COVER PAGE

TITLE: An international, multicentre, efficacy and safety study of I10E in initial and maintenance treatment of patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy

NCT Number: NCT02293460

DOCUMENT: Statistical analysis plan (v3.0)

VERSION & DATE OF DOCUMENT: Version 3.0; December 7, 2018

STATISTICAL ANALYSIS PLAN

An international, multicentre, efficacy and safety study of I10E in initial and maintenance treatment of patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
CLINICAL TRIAL PROTOCOL: *no. I10E-1302* /EUDRACT no. 2013-005557-73
Version 6.0 dated 3 May 2017

Investigational Medicinal Product:	***I10E, a ready-to-use liquid human normal immunoglobulin for intravenous administration (IVIG), 100 mg/mL***
Indication:	***Initial and maintenance treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)***
Study design:	Phase III, international, multicentre, single-arm, open-label prospective study.
Sponsor:	**Laboratoire français du Fractionnement et des Biotechnologies (LFB) BIOTECHNOLOGIES** 3 avenue des Tropiques BP 50052 91942 COURTABOEUF Cedex - France
Clinical Project Manager:	[redacted]
Clinical Research Physician:	[redacted]
Project Statistician:	[redacted]

Clinical trial number: I10E-1302
Version number: 3.0
Version date: 07DEC2018
Prepared by: [redacted]

MODIFICATION HISTORY

Unique Identifier for this version	Author	Changes from previous version
V3.0	[redacted]	Refer to Statistical Analysis Plan Amendment request form

SIGNATURE PAGE

Clinical trial number: I10E-1302
Version number: 3.0
Version date: 07DEC2018
Prepared by: [redacted]

Author:

Name	Function	Date	Signature
[redacted]	[redacted]	[redacted]	[redacted]

Reviewers:

Name	Function	Date	Signature
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Ab	Antibody
ACR	Albumin to Creatinine Ratio
AE	Adverse Event
AER	Albumin Excretion Rate
ALP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical
BAFF	B Cell Activating Factor
BMI	Body Mass Index
bpm	Beats per Minute
CGI	Clinical Global Impression
CI	Confidence Interval
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CNTN1	Contactin 1
DILI	Drug-induced Liver Injury
dps	Decimal Places
EOS	End of Study
FAS	Full Analysis Set
FCγR	FC-gamma Receptors
GFR	Glomerular Filtration Rate
γGT	γ Glutamyl Transferase
Hb	Hemoglobin
HBc	Hepatitis B core Antigen
HBs Ag	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
INCAT	Inflammatory Neuropathy Course and Treatment

IVIG(g)	Intravenous Immunoglobulin
KM	Kaplan-Meier
kPa	Kilopascal (Pressure Unit)
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LOCF	Last Observation Carry Forward
LOESS	Local Polynomial Regression
MCV	Mean Corpuscular Volume
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
NF155	Neurofascin 155
PCR	Protein to Creatinine Ratio
PER	Protein Excretion Rate
PPS	Per Protocol Set
PT	Preferred Term
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCIG(g)	Subcutaneous Immunoglobulin
SI	Standard International
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SWI	Standard Working Instruction
TAAE	Temporarily Associated Adverse Event
TEAE	Treatment Emergent Adverse Event
TTS	Total Treated Set
ULN	Upper Limit of Normal
USG	Ultrasonography
WHO	World Health Organisation

2. INTRODUCTION

2.1. Study Objectives

2.1.1. Primary objective

The primary objective of this study is to assess the efficacy of I10E in improving the disability of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

2.1.2. Secondary objectives

The secondary objective of this study is to assess the safety of I10E in patients with CIDP.

The secondary objectives also include the following exploratory objectives:

- To assess a potential relationship between serum total IgG trough levels, biomarkers levels and clinical response - as assessed by neurological scales - in patients with CIDP.
- To assess a potential relationship between ultrasonography (USG) coupled to neurophysiology analysis of nerves and clinical response - as assessed by neurological scales - in patients with CIDP (ancillary study in Italy).

2.2. Study Design

This study is a phase III, international, multicentre, single-arm, open-label, prospective study.

2.3. Sample Size

The study is designed to demonstrate superiority of I10E to an historical control in terms of responder rate. The historical responder rate with placebo is estimated from the ICE study (Hughes RA 2008). As a conservative estimate the upper boundary of the 95% confidence interval (CI) of the observed rate is used (observed rate 12/58 = 20.7%, 95% CI [11.2%, 33.3%]). Based on this historical placebo responder rate of 33.3% and a 60% responder rate with I10E, 38 evaluable patients are needed in order to obtain 90% power using an exact binomial test with a one-sided nominal level of significance α=2.5%. Presuming 10% non-evaluable patients, 42 patients will be included in the study (around one third of all patients will be either Immunoglobulin [Ig]-naïve or relapsing Ig-pre-treated).

2.4. Investigational Schedule and Randomisation

Depending on the version of protocol, the total duration of the study for a patient is approximately 24-27 weeks or 24-29 weeks. Each patient is screened during a maximum of 15 days or 4 weeks. The duration of treatment is approximately 21 weeks. A follow-up period of 3 weeks +/- 7 days will take place after the administration of the last study drug. At the end of the follow-up period, patients will undergo an EOS visit.

Randomisation is not applicable in this single-arm study.

2.5. Evaluation Criteria

2.5.1. Primary efficacy criterion

The primary efficacy criterion is response rate at the End-of-Study visit (EOS). Response is defined as a decrease ≥1 point in the adjusted inflammatory neuropathy course and treatment (INCAT) disability score between baseline and the EOS visit.

2.5.2. Secondary efficacy criterion

The secondary efficacy endpoints are the following:

- Response rate at 12 weeks
- Time to response
- Rate of patient with no change in CIDP treatment at 12 weeks and EOS visit
- Changes from baseline to 12 weeks and EOS visit in the following scores:
  - Adjusted INCAT disability score
  - Grip strength with the Martin vigorimeter in both hands
  - Rasch-built Overall Disability Scale (R-ODS)
  - Patient and Investigator Clinical Global Impression (CGI)
  - Medical Research Council (MRC) 12 muscles sum score (0 to 5)
  - Rasch-modified MRC sum score (0 to 3).

2.5.3. Safety criteria

The safety criteria include:

- Treatment emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Temporarily associated adverse events (TAAEs), i.e., AEs that begin during an infusion or within 72 hours after an infusion
- Clinically significant changes from baseline in vital signs
- Clinically significant changes from baseline in laboratory parameters

2.5.4. Exploratory criteria

Biomarker study

- Anti-Contactin 1 (CNTN1) and anti-Neurofascin 155 (NF155) antibodies titers at screening and EOS visit
- Fcγ receptor IIB (FcγRIIB) B cells marker levels at visits V2, V3 and V4
- B-cell activating factor (BAFF) at visits V2, V3, V4 and EOS visit
- Complement components (C3 and C4 antigens, CH50) at visits V2, V3, V4 and EOS visit
- Serum total IgG trough levels at each visit, within 24 hours prior to study drug administration

2.6. Study Plan Table

	Screening	First study drug administration	Day 4 after last infusion at V2	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18	Week 21	End of study visit
	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
Informed consent (before any procedure of study)	X										
Inclusion/exclusion criteria verification	X	X									
Demographics & Medical history	X										
Safety											
Adverse events assessment	X	X	X	X	X	X	X	X	X	X	X
Phone call 4 days (+/- 1 day) after study drug administration				X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Patient diary (delivery and verification)	X	X	X	X	X	X	X	X	X	X	X
Clinical assessments / Before study drug administration											
Complete physical examination	X	X	X								X
Clinical examination focused on arterial or venous thromboembolic signs				X	X	X	X	X	X	X	
Weight, Body temperature, heart rate, arterial blood pressure (systolic and diastolic)	X	X	X	X	X	X	X	X	X	X	X
Efficacy assessments / Before study drug administration											
INCAT disability score	X	X		X	X	X	X	X	X	X	X
MRC sum-score, Rash modified MRC sum-score R-ODS Grip Strength (both hands)		X					X				X
Patient and Investigator: CGI (Severity)		X					X				X
Patient and Investigator: CGI (Efficacy), CGI (Improvement)							X				X

Biological test Local lab / Before study drug administration	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
Serum Total IgG trough levels		X		X	X	X	X	X	X	X	X
HbA1c (only for patients with a known history of diabetes mellitus), serum IgA levels	X										
Urine protein reagent strip test	X[a]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Urine Pregnancy test for female of child bearing potential	X										X
C3 and C4 antigens		X	X	X							X
Anti HBs & anti HBc Ab, HBs Ag tests, HIV and HCV tests	X										X
Complete blood count and differentials, Hemoglobin, Mean corpuscular volume, platelet count, haptoglobin, LDH	X		X	X	X	X	X	X	X	X	X
Reticulocytes, direct Coombs test, total serum protein level	X										X
AST, ALT, γGT, ALP	X										X
Creatininemia, GFR[c], total and free bilirubin[d]	X		X	X	X	X	X	X	X	X	X
Serum reference sample for long term storage		X									X
Biological test Local lab in case of suspected clinical thrombosis											
D-Dimers		X	X	X	X	X	X	X	X	X	X
Biological test Local lab in case of suspected hemolysis											
Reticulocytes, direct Coombs test		X	X	X	X	X	X	X	X	X	X
Exploratory assessment Central lab / Before study drug administration											
anti-CNTN1 and anti-NF155 antibodies	X										X
BAFF, CH50		X	X	X							X
FcγRIIB (on B cells)		X	X	X							
Ultrasonography coupled to neurophysiology (Italian sites only)	X										X
Study drug administration											
I10E - 2g/kg		X									
I10E - 1g/kg				X	X	X	X	X	X	X	
Vital signs 30-45 minutes and 60-75 minutes after the start of study drug administration (each day of study drug administration)											
Body temperature, Heart rate, Arterial blood pressure (systolic and diastolic)		X		X	X	X	X	X	X	X	
Vital signs 30-45 minutes after the end of study drug administration (each day of study drug administration)											
Body temperature, Heart rate, Arterial blood pressure (systolic and diastolic)		X		X	X	X	X	X	X	X	

[a] *To be done in all patients. See below for actions dependent on urine protein reagent strip result at screening:*

Urine protein reagent strip test result	Action
Negative or Trace	No further urine test required
1 cross (1 +)	Verify eligibility after either assessing AER or PER from a 24h-urine collection sampled before the first study drug course, or assessing ACR or PCR from a spot urine sample immediately following the urine protein reagent strip test (i.e. urine obtained before study drug administration).
2 crosses (2 +) or more	Patient should be excluded

[b] *To be performed before study drug administration in patients who at screening tested for urine protein reagent strip result "1 cross 1 (+) and/or had GFRc in the range of 60-80 mL/min/1.73m^2:*

Urine protein reagent strip test result	Action
Negative or Trace	No further urine test required
1 cross (1 +) or more	Assess either AER or PER from a 24h-urine collection sampled at least 7 days after the end of the previous study drug course or assess ACR or PCR from a spot urine sample immediately following the urine protein reagent strip test (i.e. urine obtained before study drug administration). At all visits except End of Study visit: The Investigator must review these results in time prior to the next study drug administration and consider if any of the Early Discontinuation Criteria / Stopping Rules (see Section 5.4 of the protocol) apply.

c According to modification of diet in renal disease (MDRD) calculation

d Total bilirubin in all patients; if total bilirubin > ULN, free bilirubin will be assessed from the same blood sample, as total bilirubin

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. Description of Variables

Continuous data will be described using number of valid observations, number of missing observations, mean, standard deviation, median, quartiles, minimum and maximum.

Categorical data will be described using number of missing observations, number of valid observations per category and percentage. Number of missing observations will not be taken into account for the calculation of percentages.

For descriptive statistics, the following number of decimal places (dps) will generally be applied:

- 3 dps for values in [0, 0.9995)
- 2 dps for values in [0.9995, 9.995)
- 1 dp for values in [9.995, 99.95)
- 0 dp for values ≥99.95

For negative values the same rule will be followed using the absolute value.

For original case report form (CRF) variables the minimum and maximum will use the same number of dps as the raw data. Statistics on count variables (e.g. number of infusions) will generally be presented with 1 dp while the minimum and maximum will be presented without dp. Percentages will be presented with 1 dp. Exceptions from these rules might be applied when necessary.

3.2. Handling of Missing Data and Outliers

Regarding the primary criterion, a patient will be also considered as a non-responder if the patient is withdrawn due to lack of efficacy of the treatment (insufficient response to the investigational medicinal product [IMP]). In all other cases, if the INCAT score at EOS visit is missing, then the Last Observation Carried Forward (LOCF) approach will be applied and the last available adjusted INCAT disability score will replace the missing value at EOS visit.

The LOCF approach will also be used to handle the missing data of the secondary endpoint for adjusted INCAT and response at week 12 only.

When AEs are documented in the diary, dates of AE onset may be missing and as a result, TAAE cannot be defined. For AEs with a missing or incomplete start date, the response to the question "Did the AE start within 72 hours of an infusion" will be used for determining if the AE is temporally related to the infusion.

Partial dates of first symptoms and partial dates of diagnosis will be imputed by 15 if only the day is unknown and by 1st July if day and month are unknown. No imputation will be done if the year is unknown.

For the calculation of duration of AEs, partial start and end dates will be imputed with the first and last possible date within the period defined by the partial date, respectively. In general, no

calculation of duration will be made if either the start date or stop date is missing, i.e., cannot be imputed using pre-determined rules. No other general rules for the replacement of missing data are planned.

Data listings will always show the original CRF reported values and not the imputed values.

3.3. Handling of Local Laboratory Data

Local laboratory data will first be standardized. Standardization is the process of converting original local laboratory results to agreed standard international (SI) units. This process allows laboratory parameters to be presented in the same measurement units across the study.

Given that local laboratories are utilized for the study, normalization of the laboratory results will be performed (Karvanen 2003). Normalization is the process of transforming results from different local laboratories in such a way that the results are directly comparable. For normalization the parameter lower and upper limits from a local laboratory (S_{Lo},S_{Up} - see Section 5.7.6. 1) provided by Clinical Research Physician are chosen to represent a standard laboratory. The standardized reported result (R_S) and the local lower and upper limits for given parameter (I_{Lo},I_{Up}) are then placed into an expression, of which the now normalized result (R_N) may be treated as if it was obtained from a central laboratory.

$$\text{Either } R_N = S_{Lo} + \left(\frac{R_N - I_{Lo}}{I_{Up} - I_{Lo}}\right) \times \left(S_{Up} - S_{Lo}\right) \text{ known as location-scale formula}$$

$$\text{Or } R_N = R_S \times \left(\frac{I_{Lo}}{S_{Lo}}\right) \text{ known as the scale formula}$$

Note that standardization (i.e., unit conversion to SI unit) will be done prior to normalization; this allows the laboratory results to be converted to the same measurements prior to being transformed so that results can be directly comparable.

The normalized result will be used for descriptive summaries; displays of laboratory categories such as abnormalities and shifts from baseline based on Low (below lower limit of normal [LLN]), Normal (between LLN and upper limit of normal [ULN]) and High (above ULN) classifications and displays for observed and change values. When normalization of a parameter is not possible (e.g. estimated Glomerular Filtration Rate), then the untransformed standardized result will be presented.

Normalizations will be performed using the ranges provided in Section 5.7.6. 1.

3.4. Multiplicity Issues, Subgroup Analysis, Interim Analysis, Blinding and Randomisation

All analyses will be presented according to the following subgroups and overall:

- Ig-naïve patients
- Relapsing Ig-pretreated patients

However, statistical tests will be performed only for the overall population (not by subgroup).

No interim analyses will be performed and no p-value will be calculated for each subgroup separately. Therefore, no adjustment for multiplicity will be needed.

Secondary and exploratory analyses are purely descriptive even if p-values will be presented, therefore no multiplicity issues are present. No p-value will be provided by subgroup.

Summary of TEAEs will also be presented by relevant subgroups (e.g., by age group [<65 years and ≥65 years], sex, race [white, non-white and unknown], and BMI [<30 kg/m^2 and ≥30 kg/m^2]).

Likewise, blinding and randomisation is not applicable in this single-arm, open-label trial.

3.5. Definition of the Protocol Deviations and Population

3.5.1. Populations

The definition of analysis sets is as follows:

- Total Treated Set (TTS): all patients who received at least one administration of the study drug.
- Full Analysis Set (FAS): all TTS patients having an available assessment of the primary efficacy criterion.
- Per Protocol Set (PPS): all FAS patients without any major deviations from protocol (see Section 3.5.2).

If a patient is treated with a non-allowed treatment during the study period, then all efficacy variables measured after the intake of these non-allowed treatments will be censored for the efficacy analyses.

The TTS will be used for the analysis of safety data.

The FAS will be used for the primary analysis of efficacy data and the PPS to test its robustness.

3.5.2. Protocol deviations

The protocol deviations and corresponding categories are defined in the protocol deviation plan as well as their consequence for the inclusion in the different analysis sets. The following protocol deviations categories will be studied:

- Deviations regarding inclusion criteria
- Deviations regarding exclusion criteria
- Deviations regarding the study drug
- Deviations regarding safety assessments
- Deviations regarding assessment of laboratory parameters (including biomarkers)
- Deviations regarding visit windows
- Deviations regarding informed consent
- Deviations regarding forbidden treatments during the study
- Deviations regarding overdose/misuse of study drug
- Other protocol deviations
- Deviations regarding the primary efficacy endpoint
- Deviations regarding other efficacy endpoints
- Deviations regarding exploratory endpoints

- Deviations regarding the ancillary study

All the protocol deviations which occurred during the study will be examined during the final data review meeting. All adjudicated protocol deviations will be presented in data listings.

4. STATISTICAL ANALYSIS

4.1. Disposition of Patients

In order to describe population, descriptive statistics (number, or number and percentages) as well as a listing will be provided for the following patients:

- Patients screened (patients who signed informed consent)
- Patients enrolled
- Patients with a screening failure
- Patients who were re-screened
- Patients who received study treatment (TTS)
  - Patients participating in the ancillary study
  - Patients who completed the study
  - Patients withdrawn early from the study and reasons for study discontinuation [Adverse event (AE), Protocol deviation, Withdrawal of consent, Lost to follow-up, Insufficient response to IMP, Other]
  - Patients withdrawn early due to insufficient response of IMP with reason for insufficient response (INCAT, MRC sum score, R-ODS, Grip strength, CGI-Patient, CGI-Investigator, Clinical examination, Premature termination of IMP) and follow-up treatment (IVIg, Corticosteroids, Immunomodulatory or immunosuppressive agent or Other)
- Patients included in the FAS
- Patients included in the PPS

Percentages for patients enrolled, failed screening or re-screened will be calculated using the number of unique patients screened as the denominator. For the TTS, percentages will be calculated using the number of patients enrolled as the denominator, any other populations will use number of patients within the TTS as the denominator. For screen failure patients, a listing will be produced with the reason for screening failure and the specifications provided by the investigator. For patients who discontinued the study, a listing will be produced with the reasons of study discontinuation and the specifications provided by the investigator. Listings will also be produced for study entry, end of study (EOS) and patient study visits.

4.2. Protocol Deviations

The absolute number of deviations as well as the number and percentage of patients with at least one protocol deviations will be tabulated by deviation category and Minor/Major. Deviation details will be provided in a listing.

4.3. Demographic and Baseline Characteristics

Unless otherwise specified, the baseline value is defined as the last available value before the first IMP course.

The following characteristics will be summarized in patients of the TTS. If the FAS significantly differs (at least 10%) from the TTS, the characteristics will also be summarized in the FAS.

- Demographic characteristics:
  - Age at screening (years)
  - Age in class: [<65 years and ≥65 years]
  - Gender
  - Race
- Clinical examination:
  - Weight (kg)
  - Height (cm)
  - Body mass index (BMI) [kg/m²] (section 5.7.1)
  - BMI in class: [<30 kg/m^2 and ≥30 kg/m^2]
- History of CIDP disease:
  - Time since the date of first symptoms (years) (section 5.7.1)
  - Time since the date of diagnosis (years) (section 5.7.1)
  - Time between first symptoms and diagnosis (years) (section 5.7.1)
  - Diagnostic categories of CIDP
    - Clinical criteria of CIDP (typical / atypical)
    - Electrophysiological criteria of definite CIDP
    - Supportive criteria of CIDP
  - Current INCAT disability score (arms, legs and global non-adjusted INCAT scores and global adjusted INCAT score)
- Prior medications
  - Prior medications will be presented by therapeutic subgroup (level 2) and chemical subgroup (level 4) according to version WHO_DDE_B2_DECEMBER_1_2014 of the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) classification system. The term ‘prior medication’ refers to any medication given up to 2 months before screening or judged relevant by the Investigator.
- Medical and surgical history
  - Medical and surgical history will be classified by preferred term (PT) and system organ class (SOC) using the version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

4.4. Prior and Concomitant Treatment

Prior medications are any medications the patient received up to 2 months before screening or judged relevant by the Investigator. Thus, a prior medication is defined as a medication with a date of screening ≤ start date + 2 months. If a medication has a partial start date, the earliest possible date within the partial date is used.

Concomitant medications are any medications the patient received at any time during the study, i.e. from screening to EOS visit. Thus a concomitant medication is defined as a medication with a treatment period which has at least one day in common with the period of screening to EOS visit, i.e.

- Date of screening ≤ Start date of medication ≤ Date of EOS visit or
- Date of screening ≤ End date of medication ≤ Date of EOS visit or
- Start date of medication ≤ Date of screening and Date of EOS visit ≤ End date of medication

If a medication has a partial start date or end date, the earliest possible date within the partial start date is used and the last possible date within the partial end date.

Prior and concomitant medications will be summarized using TTS and will be classified according to version WHO_DDE_B2_DECEMBER_1_2014 of the WHO ATC classification system. Separate tables and listings will be produced for prior and concomitant medications presenting the number and percentage of patients with at least one medication by therapeutic subgroup (level 2) and chemical subgroup (level 4). The tables will be sorted by decreasing incidence of therapeutic subgroup and by decreasing incidence of chemical subgroup within therapeutic subgroup.

4.5. Compliance

Study treatment compliance will be summarized using the TTS. Treatment compliance will be presented by course, by infusion and by patients as described below. The term Planned refers to the treatment dose and frequency planned at enrollment. The term Prescribed refers to the treatment dose and frequency reported at each IMP course and infusion.

4.5.1. Course/infusion level

Compliance will be described on the course level using the following criteria:

- Prescribed course dose (g/kg) = Theoretical course dose (g/kg) ± 20%
  Theoretical course dose is defined according to the protocol as
  a. 2 g/kg at the first course and 1 g/kg at subsequent courses for patients with a BMI <30 kg/m^2
  b. 1.6 g/kg at the first course and 0.8 g/kg at subsequent courses for patients with a BMI ≥ 30 kg/m^2
- Time since previous course = 3 weeks ± 7 days
- Courses administered within
  a. 2 to 5 days (first course)
  b. 1 to 3 days (subsequent courses)
- Duration of the flow rate of the first course infusion remains unchanged for at least 25 minutes
- Flow rate of the first infusion of a course ≤0.5 mL/kg/h
- Overall course compliance: A course is compliant if all above course compliance criteria are fulfilled and all infusions of the course are compliant

4.5.2. Patient level

Compliance will be described by patients using the following criterion:

- Total patient compliance: A patient is compliant if all courses of the patient are compliant.

Non-compliant courses and infusions will be listed by patient showing all of the above criteria. The criterion leading to non-compliance will be flagged.

4.6. Efficacy Analyses

The efficacy analyses will be performed on the FAS. The analyses of the primary endpoint will be repeated on the PPS as sensitivity analysis (only if the PPS is different from the FAS). All efficacy endpoints will be analyzed overall and by subgroups of relapsing Ig-pretreated patients and Ig-naïve patients. Endpoints will also be listed by patient status (Ig-naïve/Ig-pretreated).

If a patient is treated with a non-allowed treatment during the study period, then all efficacy variables measured after the intake of these non-allowed treatments will be censored for the efficacy analyses. Assessments of primary and secondary criteria after a forbidden treatment will be flagged in all listings.

The following treatments are not allowed during the study:

- Any other investigational product administered within the last month prior to screening
- Plasma exchange, blood products or derivatives other than the study drug.
- Immunomodulatory or immunosuppressant agents (e.g. including but not limited to cyclophosphamide, cyclosporine, interferon-α, interferon-β1a, anti-CD20, alemtuzumab, aziathioprine, etanercept, mycophenolate mofetil, methotrexate) and hemotopoeitic stem cell transplantation.
- Oral or systemic corticosteroids therapy if administered with an increasing dosage or introduced at a dose higher than 10 mg daily prednisolone or equivalent. Topical corticosteroids are allowed.

4.6.1. Primary efficacy endpoint

The primary efficacy criterion is the response rate of the patients at EOS visit. Response is defined as a patient with a decrease of at least 1 point between baseline and the EOS visit in the adjusted INCAT disability score.

The primary analysis of the primary efficacy criterion will be done using the baseline and last available assessment of the adjusted INCAT disability score after the first study drug administration. That is, if the score at EOS visit is missing, then the Last Observation Carried Forward (LOCF) approach will be applied and the last available adjusted INCAT disability score will replace the missing value at EOS visit.

Similarly, if the assessment of the adjusted INCAT disability score is censored due to an intake of a forbidden treatment, the adjusted INCAT disability score from the last assessment before the intake of the forbidden treatment is used as replacement for the assessment of the EOS visit.

The response rate at the EOS visit will be tested against the historical response rate of 33.3% with a one-sided Clopper-Pearson test (exact binomial test (Clopper 1934) at the nominal level of significance of α=2.5% for the overall set of patients, one-sided Clopper-Pearson test will not be performed by subgroup.

The null and alternative hypotheses are as follows:

H^0: $\pi_{I10E} \leq 33.3\%$

H^1: $\pi_{I10E} > 33.3\%$

The number and percentage of responders at EOS will be presented with descriptive statistics. The associated exact 95% Clopper-Pearson confidence interval will be calculated for the proportion of responders. A table will be produced for the subgroup of patients with response at EOS visit presenting the earliest visit at which response was achieved.

The primary analysis will be performed using the FAS and a sensitivity analysis will be performed using the PPS.

4.6.2. Secondary efficacy endpoints

The following secondary efficacy endpoints will be studied.

1) Responder rate at 12 weeks
   Responder rate at 12 weeks will be presented in the same way as for the primary endpoint with exception of the sensitivity analysis using the PPS. Missing assessments at 12 weeks will be imputed using the LOCF approach.

2) Time to first response
   Time to first response will be analyzed using a Kaplan-Meier (KM) method (Kaplan 1958). Patients without response will be considered censored at their last assessment of the (adjusted) INCAT disability score. Patients with a non-allowed treatment intake before a first response will be considered censored at the date of the first intake of a forbidden treatment.
   KM estimates of the mean, median as well as the first and third quartile will be provided together with their associated 95% confidence interval. Reason for censoring will be also indicated. A KM-plot will be provided showing the incidence of a first response over time. Time of censoring will be displayed in the graph. A table will be included below the graph showing the number of patients "at risk" (i.e. without a first response), the number of patients with a first response and the number of censored patients at the time points 0, 6, 12, 18 and 24 weeks.
   Descriptive statistics will be provided for the time to first response on the subset of patients with response until EOS.

3) Percentage of patients at 12 weeks and EOS visit with no change in CIDP treatment
   The number and % of patients without change in CIDP treatment will be presented at 12 weeks and at the EOS visit. The associated exact 95% Clopper-Pearson CI will be calculated. A change in CIDP treatment is defined as at least one of the following conditions:

Average dose (g/kg) (see section 5.7.3) of the course is not within 5% of the theoretical study treatment dose (g/kg)

  - Theoretical dose is 2 g/kg at the first course and 1 g/kg at subsequent courses for patients with a BMI <30 kg/m^2
  - Theoretical dose is 1.6 g/kg at the first course and 0.8 g/kg at subsequent courses for patients with a BMI ≥30 kg/m^2
- Decrease of the time between courses
  - Time between day 1 of a course and day 1 of the following course is less than 14 days
- Addition of corticosteroids (equivalent of more than 10 mg/day of prednisone for more than 10 days) or immunosuppressive drugs. As this condition is not possible to derive by programming, the study physician will review all treatments with corticosteroids and immunosuppressive drugs prior to database lock and flag those who fulfil the condition.
- Premature discontinuation of study drug due to insufficient response to IMP and start of another CIDP treatment, corticosteroids, immunosuppressive drugs or plasma exchange

A listing will provide details about the nature of the CIDP treatment changes.

4) Adjusted INCAT disability score
   The adjusted INCAT disability score will be presented with descriptive statistics at each visit. The change from baseline in the adjusted INCAT disability score will be analyzed at 12 weeks and EOS visit.
   Several graphics will be produced:
   - Boxplots over time of a) the at-visit values and b) change from baseline
   - Waterfall plots faceted by visit of a) the at-visit values and b) change from baseline

5) Grip strength (kPa) with the Martin vigorimeter in both hands
   Actual and normalized (according to the healthy population Merkies 2000) grip strength will be presented with descriptive statistics at baseline, week 12 and EOS for the dominant hand and the non-dominant hand side by side. The change from baseline in grip strength for the dominant hand and the non-dominant hand will be analyzed at 12 weeks and at the EOS visit. The assessment at screening will be used for the determination of the dominant hand. Normalization according to a healthy population is calculated using the formula (see Section 5.7.5).

6) Rasch-built Overall Disability Scale (R-ODS)
   R-ODS will be presented with descriptive statistics at baseline, week 12 and EOS visit. The change from baseline in R-ODS will be analyzed at 12 weeks and at the EOS visit.

7) Medical Research Council (MRC) 12 muscles sum score (0 to 5)
   The MRC sum score will be presented with descriptive statistics at baseline, week 12 and EOS visit. The change from baseline in MRC score will be analyzed at 12 weeks and at the EOS visit.

8) Rasch-modified MRC (0 to 3)
   The Rasch-modified MRC sum score will be presented with descriptive statistics at baseline, week 12 and EOS visit. The change from baseline in Rasch-modified MRC score will be analyzed at 12 weeks and at the EOS visit.

9) Patient and Investigator Clinical Global Impression (CGI)
   The CGI-S (*Severity of illness*) assessment by patients and investigators will be presented side by side with descriptive statistics at the visits baseline, week 12 and EOS for the categories *Normal,*

not at all ill / Borderline ill / Mildly ill / Moderately ill / Markedly ill / Severely ill / Among the most extremely ill patients (only for the investigator judgment). A shift table will be provided for the change from baseline at week 12 and EOS.

The CGI-I (*Improvement*) assessment by patients and investigators will be presented side by side with descriptive statistics at the visits week 12 and EOS for the categories *Very much improved / Much improved / Minimally improved / No change / Minimally worse / Much worse / Very much worse*.

The CGI-E (*Efficacy index*) assessment by patients and investigators will be presented with descriptive statistics at the visits week 12 and EOS in a 4×4 cross-table crossing Therapeutic effect categories (*Marked / Moderate / Minimal / Unchanged or Worse*) with Side effect categories (*None / Do not significantly interfere with patient's functioning / Significantly interferes with patient's functioning / Outweighs therapeutic effect*). The sum over the number and % of patients shown the 4×4 cross-table (16 cells) will correspond to the number of patients with valid assessments and 100% respectively. The cross-table will also show a row and column with the Total for each dimension corresponding to the separate description of the Therapeutic effect and the Side effects.

For the endpoints 4) to 8) the one sample Hodges-Lehmann estimator (Hodges 1963 and Han 2008) and the associated 95% confidence interval will be calculated for all at-visit values, as well as for the change from baseline to 12 weeks and EOS visit for both the overall and patient subgroups. The change from baseline for the endpoints 4) to 8) will be tested using a one sample Wilcoxon signed-rank test, for the overall set of patient only. All statistical tests will be descriptive and will use a two-sided significance level of α=5%.

Statistical tests will not be performed by subgroup.

For all secondary efficacy endpoints, assessments performed after the use of a non-allowed treatment will be censored (not used in the statistical summaries).

4.7. Safety Analyses

Safety analyses will be conducted on the TTS. All safety analyses will be performed on the subgroups of relapsing Ig-pretreated patients and Ig-naïve patients as well as overall.

4.7.1. Extent of exposure

4.7.1. 1. Patient level analyses

The extent of exposure to IMPs will be summarized on the patient level using the following variables:

- Duration of study participation (month) from signing of informed consent to EOS (see section 5.7.3)
- Duration of treatment exposure (month) from the first day of IMP administration to EOS (see section 5.7.3)
- Total number of courses
- Total number of infusions (see section 5.7.3)

- Cumulative dose over all infusions (g and g/kg) (see section 5.7.3)
- Average dose per course (g and g/kg) (see section 5.7.3)
- Maximum dose over all infusions (g and g/kg)
- Maximum flow rate over all infusions (mL/kg/h)

4.7.1. 2. Course level analyses

The extent of exposure to IMPs will be summarized on the course level using the following variables:

- Total number of infusions (At course 1, all subsequent courses and all courses taken together)
- Course dose in g and g/kg (At course 1, all subsequent courses and all courses taken together)
- Initial flow rate of the first course infusion (mL/kg/h)
- Duration of initial flow rate of the first course infusion (min)
- Maximum flow rate over all infusions (mL/kg/h)
- Duration of the course in days (At course 1, all subsequent courses and all courses taken together)

4.7.1. 3. Infusion level analyses

The extent of exposure to IMPs will be summarized on the infusion level using the following variables:

- Dose (g and g/kg)
- Initial flow rate (mL/kg/h)
- Maximum flow rate (mL/kg/h)
- Duration of the infusion (min)

For patients who experienced at least one infusion with an interruption/discontinuation or a decreased flow-rate, a listing will be provided presenting information on all infusions received during the given course.

In all three analysis levels, dose (g and g/kg) will be derived based on the prescribed administered volume reported in the CRF:

- Dose (g) = Daily volume administered (mL) x batch concentration (i.e. 0.1 g/L)
- Dose (g/kg) = Dose (g) / body weight (kg) at the start of the course

A listing will be provided with the presented variables of each analysis level (patient, course, infusion).

4.7.2. Adverse events

All AEs occurring during the study will be classified by PT and SOC using the version 17.1 of the MedDRA.

Seriousness	*Serious* if one of the follow-ups is serious / *Non-serious* otherwise
Seriousness criterion	For each of the criteria listed below: Yes if at least one of the follow-ups had *Yes* for the corresponding criterion / *No* otherwise ▪ *Results in death* ▪ *Life-threatening* ▪ *In hospitalisation or prolongation of existing hospitalisation* ▪ *Persistent or significant disability / incapacity* ▪ *Congenital anomaly / birth defect* ▪ *Important medical event*
Start date time	Start date time of the first follow-up
End date time	End date time of the last follow-up
Ongoing	*Yes* if last sequence follow-up is ongoing / *No* otherwise
Did the AE start within 72h after an infusion?	Yes if the first follow-up started within the first 72h after an infusion / No otherwise
Intensity	Maximum (Intensity of follow-ups) Increasing order of importance: *Mild / Moderate / Severe*
Action taken	Maximum (Action taken of follow-ups) Increasing order of importance: *None / Dose changed / Interruption of IMP / Discontinuation of IMP*
Corrective medication	*Yes* if at least one of the follow-ups had a corrective medication / *No* otherwise
Relationship to study drug	*Yes* if at least one of the follow-ups had a relationship to study drug assessed as Yes / *No* otherwise
Outcome	Maximum (Outcome of corresponding follow-ups) Increasing order of importance: *Unknown / Recovered without sequela / Recovered with sequelae / Recovering / Not recovered / Fatal*

AEs will be classified as Pre-treatment or Treatment-Emergent according to the date of onset:

- Pre-treatment AE defined as an event with a date-time of onset before the first infusion date-time.
- TEAE defined as any event with a date-time of onset on/after the start date-time of the first infusion.

Treatment emergent adverse event flag

The following rules for the derivation of the TEAE status will be used in the order of display:

- If the date-time of the AE onset is known: TEAE = "Yes" if AE onset date-time ≥ start date-time of first IMP infusion / "No" otherwise
- If the date-time of the AE onset is not known but the complete date of the AE onset is known:

  - TEAE = “Yes” if AE onset date > start date of first IMP infusion
  - TEAE = “Yes” if AE onset date = start date of first IMP infusion and investigator’s assessment of the time of onset ≠ “Before infusion”
  - TEAE = “No” otherwise
- If the date of AE onset is a partial date and the investigator’s assessment of the time of onset is not missing: TEAE = “Yes” if investigator’s assessment of the time of onset “During infusion”, “≤72h” or “>72h”
- If the date of AE onset is a partial date and the investigator’s assessment of the time of onset is missing:
  - TEAE = “Yes” if last possible date in the period defined by the partial date ≥ start date of first IMP infusion / “No” if the last possible date in the period defined by the partial date < start date of first IMP infusion
- TEAE = “Yes” otherwise

Temporally associated adverse events (TAAEs)

TAAE will be defined according to the item “Schedule” collected in the eCRF. They will include all adverse events with Schedule “During infusion”, “Within 72 hours after the end of the infusion”. If Schedule is missing then the event will be classified as TEAE by default.

Other significant AEs

Other Significant AEs are based on the definition of relevant AESIs (Adverse Events of Special Interest) for I10E. They are defined as standardized MedDRA queries (SMQs) of interest on the narrow scope, these are:

- Anaphylactic reaction (SMQ) [20000021] narrow scope
- Anaphylactic/anaphylactoid shock conditions (SMQ) [20000071] narrow scope
- Noninfectious meningitis (SMQ) [20000134]) narrow scope
- Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ) [20000083] narrow scope
- Acute renal failure (SMQ) [20000003] narrow scope
- Hemolytic disorders (SMQ) [20000019] narrow scope
- Eosinophilic pneumonia (SMQ) [20000157] narrow scope

Interstitial lung disease (SMQ) [20000042] narrow scope

Pre-treatment Adverse Events

Pre-treatment AEs will be listed for all enrolled patients.

Summary of treatment Emergent Adverse Events (TEAE)

A summary of the total number of TEAEs, and number and percentage of patients with at least one TEAE will be presented. This summary will include the number and percentage of patients having at least one TEAE as well as the absolute number of TEAEs in each AE category:

- TEAEs
- Serious TEAEs by seriousness criterion

- Drug-related TEAEs
- TAAEs
- TEAEs by severity (Mild / Moderate / Severe)
- TEAEs by Action taken with IMP (None / Dose reduced / Dose increased / Discontinuation of IMP / Temporary interruption of IMP, (the action could also be a decrease of infusion flow rate))
- TEAEs by outcome (Resolved without sequelae / Resolved with sequelae / Not recovered / Recovering / Fatal / Unknown)
- Other significant AEs

A similar summary table will be produced for TAAEs as well as drug-related TEAEs and Serious TEAEs.

All TEAEs, SAEs, TAAEs and drug-related AEs will be summarized by SOC and PT, showing number of TEAEs, and number and percentage of patients with at least one TEAE, sorted by decreasing incidence of SOC and PT within SOC in the column "overall".

Summary of TEAEs will also be presented by relevant subgroups (e.g., by age group [<65 years and ≥65 years], sex, race [white, non-white and unknown], and BMI [<30 kg/m^2 and ≥30 kg/m^2]).

The rate of TEAEs by patient, course, infusion and drug-related AEs by course will be presented and sorted by decreasing incidence of PT in the column "overall". Rate is defined as the number of events for unique PTs divided by the total number of patients, courses and infusions respectively.

Duration of most-common (those which occurred in at least 10% of the patients in the overall safety population) drug-related AEs will be calculated as is outlined in Section 5.7.2 and will be presented with descriptive statistics on recovered AEs (i.e., AEs with an outcome of "Recovered without sequelae" or "Recovered with sequelae"). Statistical unit of analysis will be the individual who recovered from drug-related AE. No imputation will be performed for the purposes of computing duration.

The time between the stop time of the last administration of IMP (before the onset of event) to the onset of the drug-related AEs will be calculated (in days) as is outlined in Section 5.7.2 and will be presented with descriptive statistics using the individual drug-related AE as statistical unit.

All Serious TEAEs, drug-related AEs, AEs leading to dose changes (action taken is not missing, "None" or "Not-applicable") or discontinuation of IMP, and other significant TEAEs will be listed. These listings will include the event duration as well as the time elapsed (in days as is outlined in Section 5.7.2) between the stop time of the last administration to the onset of the event.

The rate of of drug-related TEAE will be presented by course number and overall. This rate will be calculated as the ratio between the number of TEAEs starting during a course and the overall number of patients treated at the corresponding course.

4.7.3. Other safety endpoints

4.7.3. 1. Laboratory data

Quantitative descriptions of laboratory data will be performed on normalized values as outlined in Section 3.3 with the exception of hematology differential counts for which standardized values will be used because values collected as a ratio of WBC count cannot be normalized into a range in absolute unit. For these parameters results expressed in percentages of WBC will be converted to absolute count by multiplying WBC count by the value collected in percentage (ranges will not be transformed).

4.7.3. 1.1. Patient level analyses

All laboratory values will be reported in SI units. Summary displays for laboratory safety data (hematology and chemistry) will be produced by visit for both observed and change from baseline values of the different laboratory analyses. Laboratory tests taken only at screening, those in case of a qualifying event (e.g., thrombosis or hemolysis), and urine protein reagent strip test results will be presented in the laboratory listings. The following clinical parameters will be summarized:

- Hematology:
  - Complete blood count + differentials, hemoglobin (Hb), mean corpuscular volume (MCV), platelet counts
  - Haptoglobin
- Biochemistry:
  - Creatininemia, glomerular filtration rate according to MDRD
  - LDH
  - Total and free bilirubin (total bilirubin in all patients; if total bilirubin > ULN, free bilirubin will be assessed from the same blood sample, as total bilirubin)
  - AST, ALT, alkaline phosphatase (ALP), γGT
  - Total serum protein level
  - Serum IgA levels

Laboratory values will be classified as normal, low, or high based on standardized normal ranges. Laboratory categories will be expressed in terms of the L (below lower limit of normal [LLN]), N (between LLN and ULN) and H (above ULN) classifications for numerical measurements and normal, abnormal for categorical measurements. The number and percentage of patients with abnormal values will be summarized for each laboratory parameter by visit. These summaries will include the number and percentage of patients with “any pre-treatment visit” and “any on-treatment visit post baseline” abnormality for each parameter. These displays will ensure that all abnormal values will be captured.

LNH shifts in clinical laboratory values (hematology and chemistry) from baseline to each visit post first dosing will be summarized by visit. Patients with values outside the normal range will be flagged.

A scatter plot of the values at the EOS assessment as well as the minimum and maximum values of each patient during the treatment follow-up against the values at baseline will be prepared for each parameter. The first diagonal will be displayed by a dotted line.

4.7.3. 1.2. Course and infusion level analyses

Descriptive statistics of laboratory parameters at screening, before and 96h after the 1st IMP course, before the start of each subsequent course and at the EOS assessment will be provided for laboratory parameters as well as for the clinical assessment. The change from before first IMP course to 96h after the 1st IMP course as well as to before subsequent courses will be presented as well as the minimum and maximum values of each patient during the complete treatment follow-up. The complete treatment follow-up of maximum and minimum presentations includes all post-baseline assessments, along with any unscheduled assessment results which do not contribute to by visit descriptive summaries. Similarly, shift tables for the clinical assessment will be produced showing the change from before the first IMP course to 96h after the 1st IMP course as well as to before subsequent courses.

A graphical display of the evolution of each laboratory parameter by course will be presented with connected box-and-whisker plots. The number of observations at each visit will be displayed in the graph.

Detection of hemolysis will be evaluated at course level. The number and percentage of course with hemolysis will be displayed by subgroup and overall in accordance with the IVIg-associated hemolysis criteria published by Health Canada (Health Canada 2009), adapted to the study as follows:

- Drop in hemoglobin by at least 1 g/dL compared to baseline and
- At least one of the two criteria below are met
  - Positive direct Coombs test
  - At least 2 of the following criteria are met (in absence of negative direct Coombs test):
    - Reticulocyte count increased by at least 50 x 10^9/L compared to baseline
    - LDH increased by at least 20% compared to baseline
    - Haptoglobin value is lower than the lower limit of normal (LLN)
    - Free bilirubin (or total bilirubin if the free bilirubin is not documented) increased compared to baseline and value is greater than the upper limit of normal (ULN)

In the following situations the courses will be excluded from the analysis:
Criterion for hemoglobin value cannot be evaluated/calculated
Criterion for hemoglobin is evaluable, direct Coombs test neither positive or negative (missing or not-done) and

- 3 or 4 out of 4 criteria (Reticulocytes, LDH, Haptoglobin, free/total bilirubin) cannot be evaluated/calculated or
- 1 or 2 out of 4 criteria (Reticulocytes, LDH, Haptoglobin, free/total bilirubin) cannot be evaluated/calculated and less than two of the remaining criteria are met

A listing of all hemoglobin, reticulocytes, LDH, haptoglobin and bilirubin values will be provided for patients with at least one blood sample for which the aforementioned criteria for hemolysis is met. A listing of the excluded courses will be also given.

All abnormalities, clinically significant or not, will be listed. Pregnancy status and test results will also be listed, including the method of contraception used (if any).

4.7.3. 2. Vital signs

Vital signs parameters including systolic and diastolic blood pressure (mmHg), heart rate (bpm), weight, and body temperature (°C) (calculated value according to the way the temperature was measured) will be summarized.

4.7.3. 2.1. Patient level analyses

Descriptive statistics of vital sign values will be presented for the following time points:

a) Screening
b) Before the 1st IMP infusion
c) 30-45 min and 60-75 min after the start of the first infusion
d) 30-45 min after the end of the first infusion
e) 96h after the end of the 1st course
f) EOS

Change from time point b) will be presented for time points c) to e). The minimum and maximum of each parameter during the patient's complete treatment follow-up will be presented. The complete treatment follow-up of maximum and minimum presentations includes all post-baseline assessments, along with unscheduled assessment results which do not contribute to by visit and by timepoint descriptive summaries.

A scatter plot of the values at the end of study assessment as well as the minimum and maximum values of each patient during the treatment follow-up against the values at baseline will be prepared for each parameter. The first diagonal will be displayed by a dotted line.

4.7.3. 2.2. Course and infusion level analyses

Descriptive statistics of vital sign values will be presented at the following time points:

a) Before the start of the course (only first infusion of a course)
b) 30-45 min and 60-75 min after the start of the infusion
c) 30-45 min after the end of the infusion

Change from before start of the course to time points b) and c) will be presented as well.

A graphical display of the evolution pre-dose values (before IMP infusion) of each vital sign parameter over time (by course). The evolution of (before start of the course, time points b) and c) at each day) will be also presented with connected box-and-whisker plots by course. The number of observations at each visit will be displayed in all graphs.

All abnormalities, clinically significant or not, will be listed in both patient level and course/infusion level formats. If a patient assessment has no timepoint attributed then these assessments are classified as unscheduled.

4.7.3. 3. Thrombo-embolic physical examination

Number and percentage of patients with at least one abnormal thrombo-embolic sign will be presented by visit together with the absolute number of signs for the following:

- Arterial thrombo-embolic signs
- Venous thrombo-embolic signs

4.7.3. 4. Complete physical examination

Physical examination results will be listed.

4.8. Pharmacokinetics

Not Applicable.

4.9. Exploratory analyses

The following exploratory endpoints will be analyzed and summarised by visit using FAS for absolute value and change from baseline.

- Anti-CNTN1 and anti-NF155 antibodies titers at EOS visit
- FcγRIIB B cells marker levels at visits V2, V3 and V4
- BAFF and complement components (C3 and C4 antigens, CH50) at visits V2, V3, V4 and EOS visit
- Serum total IgG trough levels before each course

In order to explore the relationship between the biomarkers and clinical response at EOS a univariate logistic regression model will be applied. Each biomarker will be studied separately at each visit. The by visit univariate model will use the biomarker change from baseline (quantitative) as a single exploratory variable, with the clinical response at EOS being the dependent variable.

To explore the relationship of the total IgG trough level and the adjusted INCAT disability score a linear mixed model will be used using the patient as random factor. A scatterplot will show all values and the estimated regression line and its 95% confidence band.

A non-parametric regression method will also be applied (e.g. LOESS, splines or generalised additive models) in order to explore departures from linearity. The result of the estimated regression line will also be shown in a scatterplot together with the 95% confidence band. Similar exploration of the relationship between the biomarkers and other clinical response variables will be conducted as needed using generalized linear mixed models.

A listing of the biomarker data will be produced. In addition, a listing of patients included in the ultrasonography ancillary study will be provided. However, no statistical analysis will be done (see section 4.10.3). The listing will include information on the consent date for the ancillary study and whether data were collected (Yes/No).

4.10. Changes in the Conduct of the Study or Planned Analysis

This section describes the changes from protocol.

4.10.1. Efficacy

Planned analysis associated with the ultrasonography ancillary study will not be performed due to non-collection of required data.

The protocol (section 12.9.2.2) states for secondary efficacy data that "A LOCF approach will be used to handle the missing data of secondary endpoints. All details to handling of missing data will be provided in the SAP". However LOCF approach will only be used for criteria using adjusted-INCAT.

4.10.2. Safety

The protocol (section 12.10.2) incorrectly states that "Vitals signs […] will be measured before each infusion". However, vital signs are assessed only before the start of each course and not before each infusion. Therefore, the data before start of each infusion cannot be presented.

The protocol did not prospectively define an appropriate analysis of "Detection of hemolysis" therefore an additional analysis has been defined in accordance with the IVIg-associated hemolysis criteria published by Health Canada in section 4.7.3. 1.2 of the SAP.

4.10.3. Ancillary study

For logistical reasons, no data (other than the data related to the Informed Consent) is collected. Therefore no statistical analysis will be performed for this part of the study, only the disposition will be presented.

5. APPENDICES

5.1. Listings

All data will be presented in patient listings (includes those data recorded after the use of a non-allowed treatment). All listings produced will be ordered by patient status (Ig-naïve, relapsing Ig-pretreated, other, screen failure), patient identifier, visit and date unless otherwise specified.

5.2. Statistical Software

Statistical analyses will be conducted on IQVIATM servers using SAS version 9.4.

5.3. Standard Operating Procedures

All programming activities will be performed according to CRO's Standard Operating Procedures.

At the time of v2.0 of the SAP, it was planned that the following Standard Operating Procedures will be followed:

- LFB SOP 203/05919 Statistical Analysis Plan
- LFB SOP 204/06045 Statistical Analysis Plan Template
- LFB SOP 203/05921 Statistical Programming
- LFB SOP 203/05924 Statistical Analysis
- LFB SOP 203/05897 Controlled Version of Study Documents
- LFB SOP 203/05926 Quality Control of Statistical Documents

However -because the entire set of biometry SOPs were updated in 2017 and came into force early 2018- the following SOPs will also be used regarding the oversight/Quality Control activities performed internally at LFB:

- LFB SOP 202/16747 Document versioning
- LFB SOP 202/16694 History form
- LFB SOP 203/17019 Statistical Analysis Plan
- LFB SOP 204/17029 Statistical Analysis Plan Amendment request form
- LFB SOP 202/16911 Statistical Validation Plan
- LFB SOP 202/17028 Statistical Tables, Listings and Figures production

More details are available in the Statistical Validation Plan.

5.4. Audit and Quality Control

5.4.1. Audit

An audit/inspection may be carried out by qualified Sponsor staff, by subcontracted auditors or by representatives of national or foreign Competent Authorities to ensure that the study is conducted as per protocol and in accordance with regulatory requirements, and to ensure the validity of the data.

5.4.2. Quality control

A statistical validation plan will be created describing quality control steps for analysis datasets, tables, listings and graphs.

5.5. Statistical Review

Statistical review of analysis datasets, tables, listings and graphs will be performed to ensure the accuracy and completeness of the statistical package (datasets and outputs). The outcome of review will be documented using quality control sheets.

5.6. Bibliography

Guideline (SWI) for Biostatistics and Statistical Programming

ICH E3 “Structure and Content of Clinical Study Reports”

ICH E9 “Statistical Principles of Clinical Trials”

Clopper C, Pearson ES. Ther use of confidance or fiducial limits illustrated in the case of the binomial. Bimetrika. 1934;26(4):404-13.

Han L. Calculating the point estimate and confidence interval of Hodges-Lehmann's median using SAS® software. SESUG 2008 the Proceedings of the SouthEast SAS Users Group, Paper ST-154.

Health Canada. Intravenous immune globulin (IVIg): hemolytic reactions. Canadian Adverse Reaction Newsletter, volume 19, issue 4, October 2009.

Hodges JL, Lehmann EL. Estimates of location based on ranks tests. Ann Math Statist. 1963;34(2):598-611.

Hughes RA, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, Hartung HP, Latov N, Merkies IS, van Doorn PA; ICE Study Group. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol. 2008;7(2):136-44. Erratum in: Lancet Neurol. 2008; 7(9):771.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53(282):457-81.

Karvanen J. The Statistical Basis of Laboratory Data Normalization. Drug Inf J. 2003;37:101-7 - 0092-8615/2003.

Merkies IS, Schmitz PI, Samijn JP, Meché FG, Toyka KV, van Doorn PA. Assessing grip strength in healthy individuals and patients with immune-mediated polyneuropathies. Muscle Nerve. 2000;23(9):1393-1401.

Additionally, the following reference from Lexjansen (PharmaSUG-2000) was used to implement the Hodge-Lehmann estimations:

Chris Deker. Calculating a Nonparametric Estimate and Confidence Interval Using SAS Software.

5.7. Basic Derived Variables

5.7.1. Baseline characteristics

BMI (kg/m²) $= \dfrac{Weight(kg)}{\left(Height(m)\right)^2}$

Time since the date of first symptoms (years) $= \dfrac{(\text{Date of screening} - \text{Date of first symptoms} + 1)}{365.25}$

Time since the date of diagnosis (years) $= \dfrac{(\text{Date of screening} - \text{date of diagnosis} + 1)}{365.25}$

Time between first symptoms and diagnosis (years) $= \dfrac{(\text{Date of diagnosis} - \text{date of first symptoms} + 1)}{365.25}$

5.7.2. Safety

Adverse Event Duration
The duration of AEs will be calculated as:

AE Duration (days) = AE stop date – AE start date + 1

Similar formula will be used for any duration-related calculations.

Time to AE onset
The time to onset of an AE since the previous infusion will be calculated as:

Time to AE onset (days) = AE start date – Date of previous IMP infusion+1

Similar formula will be used for any time to event-related calculations.

5.7.3. Exposure

Duration of study participation (months) $= \frac{(\text{EOS visit date} - \text{date of informed consent} + 1)}{30.4375}$

Duration of treatment exposure (months) $= \frac{(\text{EOS visit date} - \text{date of first IMP infusion} + 1)}{30.4375}$

Total number of infusions $= \sum_{j=1}^{n_C} (\text{number of infusions at course } j)$

Cumulative dose over all infusions (g and g/kg) $= \sum_{j=1}^{n_C} \sum_{k=1}^{n_{I_j}} (\text{dose at infusion } k \text{ of course } j)$

with n_{I_j} the number of infusions at course j of the patient

Average dose per course (g and g/kg) $= \frac{1}{n_C} \sum_{j=1}^{n_C} \sum_{k=1}^{n_{I_j}} (\text{dose at infusion } k \text{ of course } j)$

Actual administered dose (g) $= \frac{\left(\text{Batch titer}\left(\frac{g}{200}mL\right)\text{Volume infused}(mL)\right)}{200}$

Average dose (g/kg) $= \frac{\text{Actual dose administered (g)}}{\textit{Subject Weight (kg)}}$

Where batch is set to the theoretical level based on nominal I10E concentration of 10%.

5.7.4. Other characteristics

Body Mass Index (BMI)

BMI (kg/m^2) = Weight (kg) / (Height (m) x Height (m))

Disability Scores

INCAT/Adjusted INCAT disability score = arm disability score + leg disability score

5.7.5. Efficacy

$$\text{Normalized grip strength (\%)} = \frac{\text{Measured value (kPa)}}{\text{Median value (kPa) by age class and gender}} \times 100$$

5.7.6. Reference tables for derivations

5.7.6. 1. Reference ranges for local laboratory normalization

The following ranges have been reviewed and agreed by LFB Clinical Research Physician of the study:

Table 5–1: Reference ranges for normalization of local laboratory data

Laboratory test			Reference Ranges		Formula
Test name	**Short name**	**Standard Units**	**Lower Limit of Normal (LLN): S_{Lo}**	**Upper Limit of Normal (ULN) S_{Up}**	
Alanine Aminotransferase	ALT	IU/L	5	35	location-scale
Alkaline Phosphatase	ALP	IU/L	42	141	location-scale
Aspartate Aminotransferase	AST	IU/L	8	30	location-scale
Bilirubin	BILI	µmol/L	3	17	location-scale
Bilirubin, Free	BILIF	mg/dL	0,2	0,8	location-scale
Creatinine	CREAT	µmol/L	44	106	location-scale
D-Dimer	DDIMER	ug/L	0	500	location-scale
Ery. Mean Corpuscular Volume	MCV	fL	79	96	location-scale
Erythrocytes	RBC	10^{12}/L	4	5	location-scale
Gamma Glutamyl Transferase	GGT	IU/L	8	35	location-scale
Glomerular Filtration Rate	GFR	mL/min/1.73m^2	60	.	scale
Haptoglobin	HAPTOG	mg/dL	40	200	location-scale
Hematocrit	HCT	%	36	48	location-scale
Hemoglobin	HGB	g/dL	12	16	location-scale
Hemoglobin A1C	HBA1C	mmol/mol	20	42	location-scale
Lactate Dehydrogenase	LDH	IU/L	250	450	location-scale
Leukocytes	WBC	10^9/L	4	10	location-scale
Platelets	PLAT	10^9/L	150	450	location-scale
Protein	PROT	g/dL	6	8	location-scale
Protein Excretion Rate	PROTEXR	mg/day	0	100	location-scale

5.7.6. 2. Normative values for grip strength

Normative values (Merkies 2000) for quantitative grip strength assessment with the Martin vigorimeter for both hands in healthy subjects (kPa) are presented in Table 5–2:

Table 5–2: Normative values for grip strength

Age (year)	**Median values (KPa) per age span and gender**	
	Males	**Females**
15-19	122	90
20-24	146	106
25-29	154	112
30-34	153	109
35-39	148	104
40-44	141	104
45-49	134	98
50-54	126	92
55-59	116	84
60-64	105	76
65-69	97	71
70-74	91	67
75-79	82	63
80-84	75	59
≥85	64	54