CSL Behring

CLINICAL STUDY PROTOCOL

Substantial Protocol Amendment No. 3

Study Title:	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
Study Number:	IgPro20_3004
Study Product:	IgPro20 (Hizentra®)
IND Number:	CCI
EudraCT Number:	2013-004157-24
Sponsor:	CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg Germany
Version and Date of Study Protocol:	Amendment 3, 08 December 2015 The revision history of the study protocol is summarized on page 3.

This protocol includes information and data that contain trade secrets and privileged or confidential information, which is the property of the sponsor. This information must not be made public without written permission from the sponsor. These restrictions on disclosure will apply equally to all future information supplied to you. This material may be disclosed to and used by your personnel and associates as may be necessary to conduct the clinical study.

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator Study File. This list will be updated by the sponsor or the sponsor's agent and provided to study sites as needed.

STUDY PROTOCOL REVISION HISTORY

Document/ Document Type/ Type of Amendment	**Date/ Validity**	**Summary of Changes Covered by Amendment**
Original Study Protocol (Version 1.0)/ Full study protocol/ Not applicable	09/Dec/2013 All sites	N/A
Amendment 1/ Full study protocol/ Substantial	31/Jul/2014 All sites	In addition to the changes listed below, this amendment includes minor text changes to correct errors and/or inconsistencies and/or to provide additional clarifications that are not described below. •Study design modified to require direct transition from the completion visit of study IgPro20_3003 to the Week 1 (baseline) visit of this study. •Inclusion criteria modified to define the study population (subjects who completed the SC Period or successfully recovered from CIDP relapse during the SC Period of the IgPro20_3003 study). •Exclusion criteria modified because of study design change, ie, direct transition from study IgPro20_3003. •IgPro20 dose reduced to 0.2 g/kg bw; if CIDP relapse occurs, subject will have the dose adjusted up to 0.4 g/kg bw; subject must successfully recover within 4 weeks (±2 days) in order to continue in the study. Dose justification and maximum volume per infusion site increased to 50 mL, as tolerated. •Subjects enrolled under the original protocol will be re-consented for Amendment 1 and started on Amendment 1 dose requirements and procedures at Week 25. If a subject enrolled under the original protocol, relapses and successfully recovers from the relapse prior to Week 25, the subject will remain on 0.4 g/kg bw for the remainder of the study. If the subject relapses again, they will be discontinued. •Week 17 and Week 41 visits converted to dispensing and inventory only visits. •Viral safety testing deleted, only retention sample collected for possible future testing if a suspected treatment-emergent viral infection occurs.

Document/ Document Type/ Type of Amendment	Date/ Validity	Summary of Changes Covered by Amendment
		•Biomarker text modified to delete anonymization of samples. This should not have been required in the original protocol, because no genetics will be tested. Biomarker results will need to be correlated with the subject's treatment in both studies and other test results in order to benefit understanding of CIDP disease progression and how to treat it. Biomarker sample collection is optional for Japan. •Missing efficacy (R-ODS) and HRQL (EQ-5D) instruments added to Section 8 and the Appendix, respectively. •Statement added that IgG levels will not be disclosed to the site or CSLB until the IgPro20_3003 study is locked and unblinded. •New postmarketing adverse reactions added to Section 1. •Thromboembolic events and aseptic meningitis syndrome text added to precautions in Section 6. •A snapshot analysis will be performed when approximately 10 Japanese subjects have completed 6 months of treatment.
Amendment 2/ Full study protocol/ Substantial	22/Jun/2015 All sites	In addition to the changes listed below, this amendment includes minor text changes to correct errors and/or inconsistencies and/or to provide additional clarifications that are not described below. •Number of subjects increased to approximately 80 subjects. •IVRS language updated to more closely align with the IgPro20_3003 protocol. •Biomarker language modified to confirm that a biomarker sample is required to be collected upon a CIDP relapse, either at a scheduled visit, or an unscheduled visit whichever is more timely. An unscheduled laboratory kit should be used for biomarker sample collection for both scheduled and unscheduled visits.
Amendment 3/ Full study protocol/ Substantial	08/Dec/2015 All sites	In addition to the changes listed below, this amendment includes minor text changes to correct errors and/or inconsistencies and/or to provide additional clarifications that are not described below. •Adverse reactions were updated per current safety information. •IVRS language updated to clarify volume needed for each infusion session.

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SIGNATURE ON BEHALF OF SPONSOR

Study Number: IgPro20_3004

Study Title: 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

When signing, please use the following format for dates: DD/MMM/YYYY (eg, 01/JUN/2008)

Sponsor's Responsible Medical Officer: PPD
PPD
PPD

PPD

09 Dec 2015

(Date [DD/MMM/YYYY]) (Signature)

SIGNATURE OF COORDINATING INVESTIGATOR

Study Number: IgPro20_3004

Study Title: 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

When signing, please use the following format for dates: DD/MMM/YYYY (eg, 01/JUN/2008)

Coordinating Investigator: PPD PPD PPD PPD PPD PPD

(Date [DD/MMM/YYYY]) (Signature)

SIGNATURE(S) OF PRINCIPAL INVESTIGATOR(S)

Study Number: IgPro20_3004

Study Title: 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

_____

I have read this study protocol, including all appendices. By signing this study protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

_____

When signing, please use the following format for dates: DD/MMM/YYYY (eg, 01/JUN/2008)

Name and affiliation to be filled out by the investigator

Principal Investigator

Name and affiliation: _____

_____

_____ _____

(Date [DD/MMM/YYYY]) (Signature)

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
AMS	Aseptic meningitis syndrome
bw	Body weight
CIDP	Chronic inflammatory demyelinating polyneuropathy
CS	Clinically significant
CSLB	CSL Behring
ECG	Electrocardiogram
eCRF	Electronic case report form
EQ-5D	EuroQoL 5-Dimension Questionnaire
ER	Error
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRQL	Health-related quality of life
ICC	Intraclass correlation coefficient
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA, IgG	Immunoglobulin A, G
IgPro20	CSL Behring's 20% SCIG preparation (trade name: Hizentra®)
IMP	Investigational medicinal product
INCAT	Inflammatory Neuropathy Cause and Treatment
IRB	Institutional Review Board
ITT	Intention-to-Treat
IVIG	Normal human immunoglobulin for intravenous administration
MRC	Medical Research Council
PT	Preferred term
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SDS	Safety Data Set
SOC	System organ class
SRC	Safety Review Committee
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States of America
WPAI-GH	Work Productivity and Activity Impairment Questionnaire for General Health

DEFINITION OF TERMS

Baseline	The baseline time point for the extension study is the same time point as the completion visit for pivotal study IgPro20_3003.
Chronic inflammatory demyelinating polyneuropathy (CIDP) relapse	An increase of at least 1 point in the total adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score, except when there is a change from 0 to 1 that occurs only in the arm score (see Section 8.2.2.1 for full description). OR An unchanged total INCAT score 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).
End of study	End of study occurs at the completion of Week 49 visit.
Endpoint	Key measurement or observation used to measure the effect of experimental variables in a study.
Enrollment	The time point at which a subject starts participation in the study after having given written informed consent.
High dose	IgPro20 at 0.4 g/kg body weight (bw) per week.
Investigational medicinal product (IMP)	The study product that is to be administered in the current study (IgPro20).
Low dose	IgPro20 at 0.2 g/kg bw per week.
Primary completion	Date after which no more measurements for the primary endpoint are expected (or primary “outcome measure”, per ClinicalTrials.gov).
Snapshot analysis	A data analysis performed at a specific time point which has no influence on the conduct of the study.
Study product	The IMP that is the focus of investigation in the current study (ie, IgPro20).
Study Treatment Period	Represents the entire length of the study, from Week 1 (baseline) to Week 49. The last dose of IgPro20 is administered at Week 48.

Study start	The time point at which the first subject gives written informed consent; equivalent to first subject's first visit at the first study site to have enrolled a subject into the study.
Successful recovery following CIDP relapse	Defined as the return of the total adjusted INCAT score back to (or better than) the adjusted baseline INCAT score of extension study IgPro20_3004.

STUDY SYNOPSIS

Study Title: 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	
Study Number: IgPro20_3004	
Study Product: IgPro20 (Human Normal Immunoglobulin for Subcutaneous Administration [SCIG], 200 mg/mL) Hizentra®	
Type of Study: Open-label, prospective, multicenter study	**Indication Studied:** CIDP
Phase of Development: Phase 3	
Sponsor: CSL Behring	
Coordinating Investigator: PPD	
Estimated Duration of Individual Subject Participation: The study duration will be up to 49 weeks. The last dose of IgPro20 is administered at Week 48. • 48 weeks of low dose IgPro20. • If CIDP relapse occurs, high dose IgPro20 until Week 48.	
Objectives: **Primary objective:** To evaluate the long-term safety of IgPro20. **Secondary objectives:** • To evaluate the long-term safety of IgPro20 by dose. • To evaluate the efficacy of IgPro20. **Exploratory objectives:** • To evaluate health-related quality of life (HRQL). • To evaluate serum immunoglobulin G (IgG) levels.	

Methodology:

This is an open-label prospective, multicenter extension study for subjects who have completed subcutaneous (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 the extension study IgPro20_3004.

Eligible subjects will receive open-label IgPro20 (0.2 g/kg body weight [bw]) weekly for 48 weeks.

Subjects who relapse on IgPro20 0.2 g/kg bw will be given the option to remain in the study with an increase in the IgPro20 dose to 0.4 g/kg bw. Subjects remaining in the study on IgPro20 0.4 g/kg bw will have to successfully recover from the CIDP relapse within 4 weeks (±2 days), as confirmed by a site visit, or will otherwise be withdrawn from the study.

Successful recovery after a CIDP relapse is defined as the return of the total adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score back to (or better than) the baseline score.

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, ie, 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 subject enrolled under the original protocol (09 Dec 2013) will convert to Amendment 2 procedures at Week 25 after Amendment 2 approval at the site (conversion to Amendment 2 may be later than Week 25 if the site has not yet been granted approval). An IgPro20 dose adjustment from 0.4 to 0.2 g/kg bw will be required for subjects who did not experience a CIDP relapse during the first 25 weeks. For subjects under the original protocol (09 Dec 2013) who recovered from a CIDP relapse during the first 25 weeks, their IgPro20 dose will be maintained at 0.4 g/kg bw for the remainder of the study. If they experience a second relapse after Week 25, they will be withdrawn from the study, as per this amendment.

Number of Subjects:

It is assumed that approximately 80 subjects (thereof approximately 10 subjects from Japan) will participate in this study.

It is planned to conduct the study at approximately 25 sites participating in study IgPro20_3003.

Inclusion Criteria:

1. Written informed consent for study IgPro20_3004 before any study-specific procedures are performed.
2. Subject has completed the pivotal study IgPro20_3003 (SC Week 25), or was successfully rescued from a CIDP relapse during the SC Treatment Period of study IgPro20_3003.

Exclusion Criteria:

1. Subject is unable to directly transition from the pivotal study IgPro20_3003, ie, the subject is unable to have the baseline visit conducted at the same time as the completion

visit for the pivotal study IgPro20_3003.

2. New medical condition and/or social behavior (ie, alcohol, drug, or medication abuse) during participation in pivotal study IgPro20_3003 that in the judgment of the investigator could increase risk to the subject, interfere with the evaluation of IMP, and/or conduct of the study. See Section 6.7 (Contraindications and Precautions for Further Dosing).
3. Pregnant or intention to become pregnant during the course of the study.
4. Female subjects of childbearing potential either not using, or not willing to continue to use, a medically reliable method of contraception for the entire duration of the study, or not sexually abstinent for the entire duration of the study, or not surgically sterile.

Study Products, Doses, and Mode of Administration:

IgPro20: 20% liquid formulation of human immunoglobulin for SC use (SCIG), containing 250 mmol/L L-proline and 20 mg/L polysorbate 80 (P80).

Dosages:

- Open-label 0.2 g/kg bw IgPro20 for 48 weeks
- Open-label 0.4 g/kg bw IgPro20, if CIDP relapse on 0.2 g/kg dose.

Dosing and mode of administration:

Subjects will receive weekly SC infusions of IgPro20.

The volume administered will be rounded up or down to the next full 5 mL.

Reference Product, Dose, and Mode of Administration:

Not applicable

Duration of Treatment:

Up to 48 weeks

Criteria for Evaluation:

***Safety*:**

- Adverse events (AEs).
- Laboratory parameters (hematology, serum chemistry).
- Physical examination.
- Japan only: 12-lead standard electrocardiogram (ECG).

***Efficacy*:**

- Total adjusted INCAT score.
- Mean grip strength.
- Medical Research Council (MRC) sum score.
- Rash-built Overall Disability Scale (R-ODS).

***Health-related quality of life (HRQL) variables*:**

- EuroQoL 5-Dimension Questionnaire (EQ-5D).
- Treatment Satisfaction Questionnaire for Medication (TSQM).
- Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH).

- Subject preference for treatment.

Endpoints:

Primary endpoint:

- Overall rate of AEs per infusion.

Secondary endpoints:

Safety

- Overall rate of AEs per infusion (by system organ class [SOC], preferred term [PT], severity, causality, and seriousness).
- Percentage of subjects with AEs (overall, and by SOC, PT, severity, causality, seriousness).
- Rate of AEs per infusion (by SOC, PT, severity, causality, and seriousness) by dose.
- Percentage of subjects with AEs (overall, and by SOC, PT, severity, causality, seriousness) by dose.

Efficacy

- Changes from baseline in total adjusted INCAT score, MRC sum score, R-ODS, and mean grip strength.
- Time to first relapse based on adjusted INCAT score.

Exploratory endpoints are listed in Section 3.1.2.

Statistical Methods and Sample Size Determination:

Sample size determination: No formal sample size calculation was performed.

Statistical methods: Descriptive statistics.

Interim analysis: No interim analysis is planned. A snapshot analysis will be performed when approximately 10 Japanese subjects have completed at least 6 months of treatment.

SCHEDULE OF ASSESSMENTS

Visit[a]	1	2	3	4	5	6	7	Unscheduled visit	FU Relapse Visit	Completion visit	
Week	**Week 1 Baseline[b]**	**Week 2 ± 2 d**	**Week 9 ± 4 d**	**Week 17 ± 4 d**	**Week 25 ± 4 d**	**Week 33 ± 4 d**	**Week 41 ± 4 d**	**Any time during study**	**4 weeks after relapse ± 2 d**	**Week 49 ± 4 d (or at discontinuation)**	
Inclusion/exclusion criteria, informed consent, new medical history	X										
Concomitant medications	X➡	X➡	X➡		X➡	X➡		X➡	X➡	➡X	
Pregnancy test	X									X	
Physical examination, body weight	X				X			X	X	X	
Hematology & serum chemistry, IgG	X	X	X		X	X		X	X	X	
Biomarker samples[c]	X				X			X[g]		X	
Retention sample for possible future viral safety testing	X									X	
ECG (for Japan only)	X									X	
Dispense IgPro20 to subjects[d]	X	X	X	X	X	X	X	X	X		
Collect used/unused/partially used vials[d]	X	X	X	X	X	X	X	X	X	X	
Start/plan weekly IgPro20 infusions	X ➡	X ➡	X ➡		X ➡	X ➡		X	X		
Review IgPro20 administration information[e]	X	X	X	X[e]	X	X	X[e]	X	X	X	
Adverse events	X ➡	X➡	X ➡		X ➡	X ➡		X ➡	X➡	➡X	
HRQL questionnaires[f]	X				X					X	
INCAT, MRC, grip strength, R-ODS	X	X	X		X	X		X	X	X	

[a] A subject enrolled under the original protocol (09 Dec 2013) will convert to Amendment 2 Schedule of Assessments at Week 25 after the Amendment 2 approval at the site.

[b] Baseline visit is conducted at the same time as the completion visit of pivotal study IgPro20_3003. Where the procedure is common to both studies, the procedure will be performed and recorded as part of the pivotal study IgPro20_3003 completion visit and the data transferred to the baseline visit of the extension study. Procedures only performed for the extension study appear in bold-face type.

[c] Biomarker sample collection is optional for Japan subjects only.

[d] Week 17 and Week 41 are dispensing and inventory visits. Weekly infusion details will be collected during these visits as well. Dispensing and inventory may not be required at some unscheduled or follow-up relapse visits.

[e] Only the weekly infusion details will be collected at Week 17 and Week 41.

[f] HQRL questionnaires include EuroQoL 5-Dimension Questionnaire (EQ-5D), Treatment Satisfaction Questionnaire for Medication (TSQM), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH), Subject preference for treatment.

[g] A biomarker sample should be collected at an unscheduled visit only in the case of CIDP relapse. If a CIDP relapse is confirmed at a scheduled visit, a biomarker sample should also be collected, using the unscheduled kit for this purpose.

CIDP = chronic inflammatory demyelinating polyneuropathy; d =days; ECG = electrocardiogram; FU = Follow-up; HRQL =health-related quality of life; IgG = immunoglobulin G; INCAT = Inflammatory Neuropathy Cause and Treatment score; MRC = Medical Research Council; R-ODS = Rash-built Overall Disability Scale; SAE = serious adverse event. .

1. INTRODUCTION

1.1 BACKGROUND INFORMATION ON INDICATION STUDIED

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired neurological, demyelinating neuropathy with an assumed autoimmune-mediated pathogenesis. The clinical course can be relapsing/remitting or chronic and progressive (Köller et al., 2005), the former being much more common in young adults.

The prevalence of CIDP is estimated to be about 4.7 per 100,000 adults (EFNS and PNS joint task force, 2005) and about 0.5 per 100,000 children (Connolly, 2001; Köller et al., 2005).

Primary treatment modalities include IVIGs (normal human immunoglobulin for intravenous administration) and plasma exchange and corticosteroids, with the choice usually based on availability, cost, and side-effect profile (Toothaker and Brannagan, 2007).

1.2 BACKGROUND INFORMATION ON STUDY PRODUCT

IgPro20 is a ready-to-use formulation of human immunoglobulin G (IgG) with ≥98% purity for subcutaneous (SC) administration. It is approved in the United States of America (US), the European Union, Switzerland, Latin America, eastern Europe, Canada, Japan, and Australia under the brand name Hizentra® for primary immunodeficiency syndromes, and is manufactured at CSL Behring's (CSLB's) facility in Berne, Switzerland.

An overview of known and potential risks and benefits of the study product to human subjects is available in Section 1.5.

Further details on the study product are available in the Investigator's Brochure and the Summary of Product Characteristics, the current version of which will be available in the Investigator Study File.

1.3 BACKGROUND INFORMATION ON REFERENCE PRODUCT

Not applicable.

1.4 RATIONALE FOR CURRENT STUDY

The current study is an extension study to the pivotal study IgPro20_3003. Clinical studies have demonstrated the clinical efficacy and safety of using IVIGs to treat CIDP (Kieseier et al., 2008; Eftimov et al., 2009; Hughes et al., 2008). Study IgPro20_3003 is being 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.

The study will be conducted in compliance with this study protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and the applicable regulatory requirement(s) (see Section 12.1).

1.5 RISK-BENEFIT ASSESSMENT

Risk

In the 3 pivotal studies performed by CSLB for approval of IgPro20 in primary immunodeficiency syndromes, almost all adverse events (AEs [99%]) were mild or moderate in intensity. There was no dose-dependent increase in the overall rate of AEs, and there was no evidence in either study of severe systemic AEs.

The most frequently reported AEs in these studies were local reactions (swelling, erythema, warmth, bruising, pain, pruritis), followed by headache, diarrhea, fatigue, back pain, nausea, arthralgia, pain in extremity, cough, rash, pruritis, vomiting, upper abdominal pain, migraine, fever, and pain. In addition, in the postmarketing setting, reactions such as hypersensitivity, tremor, burning sensation and infusion site ulcer were reported; as well as rare events such as anaphylaxis, aseptic meningitis syndrome (AMS) and thrombotic events. SC infusions generally result in lower rates of headache and other systemic adverse reactions than IV infusions, which is attributed to the more stable serum IgG concentrations attained with SCIG treatment (see Hizentra Investigator's Brochure). Clinical trial and postmarketing experience with IgPro20 in pediatric and geriatric patients shows an overall similar safety profile as in adult patients.

The risk that products manufactured from plasma could transmit an infectious agent has been reduced by screening plasma donors for prior exposure to pathogens and by testing the donations for the presence of certain markers of infections. In addition, different complementary virus elimination processes used during the manufacture of IgPro20 (incubation at pH 4, virus filtration, fractionation, and depth filtration) effectively reduce the potential for viral transmission. The manufacturing process was also investigated for its capacity to eliminate hamster-adapted scrapie agent 263K, which is considered to be a model for Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease. The results demonstrated substantial removal of the infectious agent by the manufacturing process in all model systems. To date, no viral infection related to the infusion of IgPro20 was reported. However, the possibility of transmitting infective agents cannot be totally excluded.

At the start of this extension study, the pivotal study is still ongoing. Therefore, no final assessment of the efficacy and safety of IgPro20 in CIDP will have been performed. Depending on these results, the extension study may be modified, terminated, or continued as planned.

Justification for IgPro 20 Dose used in this extension study

The preplanned IgPro20_3003 safety interim analysis (March 2014) after 89 subjects were randomized to IgPro20 or placebo treatment revealed no safety issue. Altogether, a total of 2463 infusions were administered for the 3 treatment arms (IgPro20 0.4 g/kg bw; IgPro20 0.2 g/kg bw; and placebo). There were 4 (4.5%) subjects with serious treatment-emergent adverse events (2 subjects with arthralgias, 1 subject with acute allergic skin reaction, and

1 subject who required surgery of his ankle). In only 1 subject was the serious treatment-emergent adverse event (acute allergic skin reaction) assessed as related to the blinded study drug. All these events were of temporary duration and the subjects recovered completely by the end of the study. These results suggest that both doses of IgPro20 were well tolerated.

The low IgPro20 dose from Study IgPro20_3003 has been chosen for this study as it is suggested to be the minimum effective dose necessary to maintain CIDP. High IgPro20 dose subjects in Study IgPro20_3003 will have their dose reduced – which is in line with current guidelines to lower the dose after a period of stability. Low dose subjects in Study 3003 will continue with their low dose, and placebo subjects in Study 3003 will start with the low dose.

The low IgPro20 dose will be administered in a lower volume, unlike in Study 3003 where half of the low IgPro20 dose consisted of placebo in order to allow for blinding of the higher volume necessary for high IgPro20 dose treatment. It is therefore assumed that the low IgPro20 dose will be at least as safe in subjects participating in the extension study (minimizing local site reactions due to lower volume) while still being effective to control the CIDP.

In conclusion, the lowIgPro20 dose from Study 3003 has been chosen for this extension study as the probable minimum effective dose. The dose change does not pose a specific risk and is recommended by current treatment guidelines.

Also see Section 9.1.3 “Adverse Events of Special Interest”.

Benefit

The expected benefit of the extension study for subjects is the continuation of SCIG therapy in subjects a) who have completed the pivotal study and were treated with either high dose or low dose IgPro20; or b) who have relapsed in the pivotal study on placebo

Volume up to 50 mL per infusion site

In Study 3003 up to 40 mL per infusion site is allowed. The preplanned safety interim analysis (March 2014) after 89 patients were randomized to IgPro20/placebo treatment revealed no safety issues with regards to infusion volume. The maximum infusion volume per site has therefore been increased to 50 mL in this study. This allows a syringe (50 mL) of IgPro20 to be used without changing infusion needles which is expected to increase comfort, decrease pain and decrease infusion time. The infusion method details are described in Section 6.4.1.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

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 – DESCRIPTION

3.1.1 Primary and Secondary Endpoints

3.1.1.1 Primary Endpoint

Safety
- Overall rate of AEs per infusion.

3.1.1.2 Secondary Endpoints

Safety
- Overall rate of AEs per infusion (by system organ class [SOC], preferred term [PT], severity, causality, and seriousness).
- Percentage of subjects with AEs (overall, and by SOC, PT, severity, causality, seriousness).
- Rate of AEs per infusion (by SOC, PT, severity, causality, and seriousness) by dose.
- Percentage of subjects with AEs (overall, and by SOC, PT, severity, causality, seriousness) by dose.

Efficacy
- Changes from baseline in total adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score, Medical Research Council (MRC) sum score, Rasch-built Overall Disability Scale (R-ODS), and mean grip strength.
- Time to first relapse based on adjusted INCAT score.

3.1.2 Exploratory Endpoints

Safety
- Descriptive statistics of laboratory safety parameters for hematology and serum chemistry.
- Electrocardiogram (ECG) (Japan only), and physical examination.

Efficacy
- Changes from baseline in total adjusted INCAT score, Medical Research Council (MRC) score, Rasch-built Overall Disability Scale (R-ODS), and mean grip strength, by dose.
- Time to first relapse based on adjusted INCAT score by dose.
- Changes from baseline in serum IgG levels by dose.

HRQL

Changes from baseline in:

- EuroQoL 5-Dimension Questionnaire (EQ-5D),
- Treatment Satisfaction Questionnaire for Medication (TSQM),
- Work Productivity and Activity Impairment Questionnaire for General Health (WPAI-GH),
- Subject preference for treatment.

3.1.3 Study Design

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 receive open-label IgPro20 (0.2 g/kg bw) weekly for 48 weeks.

Subjects who relapse on IgPro20 0.2 g/kg bw will be given the option to remain in the study with an increase in the IgPro20 dose to 0.4 g/kg bw. Subjects remaining in the study on IgPro20 0.4 g/kg bw will have to successfully recover from the CIDP relapse within 4 weeks (±2 days), as confirmed by a site visit, or will otherwise be withdrawn from the study.

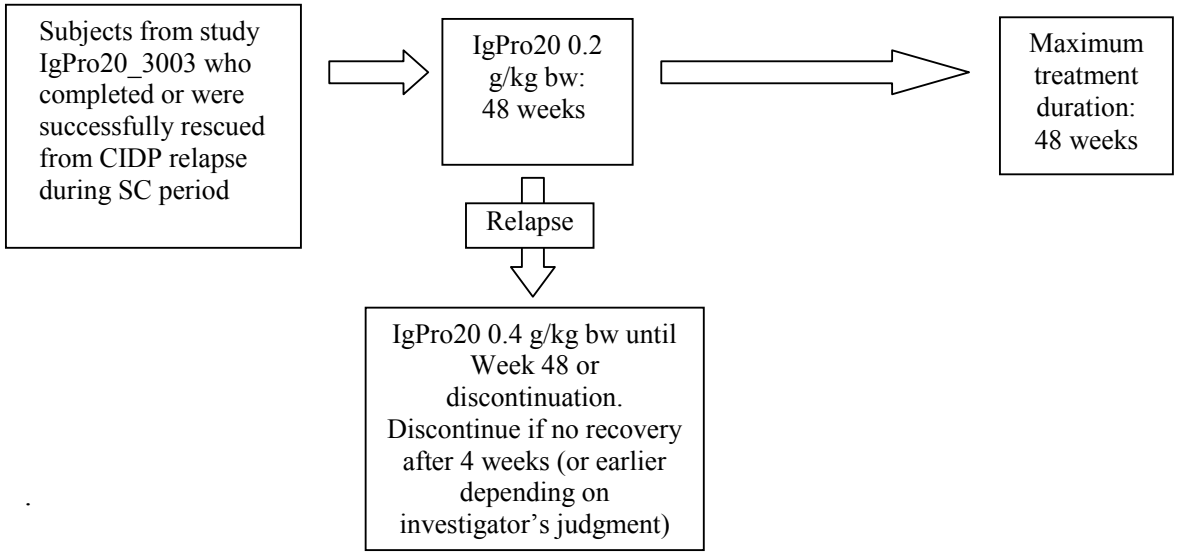
Successful recovery after a CIDP relapse is defined as the return of the total adjusted INCAT score back to (or better than) the baseline score.

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, ie, 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 subject enrolled under the original protocol (09 Dec 2013) will convert to Amendment 2 procedures at Week 25 after Amendment 2 approval at the site (conversion to Amendment 2 may be later than Week 25, if the site has not yet been granted approval). An IgPro20 dose adjustment from 0.4 to 0.2 g/kg bw will be required for subjects who did not experience a CIDP relapse during the first 25 weeks of the study. For subjects under the original protocol (09 Dec 2013) who recovered from a CIDP relapse during the first 25 weeks, their IgPro20 dose will be maintained at 0.4 g/kg bw for the remainder of the study. If they experience a second relapse after Week 25, they will be withdrawn from the study, as per this amendment.

A study design schematic is presented in Figure 1.

Figure 1: Study Design



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3.2 DISCUSSION OF STUDY DESIGN

See Section 3.1.3.

3.3 NUMBER OF SUBJECTS

It is assumed that approximately 80 subjects (includes approximately 10 subjects from Japan) from the pivotal study IgPro20_3003 will participate in this study.

3.4 STUDY DURATION

The study will end at the completion visit (Week 49). The last dose of IgPro20 is administered at Week 48.

3.5 PREMATURE TERMINATION OF STUDY

CSLB reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the CSLB Study Monitor (or delegate) will discuss this with the investigator at each study site at that time and notify the investigators in writing. If the study is suspended or terminated for safety reasons all investigators and the relevant regulatory agencies will be immediately notified of the action as well as the reason for it. The investigator at each study site will advise the Institutional Review Board (IRB)/IndependentEthics Committee (IEC) overseeing the study at their site. In accordance with applicable regulatory requirements, the sponsor will promptly inform the competent regulatory authorities of the termination and its reason(s).

If the study is terminated prematurely for any reason, the investigator should promptly inform the subjects participating at his or her study site and should ensure that appropriate alternative therapy is available and that follow-up procedures are conducted, as described in Section 7.10.

All study materials, except documents needed for archiving requirements, will be returned to the sponsor. The study monitor will ensure that any outstanding data clarification issues and queries are resolved, and that all study records at the study site are complete.

3.6 COMMITTEES

3.6.1 Steering Committee

The Steering Committee will have the following tasks:

- Provide overall supervision of the study.
- Provide scientific support.
- Provide scientific expertise for substantial amendments to the protocol.
- Provide advice to the investigators on all aspects of the study.
- Support recruitment/feasibility of the study (ie, education or lectures).
- Support preparation of publication(s).

3.6.2 Safety Review Committee

The Safety Review Committee (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 that will be finalized before first subject enrollment.

4. SELECTION OF STUDY POPULATION

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Before evaluating these criteria and deciding on the eligibility of subjects to participate in the study, it is important that the investigator is familiar with the safety profile of the study product by referring to the Investigator's Brochure, and/or appropriate product information, as supplied by the sponsor.

4.1 INCLUSION CRITERIA

Subjects meeting all of the following inclusion criteria may be enrolled into the study:

1. Written informed consent for study IgPro20_3004 before any study-specific procedures are performed.

2. Subject has completed the pivotal study IgPro20_3003 (SC Week 25), or was successfully rescued from a CIDP relapse during the SC Treatment Period of study IgPro20_3003.

4.2 EXCLUSION CRITERIA

1. Subject is unable to directly transition from the pivotal study IgPro20_3003, ie the subject is unable to have the baseline visit conducted at the same time as the completion visit for the pivotal study IgPro20_3003.
2. New medical condition and/or social behavior (ie, alcohol, drug, or medication abuse) during the pivotal study IgPro20_3003 that in the judgment of the investigator could increase risk to the subject, interfere with the evaluation of investigational medicinal product (IMP), and/or conduct of the study. See Section 6.7 (Contraindications and Precautions for Further Dosing).
3. Pregnant or intention to become pregnant during the course of the study.
4. Female subjects of childbearing potential either not using, or not willing to continue to use, a medically reliable method of contraception for the entire duration of the study, or not sexually abstinent for the entire duration of the study, or not surgically sterile.

4.3 SUBJECTS OF REPRODUCTIVE POTENTIAL

Female subjects of childbearing potential must use a medically reliable method of contraception (oral, injectable, or implantable hormonal contraceptives, or spermicide plus barrier, or intrauterine contraceptive device, or vasectomized partner) for the entire duration of the study, unless they are surgically sterilized or have undergone a hysterectomy or have been post-menopausal for more than 1 year.

The procedures for reporting and following up on any cases of pregnancy arising during this study are described in Section 9.7.

4.4 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

Subjects can withdraw their consent to participate in the study at any time without having to justify the reason for doing so. The decision to withdraw consent and discontinue participation in the study will not prejudice the subject's future medical treatment in any way.

Subjects must be discontinued from receiving IgPro20 and/or participating in any further study procedures (except for completion visit and related procedures) under the following circumstances:

- The subject has not successfully recovered at the 4-week follow-up visit after relapse.
- The subject or subject's legally authorized representative wishes to discontinue participation in the study.
- The investigator advises that the subject's safety or well-being could be compromised by further participation in the study. Example: After a relapse, the investigator may discontinue the subject at any time within 4 weeks if the subject's clinical status mandates it.
- If a subject has a grade 3 or above hemolysis (Table 3).

- The sponsor requests that a subject discontinues participation in the study (eg, due to suspicion of fraud, multiple enrollments in clinical studies, lack of compliance, etc.).
- Pregnancy.

Concern for the interests of the subject must always prevail over the interests of the study.

The reason for, and date of, discontinuation from participation in the study must be recorded in detail in the electronic case report form (eCRF) and in the subject's medical records (eg, AE, lack of compliance, lost to follow-up, etc.). If possible, the subject should confirm his or her decision in writing.

The investigator will attempt to complete all procedures usually required during follow-up or at the end of the study at the time when the subject's participation in the study is discontinued. Specific procedures required are described in Section 7.9. As far as possible, a complete final examination must be performed on all subjects who do not complete the study according to the study protocol.

Data collected until the time a subject discontinues participation in the study will be handled in the same manner as data for subjects completing the study. Where possible, further information will be collected if any AEs are experienced by a subject after discontinuing participation in the study.

4.5 REPLACEMENT OF SUBJECTS

Not applicable.

5. TREATMENTS

5.1 IDENTITY OF INVESTIGATIONAL MEDICINAL PRODUCT

	Study Product
Substance Code	IgPro20
Active Substance- International Nonproprietary Name (INN)	Human normal IgG
Trade Name (if applicable)	Hizentra®
Formulation (including dosage form and strength)	Liquid, ready-to-use 20% IgG solution stabilized with 250 mmol/L L-proline and 20 mg/L polysorbate 80 (P80). IgPro20 will be provided as a 20% IgG solution in a vial containing 4 g IgG in a volume of 20 mL.
Route/Mode of Administration	SC infusion
Manufacturer	CSL Behring AG, Berne, Switzerland

All IgPro20 supplied by the sponsor for use in this study will have been manufactured, tested, and released according to current Good Manufacturing Practice guidelines.

Any technical complaints arising from defects in the quality of the IMP, or defects in the packaging or labeling of the IMP must be reported to the sponsor at the earliest opportunity.

5.2 LABELING AND PACKAGING

IgPro20 will be packaged and labeled according to current ICH Good Manufacturing Practice and GCP guidelines and national legal requirements.

IgPro20 will be supplied in open-label packages. The lot number on IgPro20 identifies the packaging operation of a given amount of IgPro20. In addition, each vial has a unique vial number stated on the label. These numbers will be allocated to enrolled subjects by CSLB Clinical Supplies.

5.3 SHIPMENT AND STORAGE

IgPro20 will be supplied (initial and re-supplies) by external providers on behalf of CSLB. The Interactive Web Response System (IWRS) system supports the IgPro20 supply process.

IgPro20 will be shipped under appropriate temperature conditions as indicated on the label. The shipment process as well as actions that have to be taken in case of transport temperature deviations are described in the IMP Handling Instructions.

IgPro20 must be stored under labeled conditions/handling instructions, protected from light, and must not be frozen.

Control of the storage conditions at the study site is mandatory. For a more detailed description of storage of IgPro20, refer to the IMP Handling Instructions and the labels.

All IgPro20 must be stored separately from normal hospital or practice inventories, in a locked facility with access limited to the investigator and authorized personnel. The investigator must ensure that IgPro20 is dispensed only to subjects enrolled in this study according to this study protocol.

Storage and handling of IgPro20 at the subject's home are described elsewhere (ie, in the infusion training manual).

5.4 ACCOUNTABILITY

The investigator or delegate will confirm receipt of all shipments of IgPro20 in the Interactive Web Response System (IWRS).

All supplies must be accounted for throughout the study. Records for the delivery of the IgPro20 to the study site, the inventory at the study site, the use by each subject, and the destruction or return of the IgPro20 to the sponsor must be maintained by the investigator (or delegate). The

investigator must maintain records documenting that subjects were provided with the doses of IgPro20 specified in this study protocol. Furthermore, the investigator must account for all IgPro20 received from the sponsor. The investigator must provide reasons for any discrepancies in drug accountability. Forms/reports will be provided by the sponsor to ensure standardized and complete drug accountability. Detailed information on site accountability is provided in the IMP Handling Instructions.

Used, unused, and partially used vials of IgPro20 provided to the subject will be returned by the subject to the investigator at every visit.

Further details regarding drug accountability are provided in the IMP Handling Instructions.

For Japanese sites only, the drug inventory and accountability logs/reports must be dated and signed by the head of the medical institute or the study drug storage manager (if assigned by the head of medical institute).

5.5 DESTRUCTION OF INVESTIGATIONAL MEDICINAL PRODUCT

Any unused, partially used, or empty IgPro20 vials must not be destroyed until the drug accountability documentation has been checked by the study monitor and any necessary permission for destruction has been given by the sponsor. Any destruction of the IgPro20 must be documented and provided to the sponsor.

All drug accountability records must be stored in the site file and must be readily available for inspection by the study monitor and/or auditor, and open to regulatory inspection at any time.

6. PROCEDURES FOR ADMINISTRATION OF TREATMENTS

6.1 TREATMENTS TO BE ADMINISTERED

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

Subjects have been trained on the SC technique during the pivotal study. An investigator/study nurse can be contacted to discuss any problems with SC infusion, and if needed, additional training can be performed in the context of this study.

All subjects enrolled in this study will receive a weekly dose of IgPro20 0.2 g/kg bw for 48 weeks.

Subjects who relapse will receive weekly administrations of IgPro20 0.4 g/kg bw until completion visit or withdrawal from the study.

A subject enrolled under the original protocol (09 Dec 2013) will convert to Amendment 2 procedures at Week 25 after Amendment 2 approval at the site (conversion to Amendment 2 may be later than Week 25, if the site has not yet been granted approval). An IgPro20 dose adjustment from 0.4 to 0.2 g/kg bw will be required for subjects who did not experience a CIDP relapse

during the first 25 weeks of the study. For subjects under the original protocol (09 Dec 2013) who recovered from a CIDP relapse during the first 25 weeks, their IgPro20 dose will be maintained at 0.4 g/kg bw for the remainder of the study. If they experience a second relapse after Week 25, they will be withdrawn from the study, as per this amendment.

6.2 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

Not applicable, as this is a single-arm study.

6.3 SELECTION OF DOSES IN THE STUDY

The IgPro20 dose (0.2 g/kg bw) used in this study has been investigated in the pivotal study IgPro20_3003. As the extension study will start before termination of the pivotal study, the pivotal study will still be blinded and the final analysis of efficacy and safety of the 2 IgPro20 doses versus placebo will not yet have been performed. All subjects will be treated with 0.2 g/kg bw IgPro20 in this extension study, and will receive 0.4 g/kg bw IgPro20 only if CIDP relapse occurs. For dose justification, see Section 1.5.

6.4 SELECTION AND TIMING OF DOSE FOR EACH SUBJECT

6.4.1 Dosing Procedure

Before SC administration, the solution of IgPro20 must be allowed to reach room temperature.

For best practice, IgPro20 should be administered during 1 session for the **0.2 g/kg bw** dose, and 2 equal volume sessions for the **0.4 g/kg bw** dose during 1 or 2 consecutive days.

The total dose/volume of IgPro20 will be calculated on the basis of the body weight (kg, to 1 decimal place). The volume needed for each **infusion session** will be calculated by the Interactive Web Response System (IWRS) in the following manner:

Example for 0.2 g/kg bw dose:

- Weight = 77kg
- Volume of IgPro20 in mL rounded up or down to nearest full 5mL, 75mL in a single session

Example for 0.4 g/kg bw dose:

- Weight = 77kg
- Volume of IgPro20 in mL rounded up or down to nearest full 5mL per session, 75mL + 75mL = 150mL total volume given in two sessions

The time points for body weight measurements relevant for dose calculation and potential dose adjustments are presented in the Schedule of Assessments.

The SC infusions should be performed at appropriate infusion sites, eg, on the abdomen, thighs, and/or lateral hip. The number of infusion sites depends on the total volume to be administered. The maximum rate and the maximum volume per infusion site should not be exceeded (see Table 1). It is recommended to change the infusion site(s) with each administration. Two infusion pumps with a maximum volume of 50 mL each will be provided to the subject. The total volume to be infused can be subdivided over multiple injection sites. Two infusion pumps may be used in parallel. If needed, additional infusion sites may be used consecutively.

Table 1: Maximum infusion rate and volume for IgPro20

Rate of infusion per site	Up to 35 mL/h, as tolerated
Volume per site	Up to 50 mL, as tolerated

The goal should be increasing the subject's comfort while decreasing the pain and infusion time. A subject who does not tolerate a specific volume per infusion site can reduce the volume per site as needed. Any change of volume or rate per infusion site should be approved by the investigator.

6.4.2 Dosing Procedure in Case of Relapse

Subjects who relapse on IgPro20 0.2 g/kg bw will be given the option to remain in the study and start immediately on IgPro20 0.4 g/kg bw after the relapse has been confirmed at a site visit or be withdrawn from the study. Subjects who meet the criteria to stay on study after a relapse will remain on IgPro20 0.4 g/kg bw until Week 48 or until they are withdrawn from the study.

6.5 BLINDING

Not applicable as this is an open-label study.

6.6 CONCOMITANT THERAPY

All medications currently being taken by a subject at enrollment into the study and which continue to be taken in addition to the IgPro20 during the study, are regarded as concomitant therapy and must be documented as such in the eCRF.

6.6.1 Concomitant Therapy – Not Permitted

The following CIDP treatments are NOT PERMITTED during the treatment period for IgPro20_3004:

- Other non-study IgGs
- Rituximab
- Alemtuzumab
- Plasma exchange
- Interferon
- Tumor necrosis factor (TNF)-α inhibitors
- Fingolimod

- Cyclophosphamide
- Any other systemic immunosuppressive medications, except those medications permitted during IgPro20_3003 participation, see Section 6.6.2.

Subjects who receive prohibited medication during the study before the completion visit may be discontinued each case will be assessed individually.

6.6.2 Concomitant therapy - Permitted

Concomitant CIDP treatments other than those listed above are permitted, provided their dose and frequency are kept stable during the whole study, eg, methotrexate, azathioprine, mycophenolate, or corticosteroids (maintenance dose ≤20 mg).

6.7 CONTRAINDICATIONS AND PRECAUTIONS FOR FURTHER DOSING

IgPro20 is contraindicated in subjects:

- Who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of the immunoglobulin formulation, such as polysorbate 80 (P80) in IgPro20.
- With hypersensitivity to homologous immunoglobulins, especially in the very rare cases of immunoglobulin A (IgA) deficiency when the subject has antibodies against IgA.
- With hyperprolinemia type I or II.

Thrombotic events: Thrombotic events can occur in treatment with IgPro20. Subjects should be informed about first symptoms of thrombotic events including shortness of breath, pain and swelling of a limb, focal neurological deficits, and chest pain and should be advised to contact their physician immediately upon onset of symptoms. Subjects should be sufficiently hydrated before use of IgPro20.

Aseptic meningitis syndrome: AMS can occur in treatment with IgPro20. The syndrome usually begins within several hours to 2 days following treatment. AMS is characterized by the following signs and symptoms: severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Subjects exhibiting signs and symptoms of AMS should receive a thorough neurological examination, including cerebral spinal fluid studies, to rule out other causes of meningitis. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

Hemolysis: Cases of hemolysis can occur in treatment with IgPro20. If a subject experiences a confirmed hemolysis of grade 3 (see Section 9.1.3) during the study, the subject should be withdrawn.

Hypersensitivity and anaphylactic reactions: True hypersensitivity reactions can occur in cases of IgA deficiency with anti-IgA antibodies.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in subjects who had tolerated previous treatment with human normal immunoglobulin.

In case of an adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the reaction. In case of shock, standard medical treatment for shock should be implemented.

Vaccination: Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella for a period of at least 6 weeks and up to 3 months. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore subjects receiving measles vaccine should have their antibody status checked.

6.8 OVERDOSE

Consequences of an IgPro20 overdose are not known. In case of an overdose, the occurrence of an adverse drug reaction should be closely monitored and, if necessary, supporting measures should be offered.

6.9 TREATMENT COMPLIANCE

Subjects will bring their vials of IgPro20 (used, unused, and partially used) at every scheduled or unscheduled (if needed) visit to the study site. Treatment compliance will be monitored by an accurate and current accounting of the dispensing of study medication, to be maintained on an ongoing basis in the Drug Accountability Form by the person responsible for the distribution of the study medication to the subject for home-based treatment. The study medication label will include a unique vial number, so that the number of vials used can be checked against the details given in the Drug Accountability Form to ensure compliance. In addition, information on discrepancies to the planned infusion scheme will be recorded.

7. VISIT SCHEDULE

A subject enrolled under the original protocol (09 Dec 2013) will convert to Amendment 2 procedures at Week 25 after Amendment 2 approval at the site (conversion to Amendment 2 may be later than Week 25, if the site has not yet been granted approval). An IgPro20 dose adjustment from 0.4 to 0.2 g/kg bw will be required for subjects who did not experience a CIDP relapse during the first 25 weeks of the study. For subjects under the original protocol (09 Dec 2013) who recovered from a CIDP relapse during the first 25 weeks, their IgPro20 dose will be maintained at 0.4 g/kg bw for the remainder of the study. If they experience a second relapse after Week 25, they will be withdrawn from the study, as per this amendment.

At the Week 2 visit, the subject will receive a laminated card with the following self-help questions to assess CIDP status prior to each weekly IgPro20 infusion:

- Have I noticed any changes to my hands or arms?, ie, my ability to undo buttons?, wash/brush my hair?, eat with utensils?, or handle small coins? Yes or No.
- Have I noticed any changes in my ability to walk?, ie, outdoors?, up/down stairs?, need a walking stick or 2? Yes or No.

Any increase in signs of CIDP deterioration should prompt the subject to call the site to discuss CIDP status and the potential for an unscheduled visit (see Section 7.7).

7.1 WEEK 1 (BASELINE)

Subjects must transition directly from pivotal study IgPro20_3003 to this extension study. The baseline visit assessments will be performed at the same time as the completion visit assessments of the pivotal study IgPro20_3003.

The procedures associated with each study appear in Table 2. The data from the procedures performed as part of the completion visit of the pivotal study IgPro20_3003 will be transferred electronically to the safety extension study database for the baseline visit.

Table 2: Completion Visit IgPro20_3003 vs Baseline Visit IgPro20_3004 Assessments

Completion visit of pivotal study IgPro20_3003	Week 1/Baseline visit of extension study IgPro20_3004
Review and record concomitant medications (ongoing medications from Study IgPro20_3003 will be transferred to the study database)	Obtain written informed consent for extension study from the subject
Perform physical examination and measure body weight (This body weight should be used for Study IgPro20_3004 IWRS dose calculation for Week 1 baseline visit.)	Review in-/exclusion criteria for extension study
Obtain blood samples for hematology, serum chemistry, IgG concentration	Review and record new medical history (ongoing AEs, any resolved serious, severe, and/or AEs of special interest from Study 3003 will be transferred as medical history to the study database, old medical history from Study 3003 will be transferred to the study database)
Retention sample for viral safety testing	Dispense IgPro20 – the site should ensure that there is 1 week (+2 days) between the last dose of IgPro10 or IgPro20 administered in Study 3003 and the first dose of IgPro20 administered in Study IgPro20_3004.
Urine pregnancy test for all female subjects	Obtain biomarker sample (Optional for Japan)
Perform ECG (Japan only)	
Review IgPro20 administration information	
Review and record AEs	
Assess INCAT score, MRC sum score, grip strength, R-ODS, and HRQL questionnaires	

7.2 WEEKS 2 AND 9

The following assessments/tasks will be performed:

1. Review and record concomitant medications.
2. Obtain blood samples for hematology, serum chemistry, and IgG concentration.
3. Dispense IgPro20.
4. Collect vials (used, unused, and partially used) from the subject for reconciliation.
5. Plan weekly IgPro20 infusions.
6. Review SC administration information.
7. Review and record AEs.
8. Assess scores (INCAT score, MRC sum score, grip strength, and R-ODS).

The subject should report any increase in signs of CIDP deterioration or any other safety concerns to the site, prompting additional procedures required for an unscheduled visit (see Section 7.7)

7.3 WEEK 17

The following assessments/tasks will be performed:

1. Collect vials (used, unused, and partially used) from the subject for reconciliation.
2. Collect weekly SC administration information.
3. Dispense IgPro20.

The subject should report any increase in signs of CIDP deterioration or any other safety concerns to the site, prompting additional procedures required for an unscheduled visit (see Section 7.7)

7.4 WEEK 25

The following assessments/tasks will be performed:

1. Review and record concomitant medications.
2. Measure body weight.
3. Physical examination.
4. Obtain blood samples for hematology, serum chemistry, and IgG concentration.
5. Obtain biomarker sample (optional for Japanese subjects).
6. Dispense IgPro20.
7. Collect vials (used, unused, and partially used) from the subject for reconciliation.
8. Plan weekly IgPro20 infusions.
9. Review SC administration information.
10. Review and record AEs.
11. Assess patient-reported outcomes (TSQM, WPAI-GH, subject preference, and EQ-5D).
12. Assess scores (INCAT score, MRC sum score, grip strength, and R-ODS).

For a subject enrolled under the original protocol (09 Dec 2013) who has not relapsed during the first 25 weeks of the study, the IgPro20 dose will be decreased to 0.2 g/kg bw at Week 25 (or later than Week 25, if the site has not yet been granted amendment approval). The subject should be given the laminated self-help card (see Section 7) to review the CIDP status before each weekly SC dose. Any increase in signs of CIDP deterioration should prompt the subject to call the site to discuss CIDP status and the potential for an unscheduled visit (see Section 7.7).

For a subject enrolled under the original protocol (09 Dec 2013) who successfully recovered from a CIDP relapse during the first 25 weeks of the study, the IgPro20 dose will remain unchanged at Week 25 (0.4 g/kg bw).

7.5 WEEK 33

The following assessments/tasks will be performed:

1. Review and record concomitant medications.
2. Obtain blood samples for hematology, serum chemistry, and IgG concentration.
3. Dispense IgPro20.

4. Collect vials (used, unused, and partially used) from the subject for reconciliation.
5. Plan weekly IgPro20 infusions.
6. Review SC administration information.
7. Review and record AEs.
8. Assess scores (INCAT score, MRC sum score, grip strength, and R-ODS).

The subject should report any increase in signs of CIDP deterioration or any other safety concerns to the site, prompting additional procedures required for an unscheduled visit (see Section 7.7)

7.6 WEEK 41

The following assessments/tasks will be performed:

1. Collect vials (used, unused, and partially used) from the subject for reconciliation.
2. Collect weekly SC administration information.
3. Dispense IgPro20.

The subject should report any increase in signs of CIDP deterioration or any other safety concerns to the site prompting additional procedures required for an unscheduled visit (see Section 7.7).

7.7 UNSCHEDULED VISIT

Unscheduled visits are additional visits to the planned visits in the study. They do not replace the regular, scheduled visits. An unscheduled visit can be arranged at any time during the study triggered by the investigator or the subject. An unscheduled site visit must be scheduled as soon as possible when a CIDP relapse is suspected if a regular scheduled visit is not timely. The following assessments should be performed at an unscheduled visit:

1. Review and record concomitant medications.
2. Measure body weight.
3. Physical examination.
4. Obtain blood samples for hematology, serum chemistry, and IgG concentration.
5. Obtain biomarker sample in case of CIDP relapse only (optional for Japanese subjects).
6. Plan weekly IgPro20 infusions (if required).
7. Review SC administration information.
8. Review and record AEs.
9. Assess scores (INCAT score, MRC sum score, grip strength, and R-ODS).
10. Dispense IgPro20, if needed (ie, in case of confirmed relapse and switch from 0.2 g/kg IgPro20 to 0.4 g/kg IgPro20).
11. Collect vials, if needed (used, unused, and partially used) from the subject for reconciliation.

If a CIDP relapse is confirmed at an unscheduled visit, the site should also discuss the self-administrations of IgPro20 with the subject to see if any re-training is necessary to improve compliance.

7.8 RELAPSE FOLLOW-UP VISIT

This visit is scheduled 4 weeks (±2 days) after a CIDP relapse has been confirmed (a CIDP relapse can be confirmed at a scheduled or an unscheduled site visit).

Note: Should a subject not meet the criteria for successful recovery (see Definition of Terms for "Successful recovery") from relapse at this visit, the subject will be withdrawn and will need to complete the tasks under the completion visit. If the subject is not able to come in for the relapse follow-up visit within the 4 weeks (±2 days), the investigator must confirm successful recovery by INCAT assessment by phone and schedule the relapse follow-up visit as soon as possible.

The following assessments/tasks will be performed at the relapse follow-up visit:

1. Review and record concomitant medications.
2. Measure body weight.
3. Physical examination.
4. Obtain blood samples for hematology, serum chemistry, and IgG concentration.
5. Assess scores (INCAT score, MRC sum score, grip strength, and R-ODS).
6. Subject's total adjusted INCAT score is determined:

   If the subject's adjusted INCAT is not at least as good as the INCAT score from the baseline visit, the subject will need to complete all tasks under the completion visit below not already completed at this visit, and be withdrawn from the study.

   If the subject's adjusted INCAT is at least as good as the INCAT score from the baseline visit, the subject will remain in the study on the 0.4 g/kg bw dose.
7. Dispense IgPro20 (if needed).
8. Plan weekly IgPro20 infusions (if needed).
9. Review SC administration information.
10. Review and record AEs.
11. Collect vials, if needed (used, unused, and partially used) from the subject for reconciliation.

7.9 COMPLETION VISIT (WEEK 49 OR AT DISCONTINUATION)

The following assessments will be performed:

1. Review and record concomitant medications.
2. Measure body weight.
3. Physical examination.
4. Obtain blood samples for hematology, serum chemistry, and IgG concentration.
5. Obtain biomarker sample (optional for Japanese subjects).
6. Obtain retention sample for viral safety testing.
7. Pregnancy test (all female subjects)
8. ECG (Japan only).
9. Collect vials (used, unused, and partially used) from the subject for reconciliation.
10. Review SC administration information.
11. Review and record AEs.

12. Assess patient-reported outcomes (TSQM, WPAI-GH, subject preference, and EQ-5D).
13. Assess scores (INCAT score, MRC sum score, grip strength, and R-ODS).
14. Return subject to standard of care therapy, CIDP treatment prescribed by treating physician.

If it is determined that a subject has not successfully recovered from a CIDP relapse at the 4-week follow up visit, or if a second relapse is confirmed, and the subject must be withdrawn from study, the HRQL assessments required for the Completion visit will be performed following the efficacy determination.

7.10 DISCONTINUATION PROCEDURES

In case of discontinuation, the tasks/assessments as listed in Section 7.9 (completion visit) should be performed.

8. STUDY VARIABLES AND METHODS OF ASSESSMENT

8.1 SUBJECT CHARACTERISTICS

8.1.1 Overview of Variables

- Demographic data (date of birth, sex, race/ethnic group).
- Body weight and height.
- Medical and surgical history prior to baseline, including all diagnoses from Study IgPro20_3003 will be transferred to the study database. New medical conditions, any ongoing AEs, any resolved serious, severe, and/or AEs of special interest from Study IgPro20_3003 should be recorded as medical history.
- Concomitant medications (ongoing medications from Study IgPro20_3003 will be transferred to the study database).
- Pregnancy test.

Variables used to measure treatment compliance with respect to administration of the IMP, and their methods of assessment, are described in Section 6.9.

8.1.2 Methods of Assessment

The diagnosis of CIDP, prior therapies, demographics, and medical history have been collected within the pivotal study IgPro20_3003. Any additional information regarding prior and concomitant diseases or AEs will be assessed at baseline (Week 1) of this extension study.

8.2 EFFICACY VARIABLES

8.2.1 Overview of Variables

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

- INCAT score.

- Mean grip strength as assessed by the Martin Vigorimeter.
- MRC sum score (8 muscle groups).
- R-ODS.

8.2.2 Method of Assessment

For all clinical outcome scores, a mandatory training will be performed for all new treating physicians without previous experience in the pivotal study IgPro20_3003. Should a substitute/delegate be necessary, this person must also be trained in the use of the scores. If possible, a given subject should always be assessed by the same evaluator throughout the study.

8.2.2.1 Inflammatory Neuropathy Cause and Treatment (INCAT) Score

The INCAT score is a 10-point scale that covers the functionality of legs and arms (Hughes et al., 2001). **Clinically meaningful changes** are based on the **total adjusted INCAT score** that does not consider total INCAT scale changes of 1 point if these are from 0 to 1 or from 1 to 0 in the arms only.

Relapse according to INCAT score

In general, an increase of 1 point in the total INCAT score is considered a relapse. However, there are 2 exceptions:

1. If the increase in total INCAT score is only due to an increase in the arm score from 0 to 1, then this is not regarded as a relapse. The INCAT score increase will be documented but no tasks related to a relapsed subject (eg, 4-week relapse follow-up visit) will be performed.

2. If a subject has no INCAT increase, a relapse may still have occurred. This is the case if there is an increase in the leg score by 1 point, and in parallel a decrease in arm score from 1 to 0. While the change in arm score from 1 to 0 is not regarded as clinical meaningful, the increase in leg score still classifies this subject as a relapser. Any other parallel increase in 1 subscore and a likewise decrease in the other, where the total INCAT score will remain the same, will not be regarded as a relapse.

INCAT SCORE

ARM disability	**Classification:** 0 = No upper limb problems. 1 = Minor symptoms, in 1 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. 2 = Disability, in 1 arm or both arms, affecting but not preventing any of the above mentioned functions. 3 = Disability, in 1 arm or both arms preventing 1 or 2 functions listed above. 4 = Disability, in 1 arm or both arms preventing 3 or all functions listed above, but some purposeful movements still possible. 5 = Inability to use either arm for any purposeful movement.	
	INCAT score for ARM disability:	
LEG disability	**Classification:** 0 = Walking not affected. 1 = Walking affected, but walks independently outdoors. 2 = Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors. 3 = Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors. 4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps. 5 = Restricted to wheelchair, unable to stand and walk a few steps with help.	
	INCAT score for LEG disability:	
	Total INCAT score (= sum of arm and leg disability scores)	

Source: Hughes, 2009.

8.2.2.2 Grip Strength Measured by the Martin Vigorimeter

The hand-held Vigorimeter from Martin (Tuttlingen, Germany) is a device that measures the strength of small muscles in the hand, ie, grip strength. The subject squeezes a rubber bulb lying between the palm of the hand and the thumb and index fingers. The pressure is recorded via a rubber tube on a nanometer and expressed in kiloPascal. At each assessment, the subject squeezes 3 times with each hand (Merkies et al., 2000). The mean grip strength of each hand will be determined.

8.2.2.3 Medical Research Council (MRC) Sum Score

An adapted version of the MRC sum score as published by Kleyweg and the RMC trial group will be used (Kleyweg et al., 1991; Leger et al., 2001). With the MRC sum score, the following 8 bilateral muscle pairs are assessed, and individual muscle scores as well as the sum score documented:

- Shoulder abduction.
- Elbow flexion.
- Wrist extension.

- Index finger abduction.
- Hip flexion.
- Knee extension.
- Foot dorsiflexion.
- Great toe dorsiflexion.

Medical Research Council (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 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.

8.2.2.4 Rasch-built Overall Disability Scale (R-ODS)

The R-ODS is a recently published outcome measure that captures activity and social participation in subjects with Guillain-Barré Syndrome, CIDP, and monoclonal gammopathy of

uncertain significance (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 difficulty”, or “easy to perform”.

Rasch-built Overall Disability Scale (R-ODS)

Activity Are you able to:	Impossible to perform 0	Performed with difficulty 1	Easy to perform 2	Not applicable
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 (eg, 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				

tems are sorted in order of increasing difficulty to perform, based on data from subjects with peripheral neuropathies (chronic inflammatory demyelinating polyneuropathy, Guillain-Barré Syndrome, or monoclonal gammopathy of uncertain significance) and subjects recruited at the university outpatient clinics of PPD and PPD).
Source: van Nes et al, 2011.

8.3 SAFETY VARIABLES

8.3.1 Overview of Variables

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

- AEs.
- Laboratory safety parameters (hematology and serum chemistry).
- Physical examination.
- Japan only: 12-lead ECG.

8.3.2 Methods of Assessment

8.3.2.1 Adverse Events

Incidence, severity, and causality of AEs will be evaluated per infusion and subject according to the criteria specified in Section 9.1.1 during the observation period for AE reporting specified in Section 9.2. At the study site, the investigator or study nurse will specifically inquire (via non-leading questioning) about any AEs that might have occurred since the last infusion.

AEs will be recorded on the appropriate eCRF page.

Each individual manifestation of an AE should be graded individually for severity (see Section 9.1.1) or if it is temporally associated with the infusion (ie, during infusion or up to 72 hours after end of last infusion).

Details of the definitions and categorization of AEs, and procedures for the reporting of AEs, are available in Section 9.

8.3.2.2 Laboratory Safety Parameters

The following laboratory safety parameters will be assessed using standard validated methods:

- 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.

Information on the volume of blood to be sampled during the study for assessing laboratory safety parameters will be available in the laboratory manual. Further details on the timing of safety laboratory samples are available in the Schedule of Assessments.

Before starting the study, the central laboratory will supply the sponsor with accreditation certificates and a list of the reference ranges and units of measurement for the laboratory parameters to be determined.

All blood samples will be collected, prepared, and transferred according to the instructions provided by the central laboratory. The laboratory will provide the study sites with the appropriate material prior to study start. Pregnancy tests will be conducted at the study sites by urine dip stick.

The investigator will printout the laboratory report from the central laboratory vendor website. After reviewing the report and assessing any results that are outside the reference range, the investigator will add the assessment to the laboratory print out. Verification of the laboratory values, if applicable, will be recorded in the source data.

All abnormal laboratory values will require a comment on the lab printout. The following codes should be used:

- Error (ER), eg, laboratory error, improper sample preparation, hemolysis, delayed transit to laboratory, etc.
- Not clinically significant (NCS).
- Clinically significant (CS).

At baseline (Week 1), any laboratory values that deviate from the reference ranges and are considered by the investigator as clinically relevant have to be documented on the medical history page of the eCRF. Any deviation outside of the reference range considered by the investigator as CS at any later visit also has to be documented in the eCRF as an AE (see Section 9.1.1). Followup laboratory investigations due to an AE will be performed at the local laboratory at the discretion of the investigator.

8.3.2.3 Physical Examination

Physical examination should include an evaluation of the following body systems: general appearance, skin, eyes, ears/nose/throat, cardiovascular, pulmonary, and abdomen. Further examinations may be performed at the discretion of the investigator. Information about the physical examination must be present in the source documentation at the study site. 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.

8.3.2.4 Electrocardiogram (Japan only)

Evaluation of a 12-lead ECG will be performed by a local ECG-reader. The following ECG measures will be done: Mean heart rate, PR/PQ duration, QRS duration, and QT duration. The ECG printout will be regarded as source data. The findings will be reported to the investigator. Assessment will include a general statement about normal/unchanged, abnormal or new abnormal findings. Abnormalities will be documented in the eCRF.

8.3.2.5 Viral Safety

A retention sample for possible future viral safety analysis will be obtained at the completion visit of the extension study and will be stored for 1 year after the last subject's last visit at the central laboratory at -20°C. In case of any evidence for a potential treatment emergent virus infection within 1 year after study completion, the retention sample will be analyzed in the central

laboratory. Note: The retention sample for viral safety analysis obtained at the completion visit of the pivotal study IgPro20_3003 will also be considered the baseline retention sample for viral safety analysis for this study, ie, the retention sample will only be collected once.

8.3.2.6 Other Variables - Biomarkers

Blood samples will be collected and stored to assess potential biomarkers in CIDP in a separate, future study. These exploratory assessments may include, but will not be limited to the following: chemokines, cytokines, complement, protein expressions, and others. The blood draws for evaluation of the biomarkers will be clearly mentioned in the informed consent form (ICF) of this study. No DNA, RNA, mRNA or any other genetic testing will be done on the biomarker samples. Therefore, samples do not require anonymization by the central laboratory before transfer to CSL Australia for analysis at the end of the study. These potential CIDP biomarkers may allow for better understanding of prognosis, disease course, and correlation to treatment in CIDP subjects and therefore might allow for individualized treatment. In order to understand how the biomarker results might inform on these aspects of CIDP, they will need to be correlated with the subject's treatment in studies IgPro20_3003 and IgPro20_3004, hematology, serum chemistry and IgG, INCAT, and HRQL assessments. The CSL laboratory is located at PPD . All biomarker samples will be retained for a maximum of 10 years. The biomarker blood sample collection is optional for Japanese subjects and not required for Japanese subject study participation.

8.4 REPORTING OF INFUSION DETAILS

Infusion details as listed in Appendix 1 will be documented during the SC treatment. The information reported by the subject will be reviewed by the investigator at the site visits and recorded on the eCRF.

8.5 SERUM IMMUNOGLOBULIN G LEVELS

Blood samples for IgG level determination will be collected at each visit (scheduled and unscheduled) and will be analyzed by the central laboratory by immunoturbidimetry. IgG levels will not be disclosed to site or CSLB study personnel until the pivotal study IgPro20_3003 database is locked and unblinded.

8.6 HEALTH-RELATED QUALITY OF LIFE VARIABLES

8.6.1 Overview of Variables

The following HRQL variables will be collected:

- EQ-5D.
- TSQM.
- WPAI-GH.
- Subject preference for treatment.

8.6.2 Methods of Assessment

All HRQL instruments will be completed by the subjects themselves to assess both generic and treatment-specific subject status. The HRQL assessments should be performed before any sampling or clinical determination is performed, except if it is determined that a subject has not successfully recovered from a CIDP relapse at the 4-week follow up visit, or if a second relapse occurs, and therefore must be withdrawn from study. In that case, the HRQL assessments will be performed following the efficacy determination. EuroQoL 5-Dimension Questionnaire (EQ-5D).

The EQ-5D is a 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 Appendix 2).

8.6.2.1 Treatment Satisfaction Questionnaire for Medication (TSQM)

The original TSQM is a 14-item general instrument that measures the major dimensions of satisfaction with a medication (Atkinson et al., 2004). Scores on the TSQM range from 0 (indicating poor satisfaction) to 100 (indicating perfect satisfaction). This instrument usually requires less than 5 minutes for completion and was developed to be used with any medication and across cultural and different language settings. Scores on the Effectiveness (3 items), Side Effects (5 items), Convenience (3 items), and Global Satisfaction (3 items) scales will be assessed in a cross-sectional manner (see Appendix 3).

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

Healthcare and related services questions will be asked to assess work days lost because CIDP can be a disabling condition. For the assessment of work days lost, the WPAI-GH will be used (Reilly et al., 1993) (see Appendix 4).

8.6.2.3 Subject Preference for Treatment Questionnaire

Subject preference for pre-study intravenous treatment or on-study SC treatment will be assessed via a questionnaire consisting of 3 questions, with a selection option of predefined reasons for the preference (see Appendix 5).

8.7 APPROPRIATENESS OF MEASUREMENTS

In the present study, the changes in the course of CIDP are assessed using clinically relevant responses with well-established rating scales of limb disability (INCAT score) and muscle strength (MRC sum scores), and tests of actual grip strength.

INCAT and MRC sum score: Both scores have been widely used in other studies and publications (INCAT score: Hughes et al., 2001; Hughes et al., 2008; Hughes, 2009; Matsuda et al., 2004; MRC score: Gorson et al., 1998; Gorson et al., 2004; Hadden et al., 1999; Hughes et al., 2008; Thompson et al., 1996). Validity, reliability, and responsiveness of the INCAT score have been tested in different neurological indications.

The following adjustment of the INCAT score is applied throughout the study: changes in the function of the upper limbs from 0 (normal) to 1 (minor symptoms) or from 1 to 0 are not considered as deterioration or improvement in the INCAT score, because these changes are not considered by regulatory agencies to be clinically meaningful in all patients (Hughes et al., 2008).

Grip strength: Grip strength was found to be significantly associated with arm disability values over time, implying that grip strength can be applied as an index of arm function recovery in patients with immune-mediated polyneuropathies (Merkies et al., 2000; Merkies et al., 2003; Vanhoutte et al., 2013).

R-ODS: The R-ODS is currently the only linearly weighted "activity and social participation limitation" scale, which was developed and validated in 294 patients with Guillain-Barré Syndrome, CIDP, and monoclonal gammopathy of uncertain significance. The R-ODS captures a very broad range of difficulty items and has successfully been validated against the Overall Disability Sum Score with an intraclass correlation coefficient (ICC) of 0.85 and a very high test reliability of repeated measurements with an ICC of 0.97-0.99 (van Nes et al., 2011).

HRQL measurement

- **EQ-5D:** The EQ-5D measures quality of life as health outcome, including questions on mobility, ability to care for oneself, and do daily activities, as well as on pain and anxiety. The EQ-5D has been extensively validated in numerous therapeutic areas and has shown to be robust based upon sensitivity, reliability, and internal consistency. The scores of the EQ-5D will be calculated according to the published scoring algorithm.
- **TSQM:** The TSQM measures patients' satisfaction with a certain medication, covering positive and negative effects of the medication as experienced by the patient. The TSQM was developed based on data from patient focus groups and interviews, and was further validated in patients with chronic conditions (arthritis, asthma, depression, diabetes, hypercholesterolemia, hypertension, migraine, and psoriasis) (Atkinson et al., 2004). It has been used successfully in many other conditions. The TSQM has been shown to have good reliability and validity in a range of chronic and acute conditions (Atkinson et al., 2004).
- **WPAI-GH:** The WPAI has been developed to measure work productivity and activities in patients in a number of different diseases. The validated WPAI questionnaire has a broad acceptance in the scientific community and has been used since 1993 in several indications ranging from general health to rheumatoid arthritis or psoriasis (Reilly et al., 1993).
- **Subject Preference for Treatment Questionnaire:** For the comparison of different treatments, it is important to assess the subject's preference, which will be done with this questionnaire.

The safety measures used in this study (AEs, physical examinations, laboratory investigations, and viral safety) are routine procedures for clinical studies.

9. ADVERSE EVENT REPORTING

9.1 DEFINITIONS

9.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered an IMP (whether it is the study product or any reference product[s]). An AE does not necessarily have a causal relationship with the IMP.

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

AEs may include:

- The significant worsening of the disease or symptoms of the disease under investigation following administration of an IMP.
- Illnesses that coincide with an onset after administration of an IMP.
- Exacerbation (ie, increase in frequency or severity) of a pre-existing condition. Chronic illnesses present prior to study entry, other than the indication under study, should be recorded in the medical history page of the eCRF and be reported as AEs only if there is an increase in the frequency or severity of the condition during the study.

For laboratory safety parameters, any absolute values outside the reference range or changes at any visit after baseline that are considered by the investigator as CS have to be recorded in the eCRF as AEs.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at baseline.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE).

In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

AEs do not include:

- Medical or surgical procedures: the condition that leads to the procedure is an AE.
- Untoward medical findings that occur prior to administration of any IgPro20 if they occur in the scope of investigations that are performed for checking inclusion and exclusion criteria (eg, results of laboratory tests conducted at baseline).

- Situations where an untoward medical occurrence has not occurred, eg, planned hospitalizations due to pre-existing conditions that have not worsened, hospitalizations that occur for procedures not due to an AE (eg, elective surgery or social admission), or hospitalizations for a diagnostic procedure that takes less than 24 hours.
- Overdose of IgPro20 or any concomitant therapy that does not result in any adverse signs or symptoms. Details of the dosing (volume, location of infusions, infusion rate) of IgPro20 will be recorded by the subject during home treatment.

At each clinical evaluation the investigator (or delegate) will determine whether any AEs have occurred. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms.

All AEs are to be recorded on the "adverse event" pages in the subject's eCRF. The investigator must continue to follow-up on the course of an AE until resolution or until the AE is recognized as a permanent condition.

Severity of Adverse Events

The severity of each AE is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Severity Intensity Scale for Adverse Event Terminology.

Causality of Adverse Events

The causal relationship of an AE to IgPro20 should always be assessed by the investigator. Even if the investigator considers that there is no causal relationship to IgPro20, the AE must still be reported.

One of the following categories will be used for assessing the causal relationship of each AE, including a laboratory test abnormality, to IgPro20:

- *Not related*:
  - Event or laboratory test abnormality with a time to IgPro20 intake that makes a relationship impossible.

  - Is most likely explained by concurrent disease or other drugs or chemicals (either pathophysiologically or clinically).
  - Has occurred prior to administration of IgPro20 in comparable severity and/or frequency.
- *Related*:
  - Event or laboratory test abnormality with plausible time relationship to IgPro20 intake.
  - Cannot be explained by disease or other drugs.
  - Response to withdrawal plausible (pharmacologically, pathologically).
  - Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacological phenomenon).
  - Rechallenge satisfactory, if necessary.

The degree of certainty with which an AE is attributed to IgPro20 or an alternative cause (eg, natural history of the underlying disease, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of:

- Known pharmacology of IgPro20.
- Clinically and/or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related, eg, headache, facial flushing, and pallor.
- Plausibility supported by the temporal relationship, eg, the event being related by time to administration or termination of treatment with IgPro20, drug withdrawal, or reproduced on rechallenge.

9.1.2 Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose:

- *Results in death* – The event must be the cause of death for the AE to meet the criterion for being serious.
- *Is life-threatening* – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- *Requires in-patient hospitalization or prolongation of existing hospitalization* – The sponsor considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- *Results in persistent or significant disability or incapacity*.
- *Is a congenital anomaly or birth defect*.
- *Is medically significant* – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject's health or wellbeing or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

9.1.3 Adverse Events of Special Interest (AESIs)

An AESI is an AE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor is appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the sponsor to other parties (eg, regulators) might also be warranted.

The safety risk management plan of IgPro20 specifies the "Important Identified/ Potential Risks" for IgPro20. This involves systemic reactions reported to occur with IVIG treatment and discusses if they may potentially occur with SCIG treatments.

The following systemic AEs are therefore treated as AESIs:

- Acute systemic hypersensitivity reactions, ie, anaphylaxis.
- Aseptic meningitis syndrome (AMS).
- Suspicion of clinically relevant hemolysis.
- Thrombotic events.

All AESIs will be recorded on SAE forms, and narratives will be generated even if an AESI does not fulfill SAE criteria. AESIs which also qualify for SAE by SAE criteria will be recorded in the appropriate SAE section in the eCRF. In addition, for all AEs with hemolysis, a grading according to Table 3 should be performed. Subjects with grade 1 and 2 will continue treatment with IgPro20 and carefully monitored, while treatment with IgPro20 will be stopped in subjects with grade 3 or above hemolysis. Note: Not all cases of hemolysis necessarily qualify for AESIs, only those with suspicion of clinical relevance.

Table 3: Grading of hemolysis

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hemolysis	Laboratory evidence of hemolysis only (eg, DAT, schistocytes, decreased haptoglobin)	Clinical evidence of hemolysis and ≥2 g/dL decrease in hemoglobin	Transfusion or medical intervention indicated (eg, steroids)	Life-threatening consequences; urgent intervention indicated	Death

DAT = direct antiglobulin test.

Source: Common Terminology Criteria for Adverse Events (CTCAE), v4.03: 14/JUN/2010, U.S. Department of Health and Human Services.

9.2 OBSERVATION PERIOD FOR ADVERSE EVENT REPORTING

The observation period for AE (and SAE) reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish with the completion visit (Week 49 or discontinuation). If the investigator becomes aware of an SAE that has started after this completion visit (Week 49 or discontinuation) and the event could be associated with IgPro20 (irrespective of whether or not it is considered by the investigator to be causally related to the IgPro20), then this must also be reported to the sponsor (see Section 9.3).

9.3 REPORTING OF SERIOUS ADVERSE EVENTS BY INVESTIGATOR TO SPONSOR

SAEs will be recorded on the "AEs/SAEs" form of the eCRF, which contains specific questions for events regarded serious. Adverse events forms representing an SAE have to be printed out from the eCRF system, dated, wet signed, and a copy forwarded to CSLB together with relevant additional information via e-mail or facsimile. The signed print-out together with its attachments will be added to the subject's documents in the Investigator Study File at the study site. Whenever updates to the form become necessary this procedure will be repeated until the SAE has resolved or, in case of permanent impairment, until the SAE has been stabilized.

In case the eCRF system is not available for timely entry of SAEs a paper copy of the form located in the Investigator Study File must be used to document the SAE. Forwarding to CSLB and filing should follow the above mentioned rules. As soon as the eCRF system is available again, the information documented on the paper copy must be transcribed into the eCRF system.

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

ALL SAEs (INCLUDING SAEs LEADING TO DEATH) THAT OCCUR DURING THE COURSE OF THE STUDY, WHETHER OR NOT CAUSALLY RELATED TO THE IMP, **MUST BE REPORTED IMMEDIATELY** (WITHIN 24 HOURS OF THE INVESTIGATOR BECOMING AWARE OF THE EVENT) TO THE SPONSOR.

CONTACT DETAILS AND GUIDANCE FOR REPORTING SAEs ARE LOCATED IN THE INVESTIGATOR'S STUDY FILE AND ON THE SAE FORMS.

Prompt notification of SAEs to the sponsor, as described above, is essential so that regulatory requirements and ethical obligations to the subjects involved in the study can be met.

For SAEs occurring during the study, the investigator (or delegate) will complete the sponsor's AE/SAE reporting form, which should include all the available information regarding the event. If the minimum requirements for reporting are known, the investigator should notify the sponsor immediately and not wait for additional information to fully document the event. Follow-up reports will be submitted by the investigator to the sponsor at appropriate intervals until the SAE has resolved or, in the case of permanent impairment, until it has stabilized.

The minimum reporting requirements for immediate reporting of SAEs include:

- Identifiable subject.
- Suspected IMP and/or procedure.
- Event description.
- Identifiable reporting source.

When submitting SAE reports to the sponsor, subjects should be identified only by their subject number and study number. The investigator should not include the subject's name and address.

In cases of death, the investigator should provide the sponsor and the IEC/IRB (as applicable, see Section 9.4 with any additional requested information as it becomes available (eg, autopsy reports and detailed medical reports).

The observation period for SAEs will be specified for each clinical study (see Section 9.2) and is dependent on the nature of the study and the specific regulatory requirements. All SAEs must be reported from the time the subject gives written informed consent for participation in the current study until the end of the observation period for SAEs designated for the study.

The procedure to be followed if an ongoing AE becomes an SAE after the end of the observation period for AEs is described in Section 9.5.

Clinical events occurring in the period between the times the subject gave written informed consent and the first exposure to the IMP that meets 1 or more of the seriousness criteria for AEs must be reported to the sponsor in the same manner as SAEs and will be included in the clinical study database.

Further details on SAE reporting are available in the "Serious Adverse Event Reporting Plan".

9.4 REPORTING OF SERIOUS ADVERSE EVENTS BY INVESTIGATOR TO IEC/IRB

The timeframe within which an IEC/IRB must be notified of a death or an unexpected SAE considered at least possibly related to the IMP is stipulated by each individual IEC/IRB. The investigator is responsible for complying with the requirements for IEC/IRB notification. The investigator will notify the relevant IEC/IRB within the applicable timeframe by forwarding the safety report (eg, The Council for International Organizations of Medical Sciences [CIOMS] form) completed by the sponsor for the notifiable event.

9.5 FOLLOW-UP OF ADVERSE EVENTS ONGOING AT END OF STUDY

The investigator must make every effort to follow-up on subjects with an SAE that is still ongoing at the end of the study (ie, beyond the observation period specified in Section 9.2). This follow-up must be continued until the SAE resolves or is recognized as a permanent condition, whichever occurs later. Details of the subject's progress should be recorded in the subject's documents located in the Investigator Study File and submitted to the sponsor's study monitor.

If an ongoing AE should become an SAE (or an SAE leading to death) during a period of 30 days after the end of the study, then the investigator should follow the reporting procedures for SAEs and deaths described in Section 9.3 and Section 9.4.

9.6 REPORTING OF EVENTS OTHER THAN SERIOUS ADVERSE EVENTS BY INVESTIGATOR TO SPONSOR, IF APPLICABLE

There is no need for specifically reporting these types of AEs to the sponsor. All AEs will be documented in the eCRF.

For Japanese sites only, investigators must inform the head of medical institution, CSLB, regulatory authorities, and the relevant parties of the SAE and related information in accordance with the Japanese regulatory requirements and ICH GCP.

9.7 PREGNANCY

Pregnancy, by definition, is not considered as an AE unless it results in a complication (such as a maternal complication during pregnancy) that meets the definition of an AE, results in spontaneous abortion or stillbirth, or is associated with a congenital anomaly or birth defect in the fetus. Any such complication must then be reported accordingly as an SAE.

A subject with an estimated day of conception occurring while participating in the study must notify the investigator immediately and her participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in Section 4.4.

The sponsor must be notified within 5 days of the investigator becoming aware of the pregnancy.

Whenever possible, a pregnancy in subjects exposed to IgPro20 should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to the sponsor using a Pregnancy/Outcome Reporting Form.

10. DATA HANDLING PROCEDURES

10.1 RECORDING OF DATA

The investigator (or delegate) will maintain individual records for each subject. These records should include date of informed consent obtained, dates when a subject visits the study site, medical history, and physical examinations, administration of IgPro20 or other concomitant medications, any AEs experienced, and other records/notes as appropriate (eg, HRQL questionnaires). The investigator is responsible for maintaining individual records regarding the outcome scores, eg, scoring evaluation forms. All these records constitute source data.

The investigator is responsible for ensuring accurate and proper completion of the eCRF for recording data according to the instructions given in the eCRF, for the respective data responsible. All entries in the eCRF must be backed up by the relevant source data.

All source data will be kept according to all applicable regulatory requirements (see Section 13.8). Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate). In case of electronic source data, the investigator will provide printouts of the subject records at each monitoring visit. These printouts have to be dated and signed by the investigator (or delegate) and the sponsor's delegate.

The eCRF must be completed in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study.

10.2 DATA QUALITY ASSURANCE

An initiation meeting will be held before starting the study, during which the study design, procedures to be followed, and measures for ensuring standardized performance will be explained by a delegate from the sponsor, and a common understanding of the requirements of the study will be reached with the investigator and other relevant personnel at the study site.

Laboratory safety parameters based upon blood tests will be analyzed by a central laboratory (Section 8.3.2.2).

Data generated throughout the study will be monitored and the eCRFs checked against the subject records for completeness and accuracy. The sponsor's study monitor or delegate will perform this function.

Following completion of eCRFs, the data will be checked electronically for consistency and plausibility. Queries will be generated for questionable data. Furthermore, queries resulting from manual review of the data will be entered into the eCRF system. All queries must be resolved in a timely manner by the investigator (or delegate) and before closure of the clinical database.

10.3 RECORD RETENTION

A study document binder will be provided by the sponsor for the investigator at each site for all requisite study documents (constituting the "Investigator Study File").

Following completion of the study, the investigator will retain copies of the approved study protocol, ICF(s), relevant source documents, and all other supporting documentation related to the study according to applicable regulatory requirements, including PDF reports representing the eCRF data.

The investigator is responsible for archiving the Investigator Study File, the subject's records, and the source data according to applicable regulatory requirements. These documents have to be archived for at least 15 years, but should be retained for longer if required by regulatory requirements or by agreement with the sponsor.

If the investigator can no longer maintain the archive of study records (eg, due to retirement or relocation), the sponsor must be informed in writing about any change in responsibility for record retention, including the name of the new responsible party, contact information, and location of the study records. Records may not be destroyed without prior written consent from the sponsor.

11. STATISTICS

11.1 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.

11.2 RANDOMIZATION AND BLINDING

Not applicable.

11.3 ANALYSIS SETS AND ANALYSIS

11.3.1 Analysis Sets

Analyses will be based on the following sets: the Intention-to-Treat (ITT) Data Set and the Safety Data Set (SDS).

11.3.1.1 Intention-to-Treat (ITT) Data Set

The ITT Data Set consists of all subjects included into the study, ie, subject's informed consent has been obtained.

11.3.1.2 Safety Data Set (SDS)

The SDS is based on all subjects of the ITT Data 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.

11.3.2 Analysis of Efficacy

11.3.2.1 Intention-to-treat analysis

The ITT analysis will be based on the ITT Data Set. A subject must have at least 1 available measurement of a specific variable during the study period in order to be analyzed for that variable. Depending on the analysis, a baseline value may also be required. Therefore, some subjects may not be included in the analysis of a particular variable, although they are part of the ITT. The rules of application of imputation procedures will be specified in detail in the statistical analysis plan (SAP).

Invalid measurements will be acceptable for the ITT analysis.

11.3.3 Analysis of Safety

Analyses of safety after administration of the first dose of IgPro20 will be performed on the SDS

11.3.4 Missing Data

In case of missing data for a specific analysis variable, no imputation will be done for the analyses, except for R-ODS. For sensitivity analyses appropriate imputation procedures may be applied. Detailed description of the procedures will be documented in the SAP.

In the analysis of time to first relapse, missing data due to dropout will be accounted for by censoring.

11.4 STATISTICAL ANALYSES AND METHODS

A complete description of the statistical analyses and methods will be available in an SAP that will be finalized before the database is locked.

Descriptive statistics for continuous variables will include: N, mean, standard deviation, median, 25% and 75% quartiles, and minimum and maximum. For categorical variables, descriptive statistics will include n and percentages and – if applicable – shift tables indicating change from baseline will be presented.

If applicable, differences will be summarized descriptively after intra-subject calculation of the difference.

ITT analyses will be presented for efficacy and HRQL variables; safety variables will be analyzed based on the SDS.

Subject data listings will be presented.

11.4.1 Subject Disposition and Characteristics

11.4.1.1 Subject Disposition

The number of subjects enrolled as well as the number of subjects withdrawn will be presented. The reason for withdrawal will be listed by subject.

11.4.1.2 Subject Characteristics

Descriptive statistics will be calculated for all demographic variables. Percentages will be presented where appropriate. Age will be described as continuous.

11.4.2 Efficacy Analyses

11.4.2.1 Primary Efficacy Analysis

None

11.4.2.2 Secondary Efficacy Analyses

Analyses for changes from baseline in total adjusted INCAT score, MRC sum score, R-ODS, and mean grip strength will be summarized using descriptive statistics.

Time to first CIDP relapse will be analyzed using the Kaplan-Meier estimator. A plot will be presented as well as summary tables including median time to first relapse along with 95% confidence interval and the Kaplan-Meier estimate of the risk of experiencing a relapse until study completion.

11.4.2.3 Exploratory Efficacy Analyses

Changes from baseline will be summarized using descriptive statistics; time to first relapse will be analyzed as described in Section 11.4.2.2.

11.4.3 Safety Analyses

11.4.3.1 Adverse Events

Descriptive statistics will be provided for the primary and secondary safety AE endpoints.

11.4.3.2 Laboratory Safety Parameters

Hematology and serum chemistry values are considered exploratory safety variables. Abnormal laboratory data will be flagged.

Values flagged "ER" will be considered as missing and will not be included in the summarizing analysis.

11.4.3.3 Physical Examination

Any unfavorable findings recorded will be recorded as an AE and listed.

11.4.3.4 Electrocardiogram (Japan Only)

All new abnormal findings will be listed.

11.4.3.5 Other Safety Variables

Not applicable.

11.4.4 Pharmacokinetic and Pharmacodynamic Analyses

Not applicable.

11.4.5 Analyses of HRQL

Analyses of HRQL will include descriptive statistics of quality of life (EQ-5D), treatment satisfaction (TSQM), work productivity (WPAI-GH), and subject preference for treatment. Changes from baseline will be summarized using descriptive statistics.

11.4.6 Analyses of Other Variables

Treatment compliance will be measured as a percentage (= 100 *[used vials divided by planned vials]) overall and summarized using descriptive statistics. A percentage between 80% and 120% is regarded as compliant to treatment.

11.4.7 Subgroup Analyses

No subgroup analyses are planned.

11.5 INTERIM ANALYSIS

No interim analysis is planned. A snapshot analysis will be performed when approximately 10 Japanese subjects have completed at least 6 months of treatment. The snapshot analysis will not influence the conduct of this extension study.

11.6 ADAPTIVE DESIGN

Not applicable.

11.7 ANALYSES PROVIDED TO A SAFETY REVIEW COMMITTEE

The SRC will receive regular safety outputs, as described in the SRC Charter.

11.8 STATISTICAL SOFTWARE

The data obtained in this study will be analyzed statistically using SAS Software, version 9.2 or higher. For this purpose, data will be transferred from the eCRF system to SAS.

12. ETHICAL & REGULATORY CONSIDERATIONS

12.1 ETHICAL CONSIDERATIONS

The procedures set out in this study protocol are designed to ensure that the sponsor and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation, and documentation of this study, as described in ICH Topic E6 (Guideline for Good Clinical Practice). ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, and that the clinical study data are credible.

The study will also be carried out according to all applicable international and national regulatory requirements.

The sponsor and the investigator must inform each other (eg, during a study initiation visit, via e-mail, etc.) that all ethical and legal requirements have been met before the first subject is enrolled into the study.

12.2 SUBJECT INFORMED CONSENT

The investigator is responsible for obtaining a subject's written informed consent to participate in the study.

A Subject Information Sheet and a master ICF will be prepared by the sponsor or delegate according to the provisions of ICH GCP and local legal requirements, and will be approved by the sponsor.

All subjects will be informed that the study will be registered in the public database at ClinicalTrials.gov in accordance with the Food and Drug Administration (FDA) Amendments Act of 2007 (see Section 13.3).

Before undergoing any study-specific procedures, subjects must be informed, in an understandable form, about the nature, scope, and possible consequences of the study. This information must be given orally to subjects by a physician or medically qualified person (according to applicable regulatory requirements) who is well informed about the nature, scope, and possible consequences of the study. Written information about the study will also be provided in a Subject Information Sheet. The date on which this oral and written information on the study was provided to the subject, and by whom it was provided, must be documented in the ICF.

As specified in ICH GCP Section 4.8 and the US 21 Code of Federal Regulations Section 50.25, the informed consent discussion must emphasize that participation in the study is voluntary and that subjects have the right to withdraw their consent at any time without giving a reason and without any disadvantage for their subsequent care.

Subjects must be given ample time and opportunity to inquire about details of the study and to consider their participation in the study. If, after reading the Subject Information Sheet and the ICF, consent is given to participate in the study, then the ICF must be signed and personally dated by the subject and the person conducting the informed consent discussion (and an impartial witness, if required). The subject will be provided with a copy of the signed ICF.

Verification of the signed ICF will be recorded in the subject's eCRF. The original signed ICF will be filed with the subject's records.

The Subject Information Sheet and ICF have to be approved by the IEC/IRB before they can be used in the study.

The Subject Information Sheet and ICF must be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revision of these documents must be approved by the IEC/IRB before they can be used in the study. Subjects must be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the study. The communication of this information should be documented by having all parties' concerned sign and personally date the revised ICF.

12.3 REGULATORY CONSIDERATIONS AND INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

The sponsor (or delegate) will submit the appropriate documents to all applicable competent regulatory authorities and IEC/IRBs, and will await all relevant approval before enrolling any

subjects into the study. Written approval should mention the study protocol by study title, study number, and version date.

This study will be conducted under an Investigational New Drug Application (CCI [redacted]) and documented in accordance with the applicable regulatory guidelines and requirements.

The sponsor will ensure that the investigators conduct the study as stipulated in this study protocol and in accordance with all applicable regulatory requirements. The sponsor is obliged to obtain evidence of the investigator's qualification to perform the clinical study. Therefore, the investigator has to provide a signed and dated copy of his or her professional curriculum vitae (prepared no more than 2 years beforehand and preferably written in English) before the start of the study, including information on his or her experience in conducting clinical studies according to ICH GCP and other applicable regulatory requirements.

Written notification of the identity and occupation of the members of the IEC/IRB is also required by the sponsor. Should the IEC/IRB be unwilling to provide this information, a letter stating that the committee was constituted in accordance with applicable regulatory requirements should be provided.

12.4 PROTOCOL COMPLIANCE

The investigator must conduct the study in compliance with this study protocol as agreed to by the sponsor and, if required, by any competent regulatory authority, and which has been approved by, or given a favorable opinion by, the IEC/IRB.

The investigator should not implement any deviation from, or changes to, the study protocol without agreement by the sponsor and prior review and documented approval or favorable opinion from the IEC/IRB of an amendment to the study protocol. Exceptions include only cases of medical emergency to address immediate hazards to study subjects, or when the changes involve only logistic or administrative aspects of the study.

In the event of a medical emergency, the investigator at each site may institute any medical procedures deemed appropriate to address an immediate hazard to a subject without prior IEC/IRB approval or favorable opinion. As soon as possible, the implemented deviation or change, the reason(s) for it, and, if appropriate, the proposed study protocol amendment(s) should be submitted to:

- The sponsor for agreement.
- The IEC/IRB for review and approval or favorable opinion (if required).
- The applicable competent regulatory authority (if required).

Details of the procedure for implementing study protocol amendments are available in Section 13.10.

At the earliest opportunity, the investigator (or delegate) must inform the sponsor about any notable protocol deviations and explain any deviation from the approved study protocol in the eCRF and/or in the Protocol Deviation Log, if applicable.

13. ADMINISTRATIVE ASPECTS

13.1 CLINICAL TRIAL AGREEMENT

This study will be conducted under a Clinical Trial Agreement between the sponsor (or delegate) and the respective institutions representing the study sites. Any financial support given to the study sites will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement, which must be signed before the start of any study related procedures, will clearly delineate the responsibilities and obligations of the investigator and the sponsor, and will form the contractual basis upon which the study will be conducted.

13.2 FINANCIAL DISCLOSURE BY INVESTIGATOR

Prior to study initiation, the investigator and any sub-investigator(s) to be directly involved in the treatment or evaluation of study subjects at each study site will disclose to the sponsor any relevant financial or proprietary interests in either the study product or the sponsor company. The appropriate disclosure form(s) will be provided by the sponsor for this purpose. Any relevant updates to the financial disclosure information that occur during the conduct of the study, or during 1 year after completion of the study, will be provided by the investigator and sub-investigator(s) to the sponsor. All financial disclosure information provided by the investigator and sub-investigator(s) will be submitted to appropriate competent authorities according to the applicable regulatory requirements.

13.3 CLINICAL STUDY REGISTRATION AND RESULTS DISCLOSURE

The sponsor will provide the relevant study protocol information in a public database (ClinicalTrials.gov) before or at commencement of the study, as required by the 2007 FDA Amendments Act. The sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential subject contacts the sponsor regarding participation in the study, the investigator agrees that the sponsor may forward the relevant study site and contact details to the subject. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the subject for enrollment into the study.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record on ClinicalTrials.gov.

13.4 STUDY FILES AND MATERIALS

Before the start of any study related procedures, all essential documents specified by ICH GCP and other applicable regulations must be available in the relevant files maintained by the sponsor (or delegate) and the investigator. An Investigator Study File prepared by the sponsor (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. A list of personnel and organizations responsible for

conduct of the study as well as the list of investigators will be included in the Investigator Study File. The respective files will be kept and updated by the sponsor (or delegate) and the investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by the sponsor's study monitor (or delegate) to determine that all required documentation is present and correct (see Section 13.9).

The study may be audited or inspected by qualified delegates from the sponsor or a competent regulatory authority (see Section 13.11).

13.5 INITIATION OF THE STUDY

Before the start of the study at each study site, the sponsor's study monitor (or delegate) will visit the study site to ensure adequacy of the facilities and to discuss responsibilities regarding study protocol adherence with the investigator and other personnel involved in the study.

The investigator may not enroll any subjects into the study before the sponsor has received written approval or a favorable opinion from the IEC/IRB for conducting the study and a formal meeting has been conducted by the sponsor's study monitor (or delegate) to initiate the study (study initiation visit). This meeting will include an inventory of study supplies and a detailed review of the study protocol, the eCRF, and the subject diary (if applicable).

13.6 SUBJECT REIMBURSEMENT

Where relevant, subjects will be reimbursed for travel costs associated with participation in this study, at a rate to be approved by the IEC/IRB.

13.7 LIABILITY AND INSURANCE

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise as a result of this study being conducted are governed by the applicable legal requirement(s).

The sponsor will provide insurance to the investigator if required by the applicable regulatory and legal requirement(s).

If required by local law, subjects taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

13.8 SUBJECT IDENTIFICATION AND CONFIDENTIALITY

All study documents, including the study protocol and eCRFs, are the confidential property of the sponsor and should be treated as such.

The investigator will maintain a personal list of subject names and subject numbers (Subject Identification List) for participants in the study to enable records to be identified at a later date.

These records should be retained in a confidential manner for the duration stipulated by applicable regulatory requirements. All subject names will be kept in confidence and will not be revealed to the sponsor. Subject names must be made unreadable on any documents made available to the sponsor.

Subjects participating in the study will be identified in the eCRF by the subject number allotted to them during the study.

The ICF will include a statement that all study findings, irrespective of the medium on which they are stored, will be handled in strictest confidence in accordance with applicable data protection laws (eg, the European Data Protection Directive [95/46/EC] and the US Health Insurance Portability and Accountability Act), and will be evaluated by the sponsor and/or a competent regulatory authority in an anonymized form. The subjects are also to be informed that their medical records may be audited or inspected by qualified delegates from the sponsor or a competent regulatory authority. The subject's written consent authorizing direct access to his or her medical records, and computer processing and publishing of his or her anonymous personal data, must be obtained prior to participation in the study.

A subject's identity will be disclosed by the investigator only in case of emergency (ie, to address any immediate health hazard).

13.9 MONITORING OF THE STUDY

The investigator at each site will allow the sponsor's study monitor (or delegate) reasonable access to the eCRFs and direct access to related source documents for monitoring purposes as frequently as the sponsor deems necessary. These documents include records of tests performed as a requirement for participating in the study as well as other medical records required to confirm information contained in the eCRF, such as past history and secondary diagnoses.

The investigator (or delegate) should record all data generated in the eCRF in a timely manner, so that they are available for off-site monitoring and query management in due time. The investigator and other relevant personnel at each study site will be expected to cooperate with the sponsor's study monitor to assist in providing any missing information.

During on-site monitoring, the study monitor will require access to the Investigator Study File to ensure completeness of all documentation required for the study. The study monitor will ensure that the investigator at each site has been provided with adequate means for organization and filing of study documentation (see Section 13.4).

The date on which the study monitor (or delegate) visits the study site will be recorded in the Site Visit Log. During monitoring visits, the study site's coordinator (if applicable) and the investigator should be available, the source documentation should be accessible, and a suitable environment should be provided for the study monitor to review study related documentation.

The main objectives of monitoring visits conducted by the study monitor include:

- Resolution of any problems.

- Examination of all study documentation for completion, adherence to the study protocol, and possible AEs.
- Clarification of inconsistencies or missing data.
- Verification of study data against source documents.
- Checks that investigator obligations have been fulfilled.
- Review of ICFs and dates of consent.
- Inspection of the IgPro20 with respect to storage, labeling, and documentation.

After each subject's visit to the study site, the investigator (or delegate) will ensure that all data have been entered into the eCRF correctly and in a timely manner, after which the investigator will sign the eCRF.

13.10 PROTOCOL AMENDMENTS

A "substantial" amendment of a study protocol is any written description of change(s) to, or formal clarification of, a study protocol that may have a significant impact on the safety or physical or mental integrity of subjects, the scientific value of the study, the conduct or management of the study, or the quality or safety of any IgPro20 used in the study. The IEC/IRB must approve all substantial protocol amendments prior to their implementation. If required by applicable local regulatory requirements, the local regulatory authority must also approve all substantial protocol amendments prior to their implementation.

A "non-substantial" amendment of a study protocol includes minor corrections or clarifications that have no significant impact on the way the study is to be conducted and no effect on the safety of participating subjects (eg, change in study monitor, contact details, etc.). If required by applicable local regulatory requirements, the IEC/IRB, and/or the local regulatory authority should be notified of all non-substantial protocol amendments.

The substantial and non-substantial protocol amendments will be integrated into an updated study protocol at the discretion of the sponsor if the changes to the original study protocol are numerous, or if required by applicable regulatory requirements.

13.11 AUDITS AND INSPECTIONS

The study may be audited or inspected by qualified delegates from the sponsor or a competent regulatory authority.

In the event of an audit by the sponsor, the investigator must make all study related documentation available to the auditor(s). Regulatory authorities may request access to all study related documentation, including source documents, for inspection and copying in keeping with applicable regulations. The sponsor will immediately notify the investigator (or vice versa) of an upcoming audit or inspection.

If an audit or inspection occurs, the investigator and relevant personnel at the study site must allocate sufficient time to discuss the findings and any relevant issues.

13.12 CLINICAL STUDY REPORT

After completion of the study, a clinical study report covering clinical and statistical aspects of the study will be prepared by the sponsor (or delegate) in consultation with the Steering Committee. As required by the applicable regulatory requirements, the clinical study report will be signed by the sponsor's responsible medical officer as well as the coordinating investigator.

Progress reports and/or a summary of the clinical study report will be provided to the IEC/IRB and competent regulatory authorities in accordance with applicable requirements.

13.13 USE OF DATA AND PUBLICATIONS

The rights and obligations of investigators and the sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study (see Section 13.1).

For multicenter studies, the first publication must be based upon all data obtained from all analyses, as stipulated in the study protocol by the biostatistician and not by the investigators. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of study sites before the full, initial publication is available, unless this has been agreed to by all other investigators and by the sponsor.

The sponsor must receive a copy of any intended communications in advance of the proposed submission date. This is to allow the sponsor time to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential and/or proprietary information is not inadvertently divulged, to provide any relevant supplementary information, and to allow establishment of co-authorship (as appropriate). The authorship of communications arising from pooled data will include investigators from study sites that contributed data as well as relevant personnel from the sponsor. Ownership of all data will remain with the sponsor.

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15. APPENDIX

APPENDIX 1: INFUSION DETAILS

- Location of infusion (clinic or at home)
- Number of days for infusion sessions
- Dates of weekly infusion sessions
- Duration of the infusion sessions
- Number of injection sites used
- Maximum pump rate (mL/h) of each pump
- Volume (mL) applied
- Maximum volume (mL)/site used

APPENDIX 2: EUROQOL 5-DIMENSION QUESTIONNAIRE (EQ-5D)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*eg, work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

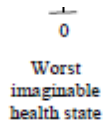
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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APPENDIX 3: TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION (TSQM)

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?
(if No, then please skip to Question 9)

1 Yes ☐
2 No ☐

5. How bothersome are the side effects of the medication you take to treat your condition?

1 Extremely bothersome ☐
2 Very Much bothersome ☐
3 Somewhat bothersome ☐
4 A Little bothersome ☐
5 Not at all bothersome ☐

(continued on next page)

6. To what extent do the side effects interfere with your *physical* health and ability to function (eg, 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 (eg, 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 ☐

(continued on next page)

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	☐
6 Very Confident	☐
7 Extremely Confident	☐

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	☐
6 Very Certain	☐
7 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	☐

Source: Atkinson et al, 2004

APPENDIX 4: WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: GENERAL HEALTH V2.0 (WPAI-GH)

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. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES

   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.*

   _____HOURS

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?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your 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.

   Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

   CIRCLE A NUMBER

(continued on next page)

6. 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.

   Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

   CIRCLE A NUMBER

Source: Reilly et al., 1993

APPENDIX 5: SUBJECT PREFERENCE FOR TREATMENT SCORE

Please choose one:

[ ] I prefer to continue using my 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 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

[ ] I have no preference for using either my current medication or the medication I was using before the study began.

Signature Page

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Signed By	Date (GMT)

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