-term safety and efficacy of treatment with IgPro20.

This statistical analysis plan (SAP) is based upon the following study documents:

- Study Protocol IgPro20_3004, Amendment 3.0 (December 8, 2015)
- Electronic Case Report Form (eCRF), Version 4.0 (May 08, 2015).

2 STUDY OBJECTIVES

2.1 Primary Objectives

To evaluate the long-term safety of IgPro20.

2.2 Secondary Objectives

- To evaluate the long-term safety of IgPro20 by dose.
- To evaluate the efficacy of IgPro20.

2.3 Exploratory Objectives

- To evaluate health-related quality of life (HRQL).
- To evaluate serum IgG levels.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label prospective, multicenter extension study for subjects who have completed SC Week 25 or were successfully rescued from a CIDP relapse during the SC Treatment Period of the preceding pivotal study IgPro20_3003. All eligible subjects must transition directly from study IgPro20_3003 to study IgPro20_3004. Eligible subjects will initially receive an open-label IgPro20 dose of either 0.2 or 0.4 g/kg bw, and will be treated weekly for 48 weeks. Predefined dose adjustments will be applied either at the Week 25 assessment or at any other point during treatment, depending on subject cohort and CIDP outcome during IgPro20 exposure.

There are two cohorts of subjects participating in this extension study:

Subjects receiving an initial IgPro20 dose of 0.4 g/kg bw

Subjects meeting eligibility criteria prior to Amendment 1 approval will receive an initial IgPro20 dose of 0.4 g/kg bw. Subjects who experience and successfully recover from CIDP relapse prior Week 25 (successful recovery is defined as a confirmed return of the total adjusted INCAT score back to, or better than, the baseline score within 4 weeks \pm 2 days) will remain at this maintenance dose until Week 48, or until the next CIDP relapse, at which time the subject will be discontinued from IgPro20 treatment. Subjects who have been CIDP relapse-free at Week 25 will be dose-adjusted to 0.2 g/kg bw, and will remain at this reduced dose until Week 48 or the next CIDP relapse, whichever occurs first. Any subject who experiences a CIDP relapse after Week 25 will be dose-adjusted to 0.4 g/kg bw, and will remain at this maintenance dose until Week 48 if the subject successfully recovers from the CIDP relapse. Subsequently, if the subject has another CIDP relapse after recovering from the first CIDP relapse, or does not recover from the first CIDP relapse, this subject will be discontinued from IgPro20 treatment.

Subjects receiving an initial IgPro20 dose of 0.2 g/kg bw

Subjects meeting eligibility criteria after Amendment 1 approval will receive an initial IgPro20 dose of 0.2 g/kg bw. Any subject who experiences a CIDP relapse at any point during treatment exposure will be dose-adjusted to 0.4 g/kg bw, and will remain at this maintenance dose until Week 48 if the subject successfully recovers from the CIDP relapse. Subsequently, if the subject has another CIDP relapse after recovering from the first CIDP relapse, or does not recover from the first CIDP relapse, this subject will be discontinued from IgPro20 treatment.

The last dose of IgPro20 is administered at Week 48; after the completion visit (Week 49), the subject is treated at the discretion of the investigator with standard of care therapy, i.e. the subject will return to the CIDP treatment prescribed by the treating physician. If a subject has a CIDP relapse with less than 4 weeks remaining before the completion visit (Week 49), the subject will continue on the study and have the completion visit (Week 49) as planned followed by treatment at the discretion of the investigator with standard of care therapy.

A steering committee and a safety review committee (SRC) have been created. The steering committee will provide overall study supervision, scientific support, oversight for substantial amendments to the protocol, and advice to the investigators on all aspects of the study, including support on recruitment/feasibility of the study (i.e., education or lectures) and the preparation of publication(s). The SRC will be an advisory group of experts with a mandate to periodically review and evaluate safety data to provide recommendations regarding ongoing safety of study subjects. See [Section 4.8.8](#) for further details.

Analyses presented to the SRC for safety review and interim analyses are described in the SRC Charter and SRC SAP and are not addressed in this SAP.

3.1.1 Treatment Period

The investigator (or delegate) will administer or dispense IgPro20 only to subjects included in this study following the procedures set out in the study protocol.

All subjects enrolled in this study will receive an initial weekly dose of either IgPro20 0.4 or 0.2 g/kg bw. Depending on when the subject is evaluated for eligibility, dose adjustments will be applied as described in [Section 3.1](#).

3.1.2 Completion visit and follow up

The completion visit will be performed at Week 49 for subjects who complete the study or at the time of discontinuation for subjects who discontinue.

3.2 Study Variables

3.2.1 Efficacy Variables

Efficacy will be assessed on the basis of the following variables:

3.2.1.1 INCAT Total Score

The INCAT total score is a scale ranging from 0 to 10 that covers the functionality of legs and arms (see [Appendix 1: INCAT Score](#)). Arm and leg scores are recorded which range from 0 to 5. The INCAT total score is the sum of these 2 scores. Lower INCAT scores correspond to higher functionality.

3.2.1.2 Mean Grip Strength

Grip strength in kiloPascal (kPa) will be measured by the Martin Vigorimeter (Tuttlingen, Germany). At each assessment, the grip strength for each hand will be measured 3 times. The mean grip strength from the 3 measurements will be recorded for each hand (dominant / non-dominant).

3.2.1.3 Medical Research Council (MRC) Sum Score

The following 8 bilateral muscle pairs will be assessed using an adapted version of the MRC sum score (Kleyweg et al., 1991; Leger et al., 2001; see [Appendix 2: MRC Sum Score](#)).

- Shoulder abduction
- Elbow flexion
- Wrist extension
- Index finger abduction
- Hip flexion
- Knee extension
- Foot dorsiflexion
- Great toe dorsiflexion

Scores are documented for the left and right side of the body, for each muscle pair. Higher scores correspond to higher functionality. The MRC sum score is the sum of all 16 muscle scores, and ranges from 0 (paralysis) to 80 (normal strength).

3.2.1.4 R-ODS

The R-ODS is an outcome measure that captures activity and social participation in subjects with immune-mediated peripheral neuropathies (CIDP, Guillain-Barré Syndrome [GBS], or monoclonal gammopathy of uncertain significance [MGUS]; [van Nes et al., 2011](#)). The 24-item questionnaire covers a wide range of tasks of daily life that are each to be rated as “impossible to perform”, “able to perform with difficulties”, “easily performed” or “not applicable” (see [Appendix 3: R-ODS](#)). The responses are given a numerical score of 0, 1, and 2 respectively.

The R-ODS summed raw score is calculated by summing the numerical scores, with values ranging from 0 to 48. Missing item responses will be dealt with as detailed in [Appendix 3](#). The summed raw score will then be transformed to a centile score (see [Appendix 3: R-ODS](#) which ranges from 0 (most severe activity and social participation limitations) to 100 (no activity and social participation limitations). Higher scores correspond to higher functionality.

3.2.2 Safety Variables

Subject safety will be continually monitored throughout the study. AEs, including serious adverse events (SAEs), will be documented at each site visit. Concomitant medications will be reviewed at each site visit. Other safety measures are as follows:

- Hematology: hemoglobin, hematocrit, platelets, erythrocytes, leukocytes, differential count (neutrophils, basophils, eosinophils, lymphocytes, and monocytes), reticulocytes, and direct antiglobulin test. Serum chemistry: total bilirubin, indirect bilirubin, creatinine, blood urea nitrogen, lactate dehydrogenase, creatine kinase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, C-reactive protein, haptoglobin, and gamma glutamyl transferase.
- Virology assessments to exclude Human immunodeficiency virus type 1/type 2 (HIV-1, HIV-2), hepatitis C virus, and hepatitis B virus.
- Urine pregnancy test.
- Physical examination: general appearance, skin, eyes, ears/nose/throat, cardiovascular, pulmonary, abdomen, and neurological. Any unfavorable findings considered by the investigator as CS at baseline will be documented in the medical history of the subject. Unfavorable changes occurring thereafter until the completion visit will be documented in the electronic case report form (eCRF) as an AE.
- Neurological examination: cranial nerves, motor system and reflexes, coordination and gait, sensory system. Any unfavorable findings considered by the investigator as CS at baseline will be documented in the medical history of the subject. Unfavorable changes occurring thereafter until the completion visit will be documented in the eCRF as an AE.
- Japan subjects only: 12-lead electrocardiograms (ECGs)

3.2.3 Pharmacokinetic and Pharmacodynamic Variables

Pharmacokinetic variables will be restricted to serum IgG levels

No pharmacodynamic analysis will be performed.

3.2.4 Health-related Quality of Life Variables

The effect of IgPro20 on quality of life will be assessed on the basis of the following instruments. All HRQL instruments will be completed by the subjects themselves.

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

The EQ-5D is a simple, generic measure of health status, consisting of 2 components: a 0 to 100 mm visual analog scale (VAS) assessing overall health on the day of assessment and 5 questions covering the following 5 health dimensions: mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some/moderate problems, and extreme problems (see [Appendix 4: EQ-5D-3L](#)).

The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled 0 = "worst imaginable health state" and 100 = "best imaginable health state". This information will be used as a quantitative measure of health state.

3.2.4.2 Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM (version 1.4) is a 14-item general instrument that measures the major dimensions of satisfaction with a medication ([Atkinson et al., 2004](#)). Scores will be calculated for the effectiveness (3 items), side effects (5 items), convenience (3 items), and global satisfaction (3 items) scales (see [Appendix 5: TSQM \(version 1.4\)](#)). Scores on the TSQM scales range from 0 (indicating poor satisfaction) to 100 (indicating perfect satisfaction).

3.2.4.3 Work Productivity and Activity Impairment Questionnaire for General Health (WPAI-GH)

The WPAI-GH questionnaire was developed to measure the effect of general health and symptom severity on work productivity and regular activities ([Reilly et al., 1993](#)). WPAI-GH outcomes can be expressed as impairment percentages (or item scores), with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, in the following areas: absenteeism, work impairment, work productivity loss and activity impairment. See [Appendix 6: WPAI-GH V2.0](#) for the questions of the WPAI-GH and the derivation of the item scores.

3.2.4.4 Subject Preference for Treatment

Subject preference for pre-study IV treatment or on-study SC treatment will be assessed via a questionnaire consisting of 2 options (prefer current treatment [SCIG] or prefer previous treatment [IVIG]), with a selection option of predefined reasons for the preference (see [Appendix 7: Subject Preference for Treatment Score](#)).

4 STATISTICAL METHODS

4.1 General Considerations

The reference visit (baseline) is used to assess changes from baseline using summary statistics and is defined as the Week 1 visit.

In case of multiple measurements, the last measurement before first intake of study medication will be used.

Descriptive statistics for continuous data will include the number of observations, mean, standard deviation (SD), median, lower and upper quartiles (25th and 75th percentiles), minimum, and maximum, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to 1 more decimal place than the raw data recorded in the database. The SD will be reported to 2 more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be 4 for any summary statistic.

Descriptive statistics for categorical data will include the number of subjects providing data at the relevant time point (N), frequency counts and percentages.

Percentages will be presented to 1 decimal place. Percentages will not be presented for zero counts (the zero count will be presented). Percentages will be calculated using the number of subjects in the population/treatment group as the denominator, unless otherwise specified.

Changes from baseline will be calculated as: (post baseline value) – (baseline value). Categorical data will be summarized using shift tables where appropriate.

Confidence intervals (CIs) will be presented to 1 more decimal place than the respective point estimate.

The treatments will be labeled as ‘0.2 IgPro20’ and ‘0.4 IgPro20’.

Results from unscheduled visits will be listed but not included in summary tables.

Listings will be presented by subject, visit and treatment, as appropriate. Age, sex and race will be reported on all by-subject listings unless otherwise specified. Age will be presented as the number of complete years based on the derived age according to [Section 4.4](#). Sex will be abbreviated as follows: female (F) and male (M). Race will be abbreviated as follows: American Indian or Alaska Native (AI), Asian (AS), Black or African American (BL), Native Hawaiian or other Pacific Islander (NH), White (WH) and Other (OR).

All report outputs will be produced using SAS[®] version 9.1.3 or higher in a secure and validated environment.

4.1.1 Assignment of Treatment Periods

Treatment periods for 0.2 IgPro20 and 0.4 IgPro20 start with the first infusion of respective treatment and end with the first infusion of another dose group or withdrawal date or last study visit.

Non-adjacent periods for the same dose group will be listed separately but combined for summary tables.

For tabular summaries presented by dose group, subjects who underwent dose changes, either by receiving a reduced dose of 0.2 g/kg bw at Week 25 or an increased dose of 0.4 g/kg bw due to a CIDP relapse, will be summarized using the most recent dose prior to the subject's assessment. Therefore, it is possible that a subject will be tabulated in both 0.2 g/kg and 0.4 g/kg groups.

Each visit of a subject will be assigned to the dose group the subject received prior to that visit. The following virtual visit will be additionally created per dose group:

- the last post-dose observation
- relapse visit

All events (AEs, concomitant medication, etc) will be assigned to the treatment periods in which the events started, ie by comparison of start and stop dates and times of the treatment periods to the start date and time of the event. Partial dates will be handled according to [Section 4.7.4.3.1](#).

4.2 Study Subjects

4.2.1 Disposition of Subjects

The number and percentage, where applicable, of subjects will be presented overall for the total set:

- enrolled,
- For subjects meeting eligibility criteria under original Protocol
 - treated with initial dose of 0.4 g/kg bw IgPro20
 - experienced CIDP relapse §
 - switched at Week 25 to 0.2 g/kg bw
 - experienced CIDP relapse §
 - titrated to 0.4 g/kg bw
 - recovered from CIDP relapse ~
 - experienced new CIDP relapse §
 - completed the study as planned at Week 49
 - discontinued the study
 - with each reason for discontinuation #
- For subjects meeting eligibility criteria under Protocol Amendment 1 onwards
 - treated with initial dose of 0.2 g/kg bw IgPro20
 - experienced CIDP relapse
 - titrated to 0.4 g/kg bw
 - recovered from CIDP relapse ~
 - experienced new CIDP relapse §
 - completed the study as planned at Week 49
 - discontinued the study

- with each reason for discontinuation #
- Overall
 - experienced CIDP relapse §
 - recovered from CIDP relapse ~
 - completed the study as planned at Week 49
 - discontinued the study
 - with each reason for discontinuation#

Percentages will be calculating using

- the number of subjects in the total set for the overall group
- the number of subjects in the total set who met eligibility criteria under the original protocol
- the number of subjects in the total set who met eligibility criteria under protocol Amendment 1

except in the following cases:

- ~ percentages calculated using the number of subjects who relapsed
- § percentages calculated using the number of subjects treated at respective dose
- # percentages calculated using the number of subjects who discontinued.

A summary of the length of time in the treatment period, in weeks, will also be provided overall and by treatment (i.e. dose group) using descriptive statistics and based on SDS. In weeks this is defined as:

Length of time in the treatment period (weeks) =
 $(\text{date of last dose} - \text{date of first dose} + 1) / 7.$

Non-adjacent periods of the same treatment (i.e. dose group) will be summed up. Note: Subjects treated both with 0.2 g/kg bw and 0.4 g/kg bw IgPro20 will be counted in both groups with the corresponding time in the respective treatment period.

Length of time in the treatment period will also be analyzed by pre-study treatment group and status at end of Study IgPro20_3003 defined in [Section 4.7.4.6](#).

In addition, a summary of the time on study, in weeks, will also be provided overall using descriptive statistics and based on SDS. This is defined as:

Time on study (weeks) =
 $(\text{date of completion or withdrawal} - \text{date of first dose} + 1) / 7.$

The gap (days) between the last visit in study IgPro20_3003 and the first visit in study IgPro20_3004 will be derived for each subject and analyzed using descriptive statistics.

Gap between study IgPro20_3003 and IgPro20_3004 (weeks) =
 $(\text{date of first visit in IgPro20_3004} - \text{date of last visit in IgPro20_3003}) / 7.$

The following by-subject listings will be provided for subjects in the total set:

- Dates and labels of all visits (scheduled and unscheduled as well as phone calls) and start/stop times of all infusions.
- Subject disposition including reasons for withdrawal if applicable. The number of days in the treatment (i.e. dose) period(s) will also be calculated as defined above and presented.

4.2.2 Protocol Deviations

Any change, divergence, or departure from the study design or procedures of a research protocol that affects the subject's rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data constitutes a protocol violation. Changes or alterations in the conduct of the trial which do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are considered protocol deviations.

Protocol violations and the subjects and data affected by them will be determined at the data review meeting (DRM; see Section 4.3).

The impact of the protocol violations will be investigated by using the Total set and Per protocol set (PPS).

The number and percentage of subjects with a protocol violation will be provided, by treatment and type of deviation, based on the Total set. Deviations will be assigned to the treatment being administered at the time of the deviation. A deviation may be assigned to both treatments if it was a deviation which covered a study period during which both treatments were administered.

A by-subject listing of all protocol violations will be provided.

4.3 Analysis Populations

Analyses will be based on the following populations: total set, SDS and PPS.

A DRM (see Section 4.3) will be arranged to discuss all protocol deviations to decide which subjects will be excluded from certain analyses, and the minutes of this meeting will be documented and approved by CSL Behring prior to database lock.

The number and percentage of subjects in each analysis population will be presented, overall and by treatment, where appropriate. A by-subject listing of analysis population details will also be provided. This listing will include: center, subject identifier, an

inclusion/exclusion flag for each population and reason(s) for exclusion from each population. This listing will be based on the total set.

The primary population for the analysis of efficacy, serum IgG levels, and HRQL endpoints is the Total set. Efficacy, serum IgG levels, and HRQL summaries and analyses will also be performed for the PPS to assess the robustness of the results. The primary population for the analysis of the safety of the study treatment is the SDS. The total set will be used for disposition summaries.

For analyses based on a certain analysis population, a subject must have at least 1 post-reference visit assessment of a specific variable in order to be analyzed for that variable. For change from reference visit analyses, a valid reference visit value will also be required. Therefore, some subjects may not be included in the analysis of a particular efficacy variable, even though they are part of that analysis population.

4.3.1 Total Set

The total set consists of all subjects enrolled into the study, i.e., the subject's informed consent has been obtained. In the protocol this analysis set is referred to the Intention-to-Treat (ITT) Data Set.

4.3.2 Safety Data Set (SDS)

The SDS is based on all subjects of the Total Set who received at least 1 dose of IgPro20 in this study. The documented failure to take at least 1 dose of IgPro20 will lead to the exclusion of the subject from the SDS.

4.3.3 Per Protocol Set

The PPS consists of all subjects of the Total set without any protocol violation with a potential impact on the validity of the efficacy measurements. It is the set of subjects that participated in the study as intended. Protocol violations, their impact on the validity of the efficacy measurements, and their occurrence in individual subjects will be determined and documented in the Data Review Meeting prior to database lock. Premature withdrawal of subjects from the study is not considered as major protocol violation.

4.4 Demographic and Other Baseline Characteristics

Demographic variables (age [years], age category[18-65 years, > 65 years], sex, race, ethnicity, country, height [cm], body weight [kg], body mass index [BMI; kg/m²]), and BMI category [$< 25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$] will be summarized for Total set and PPS. Further, INCAT total score, mean grip strength [kPa], MRC sum score and R-ODS

centile score will be summarized using baseline values for Total set and PPS. All demographic analyses will be done by treatment (i.e. dose group) and overall.

Missing data will be handled as outlined in [Section 4.7.4.3](#).

Age at informed consent (in years) will be calculated as (Date of informed consent – Date of birth) / 365.25.

BMI at baseline will be calculated as Weight at baseline (kg) / (Height (m))². Height is recorded at the Screening visit of the IgPro20_3003 study.

Variables will be summarized using descriptive statistics.

Medical and surgical history will be summarized by treatment (i.e. dose group) and overall for the Total set.

Medical and surgical history will be classified using version 14.1 of the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized using counts and percentages and presented by system organ class (SOC) and preferred term. Subjects will only be counted once, regardless of how many conditions are included under the same SOC and preferred term.

A by-subject listing of demographic and baseline characteristics will be provided (including weight and BMI at baseline). By-subject listings of medical and surgical history will also be provided.

4.5 Concomitant Therapy

All concomitant therapy summaries will be based on the Total set.

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the September 2011 version of the World Health Organization (WHO) drug dictionary. Medication start and stop dates will be compared to the date of enrollment to allow medications to be classified as ‘prior’ or ‘concomitant’ for the study. Medications starting on or after the completion/withdrawal date will be listed but will not be summarized.

Medications with start and stop dates prior to the date of enrollment will be classified as prior medications for the study. Medications which are ongoing at enrollment or have a start date on or after the date of enrollment, and have a stop date after the date of enrollment, will be classified as concomitant medications for the study.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of enrollment. Medications will be assumed to be ‘concomitant’, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the date of enrollment.

Medications will also be classified as ‘concomitant’ if they are ongoing at (i.e. stop after) the date of enrollment or have a start date on or after the date of enrollment and prior to the date of completion/withdrawal. Concomitant medications will be assigned to all treatments received in the same time period as the concomitant medication (i.e. a medication may be assigned to both 0.4 and 0.2 IgPro20).

The following summaries of prior medications will be provided by treatment (i.e. dose group) and overall and the following summaries of concomitant medications will be provided by treatment group (i.e. dose group) and overall.

- Prior CIDP medications taken between completion visit of the pivotal study IgPro20_3003 and enrollment of study IgPro20_3004.
- Concomitant CIDP medications during the study.
- Other prior medications taken between completion visit of the pivotal study IgPro20_3003 and enrollment of study IgPro20_3004.
- Other concomitant medications taken during the study.

The number and percentage of subjects taking medications will be presented, by ATC class and preferred term. Note that a subject will only be counted once regardless of how many times they took medication included under the same preferred term.

Prior CIDP medications are defined as medications recorded on the *Prior and Concomitant Medications* eCRF page with an end date prior to the date of enrollment and the indication recorded as “Study Indication”. Concomitant CIDP medications are defined as medications recorded on the *Prior and Concomitant Medications* eCRF page with a start or end date on or after the date of enrollment and the indication recorded as “Study Indication”.

Other prior medications are defined as medications recorded on the *Prior and Concomitant Medications* eCRF page with an end date prior to the date of enrollment and the indication recorded as anything other than “Study Indication”. Other concomitant medications are defined as medications recorded on the *Prior and Concomitant Medications* eCRF page with a start or end date on or after the date of enrollment and the indication recorded as anything other than “Study Indication”.

A by-subject listing of all prior and concomitant medications will be provided, for subjects in the total set, and will include the dates of enrollment, start and stop date of medication and date of first IgPro20 infusion.

Prior and on-study prohibited medication use (includes other non-study IgGs, rituximab, alemtuzumab, plasma exchange, interferon, tumor necrosis factor-alpha inhibitors, fingolimod, cyclophosphamide, and any other systemic immunosuppressive medications, except those medications permitted during IgPro20_3003 participation) will be provided by subject listings only. A list of ATC codes for potentially prohibited medications is provided in [Appendix 8: Prohibited medications list](#).

4.6 Treatment Compliance

Weekly treatment compliance will be measured as a percentage ($= 100 \times [\text{volume administered per week} / \text{planned volume per week}]$) and summarized using descriptive statistics. A subject will be considered to be compliant for an SC week if the weekly compliance rate is between 80% and 120%. If a subject's weekly compliance rate is less than 80% or greater than 120%, they will be considered to be non-compliant with the study treatment for that week.

For the study duration of a subject, a subject will be considered to be compliant with the study treatment if they are compliant for at least 80% of his/her study duration in the SC Treatment Period. If a subject is non-compliant at more than 20% of his/her SC weeks, they will be considered to be non-compliant with the study treatment for the study overall.

Treatment compliance rates will be summarized for each SC week and overall for the SC Treatment Period, using descriptive statistics. The number and percentage of subjects that are compliant and non-compliant will also be presented, for each SC week and for the study overall.

Treatment compliance will be listed by subject.

4.7 Efficacy Evaluation

4.7.1 Primary Efficacy Endpoint

There is no primary efficacy endpoint in this study.

4.7.2 Secondary Efficacy Endpoints

4.7.2.1 Time Course of Total INCAT Score Over all Study Visits

INCAT arm, leg and total scores will be calculated as outlined in [Appendix 1: INCAT Score](#) and summarized by treatment (i.e. dose group) and visit, using descriptive statistics. The changes from baseline visit will be summarized at all post-baseline scheduled visits. Each visit of a subject will be assigned to the treatment (dose group) the subject received prior to that visit.

A by-subject listing of all INCAT scores (including total, arm and leg scores) will be provided for the entire study period, based on the total set and presenting visit and treatment. Total scores indicating a CIDP relapse (see [Section 4.7.2.2](#)) will be flagged, and date of relapse presented.

Analyses will be performed based on the Total set, and repeated for the PPS.

4.7.2.2 Time to First CIDP relapse

CIDP relapse based on adjusted INCAT score is defined as (*):

An increase of at least 1 INCAT total score point at post-baseline visit compared to baseline, excluding an increase in total INCAT total score of 1 point if this is only due to an increase in the arm score from 0 to 1.

OR

An unchanged total INCAT total score at a post-baseline visit compared to baseline, where the arm score decreased from 1 to 0 (not clinically meaningful improvement) and the leg score increased by 1 point (clinically meaningful worsening).

A CIDP relapse will be documented on the dedicated relapse form where the date of confirmed relapse will be recorded.

Analysis of CIDP relapse will be done by treatment group (i.e. dose group) and overall.

Time to first CIDP relapse (days) in the respective treatment (dose) group is defined as (date of first confirmed relapse in the respective treatment group – date of first infusion in the respective treatment group + 1).

Subjects who do not relapse in the respective treatment (dose) group will be censored at the date of completion/discontinuation or the last day in the respective treatment (dose) group whatever occurs first. Thus the time to censoring (days) will be calculated as (date of censoring in the respective treatment group – date of first infusion in the respective treatment group + 1).

Time to first CIDP relapse by treatment group (i.e. dose group) will be analyzed using the Kaplan-Meier estimator. A plot will be presented as well as summary tables including median time to relapse along with 95% confidence interval and the Kaplan-Meier estimate of the risk of experiencing the first CIDP relapse.

In order to assess the impact of switching doses from Study IgPro20_3003 to IgPro20_3004, time to first CIDP relapse in Study IgPro20_3004 will also be calculated for the following groups:

Treatment in Study IgPro20_3003	Starting dose in Study IgPro20_3004
Placebo	0.2 g/kg
Placebo	0.4 g/kg
0.2 g/kg	0.2 g/kg
0.2 g/kg	0.4 g/kg
0.4 g/kg	0.2 g/kg

0.4 g/kg	0.4 g/kg
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In this case only the relapses in the starting dose group will be taken into account. Subjects who do not relapse in the starting dose period will be censored at the date of completion/discontinuation or the date the subject switches to another dose (whatever occurs first).

For subjects experiencing a relapse under 0.2 g/kg dosing in IgPro20_3004 and up-titrated to 0.4 g/kg, the following will be analyzed:

- The number and percentage of subjects successfully recovered will be provided. A subject is considered to be successfully recovered if he or she has reached the INCAT baseline score or lower at the visit following the dose increase to 0.4 g/kg.
- Time to first CIDP relapse (in the 0.4 g/kg group).

For the first 0.4g/kg treatment period per subject in IgPro20_3004 (i.e. subjects starting with 0.4 g/kg and subjects who started with 0.2 g/kg and uptitrated to 0.4 g/kg) the following will be analyzed:

- Time to first CIDP relapse.

In addition, descriptive analysis will be performed for the rate of relapses by treatment group and overall, i.e. relapses under a specific treatment divided by time on treatment. Analyses will be performed based on the Total set, and repeated for the PPS.

A by-subject listing of relapse information will be provided and will include the date of first infusion, the date of CIDP relapse (or date of discontinuation or completion of in case of no relapse), time to CIDP relapse (or censored time if no CIDP relapse occurred). Subjects who are censored for the time to relapse (i.e. subjects with no confirmed relapse) will be flagged.

4.7.3 Exploratory Efficacy Endpoints

All the following scores will be analyzed on an exploratory level and separately for the Total set and PPS.

Each visit of a subject will be assigned to the dose group the subject received prior to that visit. The following virtual visits will be additionally created per dose group:

- the last post-dose observation
- relapse visit

4.7.3.1 MRC Sum Score

MRC sum scores will be calculated as outlined in [Appendix 2: MRC Sum Score](#) and summarized by visit and treatment, using descriptive statistics. The changes from baseline will be summarized at all post-baseline visits.

A by-subject listing of all responses to all questions and scales will be provided based on the total set and presenting visit and treatment.

4.7.3.2 R-ODS

R-ODS centile scores will be calculated as outlined in [Appendix 3: R-ODS](#) and summarized by visit and treatment, using descriptive statistics. The changes from baseline will be summarized at all post-baseline visits.

A by-subject listing of all responses to all questions and scales will be provided based on the total set and presenting visit and treatment.

4.7.3.3 Mean Grip Strength

Mean grip strength will be summarized by visit, treatment and by hand (dominant/non-dominant), using descriptive statistics. The changes from baseline will be summarized at all post-baseline visits

A by-subject listing of all grip strength measures will be provided for the entire study period, based on the total set and presenting visit and treatment.

4.7.4 Analysis and Data Conventions

4.7.4.1 Multi-center Studies

The term ‘Center’ will be used to define each investigator site.

No adjustment will be made for center in any analyses.

4.7.4.2 Adjustments for Covariates

Not applicable.

4.7.4.3 Handling of Dropouts or Missing Data

4.7.4.3.1 Incomplete dates/times

For the calculation of age, missing day and month of year will be replaced by the 1st of July.

By convention, incomplete and missing AE onset dates and times will be queried at the site. If the timing of the AE onset could not be determined whether it started before or after IMP dosing, the AE status will be assigned as treatment emergent.

For AEs without complete start/end dates/times, duration of AE and time to AE since last infusion will not be calculated.

For any partial dates in the initial date of CIDP diagnosis, the 1st of July will be used for missing day and month.

No other imputation for incomplete dates/times is anticipated. Partial dates/times will be reported (in listings) as they are recorded.

Missing data will be considered as such and will not be imputed.

4.7.4.3.2 Sensitivity Analyses

Not applicable.

4.7.4.4 Multiple Comparisons

Not applicable.

4.7.4.5 Interim Analyses

No interim analysis is planned.

4.7.4.6 Examination of Subgroups

IgG levels at all visits will be summarized by pre-study treatment group in the pivotal study (placebo, low-dose SCIG, high-dose SCIG, and all subjects) for subjects whose completion visit for study 3003 is at the same day of baseline visit of extension study.

To investigate the effect of age group (18-65 years, > 65 years), pre-study treatment, Status at end of Study IgPro20_3003 on key primary and secondary endpoints, the following parameters will be summarized for these subgroups:

Parameter	Age	Pre-study treatment group	Status at end of Study IgPro20_3003 ¹⁾	Pre-study treatment group and Status at end of Study IgPro20_3003 ²⁾
Primary:				
<ul style="list-style-type: none"> Overall rate (by subject and infusion) of AEs per infusion 	✓			
Secondary:				
<ul style="list-style-type: none"> Incidence rate (by subject and infusion) by SOC and PT, severity, causality, seriousness 	✓			
<ul style="list-style-type: none"> Time to first CIDP relapse 	-	✓	✓	✓

1) Non-relapsers vs relapsers

- 2) including the following 6 categories: High dose non-relapsers, Low dose non-relapsers, Placebo non-relapsers, High dose relapsers, Low dose relapsers, Placebo relapsers

Subgroup analyses will be performed for the Total set and the PPS for efficacy endpoints, and SDS for safety endpoints.

4.8 Safety Evaluation

Unless otherwise specified, safety summaries and analyses of the treatment period will be based upon the SDS. Listings of safety data for the entire study period will be based upon the total set. All safety analyses will be done descriptively.

Analysis populations are defined in [Section 4.3](#).

4.8.1 Extent of Exposure

All exposure information will be summarized by treatment (dose group) and overall.

The duration of the safety observation period for treatment (i.e. the number of days on study treatment) will be calculated as:

Duration of exposure (days) = Date of last infusion of the treatment – Date of first infusion of the treatment + 1.

Exposure for each treatment group will also be summarized in total subject years. This will be calculated on a treatment level as follows:

Exposure in subject years = Sum of duration of exposure (for all subjects receiving that treatment) / 365.25.

The duration of exposure and overall exposure in subject years will be summarized by treatment using descriptive statistics.

The total dose of each treatment received will be calculated as the sum of the doses of that treatment given at each infusion session, which in turn is calculated as follows:

Dose per infusion session for subjects (g) = Volume infused during session (mL) × 0.2

The number of infusions of each treatment received by each subject during the study will be summarized using descriptive statistics. The number and percentage of subjects receiving each number of infusions will also be presented. Each infusion session will be counted separately.

A table presenting the number and percentage of subjects with dose changes will be presented based on the SDS.

A by-subject listing of extent of exposure (including duration of exposure and total dose) will be provided.

4.8.2 Adverse Events

All AEs will be classified using version 14.1 of MedDRA. Details of AEs will be recorded at each post-baseline visit (including any unscheduled visit).

An AE is any untoward medical occurrence in a subject administered IgPro20. An AE does not necessarily have a causal relationship with IgPro20.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of IgPro20, whether or not causally related to IgPro20.

AEs will be assigned to the most recent treatment received at the time of the AE onset. Only AEs occurring during the treatment period will be presented in tables; if applicable by treatment. AEs occurring prior to first dose will be listed only. All AEs will be listed based on the total set.

Treatment-emergent AEs (TEAEs) are defined as AEs starting on or after the date of first dose in this study.

Where dates and/or times are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates and/or times or by using the flag that indicates that an AE has started before study treatment) to suggest that the AE started prior to or after first treatment.

Each individual manifestation of an AE should be graded for severity and causality. If severity is missing, the AE will be included in the summary tables using a missing category for severity. If the relationship to study drug is missing, the AE will be assessed as unrelated if it started before first infusion and as possibly related if it started after first infusion of treatment.

AE summaries will be ordered in terms of decreasing frequency for SOC, and preferred term within SOC, in the 0.4 IgPro20 group. SOCs or preferred terms with equal frequencies will be sorted alphabetically.

Analyses of AEs will be conducted on both a subject level and an infusion level.

For the subject level analyses, the number of subjects with an AE will be related to the total number of subjects in the respective study population (i.e., incidences will be presented). Incidences will be calculated for each SOC and preferred term as follows:

Incidence of AE = $100 \times (\text{Number of subjects with AE} / \text{Total number of subjects})$.

For the infusion level analyses, the number of AEs will be related to the total number of infusions among the study population (i.e., rates will be presented). Each infusion session will be counted separately. Rates will be calculated for each SOC and preferred term, as follows:

Rate of AE = $\text{Number of AEs} / \text{Number of infusions}$.

All AE summaries presented by SOC and preferred term will include a virtual SOC comprising of local reactions comprising all AEs reported within the MedDRA High level terms “Administration site reactions NEC”, “Infusion site reactions”, “Injection site reactions”. The preferred terms which make up the local reactions SOC will be finalized at the DRM. These preferred terms will be presented under their original SOC in addition to the local reactions SOC, but will be counted in the total number of subjects and events (used in the calculations of percentages and rates of AEs) once only.

An overview of AEs will be provided (by treatment and overall), with the number and percentage of subjects reporting an event (for subject level), or the number of events and rate per infusion (for infusion level), presented for the following categories, for all AEs (including local reactions) and for AEs excluding local reactions:

- Any TEAE,
- Any mild TEAE,
- Any moderate TEAE,
- Any severe TEAE,
- Any serious TEAE,
- Any causally related or temporally associated TEAEs to IgPro20,
- Any causally related or temporally associated serious TEAEs to IgPro20,
- Any TEAE causally related to IgPro20,
- Any temporally associated TEAE,
- Any TEAE leading to discontinuation,
- Any TEAE leading to withdrawal of study drug,
- Any TEAE leading to death.

An AE is considered to be temporally associated to the study drug if the onset time of the AE is between the start of the infusion and up to 72 hours after the last infusion in the infusion session.

The following summaries of AEs will be provided by treatment group and overall. The number and percentage of subjects reporting an event (for subject level) and the number of events and rate per infusion (for infusion level) will be presented.

- TEAEs, by MedDRA SOC and preferred term.
- TEAEs, by severity, MedDRA SOC and preferred term.
- TEAEs, by causal relationship to IgPro20, MedDRA SOC and preferred term.

- TEAEs, by temporal association to study drug, by MedDRA SOC and preferred term.
- Temporally associated or causally related TEAEs, by MedDRA SOC and preferred term.

The time from the start of the last infusion to the onset of the AE will be calculated, in days, as follows:

Time from start of last infusion to AE onset (hours) = (Start date and time of AE – Start date and time of previous infusion session)/3600.

The duration of an AE will be calculated, in days, as follows:

Duration of AE (days) = (End date and time of AE – Start date and time of AE)/86400.

Duration will not be calculated if the start and/or end date of the AE is missing.

The time to onset and duration of AE will be summarized using descriptive statistics, presented by MedDRA SOC, preferred term and treatment group (including overall). A table with decreasing frequency of AEs will be provided.

In addition, a summary of non-serious AEs (i.e., not including serious AEs) occurring at 5% or more in at least 1 treatment group, presented by SOC, preferred term and treatment (including overall). The number and percentage of subjects reporting each event and the number of events will be presented, along with the total number of subjects reporting at least 1 AE, and the total number of events.

A by-subject listing of all AEs occurring during the study will be provided. The listing will include: center, subject identifier, AE information (SOC, preferred term, verbatim term), start date and time, end date and time, end date and time of previous infusion session, time from last infusion to onset, duration, severity, seriousness, action taken, outcome and causality, AESI, special AE (see [Section 4.8.3.1](#)).

4.8.3 Adverse Events of Special Interest

The following systemic AEs are considered as adverse events of special interest (AESIs):

- Acute systemic hypersensitivity reactions (identified by “Anaphylactic reaction” (SMQ) [NARROW], plus PTs “hypersensitivity”, “drug hypersensitivity”, “allergic reaction”).
- Aseptic meningitis syndrome (identified by “Noninfectious meningitis” (SMQ) [NARROW])
- Suspicion of clinically relevant hemolysis (identified by “Haemolytic disorders” (SMQ) [BROAD])

- Thrombotic events (identified by “Embolic and thrombotic events” (SMQ) [BROAD])

AESIs will be documented on the AE and SAE forms. The investigator will identify AESIs by a tick mark. Final decision on AESIs will be done during the DRM.

An overview and a summary table of AESIs will be provided by treatment group and overall, on a subject level and infusion level (see [Section 4.8.2](#)), by SOC and preferred term. The number and percentage of subjects reporting an event (for subject level) and the number of events and rate per infusion (for infusion level) will be presented, for each AESI.

4.8.3.1 Causally Related Local and Systemic AEs Analyzed by Maximum Volume Infused and Maximum Infusion Rate

The following AE categories are defined:

- Any TEAEs
- Any causally related TEAEs
 - causally related local TEAEs
 - causally related non-local TEAEs

Infusions will be categorized according to the maximum infusion rate per infusion and maximum volume per infusion:

- Infusion rate categories:
maximum infusion rate <35 mL/h, =35mL/h, >35mL/h
- Infusion volume categories:
maximum infusion volume over all sites: <=25 mL, >25 -<50 mL, >= 50 mL

For each infusion rate category and each infusion site category and the respective combinations the following will be calculated:

- Number of infusions falling in the respective category
- Number of events and rate per infusion (for infusion level) will be presented for the respective category

4.8.4 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The following summaries of AEs will be provided by treatment group and overall, on a subject level and infusion level (see [Section 4.8.2](#)). The number and percentage of subjects (subject level)/number of events and rate per infusion (infusion level) will be presented.

- SAEs/Serious TEAEs, by MedDRA SOC and preferred term.
- SAEs/Serious TEAEs, by causal relationship to study drug, MedDRA SOC and preferred term.

The following summaries of AEs will be provided by treatment group and overall, on a subject level only.

- AEs leading to withdrawal of study drug, by MedDRA SOC and preferred term.
- AEs leading to study discontinuation, by MedDRA SOC and preferred term.

The following by-subject listings will be provided for the entire study period, based on the total set and presenting visit and treatment, following the same format as specified in [Section 4.8.2](#).

- Deaths
- SAEs
- AEs/TEAEs leading to study discontinuation

4.8.5 Clinical Laboratory Evaluation

Continuous clinical laboratory parameters (hematology and serum chemistry) will be summarized by visit and treatment, using descriptive statistics. The changes from baseline will be summarized descriptively and using shift tables at all post-baseline scheduled visits.

Shift tables will present the number and percentage of subjects experiencing missing, low, normal or high results (compared to normal ranges) at the baseline visit and their respective values at each visit.

A range change abnormal (RCA) value is defined as a laboratory value which was normal at the baseline visit and high or low at a further evaluation. A range change abnormal low (RCAL) value is defined as a laboratory value which was normal or high at the baseline visit and low at a further evaluation. A range change abnormal high (RCAH) value is defined as a laboratory value which was normal or low at the baseline visit and high at a further evaluation. The number and percentage of subjects with RCA, RCAH and RCAL values at any time during a respective period will be summarized, by treatment group (if applicable), for each laboratory parameter. Scheduled, unscheduled and repeat assessments will be included.

Values flagged as erroneous records (ER) will not be included in the summary tables containing descriptive statistics, but will be included in the data listings and will be regarded as 'missing' in the shift tables.

A by-subject listing of all laboratory data (including virology results if any samples are analyzed) will be provided based on the total set and presenting visit and treatment, and will include laboratory reference ranges. Clinically significant abnormal values will be flagged.

Signs and symptoms of potential hemolysis will be documented by listing for each subject (and their blood group at screening) the results and changes from reference visit over time in hemoglobin, direct antiglobulin test, erythrocytes, haptoglobin, indirect bilirubin, LDH and reticulocytes.

Selection of potential hemolysis was based on 2 sets of criteria:

Criteria A:

- Drop in hemoglobin of >1 g/dL within the defined period (see below) without clinical evidence of blood loss from gastrointestinal bleeding, menorrhagia, hemoptysis, major hematoma, or injury and not explained by repeated phlebotomy.
- DAT positive after infusion (only strictly negative results were not considered).

Criteria B - Presence of minor criteria documented at any time within the defined period (see below), consisting of:

- Haptoglobin <LLN
- LDH >ULN
- Total or indirect (unconjugated) bilirubin >ULN *or jaundiced.*
- *hemoglobinuria or red/dark urine, **
- *hemoglobinemia, **
- *spherocytosis, **
- *hepatosplenomegaly. **

(* *criteria in italics*: Criteria will be assessed by medical review. If no clinical signs occur these criteria will be disregarded)

The following groups will be assessed:

- “hemolysis”: subjects fulfilling the 2 criteria A) and 1 of criteria B).
- “no hemolysis”: subjects not fulfilling criteria for hemolysis, even if reference data for HB is missing and all post treatment DATs are negative and/or none of criteria B is fulfilled.
- “Insufficient data to evaluate” : Subjects will be assigned to 'insufficient data to evaluate' (a) if the reference data for HB is missing and at least one DAT positive

and one of criteria B met post treatment (b) if no post treatment lab data is available.

In case there are not sufficient data captured to fulfil the criteria required for hemolysis, a subject will be assigned to 'no hemolysis' group.

Listings will be provided with the results of the specific laboratory parameters as outlined above. If present, this listing will also comprise the clinical signs (marked with * above) in a comment field.

Further, listings showing which criteria were fulfilled by each subject and his/her assignment to the respective laboratory hemolysis group following above classification.

Summary tables will be provided based on the SDS, presenting the number and percentage of subjects in the laboratory hemolysis group and the number and percentage of subjects with resolved/unresolved hemolysis. A hemolysis is considered resolved if hemolysis was reported but last visit compared to reference visit do not indicate hemolysis criteria fulfilled.

4.8.6 Physical Findings

Physical findings (weight [kg] and BMI [kg/m^2]) will be summarized in the same way as the continuous laboratory parameters (see [Section 4.8.5](#)).

4.8.7 Electrocardiograms (Japan Subjects Only)

Findings in ECG (normal/abnormal) will be listed by subject presenting visit and treatment. Shift tables presenting the number and percentage of subjects with normal, abnormal and missing findings at Week 1 and their respective values at the completion visit will be produced based on Japanese subjects in the SDS.

4.8.8 Committees

4.8.8.1 Steering committee

The steering committee will have the following tasks:

- Provide overall supervision of the study.
- Provide scientific support.
- Provide oversight for substantial amendments to the protocol.
- Provide advice to the investigators on all aspects of the study.
- Support recruitment / feasibility of the study (i.e. educational training or lectures).
- Support preparation of publication(s).

4.8.8.2 SRC

The SRC will be an advisory group of experts with a mandate to periodically review and evaluate safety data to provide recommendations regarding ongoing safety of study subjects.

The SRC can recommend that the study should be stopped, temporarily suspended or amended or continued as planned.

Further details of the role of the SRC are described in the SRC Charter.

4.9 Pharmacokinetic Analyses

Serum IgG levels will be summarized, by visit, using descriptive statistics for the Total set and PPS separately. The changes from baseline will be summarized at all post-baseline scheduled visits

Subgroup analyses will be performed as described in [Section 4.7.4.6](#).

A by-subject listing of all IgG measures will be provided for the entire study period, based on the total set and presenting visit and treatment.

4.10 HRQL Analyses

All HRQL analyses are considered to be exploratory analyses. Unless otherwise specified, HRQL endpoints will be analyzed separately for the Total set and PPS.

For each HRQL endpoint, a by-subject listing will be provided for the entire study period, based on the total set and presented by visit and treatment.

4.10.1 EQ-5D-3L

Responses to the 5 dimensions of the EQ-5D (see [Appendix 4: EQ-5D-3L](#)) will be summarized by visit and treatment (i.e. dose group), using descriptive statistics presenting the number and percentage of subjects showing no problems, some/moderate problems, extreme problems and the number and percentage of subjects who have maintained, improved or worsened their EQ-5D status as compared to the reference visit

For the VAS, the changes from baseline will be summarized using descriptive statistics at all post-baseline scheduled visits in the treatment period.

A by-subject listing of all responses to all dimensions will be provided based on the total set and presenting visit and treatment.

4.10.2 TSQM

Responses to the 14 items of the TSQM (version 1.4) will be converted to the 4 scales “Effectiveness”, “Side effects”, “Convenience” and “Overall satisfaction” using the rules outlined in [Appendix 5: TSQM \(version 1.4\)](#)

Scores for these scales will be analyzed in the same way as the EQ-5D VAS (see [Section 4.10.1](#)).

A by-subject listing of all responses to all questions and scales will be provided based on the total set and presenting visit and treatment.

4.10.3 WPAI-GH

Responses to the 6 items of the WPAI-GH will be converted to the 4 scales “Absenteeism score”, “Work impairment score”, “Work productivity loss score” and “Activity impairment score” using the rules outlined in [Appendix 6: WPAI-GH V2.0](#).

These will be analyzed in the same way as the EQ-5D VAS (see [Section 4.10.1](#)).

A by-subject listing of all responses to all questions and scales will be provided based on the total set and presenting visit and treatment.

4.10.4 Subject Preference for Treatment

Subject preference for treatment questionnaire responses will be summarized, by visit. The number and percentage of subjects with each response and reasons for the response (where applicable) will be provided.

A shift table showing the change in response based on a comparison to baseline will be provided. The number and percentage of subjects reporting “prefer current SC treatment”, “prefer previous IV treatment”, “no preference” and missing responses at baseline and their respective responses at Week 25/Week 49 will be presented.

A by-subject listing of all responses to all questions will be provided based on the total set and presenting visit and treatment.

4.11 Infusion Data

Infusion data at the subject level will be summarized by time point (e.g. Week 1 Session 1) and treatment (dose group) for the SDS. Each infusion session will be treated as a separate time point. Variables will be summarized using descriptive statistics. In addition, infusion data will be summarized per treatment (dose group) and overall.

The variables to be summarized will include: duration (h), number of infusion sites, maximum volume infused per site (mL), maximum infusion rate per site (mL/h), maximum number of sites used in parallel, and volume of study treatment infused (mL).

Duration of infusion will be calculated as follows. Start and end time of the infusion are given in hours and minutes. The difference between the 2 times is assumed to be calculated in minutes.

Duration of infusion (h) = (Start time of infusion – End time of infusion) / 60.

A by-subject listings will be provided for all infusion data for the entire study period, based on the total set and presenting visit, treatment and dispensing details (including vial number and actual treatment).

A table presenting the number and percentage of subjects with changes in dose will be presented.

4.12 Determination of Sample Size

No formal sample size calculation was performed. It is expected that approximately 80 subjects (approximately 10 subjects from Japan) will participate in this study.

4.13 Changes in the Conduct of the Study or Planned Analysis

A snapshot analysis was planned to be performed when approximately 10 Japanese subjects completed at least 6 months of treatment to coincide with the Japanese CIDP submission of the pivotal study. The criterion cannot be fulfilled by the study and the timing of the Japanese submission of this study has changed to include the full study report. Since the snapshot analysis was not supposed to influence the conduct of this extension study, interim analysis will not be performed.

In order to support the 4-month safety update of the Hizentra BLA submission an analysis will be performed including all subjects fully disposed by 31Dec2016. This analysis will include disposition, demography, and adverse events data by dose group. This analysis will be based on the SDS.

5 REFERENCES

Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, Rowland CR (2004). Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2:12.

Atkinson MJ, Kumar R, Cappelleri JC, Hass SL (2005). Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. *Value Health* 8 Suppl 1:S9-S24.

Eftimov F, Winer JB, Vermeulen M, de HR, van Schaik IN (2009) Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev*CD001797.

Hughes RA, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, Hartung HP, Latov N, Merkies IS, van Doorn PA (2008). Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomized placebo-controlled trial. *Lancet Neurol* 7:136-144.

Hughes RA (2009). Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: the ICE trial. *Expert Rev Neurother* 9:789-795.

Kieseier BC, Meyer zu HG, Lehmann HC, Gold R, Hartung HP (2008). Intravenous immunoglobulins in the treatment of immune neuropathies. *Curr Opin Neurol* 21:555-562.

Kleyweg RP, van der Meche FG, Schmitz PI (1991). Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle Nerve* 14:1103-1109.

Leger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N (2001). Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 124:145-153.

Reilly MC, Zbrozek AS, Dukes EM (1993). The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 4:353-365.

van Nes SI, Vanhoutte EK, van Doorn PA, Hermans M, Bakkers M, Kuitwaard K, Faber CG, Merkies IS (2011). Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology* 76:337-345.

WPAI-GH Scoring. http://www.reillyassociates.net/WPAI_Scoring.html. Accessed on 27 November 2013.

Appendix 1: INCAT Score

ARM disability	<p>Classification:</p> <p>0 = No upper limb problems</p> <p>1 = Minor symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zippers and buttons, wash or brushing hair, using knife and fork together, handling small coins.</p> <p>2 = Disability, in 1 arm or both arms, affecting but not preventing any of the above mentioned functions.</p> <p>3 = Disability, in 1 arm or both arms preventing 1 or 2 functions listed above.</p> <p>4 = Disability, in 1 arm or both arms preventing 3 or all functions listed above, but some purposeful movements still possible.</p> <p>5 = Inability to use either arm for any purposeful movement.</p>	
	INCAT score for ARM disability:	
LEG disability	<p>Classification:</p> <p>0 = Walking not affected.</p> <p>1 = Walking affected, but walks independently outdoors.</p> <p>2 = Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors.</p> <p>3 = Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors.</p> <p>4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps.</p> <p>5 = Restricted to wheelchair, unable to stand and walk a few steps with help.</p>	
	INCAT score for LEG disability:	
	<p>INCAT total score (=sum of arm and leg disability scores)</p>	

Source: [Hughes, 2009](#).

Appendix 2: MRC Sum Score

MRC grading		
	Left side of the body	Right side of the body
Movement ^a		
Shoulder abduction.		
Elbow flexion		
Wrist extension		
Index finger abduction		
Hip flexion		
Knee extension		
Foot dorsiflexion		
Great toe dorsiflexion		
Total for each body side		
Total (MRC sum score)		
MRC grades:	Description:	
0	No visible contraction	
1	Visible contraction without movement of the limb (not existent for hip flexion)	
2	Movement of the limb but not against gravity	
3	Movement against gravity over (almost) the full range	
4	Movement against gravity and resistance	
5	Normal	

^a The subject is investigated in sitting posture and/or lying supine.

The MRC sum score ranges from 0 (paralysis) to 80 (normal strength).

Sources: Kleyweg et al., 1991; RMC trial group 2009.

Appendix 3: R-ODS

Activity Are you able to:	Impossible to perform	Performed with difficulty	Easy to perform	Not applicable
	0	1	2	
1) Read a newspaper/book				
2) Eat				
3) Brush your teeth				
4) Wash upper body				
5) Sit on a toilet				
6) Make sandwich				
7) Dress upper body				
8) Wash lower body				
9) Move a chair				
10) Turn a key in a lock				
11) Go to general practitioner				
12) Take a shower				
13) Do the dishes				
14) Do the shopping				
15) Catch an object (e.g., ball)				
16) Bend & pick up an object				
17) Walk 1 flight of stairs				
18) Travel by public transport				
19) Walk and avoiding obstacles				
20) Walk outdoors <1 km				
21) Carry & put down a heavy object				
22) Dance				
23) Standing for hours				
24) Run				

Items are sorted in order of increasing difficulty to perform, based on data from subjects with peripheral neuropathies (CIDP, GBS, or MGUS) and subjects recruited at the university outpatient clinics of PPD and PPD.

If 1 of the 24 item responses is missing or ticked ‘not applicable’, the score for that item will be imputed using the adjacent responses. Due to the activities progressing in terms of difficulty, a missing item response will be calculated using the mean of the preceding and

following item responses, and rounded to nearest integer. If the first item response is missing, it will be assumed to be the same as the score of the second item. If the last (24th) item response is missing, it will be assumed to be the same as the score of the 23rd item.

The R-ODS summed raw score is then the sum of all the item responses (imputed or as recorded).

If 2 or more of the 24 item responses are missing or ticked ‘not applicable’, the individual item scores will not be imputed, and the R-ODS summed raw score will not be calculated.

The summed raw scores of the R-ODS will be transformed into a centile score using the following table.

R-ODS summed raw score	R-ODS centile score
0	0
1	6
2	11
3	14
4	16
5	19
6	21
7	22
8	24
9	26
10	27
11	28
12	30
13	31
14	32
15	34
16	35
17	36
18	37
19	39
20	40
21	41
22	42
23	43
24	45
25	46
26	47
27	48

R-ODS summed raw score	R-ODS centile score
28	50
29	51
30	52
31	54
32	55
33	57
34	58
35	60
36	61
37	63
38	65
39	67
40	69
41	71
42	73
43	76
44	80
45	83
46	88
47	93
48	100

Source: [van Nes et al, 2011](#)

Appendix 4: EQ-5D-3L

The EQ-5D is a simple generic measure consisting of 2 parts: a visual analogue scale assessing overall health on the day of assessment and 5 questions covering the following 5 health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (see <http://www.euroqol.org/eq-5d/eq-5d-products.html> for sample versions).

Appendix 5: TSQM (version 1.4)

Question	Response
1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?	1 Extremely Dissatisfied 2 Very Dissatisfied 3 Dissatisfied 4 Somewhat Satisfied 5 Satisfied 6 Very Satisfied 7 Extremely Satisfied
2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?	1 Extremely Dissatisfied 2 Very Dissatisfied 3 Dissatisfied 4 Somewhat Satisfied 5 Satisfied 6 Very Satisfied 7 Extremely Satisfied
3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?	1 Extremely Dissatisfied 2 Very Dissatisfied 3 Dissatisfied 4 Somewhat Satisfied 5 Satisfied 6 Very Satisfied 7 Extremely Satisfied
4. As a result of taking this medication, do you experience any side effects at all?	1 Yes 0 No
5. How bothersome are the side effects of the medication you take to treat your condition?	1 Extremely Bothersome 2 Very Bothersome 3 Somewhat Bothersome 4 A Little Bothersome 5 Not at All Bothersome

Question	Response
6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?	1 A Great Deal 2 Quite a Bit 3 Somewhat 4 Minimally 5 Not at All
7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?	1 A Great Deal 2 Quite a Bit 3 Somewhat 4 Minimally 5 Not at All
8. To what degree have medication side effects affected your overall satisfaction with the medication?	1 A Great Deal 2 Quite a Bit 3 Somewhat 4 Minimally 5 Not at All
9. How easy or difficult is it to use the medication in its current form?	1 Extremely Difficult 2 Very Difficult 3 Difficult 4 Somewhat Easy 5 Easy 6 Very Easy 7 Extremely Easy
10. How easy or difficult is it to plan when you will use the medication each time?	1 Extremely Difficult 2 Very Difficult 3 Difficult 4 Somewhat Easy 5 Easy 6 Very Easy 7 Extremely Easy
11. How convenient or inconvenient is it to take the medication as instructed?	1 Extremely Inconvenient 2 Very Inconvenient 3 Inconvenient 4 Somewhat Convenient 5 Convenient 6 Very Convenient 7 Extremely Convenient
12. Overall, how confident are you that taking this medication is a good thing for you?	1 Not at All Confident 2 A Little Confident 3 Somewhat Confident 4 Very Confident 5 Extremely Confident

Question	Response
13. How certain are you that the good things about your medication outweigh the bad things?	1 Not at All Certain 2 A Little Certain 3 Somewhat Certain 4 Very Certain 5 Extremely Certain
14. Taking all things into account, how satisfied or dissatisfied are you with this medication?	1 Extremely Dissatisfied 2 Very Dissatisfied 3 Dissatisfied 4 Somewhat Satisfied 5 Satisfied 6 Very Satisfied 7 Extremely Satisfied

TSQM scale scoring algorithm

TSQM scale scores range from 0 to 100 and no computed score should be lower or higher than these limits. If more than 1 item score is missing, the scale score should not be computed, and set to missing. If a subject answers “No” to item 4, the side effects scale score will not be computed.

Effectiveness

Effectiveness scale score = $[(\text{Item 1} + \text{Item 2} + \text{Item 3} - 3) / 18] \times 100$

If 1 item is missing:

Effectiveness scale score = $[(\text{Item 1?} + \text{Item 2?} + \text{Item 3?} - 2) / 12] \times 100$

Side effects

Side effects scale score = $[(\text{Item 5} + \text{Item 6} + \text{Item 7} + \text{Item 8} - 4) / 16] \times 100$

If 1 item is missing:

Side effects scale score = $[(\text{Item 5?} + \text{Item 6?} + \text{Item 7?} + \text{Item 8?} - 3) / 12] \times 100$

Convenience

Convenience scale score = $[(\text{Item 9} + \text{Item 10} + \text{Item 11} - 3) / 18] \times 100$

If 1 item is missing:

Convenience scale score = $[(\text{Item 9?} + \text{Item 10?} + \text{Item 11?} - 2) / 12] \times 100$

Overall satisfaction

First recode create Item 14_R: $\text{Item 14_R} = (\text{Item 14} - 1) \times 4/6 + 1$

Overall satisfaction scale score = $[(\text{Item 12} + \text{Item 13} + \text{Item 14_R} - 3) / 12] \times 100$

If 1 item is missing:

Overall satisfaction scale score = $[(\text{Item 12?} + \text{Item 13?} + \text{Item 14_R?} - 2) / 8] \times 100$

Source: [Atkinson et al, 2005](#)

Appendix 6: WPAI-GH V2.0

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom.

1. Are you currently employed (working for pay)? *If NO, check "NO" and skip to question 6.*

The next questions are about the **past 7 days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*
3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
4. During the past seven days, how many hours did you actually work? *If "0", skip to question 6.*
5. On a scale of 0 to 10 (0 = health problems had no effect on my work, 10 = health problems completely prevented me from working), during the past seven days, how much did your health problems affect your productivity while you were working?

Consider only how much health problems affected productivity while you were working. Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

6. On a scale of 0 to 10 (0 = health problems had no effect on my daily activities, 10 = health problems completely prevented me from doing my daily activities), During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

WPAI-GH scoring algorithm

Multiply scores by 100 to express in percentages:

$$\text{Absenteeism score} = Q2/(Q2 + Q4)$$

$$\text{Work impairment score} = Q5/10$$

$$\text{Work productivity loss score} = Q2/(Q2 + Q4) + [(1 - Q2/(Q2 + Q4)) \times (Q5/10)]$$

$$\text{Activity impairment score} = Q6/10$$

The absenteeism, impairment and work productivity loss scores will only be calculated if the first question is answered with “yes”. Otherwise they will be set to missing regardless of any answers given to questions 2 to 5.

Source: Reilly et al., 1993; http://www.reillyassociates.net/WPAI_Scoring.html)

Appendix 7: Subject Preference for Treatment Score

Please choose one:

I prefer to continue using my current medication (subcutaneous Ig treatment)

Select all the reasons that apply

- I prefer the frequency of administration of my current therapy
- I believe that my current therapy offers me more independence for doing the things I want to do
- I seem to feel fewer side effects from my current therapy
- I believe that overall I will spend less time dealing with my current therapy
- My current therapy works better
- I prefer my current therapy for another reason

I prefer to use the medication I was given before the study began (intravenous Ig treatment)

Select all the reasons that apply

- I prefer the frequency of administration of my previous therapy
- I believe that my previous therapy offered me more independence for doing the things I want to do
- I seem to feel fewer side effects from my previous therapy
- I believe that overall I spent less time dealing with my previous therapy
- My previous therapy worked better
- I prefer my previous therapy for another reason

Appendix 8: Prohibited medications list

The following ATC codes will be used to select potentially prohibited medication. Final decisions will be made during the Data Review Meeting prior to database lock.

WHODrug / ATC codes

	PREFNM_TEXT	ATC4_TEXT	ATC4_CODE
Other non-study IgGs		Immunoglobulins, normal human	J06BA
		Specific immunoglobulins	J06BB
		Other immunoglobulins	J06BC
Rituximab	Rituximab (code: 01402501001)	Monoclonal antibodies	L01XC
Alemtuzumab	Alemtuzumab (code: 01268601001)	Monoclonal antibodies	L01XC
		Selective immunosuppressants	L04AA
Plasma exchange	Plasma protein fraction (human) (code: 00357601001)	Blood substitutes and plasma protein fractions	B05AA
	Other plasma protein fractions (code: 07913401001)	Blood substitutes and plasma protein fractions	B05AA
	Bloodplasma (code: 03592501001)	Other blood products	B05AX
	Plasma (code: 00462801001)	Other blood products	B05AX
	Dried human plasma (code: 00197001001)	Blood transfusion, auxiliary products	V07AC
Interferon	Interferon (code: 00596801001)	Interferons	L03AB
Tumor necrosis factor-alpha inhibitors		Tumor necrosis factor alpha (TNF-) inhibitors	L04AB

	PREFNM_TEXT	ATC4_TEXT	ATC4_CODE
Fingolimod	Fingolimod (code: 01789701001)	Selective immunosuppressants	L04AA
Cyclophosphamide	Cyclophosphamide (code: 00021101001)	Nitrogen mustard analogues (regarding combination products with multi- ingredients check for additional ATC codes below L01)	L01AA
Any other systemic immunosuppressive medications		Selective immunosuppressants	L04AA
Others		Interleukin inhibitors	L04AC
		Calcineurin inhibitors	L04AD
		Other immunosuppressants	L04AX
		Folic acid analogues	L01BA
		Platelet aggregation inhibitors excl. Heparin	B01AC
		Direct thrombin inhibitors	B01AE
		Other antithrombotic agents	B01AX
		Corticosteroids, dermatological preparations	D07
		Glucocorticoids	H02AB
		Corticosteroids for systemic use, combinations	H02BX
		Other specific antirheumatic agents	M01CX
		Corticosteroids	R01AD
		Glucocorticoids	R03BA
		Corticosteroids	S03BA

Signature Page

IGPRO20_3004 - Statistical Analysis Plan - v1.0 - 24Feb2017

Signed By	Date (GMT)
PPD	14-Jun-2017 13:57:08
Approved-Technical Approval	

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