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: Protocole (v6.0)

VERSION & DATE OF DOCUMENT: Version 6.0; May 3, 2017

CLINICAL STUDY PROTOCOL n° I10E-1302

EUDRACT N° 2013-005557-73

PRISM Study

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

γGT	γ Glutamyl Transferase
Ab	Antibody
ACR	Albumine to Creatinine Ratio
AE	Adverse Event
AER	Albumin Excretion Rate
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMS	Aseptic Meningitis Syndrome
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BAFF	B Cell Activating Factor
BMI	Body Mass Index
BPWP	Blood Products Working Party
CGI	Clinical Global Impression
CHMP	Committee for Human Medicinal Product
CI	Confidence Interval
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CKD	Chronic Kidney Disease
CMAP	Compound Muscle Action Potential
CNTN1	Contactin 1
CRO	Contract Research Organization
CSA	Cross Section Area
CSP	Code de la Santé Publique
CV	Curriculum Vitae
DAT	Direct Antiglobulin Test
DCFs	Data Clarification Forms
EC	Ethics Committee
eCRF	Electronic Case Report Form

EFNS	European Federation of Neurological Societies
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
FAS	Full Analysis Set
Fc□R	Fc□□Receptor
FPI	First Patient In
FU	Follow-up
GBS	Guillain Barré Syndrome
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GM1	Ganglioside M1
HAV	Hepatitis A Virus
Hb	Haemoglobin
HBc	Hepatitis B core Antigen
HBs Ag	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee (IEC) / International Review Board (IRB)
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
INCAT	Inflammatory Neuropathy Course And Treatment
ITP	Immune ThrombocytoPenia
IVIg	Intravenous Immunoglobulin

kPa	kiloPascals
LDH	Lactate Dehydrogenase
LFB	Laboratoire Français du Fractionnement et des Biotechnologies
LLN	Lower Limit of Normal
LLT	Lowest Level Term
LOCF	Last Observation Carried Forward
LPO	Last Patient Out
MAG	Myelin-Associated Glycoprotein
MCV	Mean Corpuscular Volume
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal Gammopathy of Undetermined Significance
MMN	Multifocal Motor Neuropathy
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NCR	No Carbon Required
NCS	Nerve conduction study
NF155	Neurofascin 155
NYHA	New York Heart Association
PCR	Protein to Creatinine Ratio
PER	Protein Excretion Rate
PID	Primary Immune Deficiency
PNS	Peripheral Nerve Society
PPS	Per Protocol Set
PT	Preferred Term
RBC	Red Blood Cells
R-ODS	Rasch-built Overall Disability Scale
RR	Relative Risk
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SCIg	Sub-Cutaneous immunoglobulin
SPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected and Unexpected Serious Adverse Reaction
TAAE	Temporally-Associated Adverse Event
TEAE	Treatment-Emergent Adverse Event
TTS	Total Treated Set
ULN	Upper Limit of Normal
USG	Ultrasonography
WHO	World Health Organisation

SYNOPSIS

STUDY N° / ACRONYM	I10E-1302 / PRISM
TITLE	An international, multicentre, efficacy and safety study of I10E in initial and maintenance treatment of patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP).
SPONSOR	LFB BIOTECHNOLOGIES 3, Avenue des Tropiques, BP 40305 91958 Courtaboeuf Cedex - France
SCIENTIFIC COMMITTEE	[redacted]
COORDINATING INVESTIGATOR	[redacted]
STUDY DRUG	I10E, a ready-to-use liquid human normal immunoglobulin (Ig) for intravenous administration (IVIg), 100 mg/mL. The study drug dosage should be at 2 g/kg for the first administration, then 1 g/kg for the rest of the study. For the first day of any study drug course, the initial flow rate will not exceed 0.5 mL/kg/h during the first 30 minutes. If well tolerated, the rate of administration may be increased up to 1 mL/kg/h during 30 minutes, then, at the Investigator's discretion, gradually increased up to 2, 4 and 6 mL/kg/h as a maximum flow rate. In patients older than 65 years, the maximum infusion flow rate should be 2 mL/kg/h. On the subsequent days of any study drug course, the flow rate is at the Investigator's discretion (up to 6 mL/kg/h except for patients older than 65 years for whom the maximum infusion flow rate should be 2 mL/kg/h). For patients with BMI ≥30 kg/m², the dose must be reduced by 20% i.e 1.6 g/kg for the first administration and 0.8 g/kg for the rest of study.
STUDY DESIGN	Phase III, international, multicentre, single-arm, open-label prospective study.

STUDY N° / ACRONYM	I10E-1302 / PRISM
OBJECTIVES	Primary objective: To assess the efficacy of I10E in improving the disability of patients with CIDP. Secondary objective: To assess the safety of I10E in patients with CIDP. 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 responses, as assessed by neurological scales, in patients with CIDP (ancillary study in Italy only).
NUMBER OF PATIENTS	42 patients will be included in the trial to ensure 38 evaluable patients (around one third of all patients will be either Ig-naïve or relapsing Ig-pretreated patients). A patient will be considered evaluable if he/she has an assessment of the primary endpoint after the first study drug administration.
NUMBER OF SITES	This study will be conducted in approximately 42 recognised referral centres and/or centres of expertise for neuromuscular diseases or peripheral neuropathies in France, Italy, Spain, Tunisia, Turkey, the United Kingdom, Germany and Poland.

STUDY N° / ACRONYM	I10E-1302 / PRISM
INCLUSION CRITERIA	1. Male or female patient aged 18 years or more. 2. * Definite or probable CIDP according to the European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) guidelines 2010 clinical and neurophysiological criteria. * Pure motor CIDP, provided that a diagnosis of multifocal motor neuropathy has been ruled out. * CIDP associated with monoclonal gammopathy of undetermined significance (MGUS), provided that anti-MAG antibodies titer is lower than the used technique's negativity threshold (1000 BTU for Bühlmann ELISA technique). * Lewis-Sumner syndrome. 3. Score of at least 2 on the adjusted INCAT disability scale. 4. Patient who either : a) has never been previously treated with Ig (Ig-naïve patient) OR b) was previously treated with Ig but is in clinical relapse following treatment withdrawal. In the latter case, the last Ig course shall have been administered no less than 3 months prior to screening. 5. Covered by national healthcare insurance system as required by local regulations. 6. Written informed consent obtained prior to any study-related procedures.

STUDY N° / ACRONYM	I10E-1302 / PRISM
EXCLUSION CRITERIA	1. History of severe allergic reaction or serious adverse reaction to any immunoglobulin (Ig). 2. Clinically documented lack of response to previous Ig treatment. 3. History of IgA deficiency (IgA ≤70 mg/L), unless the absence of anti-IgA antibodies has been documented. 4. Known hypersensitivity to human Ig or to any of the excipients of I10E (glycine and polysorbate 80). 5. History of cardiac insufficiency (New York Heart Association [NYHA] III/IV), uncontrolled cardiac arrhythmia, unstable ischemic heart disease, or uncontrolled hypertension. 6. History of venous thromboembolic disease, myocardial infarction or cerebrovascular accident. 7. Risk factor for blood hyperviscosity such as cryoglobulinemia or haematologic malignancy with monoclonal gammopathy. 8. History of personal or familial congenital thrombophilia or acquired thrombophilia. 9. Factors contributing to venous stasis such as long-term bed confinement. 10. Body Mass Index (BMI) ≥40 kg/m². 11. Protein-losing enteropathy characterised by total serum protein level <60 g/L and serum albumin levels <30 g/L. 12. History of kidney transplantation, nephrotic syndrome (defined as proteinuria >3.5 g per 24 hours accompanied by hypoalbuminemia and edema), or any acute or chronic kidney disease that in the opinion of the investigator and/or nephrologist would preclude the use of I10E and/or interfere with the assessment of the safety and efficacy of I10E. AND/OR Chronic kidney disease (CKD) for more than 3 months as documented by at least one of the following: • glomerular filtration rate (GFR) <60 mL/min/1.73m² measured according to the Modified Diet in Renal Disease (MDRD) formula AND/OR • urine protein reagent strip: ≥2 crosses AND/OR • urine protein reagent strip: one cross with one of the following: o albumin excretion rate (AER) >300 mg/24 hours or protein excretion rate (PER) >500 mg/24 hours (24h-urine collection) OR o albumin to creatinine ratio (ACR) >30 mg/mmol or protein to creatinine ratio (PCR) >50 mg/mmol (spot urine sample).

STUDY N° / ACRONYM	I10E-1302 / PRISM
EXCLUSION CRITERIA	13. Serum levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times upper limit of normal (ULN) range. 14. Any other ongoing disease that may cause chronic peripheral neuropathy, such as toxin exposure, dietary deficiency, uncontrolled diabetes, hyperthyroidism, cancer, systemic lupus erythematosus or other connective tissue diseases, infection with HIV, hepatitis B virus (HBV) or hepatitis C virus (HCV), Lyme disease, multiple myeloma, Waldenström's macroglobulinaemia, amyloidosis, and hereditary neuropathy. 15. Woman with positive results on a urine pregnancy test or breastfeeding woman or woman of childbearing potential without an effective contraception. Effective contraceptives are injectable, patch or oral combined oestro progestative or progestative contraceptives, Copper T or levonorgest releasing intra-uterine devices, depot intramuscular medroxyprogesterone, subcutaneous progestative contraceptive implants, condoms or occlusive caps (diaphragm or cervical/vault caps) with spermicide, true abstinence (when this is in line with the preferred and usual lifestyle of the patient). 16. Any other serious medical condition that would interfere with the clinical assessment of CIDP or use of I10E or prevent the patient from complying with the protocol requirements. 17. Increasing dosage or introduction of a systemic corticosteroids therapy, or corticosteroids therapy at a dose higher than 10 mg prednisolone per day, or equivalent within the last 3 months prior to screening. Topical corticosteroids are permitted. 18. Treatment within 12 months prior to screening with immunomodulatory or immunosuppressant agents (including but not limited to cyclophosphamide, cyclosporine, interferon-α, interferon-β1a, anti-CD20, alemtuzumab, aziathioprine, etanercept, mycophenolate mofetil, methotrexate) or haemopoetic stem cell transplantation. 19. Plasma exchange, blood products or derivatives administered within the last 3 months prior to screening. 20. Administration of another investigational product within the last month prior to screening. 21. Drug or alcohol abuse. 22. Anticipated poor compliance of patient with study procedures.

STUDY N° / ACRONYM	I10E-1302 / PRISM
STUDY PERIODS	Screening: From signature of informed consent to the first study drug administration. The screening biological tests should be performed and their results checked by the Investigator within a period of 4 weeks before the first study drug administration. The exclusion and inclusion criteria (except those related to screening biological assesments) will be verified prior to screening. The screening biological test results will be verified before the first study drug administration. Duration of screening: a maximum of 4 weeks. Baseline: Baseline data are those obtained during the screening period before first study drug administration. If multiple results are available for one single test, the most recent one will be considered. Inclusion: A patient is considered included once he/she receives the first study drug administration. Treatment: Patients who meet all eligibility criteria will receive one dose of study drug at 2g/kg over 2 to 5 days and 7 doses of study drug at 1g/kg over 1 to 2 day(s), every 3 weeks (+/- 7 days). Duration of treatment period will be approximately 21 weeks. Follow-up: A follow-up period of 3 weeks +/- 7 days will take place after the last study drug administration. At the end of the follow-up period, patients will undergo an end of study (EOS) visit. This visit occurs 3 weeks after the 8th course of study drug. In the event of premature discontinuation from the study drug or patient withdrawal from the study, an EOS visit is performed within 7 days and prior to administration of any other treatment for CIDP (See Section 8.2.7). The reason for premature study drug discontinuation / study withdrawal should be accurately assessed and entered into the electronic Case Report Form (eCRF). The total duration of the study for a patient is approximately 24-29 weeks.

STUDY N° / ACRONYM	I10E-1302 / PRISM
STUDY PLANNING	First Patient In (FPI): Q1 2015 Last Patient Out (LPO): Q4 2017
EFFICACY ENDPOINTS	**Primary efficacy endpoint:** Responder rate at EOS visit. Responders are defined as patients with a decrease ≥1 point in the adjusted INCAT disability score between baseline and the EOS visit. **Secondary efficacy endpoints:** – Responder rate at 12 weeks. – Time to response. – Percentage of patients at 12 weeks and EOS visit with no change in CIDP treatment. – 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) and Rasch-modified MRC (0 to 3).
SAFETY ENDPOINTS	Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), from first study drug administration to the EOS visit. Temporally-associated Adverse Events (TAAEs), defined as AEs occurring during study drug administration or within 72 hours post-administration (end of infusion). Clinically significant changes from baseline in vital signs and laboratory tests.

STUDY N° / ACRONYM	I10E-1302 / PRISM
EXPLORATORY ENDPOINTS	Biomarker study: • Anti-contactin1 (CNTN1) and anti-neurofascin 155 (NF155) antibodies titers at screening and EOS visit. • FcγRIIB B cells marker levels at visits V2, V3 and V4. • B cell activating factor (BAFF) and 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 before study drug administration. Ancillary study in Italian sites only: • Change from baseline to EOS visit in nerve conduction velocities, distal latencies, amplitude of the negative phase of compound muscle action potentials and F wave for the following peripheral nerves: median nerve, ulnar nerve and deep fibular nerve (F wave assessed on ulnar nerve only). • Change from baseline to EOS visit in nerve maximal/minimal cross section area (CSA), intra-nerve and inter-nerve variability and USG immune-related classification (see Section 1.4.4 Electrophysiology examination and peripheral nerve ultrasonography), in the following peripheral nerves: median nerve, ulnar nerve, fibular nerve and sural nerve.
STATISTICAL METHODOLOGY	**Sample size:** The study is designed to demonstrate superiority of I10E to an historical control in terms of responder rate. Based on an historical response rate of 33.3% (defined as the upper limit of the 95% confidence interval of the responder rate with placebo in the ICE study) 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 a non-evaluable rate of 10 %, 42 patients (around one third of all patients will be either Ig-naïve or relapsing Ig-pretreated patients).

STUDY N° / ACRONYM	I10E-1302 / PRISM
STATISTICAL METHODOLOGY	**Statistical analyses:** The primary efficacy endpoint will be the responder rate at EOS visit. Responders are defined as patients with a decrease ≥1 point in the adjusted INCAT disability score between baseline and the EOS visit. The responder rate will be tested against the historical responder rate of 33.3% with a one-sided Clopper-Pearson test (exact binomial test) at the nominal level of significance of 2.5%. All other efficacy and safety endpoints will be analysed using descriptive statistics. The Full Analysis Set (FAS) will be used as primary efficacy analysis population. For the safety analyses, The Total Treated Set (TTS) will be used as the analysis population.

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, Haemoglobin, 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 haemolysis											
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) apply.

[c] *According to 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*

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Disease and context

CIDP is an acquired paralytic illness affecting peripheral nerves and caused by a demyelinating process. The underlying pathologic mechanisms are still unclear. Yet, an autoimmune aetiology is largely thought to be probable.

CIDP is a rare disease. The various epidemiological studies show that prevalence may vary from 1.24 to 8.9/100 000 [1] [2]. Due to the ambiguities of diagnosing CIDP, the true prevalence of the disease may be underestimated or overestimated [3].

1.1.1. Diagnostic criteria for CIDP

Diagnostic criteria for CIDP have been defined by expert groups. These diagnostic criteria sets combine clinical, electrophysiological and biological features.

The typical clinical presentation of CIDP includes symmetric sensory and motor symptoms in the proximal and distal segments of all four limbs, associated with areflexia and evolving over more than 2 months. The disease may show either continuous or stepwise progression over months to years or may take a more fluctuating course.

However, clinical features are heterogeneous and there are many borderline clinical forms, such as purely motor forms, purely sensory forms or Lewis-Sumner syndrome. Furthermore, frequent association with other diseases such as diabetes mellitus, monoclonal gammopathy with or without antibodies to myelin-associated glycoprotein, connective tissue diseases or human immunodeficiency virus infection may complicate the diagnosis.

Electrodiagnostic tests are mandatory to confirm the diagnosis of CIDP [4]. Electrodiagnostic criteria for CIDP are closely linked to diagnostic criteria of peripheral nerve demyelination. They include reduced motor nerve conduction velocity, motor nerve conduction block, abnormal temporal dispersion, prolonged motor distal latency and prolonged F wave latency or absent F waves [5].

Cerebrospinal fluid examination may assist the diagnosis. Usually there is an albumino-cytological dissociation with an elevated protein level and a leukocyte count $<10/mm^3$.

Nerve biopsy is not often used for the diagnosis as it might cause an unacceptable increase in neurological symptoms [6]. However, when an affected portion of nerve is examined, segmental demyelinating lesions are found associated with inflammatory signs such as endoneurial oedema and infiltration by macrophages and T lymphocytes. The demyelination and re-myelination process often produces the so-called "onion bulb" formations. There is usually a superimposed axonal degeneration.

Differential diagnosis

CIDP should be differentiated from amyotrophic lateral sclerosis, lower motor neuron disease, multifocal motor neuropathy (MMN) and Lewis–Sumner syndrome [7]. The differential diagnosis of CIDP is summarised in the Table 1–1: Differential diagnosis of CIDP

Table 1–1: Differential diagnosis of CIDP

Feature	CIDP	MMN	Amyotrophic lateral sclerosis	Lower motor neuron disease	Lewis-Sumner syndrome
Distribution of weakness	Symmetric	Asymmetric	Asymmetric	Asymmetric	Asymmetric
Prominent sensory symptoms	Yes	No	No	No	Yes
Tendon reflexes	General hyporeflexia or areflexia	Normal or decreased in weakened muscles*	Increased in weakened muscles	Decreased in weakened muscles	Decreased in weakened muscles
Disease course	Progressive or relapsing	Slowly progressive	Rapidly progressive	Slowly or rapidly progressive	Progressive or relapsing
CSF protein >1g/L	Yes	No	No	No	Rare
Increased titers of GM1-specific IgM antibodies	Rare	Common	Rare	Rare	Rare
Abnormal MRI signal in the brachial plexus	Symmetric	Asymmetric	No	No	Asymmetric
Response to IVIg	Yes	Yes	No	No	Yes
Response to corticosteroids	Yes	No**	No	No	Yes

**In some patients, reflexes are brisk. **May aggravate symptoms.*

Diagnostic criteria

The diagnosis of CIDP is based on clinical and electrophysiological characteristics, and may be supported by results from ancillary investigations.

The diagnostic criteria and diagnostic categories are presented in the Table 1–2 (EFNS/PNS CIDP Guideline 2010, First revision [4]):

Table 1–2: Diagnostic criteria and diagnostic categories of CIDP

Electrophysiological criteria
(1) Definite: at least one of the following (a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or (b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or (c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN values), or (d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parametera in ≥1 other nerve, or (e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parametera in ≥1 other nerve, or (f) Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥6.6 ms, ulnar ≥6.7 ms, peroneal ≥7.6 ms, tibial ≥8.8 ms)b + ≥1 other demyelinating parametera in ≥1 other nerve
(2) Probable ≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parametera in ≥1 other nerve
(3) Possible – As in (1) but in only one nerve – To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb's point and the wrist is required for probable conduction block. Temperatures should be maintained to at least 33◦C at the palm and 30◦C at the external malleolus (good practice points). – CMAP, compound muscle action potential; ULN, upper limit of normal values; LLN, lower limit of normal values.

Clinical criteria
(1) Inclusion criteria (a) <u>Typical CIDP</u> Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and Absent or reduced tendon reflexes in all extremities (b) <u>Atypical CIDP</u> (still considered CIDP but with different features) One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs): Predominantly distal (distal acquired demyelinating symmetric, DADS) or Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb) Pure motor or Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)
(2) Exclusion criteria – Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy

- Hereditary demyelinating neuropathy
- Prominent sphincter disturbance
- Diagnosis of multifocal motor neuropathy
- IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
- Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and nondiabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

Supportive criteria
1. Elevated CSF protein with leukocyte count <10/mm^3 (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumboscral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (Good Practice Points): a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or b. Conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal); or c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (Good Practice Points)

The European Federation of Neurological Society (EFNS) / Peripheral Nerve society (PNS) 2010 Guideline sets up 3 diagnostic categories for CIDP, based on presence or absence of clinical, electrophysiological and supportive criteria [4]. These categories are summarised in the Table 1–3

Table 1–3: Diagnostic Categories

Diagnostic categories
Definite CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 1; or
Probable CIDP + at least one supportive criterion; or
Possible CIDP + at least two supportive criteria
Probable CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 2; or
Possible CIDP + at least one supportive criterion
Possible CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 3
CIDP (definite, probable, possible) associated with concomitant diseases.

1.1.2. Treatment of CIDP and course of the disease

The spontaneous evolution of the disease in the absence of any therapy has not been well described in the literature. The effectiveness of treatment with corticosteroids was shown when chronic polyradiculoneuropathy was first described by Austin in 1958 [8].

Three therapeutic options have proved to be efficacious in CIDP: IVIg, oral corticosteroids and plasma exchange. The EFNS/PNS guideline recommends the use of IVIg or corticosteroids as first line treatment. Plasma exchange, which is less widely available and less tolerated, is only recommended as an alternative in case IVIg and corticosteroids are inadequate. The American Academy of Neurology considers that IVIg should be offered for the long-term treatment of CIDP (Level A recommendation) [9].

Regarding IVIg, a meta-analysis in a Cochrane review of 5 double blind placebo-controlled randomised trials showed that a significantly higher proportion of patients improved in disability within one month after IVIg treatment compared with placebo [10]. Only one study (ICE study) had a long-term follow-up; in this study, 57 responder patients were re-randomised for an extension 24 - week phase between either IVIg at 1 g/kg or placebo every 3 weeks. The percentage of relapse was 13% with the IVIg and 45% with the placebo (p=0.011) [11].

1.2. Target

The specific mechanism of action of IVIg in CIDP is not understood. However, studies in other diseases treated with IVIg have demonstrated that IVIg may inhibit autoantibody production, neutralize pathogenic antibodies, and decrease antibody-dependent cellular cytotoxicity by blocking Fc-receptors (FcγR) on macrophages [12] and upregulate inhibitory Fcγ receptor FcγRIIB on B cells [13]. Furthermore, peripheral blood from participants treated with IVIg shows increased CD8-positive suppressor T-cell function.
The B-cell activating factor BAFF contributes to B-cell homeostasis and (auto-) antibody production. BAFF was recently identified as one key molecule in the development of autoimmune diseases and acts by down-regulation in CIDP. In 2013 Bick et al identified BAFF as a new target for IVIg in CIDP treatment and provide a new FcγR independent, mechanism of action for IVIg.

1.3. Non-Clinical and Clinical Information

The study drug is I10E, a ready-to-use liquid human normal immunoglobulin preparation for IV administration (ATC Code: J06BA02). I10E is manufactured by LFB BIOMEDICAMENTS (see Section 6.1.1 Description of study drug).

Marketing Authorization Application (MAA) was submitted in Intravenous Immunoglobulin (IVIg) Core Summary of Product Characteristics (SPC) indications through the Decentralized Procedure (DCP) in the following European Union Member States: Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Italy, Luxembourg, the Netherlands, Spain, Slovakia, Sweden, and the United Kingdom.The first national marketing authorization was granted in the United Kingdom in August 2015, then in Denmark, Germany, Hungary, Belgium and Finland.

I10E MAA dossier was also submitted in Mexico and approved in April 2015 in the core SPC indications, multifocal motor neuropathy and Birdshot retinochoroidopathy.

This section summarises the available clinical and non-clinical data of I10E.

1.3.1. Non-clinical data

I10E meets specifications of the European Pharmacopoeia Monograph 0918 on IVIg. Non-clinical safety studies of I10E were performed in accordance with Good Laboratory Practice. For more information, refer to the Investigator's Brochure.

1.3.2. Clinical data

As of 08 October 2015, 107 patients have been treated with I10E in open-label clinical studies: 62 patients with primary immune deficiency (PID) in study I10E-0718 (completed), 38 patients with immune thrombocytopenia (ITP) in study I10E-0719 (completed) and 7 patients with chronic inflammatory demyelinating polyneuropathy (CIDP) in an ongoing single-arm study I10E-1302 (PRISM study). In addition, 22 patients with multifocal motor neuropathy (MMN) have been enrolled in an ongoing double-blind cross-over randomized study I10E-0901 (LIME study) and at least 17 of them were administered with I10E.

In PID patients, a total of 766 infusions at a dose ranging from 0.22 to 0.97 g/kg were administered. I10E has proved to be effective in preventing serious bacterial infections (SBIs) with an annual SBI rate below the EMA/FDA requirement of <1/patient. I10E exhibited a PK profile comparable to those of other IVIgs with a mean terminal half-life of 33.6 days.

In chronic primary ITP patients, a total of 73 infusions were administered at a median dose of 1.0 g/kg on one day, 70 of them being administered on 2 consecutive days. I10E was effective in increasing rapidly the platelet count and reducing and preventing bleedings with a response rate of 63.2% of patients using the stringent definition of response of the revised EMA guideline on the clinical investigation of IVIg and 83.8% using the primary efficacy endpoint of the previous EMA guideline.

Monitoring of adverse events (AEs), vital signs, ECG and laboratory parameters showed a safety profile comparable to that of other IVIg in patients with PID or chronic ITP.

In MMN patients, the ongoing study I10E-0901 (LIME study) compares I10E to Kiovig® maintenance therapy at a dose of 1.0 g/kg every 4 weeks up to 2.0 g/kg every 4 to 8 weeks for approximately one year. The enrolment in the study is completed.

In CIDP patients, the study I10E-1302 (PRISM study) aims at evaluating the safety and efficacy of one dose of 2.0 g/kg of I10E followed by 7 doses of 1.0 g/kg every 3 weeks. A total of 42 patients are planned to be enrolled in the study.

As of 08 October 2015, no serious adverse reactions were reported in both study I10E-0901 and study I10E-1302.

An extension of study I10E-1302, namely study I10E-1306 (PRISM-2 study) has been initiated to assess the efficacy and safety of a reduced maintenance dose of I10E in responder patients at the end of study I10E-1302. For more information, refer to the Investigator's Brochure.

I10E dose regimen required in this protocol is already commonly used in treatment of CIDP with IVIg and has shown a favourable benefit to risk ratio. The dose of I10E recommended in this protocol will not exceed the doses used in current practice in patients with CIDP as well as in other indications of immunomodulation.

This section is not intended to be all inclusive regarding risks and benefits. The investigator must become familiar with all sections of the I10E Clinical Investigator's Brochure.

1.4. Rationale of the study

LFB BIOTECHNOLOGIES wishes to develop I10E for the CIDP indication. As required by the European Guideline EMA/CHMP/BPWP/94038/2007 rev.4 [14], confirmatory data of I10E in CIDP should be provided to Health Authorities in order to get registered in this indication. Published literature already indicates a beneficial effect of IVIg in CIDP.

The objective of this study is to provide confirmatory data on the efficacy and safety of I10E in the initial and maintenance treatment phases of CIDP. In Ig-naive patients and in patients with a relapse after withdrawal of Ig treatment, an improvement of the neurological status is expected with I10E. The study will include both types of CIDP patients.

Two main studies named "ICE" and "PRIMA" have already proven the efficacy and safety of Gamunex® (IVIg 10% from Talecris Biotherapeutics, NC, USA) and Privigen® (IVIg 10% from CSL Behring GmbH) respectively.

Study design, primary endpoint and patient selection criteria in this study have been chosen as close as possible to the previous studies (ICE and PRIMA), in particular to "PRIMA" study as it was validated by EMA via a scientific advice (Privigen® EPAR EMA/CHMP/749630/2012).

CIDP patients either Ig-naive or relapsing after Ig treatment withdrawal for at least 3 months will be screened and enrolled. They will receive I10E at a dose of 2g/kg during the first course, then a dose of 1g/kg every 3 weeks during 7 following courses. The treatment and follow-up period will be 24 weeks, as recommended by the EFNS/PNS guideline [4].

The primary endpoint will be the responder rate at the EOS visit. Responders are defined as patients with a decrease ≥1 point in the adjusted INCAT disability score between baseline and the EOS visit.

1.4.1. Disability and impairment scales

In 2013, Els K. Vanhoutte, Catherina G. Faber and Ingemar S.J. Merkies [40] published outcome measures in inflammatory peripheral neuropathies on behalf of the PeriNomS study group the 196th ENMC international workshop. Their recommendations on the best scales for CIDP have been included in the current protocol. The following scales will therefore be assessed at 12 weeks and EOS visit as part of secondary endpoints:

- 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): Severity (CGI-S), Efficacy (CGI-E) and Improvement (CGI-I);
- Medical Research Council (MRC) 12 muscles sum score (0 to 5) and Rasch-modified MRC (0 to 3);
- Original INCAT disability score.

1.4.2. Immunological background and research of biomarkers

The pathogenesis of CIDP is not fully understood. T cells, B cells, macrophages, cytokines and chemokines, autoantibodies and complement are the main effectors involved in the pathogenesis of CIDP and are therefore the main target of therapies. Immune cells and soluble mediators are

regulated by IVIg and this regulation is correlated in many instances with IVIg response. Numerous biomarkers have been proposed in CIDP but none seems to predict the response to IVIg accurately. This trial gives the opportunity to assess specific biomarkers, their modulation by IVIg treatment and their correlation with clinical response.

IVIg seems to work by a direct competition and quantitative blockade of autoantibody action by different mechanisms.

In 2013 Professor Isabel Illa highlighted IgG4 anti-contactin1 (CNTN1) and anti-neurofascin (NF155) autoantibodies as poor prognostic factors after IVIg therapy: in her series, the presence of at least one of these autoantibodies identified a lack of response to IVIg [15]. Anti-CNTN1 and anti-NF155 antibodies were associated to small subgroups of CIDP patients with specific phenotypic features.

The concept of an aberrant B cell response as a pathogenic part of CIDP is widely accepted. IgG mediated effector functions require the interaction with their FcγR on effector cells. The type II FcγRIIB (CD32B) is the only inhibitory FcγR and is expressed on circulating monocytes and B cells. On B cells, signalling trough this receptor inhibits transformation of B cells into antibody secreting plasma cells [16]. Recent works has shown that this receptor is modulated by IVIg in CIDP patients [17] [18] [19].

The immune status of patients as well as their modulation by a high dose of IVIg (2g/kg) will be documented by monitoring the expression of the FcγRIIB B cell marker in blood.

Other soluble biomarkers such as (BAFF) contribute to B-cell homeostasis and autoantibody production [20].

Complement components have been shown to be modulated by IVIg [21] [22]. Scavenging of complement fragments is a mechanism believed to be important in the efficacy of IVIg. Binding of IgG molecules to potentially harmful complement fragments (C3b, C4b) blocks deposition of these fragments onto their target and the formation of amplification convertases, decreasing activation of C5 and deposition of the C5b-C9 membrane attack complex.

The modulation of the complement pathway following IVIg treatment can be monitored by the combined dosage of CH50 (ELISA-based assay) for the quantitative determination of functional classical, mannose binding lectin and alternative complement pathways, and the quantitative dosage of C3 and C4 proteins (routinely performed by nephelometry) in serum samples.

Serum concentrations of these markers in samples will be measured in order to document their modulation at both high (2g/kg) and low (1g/kg) doses of IVIg and to assess whether the modulation is dose dependent.

Analyses of these biomarkers should advance understanding of immune modulation and mechanism of action of IVIg in CIDP.

1.4.3. Neurophysiological examination (Ancillary study; Italian sites only)

Monolateral nerve conduction studies (NCS) will be performed through the following minimum neurophysiological protocol. Local laboratory standards will be employed.

Motor nerve conduction studies will be performed in the following nerves:

- median nerve: the motor response will be recorded with surface electrodes over the abductor pollicis brevis muscle and the sites of stimulation will be at the wrist (1 cm proximal volar wrist fold) and at the elbow;
- ulnar nerve: the motor response will be recorded with surface electrodes over the abductor digiti minimi muscle and the stimulation site will be at the wrist, above and below elbow (3 cm above and below elbow) and axilla;
- deep fibular nerve: the motor response will be recorded with surface electrodes over the extensor digitorum communis and the sites of stimulation will be proximal to the anterior tarsal tunnel, 2 cm distal the proximal margin of fibular head and in the popliteal fossa.

Motor nerve conduction velocities, distal latencies, and amplitude of the negative phase of compound muscle action potentials will be measured.

F wave studies will be performed in the ulnar nerve with measurement of mean F latency and frequency of F response.

Sensory nerve conduction studies:

- orthodromic sensory NCS of the median nerve will be recorded at the wrist and the stimulation with ring electrodes will be at digit III;
- orthodromic sensory NCS of the ulnar nerve will be recorded at the wrist and the stimulation with ring electrodes will be at digit V;
- antidromic sensory NCS of the sural nerve will be recorded at posterior-lateral malleolus and the site of stimulation will be at the posterior-distal leg with the cathode at 12 cm from the active electrode.

As methods differ from site to site, all participating centers must provide complete information on their laboratory's standard NCS protocols.

If clinically indicated, additional studies may be performed at the discretion of the examiner.

1.4.4. Peripheral nerve ultrasonography (Ancillary study; Italian sites only)

High-resolution ultrasound (USG) of peripheral nerves is a valuable complement to neurophysiology especially in the work-out of mononeuropathies. Less is known on polyneuropathies, where the great heterogeneity made difficult the identification of a specific alteration pattern. In previous studies in CIDP patients, nerve USG showed diffuse enlargement of cross sectional area (CSA) of peripheral nerves trunks and cervical roots [23] [24] [25] [26] [27].

Recently, USG findings in CIDP have been shown not only to contribute to the diagnosis, but also to mirror the underlying pathophysiological mechanisms. Nerve enlargement was statistically related to disability and muscle strength, and the relationship between duration of symptoms and USG classes was highly significant [28].

For the nerve USG evaluation, USG systems equipped with medium (the lowest being around 6 Hz) and high-frequency (15-18 MHz) broadband probes will be used. USG will be performed in the neurophysiologically evaluated side. Additional nerves may be evaluated at the discretion of the examiner.

Nerve assessment required and pre-determined site of measurements are:

- Median: wrist, mid-forearm, elbow, mid-humerus and axilla

- Ulnar: wrist, mid-forearm, elbow, mid-humerus and axilla
- Fibular: fibular head and popliteal fossa
- Sural: median third of the leg

Optional assessments (for skilled USG operators) are:

- Supraclavicular brachial plexus (strongly suggested)
- Radial at humeral sulcus
- Posterior interosseus nerve under the supinator muscle
- C5-C6-C7 cervical roots.

USG outcome measures will be:

1) Maximal/minimal CSA for each nerve along the visible course;
2) Intra-nerve and inter-nerve variability;
3) USG immune-related classification.

1. Maximal and minimal CSA.

The method to calculate CSA (just inside the hyperechoic rim of the nerve in transversal section) is usually the “ellipse method” when applicable (when the nerve in the transverse scan has an elliptical or roundish shape) or the “tracing method” when the nerve has an “irregular” shape. Echogenicity alteration not associated with CSA alteration will be not considered.

In addition to the pre-determined sites of imaging, maximal (MAX-CSA) and minimal (MIN-CSA) CSA enlargement along the visible course will be recorded for each nerve.

The CSA of whole plexus will be bilaterally measured. Moreover, after identification of the cervical spinal root level, CSA of each root (from C5 to C7) are measured just before entering the spine [29].

Each centre will use its own previously established CSA normative values. Every participating centre has to submit their normative values in advance. If not available, normative values adopted in the coordinating site will be used.

2. Intra- and inter-nerve variability

"Intra-nerve CSA variability" (for each nerve: maximal CSA/minimal CSA) and "inter-nerve CSA variability" (for each patient: maximal intra-nerve CSA variability/minimal intra-nerve CSA variability) will be evaluated [30] [31]. Intra-nerve variability will be evaluated only in ulnar, median and fibular nerves, having sural nerve a very short assessable segment (with only a single measure taken).

Normal values of upper cut-off of intra-nerve ratio are for median nerve 2.3 and for the ulnar nerve 2.1. Concerning inter-nerve variability the upper cut-off value is 1.9.

3. USG immune-related classification

On the basis of previous USG observations [28] USG pattern is classified as follows:

Class 1: large nerves, with hypoechoic segments and increased nerve CSA. Enlarged fascicles may be seen or the nerve may appear enlarged and hypoechoic without fascicular structure.

Class 2: large nerve, with segments with increased nerve CSA and coexistence of hyper and hypoechogenic enlarged (or normal) fascicles (in other words, in the same point we observe fascicles with hyperechoic and other fascicles with hypoechoic structure).

Class 3: normal nerve size, but changes in echogenicity (nerve appears hyperechoic with reduced CSA). The edge of the nerve and surrounding is not clear. The hyperechoic rim of epineurium is not clearly identified. Fascicles are not well visualized.

Only CIDP patients enrolled in Italian centres will undergo USG examination coupled with neurophysiology, as Italian sites already have nerve examination-trained ultra-sonographers.

2. STUDY OBJECTIVES

2.1. Primary objective

To assess the efficacy of I10E in improving the disability of patients with CIDP.

2.2. Secondary objective

To assess the safety of I10E in patients with CIDP.

2.3. 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 USG coupled to neurophysiology analysis of nerves and clinical response – as assessed by neurological scales – in patients with CIDP (ancillary study in Italy).

3. STUDY DESIGN

Study design is outlined in Figure 8–1.

3.1. Design and study periods

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

Study periods are as follows:

3.1.1. Screening

The screening period goes from signature of informed consent to first study drug administration. The screening biological tests should be performed and their results checked by the Investigator within a period of 4 weeks before first study drug administration.

The exclusion and inclusion criteria (except those related to screening biological assesments) will be verified prior to screening. The screening biological test results will be verified before the first study drug administration.

The screening period shall not exceed 4 weeks.

3.1.2. Baseline

Baseline data are those obtained during the screening period before first study drug administration. If multiple results are available for a given assessment, the most recent will be considered.

3.1.3. Inclusion

A patient is considered included once he/she receives the first study drug administration.

3.1.4. Treatment

Patients who meet all the eligibility criteria will receive one dose of study drug at 2 g/kg over 2 to 5 days. Three (3) weeks later, they will start to receive 7 doses of study drug at 1 g/kg over 1 to 2 day(s) each, every 3 weeks (+/- 7 days).

Investigators or Study Nurses will call patients 4 days (+/-1 day) after the end of each study treatment course to document potential AEs and TAAEs (see Section 8.2.4).

Duration of the treatment period will be approximately 21 weeks.

3.1.5. Follow-up and End of study

A follow-up visit will occur 3 weeks +/- 7 days after the last study drug administration. At the end of the follow-up period, patients will undergo an EOS visit. This visit occurs 3 weeks after the 8th course of study drug. In the event of premature discontinuation from the study drug or patient withdrawal from the study, an EOS visit is performed within 7 days and prior to administration of any other treatment for CIDP (See Section 8.2.7). The reason for premature study drug discontinuation / study withdrawal should be accurately assessed and entered into the eCRF.

The total duration of the study for a patient is approximately 24 to 29 weeks.

3.2. Endpoints

3.2.1. Primary efficacy endpoint:

The primary efficacy endpoint will be the responder rate at EOS visit.

Responders are defined as patients with a decrease ≥1 point in the adjusted INCAT disability score between baseline and the EOS visit.

3.2.2. Secondary efficacy endpoints

The secondary efficacy endpoints will be:

- Responder rate at 12 weeks.
- Time to response.
- Percentage of patients at 12 weeks and EOS visit with no change in CIDP treatment.
- 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) and Rasch-modified MRC (0 to 3).

3.2.3. Safety endpoints

Safety will be evaluated by the assessement of treatment-emergent adverse events (TEAEs) and temporally-associated AEs (TAAEs) – including SAEs – from first study drug administration to the EOS visit, as well as by assessment of clinically significant changes from baseline in vital signs and laboratory tests.

3.2.4. Exploratory endpoints

The following exploratory endpoints will be considered:

Biomarker study:

- Anti-CNTN1 and anti-NF155 antibodies titers at screening and EOS visit.
- FcγRIIB B cells marker levels at visits V2, V3 and V4.
- B cell activating factor (BAFF) and 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.

Ancillary study in Italian sites only:

- Change from baseline to EOS visit in nerve conduction velocities, distal latencies, amplitude of the negative phase of compound muscle action potentials and F wave for the following peripheral nerves: median nerve, ulnar nerve and deep fibular nerve (F wave assessed on ulnar nerve only).
- Change from baseline to EOS visit in nerve maximal/minimal cross section area (CSA), intra-nerve and inter-nerve variability and USG immune-related classification (see Section 1.4.4. Peripheral nerve ultrasonography), in the following peripheral nerves: median nerve, ulnar nerve, fibular nerve and sural nerve.

3.3. Study Investigational Site(s)

This study will be conducted in approximately 37 recognised referral centres and/or centres of expertise for neuromuscular diseases or peripheral neuropathies in France, Italy, Spain, Tunisia, Turkey, the United Kingdom, Germany and Poland.

Enrolment will be competitive and will take place in parallel in all sites.

Investigators are encouraged to inform their colleagues about this study, so that any eligible patient could be referred to them. Material such as doctor-to-doctor letters, posts on specialised websites or conferences could be provided by the Sponsor.

3.4. Data and Safety Monitoring Board

No DSMB will be set-up for this study for the following reasons:

- IVIgs are used in current medical practice in this indication with a favourable benefice-to-risk ratio.
- Dosages administered in this study are those recommended by scientific societies (EFNS/PNS and American Academy of Neurology) and are used in current medical practice.
- Investigators selected in this study have established competence in the treatment of CIDP, in particular in the use of IVIg for this indication and work within renowned reference centres.
- Previous human experience with I10E showed a comparable safety profile with other IVIgs.
- Neither interim analysis, nor arbitration on study continuation or early termination or redesign is planned.

3.5. Scientific Committee

A scientific committee will be set up for the following activities:

- Protocol review
- Participation in the Investigator's meeting, including training of investigators on specific scales and evaluations used in this protocol.
- Medical support for medical data review if needed.

Its membership is the following:

- Prof. Eduardo Nobile-Orazio, MD, PhD, Prof. of Neurology (Italy)
- Prof. Richard Hughes, MD, FRCP, Emeritus Prof. of Neurology (United Kingdom)
- Prof. Isabel Illa, MD, PhD, Prof. of Neurology (Spain)
- Prof. Jean-Marc Léger, MD, Co-Chair National Referral Center for rare neuromuscular diseases (France)
- Prof. Jean-Marie Grouin, PhD, Associate Professor in Statistics (France)
- Prof. Luca Padua, MD, PhD, Prof of Neurology and Ultrasonography (Italy)
- Dr. Ingemar Merkies, MD, PhD, Neurologist- Clinimetrician (The Netherlands)

4. DURATION AND DATES OF THE STUDY

The FPI is planned in Q1 2015 and the LPO is planned in Q4 2017.

5. STUDY POPULATION

5.1. Number of patients

42 patients will be included in the trial to ensure 38 evaluable patients (around one third of all patients will be either Ig-naïve or relapsing Ig-pretreated).

A patient will be considered evaluable if he/she has an assessment of the primary endpoint after the first study drug administration.

5.2. Eligibility Criteria

Before any study-related procedure is undertaken, written informed consent must be obtained (see Section 8.1.1).

A patient is eligible if all the inclusion criteria and none of the exclusion criteria are met.

5.2.1. Inclusion criteria

1. Male or female patient aged 18 years or more.
2.
   - Definite or probable CIDP according to the European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) guidelines 2010 clinical and neurophysiological criteria.
   - Pure motor CIDP, provided that a diagnosis of multifocal motor neuropathy has been ruled out.
   - CIDP associated with monoclonal gammopathy of undetermined significance (MGUS), provided that anti-MAG antibodies titer is lower than the used technique's negativity threshold (1000 BTU for Bühlmann ELISA technique).
   - Lewis-Sumner syndrome.
3. Score of at least 2 on the adjusted INCAT disability scale.
4. Patient who either :
   a) has never been previously treated with Ig (Ig-naïve patient)
      OR
   b) was previously treated with Ig but is in clinical relapse following treatment withdrawal. In the latter case, the last Ig course shall have been administered no less than 3 months prior to screening.
5. Covered by national healthcare insurance system as required by local regulations.
6. Written informed consent obtained prior to any study-related procedures.

5.2.2. Exclusion criteria

1. History of severe allergic reaction or serious adverse reaction to any immunoglobulin (Ig).
2. Clinically documented lack of response to previous Ig treatment.
3. History of IgA deficiency (IgA ≤70 mg/L), unless the absence of anti-IgA antibodies has been documented.
4. Known hypersensitivity to human Ig or to any of the excipients of I10E (glycine and polysorbate 80).
5. History of cardiac insufficiency (NYHA III/IV), uncontrolled cardiac arrhythmia, unstable ischemic heart disease, or uncontrolled hypertension.
6. History of venous thromboembolic disease, myocardial infarction or cerebrovascular accident.
7. Risk factor for blood hyperviscosity such as cryoglobulinemia or haematologic malignancy with monoclonal gammopathy.
8. History of personal or familial congenital thrombophilia or acquired thrombophilia.
9. Factors contributing to venous stasis such as long-term bed confinement.
10. Body Mass Index (BMI) ≥40 kg/m².
11. Protein-losing enteropathy characterised by total serum protein level <60 g/L and serum albumin levels <30 g/L.
12. History of kidney transplantation, nephrotic syndrome (defined as proteinuria >3.5 g per 24 hours accompanied by hypoalbuminemia and edema), or any acute or chronic kidney disease that in the opinion of the investigator and/or nephrologist would preclude the use of I10E and/or interfere with the assessment of the safety and efficacy of I10E.

    AND/OR

    Chronic kidney disease (CKD) for more than 3 months as documented by at least one of the following:

    - glomerular filtration rate (GFR) <60 mL/min/1.73m^2 measured according to the Modified Diet in Renal Disease (MDRD) formula

      AND/OR

    - urine protein reagent strip: ≥2 crosses

      AND/OR

    - urine protein reagent strip: one cross with one of the following:
        - albumin excretion rate (AER) >300 mg/24 hours or protein excretion rate (PER) >500 mg/24 hours (24h-urine collection)

          OR

        - albumin to creatinine ratio (ACR) >30 mg/mmol or protein to creatinine ratio (PCR) >50 mg/mmol (spot urine sample).
13. Serum levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times upper limit of normal (ULN) range.

14. Any other ongoing disease that may cause chronic peripheral neuropathy, such as toxin exposure, dietary deficiency, uncontrolled diabetes, hyperthyroidism, cancer, systemic lupus erythematosus or other connective tissue diseases, infection with HIV, HBV or HCV, Lyme disease, multiple myeloma, Waldenström's macroglobulinaemia, amyloidosis, and hereditary neuropathy.
15. Woman with positive results on a urine pregnancy test or breastfeeding woman or woman of childbearing potential without an effective contraception.

    Effective contraceptives are injectable, patch or oral combined oestro progestative or progestative contraceptives, Copper T or levonorgest releasing intra-uterine devices, depot intramuscular medroxyprogesterone, subcutaneous progestative contraceptive implants, condoms or occlusive caps (diaphragm or cervical/vault caps) with spermicide, true abstinence (when this is in line with the preferred and usual lifestyle of the patient).
16. Any other serious medical condition that would interfere with the clinical assessment of CIDP or use of I10E or prevent the patient from complying with the protocol requirements.
17. Increasing dosage or introduction of a systemic corticosteroids therapy, or corticosteroids therapy at a dose higher than 10 mg prednisolone per day, or equivalent within the last 3 months prior to screening. Topical corticosteroids are permitted.
18. Treatment within 12 months prior to screening with immunomodulatory or immunosuppressant agents (including but not limited to cyclophosphamide, cyclosporine, interferon-α, interferon-β1a, anti-CD20, alemtuzumab, aziathioprine, etanercept, mycophenolate mofetil, methotrexate) or haemopoetic stem cell transplantation.
19. Plasma exchange, blood products or derivatives administered within the last 3 months prior to screening.
20. Administration of another investigational product within the last month prior to screening.
21. Drug or alcohol abuse.
22. Anticipated poor compliance of patient with study procedures.

5.3. Duration of Patient participation

The duration of the treatment for a patient is approximately 21 weeks. The total duration of the study for a patient (including the screening period) is approximately 24-29 weeks.

5.4. Discontinuation criteria / Stopping rule(s)

All patients are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The Investigator must withdraw from the study any patient who requests to stop participating in the study. Patients who withdraw their consent will be asked to undergo the study assessments scheduled at the EOS visit. They will be advised that participation to the EOS visit is voluntary but is their best interest.

The Investigator must discontinue study drug administration to a patient and perform an EOS visit at the request of the Sponsor or if the patient:

- Experiences an AE - including an AE due to a clinically significant laboratory abnormality - that justifies study drug premature discontinuation.

Undergoes protocol deviation that could endanger the patient safety.

- Becomes pregnant.

Moreover, the Investigator may discontinue a patient from study drug administration if:

- Either the patient's adjusted INCAT disability score increases by 1 point, compared to baseline,

AND

Judging on the clinical examination and/or the neurological scales assessments, the Investigator considers change in patient's treatment (such as, administration of another IVIg, increase or initiation of a corticotherapy, immunosuppressive therapy, plasma exchange) is mandatory. Clinical examination findings as well as neurological scales assessments will have to be reported on the EOS visit as appropriate;

- Or the patient's adjusted INCAT disability score increases by at least 2 points compared to baseline.

If a patient is prematurely discontinued, the date and reason of discontinuation will be documented in the eCRF.

If a patient is withdrawn because of an AE, he/she will be followed up until complete resolution or stabilisation of the AE.

Patients lost to follow-up will be considered as discontinued from the study. A patient will be considered as lost to follow-up only after having exhausted all means of contact. Investigators must make every effort to contact the patient and/or his/her family or relatives to obtain the maximum of the per protocol requested information. All contact attempts will be documented in the patient's medical records.

6. STUDY DRUG AND CLINICAL SUPPLIES

6.1. Study Drug

6.1.1. Description of study drug

The study drug is I10E.

I10E will be supplied, free of charge, by LFB BIOTECHNOLOGIES.

6.1.1. 1. I10E (study drug)

Pharmaceutical form

I10E is a ready-to-use liquid human normal immunoglobulin preparation for intravenous administration (ATC Code: J06BA02). I10E is manufactured by LFB BIOMEDICAMENTS.

I10E contains 10% (100 mg/mL) of proteins, 98% at least of which are IgG. The other ingredients are glycine (18.8 mg/mL) and polysorbate 80 (0.05 mg/mL): these excipients have been chosen for their stabilising properties and good tolerance.

I10E is produced by fractioning plasma proteins and then extracting and purifying immunoglobulins.

More information is available in the current Investigator's Brochure of I10E.

6.1.1. 2. Packaging

The primary packaging of I10E is a sterile type-1 glass vial, sealed with a bromobutyl-rubber stopper.

Each I10E box will contain one vial of human normal immunoglobulin 20g/200mL or 10g/100mL.

6.1.1. 3. Labelling

The Investigational Medicinal Product will be labelled individually. A system of tear-off labels will insure traceability.

Labels will carry the following required regulatory texts. Each vial is labelled with at least the following information:

- Study LFB N° I10E-1302
- I10E - Human Normal Immunoglobulin - 100 mg/mL (vial: 20g/200mL or 10g/100mL)
- Batch Number CLIXXXX
- Use by date: MM/YYYY
- Treatment Number: XXXX
- Patient N°XX-XX (to be filled)
- Investigator name (to be filled)
- Infusion date (to be filled)
- For intravenous use only
- Solution for infusion
- Storage requirements: according to the labelling
- Protect from light, do not freeze
- The standard caution statement:
  - Medicinal Product derived from human plasma
  - For clinical use only
  - For use under medical supervision
- LFB BIOTECHNOLOGIES's name, address and phone number

Labels will be adapted to local requirements and translated into the local language when legally required.

6.1.2. Management of study drug at Hospital Pharmacy

6.1.2. 1. Shipment and study drug reception

Shipments of study drug to Hospital Pharmacy will be organised by the Sponsor's drug distributor at controlled temperature according to the labelling.

Upon receipt, the Hospital Pharmacist will inventory the study drugs and complete the acknowledgement of receipt form which has to be returned to the drug distributor. Should any abnormality of the supply boxes be observed, the Hospital Pharmacist must immediately inform the drug distributor.

Re-supply of the sites with study drug will be organised as necessary by the drug distributor upon Pharmacist's request.

6.1.2. 2. Study drug storage

The Hospital Pharmacist will be responsible for the appropriate storage of the study drug at the study site.

Study drug must be stored in a safe and locked place according to the storage temperature requirements with no access by unauthorized personnel.

I10E must be stored under controlled and monitored temperature. I10E must be protected from light (kept in their boxes) and must not be frozen.

The Hospital Pharmacist must immediately inform the Monitor of any non-respect of the required storage conditions. Any temperature deviation must be reported within 1 working day to the Sponsor, using a temperature deviation form. The official written approval for the use of treatment must be obtained from the Sponsor prior to any dispensation/administration. In the meantime, study drug under temperature deviation should be placed under quarantine at controlled temperature as per the labelling. In case of decision to not use the study drug, the vials will be stored under quarantine at ambient temperature until shipment back to the drug distributor.

6.1.2. 3. Preparation of study drug and dispensing

The Investigator will write a prescription sheet (on a quadruplicate No Carbon Required (NCR) paper) prior to the first infusion of each treatment course. The original prescription sheet, the 2nd and the 3rd NCR copy will be sent to the Hospital Pharmacist. The 4th will be kept in the Investigator site file.

The prescription will give the following information:
- Study LFB BIOTECHNOLOGIES I10E-1302
- Patient identification: Patient number
- Patient weight (in kg)
- Infusion dosage (in mL)
- Planned infusion(s) date(s).

The Hospital Pharmacist will prepare the study drug for the infusions, according to the infusion dosage indicated in the prescription. The product should be at room or body temperature before it is administered to the patient. Prior to transfer, study drug will be checked for cloudiness, colour, soapy solution or deposits. If it does not conform to the description, the study drug must not be dispensed and the Hospital Pharmacist should immediately alert the Monitor.

For each study drug vial that is to be dispensed for infusion, the Hospital Pharmacist will stick one tear-off label on the prescription sheet (original), which will be filled in the Pharmacy study file for traceability purposes.

6.1.2. 4. Study drug return, destruction and recall

When closing the investigational site, all used and unused study drug vials, including empty vials, must be returned to the Sponsor's drug distributor except in case of specific local regulatory requirements.

The Pharmacist must not destroy the used/unused study drugs without written authorization from the Sponsor.

6.1.2. 4.1. Return

The return preparation of used/unused study drugs will be performed by the Hospital Pharmacist and the Monitor.

For French sites only, return will be organised by Sponsor's drug distributor. The person in charge of study drug at site level should fill in and send (e-mail or fax) to drug distributor the "IMP Return Request Form" in which the Hospital Pharmacist will set a date and time for courier pick up. The Hospital Pharmacist or a delegate should be available at the predetermined date and time when the boxes will be collected from the investigational site.

For other countries, return will be arranged via the Monitors after obtaining the import authorization from the French Competent Authority (ANSM). The Pharmacist should inform the Sponsor's drug distributor of the expected receipt date through "IMP Return Notification Form".

6.1.2. 4.2. Destruction

After complete reconciliation, consolidated destruction of returned and stored vials will be performed by drug distributor upon Sponsor's request.

In case of any on-site destruction required, site must obtain from LFB BIOTECHNOLOGIES a written authorization for destruction which will be filed along with the certificate of destruction in the IMP section of the Pharmacy site file.
Destruction of infusion lines will be carried out by the centre under Investigator's responsibilities.

6.1.2. 4.3. Recall

The Sponsor or its representative and the Investigator/Hospital Pharmacist will inform each other of any suspected or identified study drug defect. Study drug must immediately be put in quarantine as per the storage temperature requirements and no further administration of the concerned batch(es) must be done until Sponsor’s instructions.

The Monitor or the drug distributor will organize with the Investigator/Hospital Pharmacist the return of the concerned batch(es) as per the Sponsor return procedure. Depending on the study status, new batch(es) may be sent to the investigational site.

6.1.3. Administration of study drug to patients

6.1.3. 1. Study drug dosage and treatment schedule

The study drug dosage should be at 2 g/kg for the first adminitration, then at 1g/kg for the rest of the study.

For patients with BMI ≥30 kg/m², the dose must be reduced by 20% i.e 1.6 g/kg for the first administration and 0.8 g/kg for the rest of study.

It is not recommended to change the study drug dose or frequency of administration during the study.

Under no circumstances will the Investigator/Hospital Pharmacist allow the study drug to be used other than as directed by the protocol.

Before any infusion, the Investigator will rule out any study drug over or under dosage in regards to patient's body weight and protocol requirements.

6.1.3. 2. Method of administration

Before administration to a patient, the Investigator will check that the label corresponds to his/her prescription for the patient (study number, patient number, study drug dose).

Study drug will be administered with an infusion pump.

The infusion flow rate must be compliant with the Investigator's Brochure of I10E.

For the first day of any study drug course, the initial flow rate will not exceed 0.5 mL/kg/h during the first 30 minutes. If well tolerated, the rate of administration may be increased up to 1 mL/kg/h during 30 minutes, then - at the Investigator's discretion - gradually increased up to 2, 4 and 6 mL/kg/h as a maximum flow rate.

In patients older than 65 years, the maximum infusion flow rate should be 2 mL/kg/h.

On the subsequent days of any study drug course, the flow rate is at the Investigator's discretion (up to 6 mL/kg/h; up to 2 mL/kg/h for patients older than 65 years).

6.1.3. 3. Traceability, accountability and documentation

Each study drug course should be documented in the patient's medical file, including doses, time and flow rate changes.

The prescribed dose, the date and time of administration and the exact dose administered will be recorded in the eCRF.

The Sponsor will provide specific forms for study drug accountability, which will be kept up-to-date by the Hospital Pharmacist throughout the study. At the end of the study, it must be possible to reconcile the number of study drugs sent by the drug distributor with the number of study drugs delivered to patients and the number of unused study drugs.

6.1.3. 4. Compliance

Compliance with treatment is defined as dose(s) administered within 20% of the prescribed dose(s). Both prescribed and administered doses will be recorded in the eCRF.

As the study drug will be administered only under the direct supervision of a physician familiar with the requirements of the study protocol, compliance should not be an issue. Nevertheless, the reason for any non-compliance must be recorded in the eCRF.

6.2. Medical device

Infusion pump and perfusion lines will be provided by the Sponsor.

7. PRIOR AND CONCOMITANT MEDICATION

7.1. Prior Medication

The term 'prior medication' refers to any medication given up to 2 months before screening.

All relevant prior medications taken within two months prior to screening must be recorded in the patient's medical file and documented on the appropriate pages of the eCRF. Moreover, any prior medication taken more than two months prior to screening which is, in the opinion of the investigator, clinically relevant to the patient's condition will also be recorded.

The following medications are not allowed before screening because they could interfere with the assessment of study drug efficacy:

- Any other investigational product administered within the last month prior to screening.
- Plasma exchange, blood products or derivatives administered within the last 3 months prior to screening.
- Immunomodulatory or immunosuppressant agents (including but not limiting to cyclophosphamide, cyclosporine, interferon-α, interferon-β1a, anti-CD20, alemtuzumab, aziathioprine, etanercept, mycophenolate mofetil, methotrexate) or haemopoetic stem cell transplantation administered during the last 12 months prior to screening.
- Systemic corticosteroids therapy if administered with an increasing dosage or introduced, or administered at a dose higher than 10 mg prednisolone per day, or equivalent. Topical corticosteroids are permitted.
- Loop diuretics administered during the last 24 hours before IVIg infusion planned date. In this case, the study drug infusion date will have to be postponed.

7.2. Concomitant Medication

The term 'concomitant medication' refers to any medication that the patient receives at any time during the study, i.e. from screening to EOS visit. This includes the screening/baseline period,

treatment period and follow-up as defined in the protocol. At each visit, the Investigator will ask the patient about any medication taken since the last visit. All concomitant medication must be recorded in the patient's medical file and documented on the appropriate pages of the eCRF.

Treatments not allowed during the study are the following:

- Plasma exchange, blood products or derivatives other than the study drug.

- Immunomodulators/immunosuppressors agents (e.g. including but not limited to cyclophosphamide, cyclosporine, interferon-α, interferon-β1a, anti-CD20, alemtuzumab, aziathioprine, etanercept, mycophenolate mofetil, methotrexate) and haemotopoeitic stem cell transplantation.
- Introduction or increasing dose of systemic corticosteroids therapy, and/or systemic corticosteroids therapy at a dose higher than 10 mg prednisolone per day, or equivalent. Topical corticosteroids are permitted.
- Loop diuretics administered during the last 24 hours hours before IVIg infusion planned date. In this case, the study drug infusion date will have to be postponed.

Routine pre-medication (to prevent known drug related adverse reaction) are not recommended to avoid masking potential AEs. However, patients who have routinely been receiving pre-medication with previous Ig treatments may continue to receive the same pre-medication.

Other medications which are necessary for the patient's welfare or well-being may be given at the discretion of the Investigator.

All concomitant medications must be recorded in the patient's medical records and documented on the appropriate pages of the eCRF.

8. STUDY PLAN

The method for assessing each study parameter is described in Section 10.

See also Table 1–1: study flow chart.

8.1. Patient recruitment

8.1.1. Informed Consent

The Investigator provides each patient with relevant, comprehensive, verbal and written information regarding the objectives and procedures of the study, as well as the possible risks involved. A patient information sheet will be given to the patient.

The patient should have enough time and opportunity to inquire about study details. All his/her questions should be answered in a satisfactory manner. The patient must be informed about his/her right to withdraw from the study at any time.

Signed informed consent must be obtained from the patient prior to undertaking any study-related procedure and before a blood sample is taken for the screening tests.

One original of the informed consent form, signed and dated by both the patient and the Investigator, will be given to the patient. A second original is filed at the Investigator's site. The process of obtaining consent will be documented in the patient's file.

8.1.2. Screening

The screening period starts when the patient signs his/her informed consent and ends right before study drug is first administered.

The exclusion and inclusion criteria (except those related to screening biological assesments) will be verified prior to screening. The screening biological test results will be verified before the first study drug administration.

The screening biological tests should be performed and their results checked by the Investigator within a period of 4 weeks before the first study drug administration.

Baseline data are those obtained during the screening period before the first study drug administration. If multiple results are available for one single test, the most recent one will be considered.

If the patient is a woman of childbearing potential, investigator must caution her not to become pregnant, while participating to the clinical study. The patient must be willing to employ an effective contraception mean.

Effective contraceptives are injectable, patch or oral combined oestro-progestative or progestative contraceptives, copper T or levonorgest-releasing intra-uterine devices, depot intramuscular medroxyprogesterone, subcutaneous progestative contraceptive implants, condoms or occlusive caps (diaphragm or cervical/vault caps) with spermicide, true abstinence (when this is in line with the preferred and usual lifestyle of the patient).

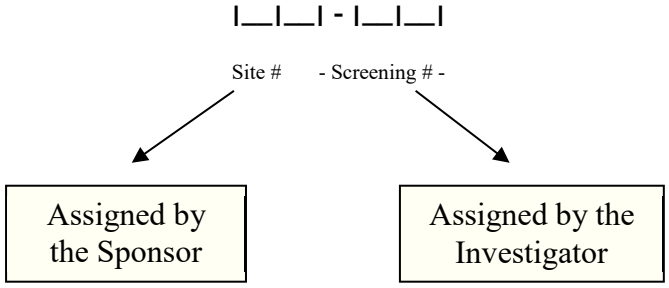
After the patient has signed his/her informed consent, a blood sample will be drawn for biological tests. The screening biologic tests should be performed and the results checked by the Investigator within a period of 4 weeks before the first study drug administration.

The 4-week period should ensure the availability of the screening tests results.

An eCRF will be completed for each patient who has signed an informed consent form. In case of screening failure, the reason will be documented in the eCRF.

8.1.3. Patient Allocation

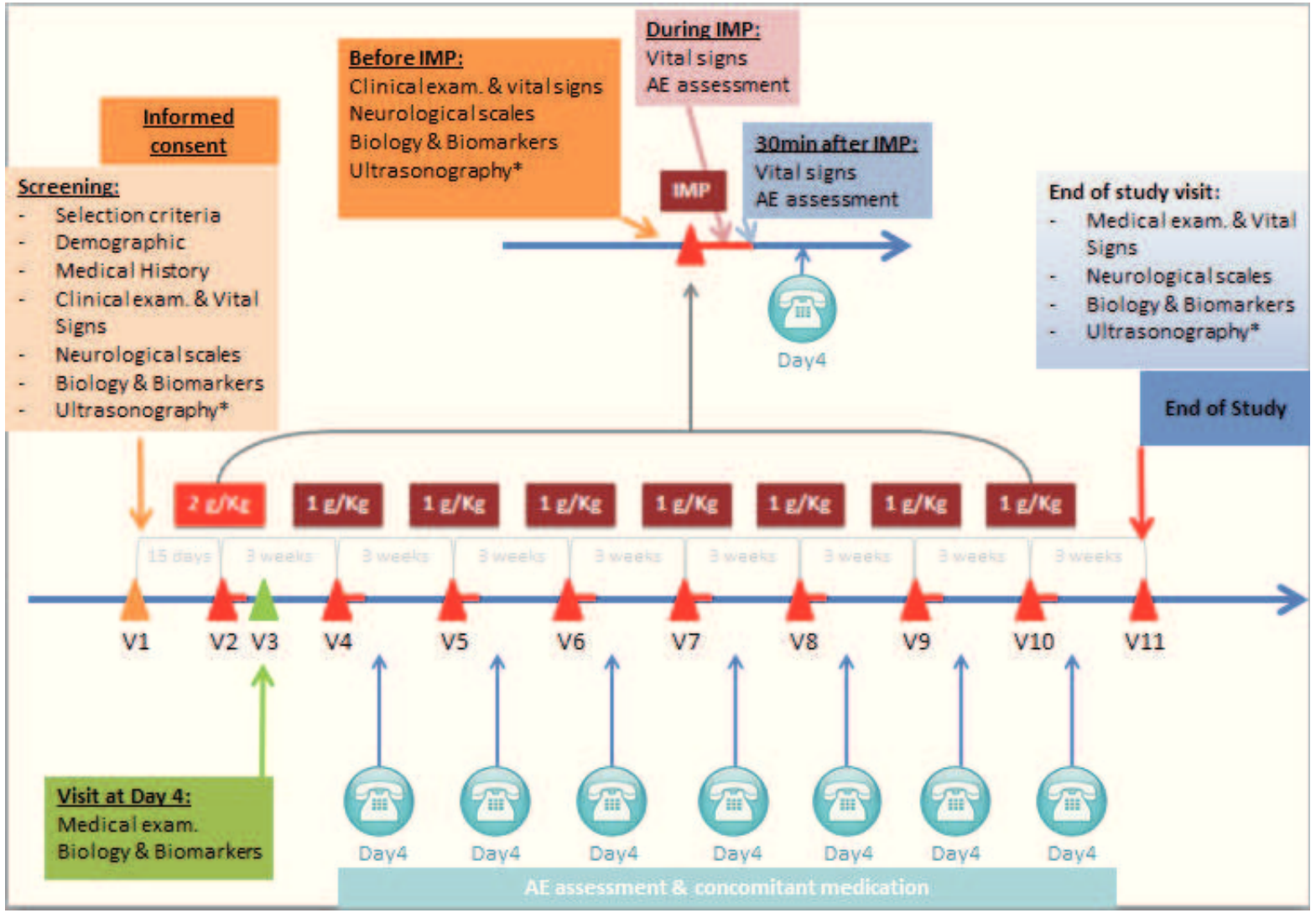
Patient numbers will be composed of 4 digit numbers as shown here below:



A two-digit numbers will be allocated to each site at the beginning of the study.

Investigators will allocate a screening number to each patient who has signed an informed consent. Screening numbers will be two-digit numbers starting with 01 and attributed sequentially according to the chronological order of informed consent signatures in the site.

Figure 8–1: Sequence of study procedure



** ultrasonography coupled to electrophysiology (only for Italian sites).*

8.2. Sequence of study procedures

8.2.1. Visit 1: Screening

The following visit procedures will be carried out during the screening:

- Informed consent signature.
- Check of inclusion and exclusion criteria.
- Demographic and biometric information (gender, age, weight, BMI…).
- Relevant medical history and ongoing concomitant diseases.
- Listing of prior medications.
- Complete physical examination.
- Vital signs: temperature, heart rate, systolic and diastolic blood pressure.

- Neurological status assessment:
  - INCAT disability score (adjusted INCAT disability score will be deduced from reported values).

- Biological tests in local laboratory:
  - Haematology:
    - Complete blood count + differentials, haemoglobin (Hb), mean corpuscular volume (MCV), platelets count.
    - Haptoglobin.
    - Reticulocytes, direct Coombs test.
  - 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, ALP, γGT.
    - HbA1c (only for patients with a known history of diabetes mellitus).
    - Total serum protein level.
    - HBs Ag, anti HBs & anti HBc Ab, HIV, HCV tests.
    - Serum IgA levels.
  - Urine protein reagent strip test:

If urine protein reagent strip test result = Negative or Trace	Action: No further urine test required
If urine protein reagent strip test result = 1 cross (1 +)	Action: 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).
If urine protein reagent strip test result = 2 crosses (2 +) or more	Patient should be excluded

  - Urine Pregnancy test for female patients of child bearing potential.

- Analysis at centralised laboratory:
  - Anti-CNTN1 and anti-NF155 antibodies.
- Ultrasonography coupled to neurophysiology (for Italian sites only).
- AEs assessment.
- Listing of ongoing concomitant treatments.
- Delivery of Patient diary with instruction for use. The patient should document in the diary any AE that occus outside of hospital (including start and end date and time) and any medication taken during the study. The patient should come back at each visit with the diary and the Investigator should assess and evaluate patient information recorded in the diary and report appropriate relevant information in the eCRF.

Abnormal findings at screening physical and biological tests should be reported as baseline findings in patient medical history. All clinical or laboratory abnormalities other than those found on mandatory study screening tests should be reported as an adverse event if clinically significant.

8.2.2. Visit 2: First study drug course

(As soon as the biologic results of screening are available, no later than 4 weeks after the start of the screening).

The following study procedured will be carried out at the 1st study drug course:

- Before the 1st study drug course (within 24 hours before study drug course)
  - Complete physical examination.
  - Biometric information: weight.
  - Vital signs: temperature, heart rate, systolic and diastolic blood pressure.

  - Baseline neurological status assessment:
    - INCAT disability score (adjusted INCAT disability score will be deduced from reported values).
    - Patient and Investigator CGI-S.
    - MRC-sum-score.
    - Rasch-modified MRC sum score.
    - R-ODS.
    - Grip strength with Martin vigorimeter in both hands.

  - Biological tests in local laboratory:
    - Serum total IgG trough levels.
    - C3 and C4 antigens.
    - Serum reference sample for long term storage.

  - Analysis at centralised laboratory:
    - BAFF.
    - CH50.
    - FcγRIIB.

- AEs assessment.
- Listing of concomitant medication.
- Patient diary verification. If information on the patient's diary is not clear, the Investigator will ask the patient questions. The investigator may annotate the patient's diary but must date and sign the annotations.

- During the course of study drug infusion:
  - Collection of infusion parameters.
  - Vital signs measured 30-45 min and 60-75 min after the beginning of the infusion: temperature, heart rate, systolic and diastolic blood pressure.
  - Listing of concomitant medication if applicable.
  - AEs assessment.
- 30-45 min after the end of study drug infusion:
  - Vital signs: temperature, heart rate, systolic and diastolic blood pressure.
  - AEs assessment.
  - Listing of concomitant medication if applicable.

8.2.3. Visit 3: 96 hours after the end of the first course (+/- 24 hours)

The following study procedures will be carried out:

- Complete physical examination.
- Vital signs: temperature, heart rate, systolic and diastolic blood pressure.
- Biological tests in local laboratory:
  - Haematology:
    - Complete blood count + differentials, Hb, MCV, platelets count.
    - Haptoglobin.
  - Biochemical:
    - Creatininemia, glomerular filtration rate according to MDRD.
    - LDH.
    - Total and free bilirubin (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).
    - C3 and C4 antigens.
  - Urine protein reagent strip test [to be performed in patients who at screening tested for urine protein reagent strip result "1 cross 1 (+) and/or had GFR in the range of 60-80 mL/min/1.73m^2]:

If urine protein reagent strip test result = Negative or Trace	Action: No further urine test required
If urine protein reagent strip test result = 1 cross (1 +) or more	Action: 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). The Investigator must review these results in time prior to the study drug administration and consider if any of the Early Discontinuation Criteria / Stopping Rules (see Section 5.4) apply.

- Analysis at centralised laboratory:
  - BAFF.
  - CH50.
  - FcγRIIB (on B cells).

- AEs assessment.
- Listing of concomitant medication if applicable.
- Patient diary verification. If information on the patient's diary is not clear, the Investigator will ask the patient questions. The investigator may annotate the patient's diary but must date and sign the annotations.

8.2.4. Visits 4, 5 and 6: Week 3, Week 6 and Week 9 (+/- 7 days)

The following study procedures will be carried out:

- Before study drug course (within 24 hours before study drug course)
  - Clinical examination focused on arterial or venous thromboembolic signs.
  - Biometric information: weight.
  - Vital signs: temperature, heart rate, systolic and diastolic blood pressure.

  - Neurological assessments:
    - INCAT disability score (adjusted INCAT disability score will be deduced from reported values).

  - Biological tests in local laboratory:
    - Haematology:
      - Complete blood count + differentials, Hb, MCV, platelets count.
      - 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).
      - C3 and C4 antigens (only at visit V4, Week 3).
    - Serum total IgG trough levels.
    - Urine protein reagent strip test [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 GFR in the range of 60-80 mL/min/1.73m^2]:

If urine protein reagent strip test result = Negative or Trace	Action: No further urine test required
If urine protein reagent strip test result = 1 cross (1 +) or more	Action: 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). 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) apply.

- Blood collection for central analysis: (Week 3 only):
  - BAFF.
  - CH50.
  - FcγRIIB (on B cells).
- AEs assessment.
- Listing of ongoing concomitant treatments.
- Patient diary verification. If information on the patient's diary is not clear, the Investigator will ask the patient questions. The investigator may annotate the patient's diary but must date and sign the annotations.

- During the course of study drug infusion:
  - Collection of infusion parameters.
  - Vital signs measured 30-45 min and 60-75 min after the beginning of the infusion: temperature, heart rate, systolic and diastolic blood pressure.
  - Listing of concomitant medication if applicable.
  - AEs assessment.
- 30-45 min after the end of study drug infusion:
  - Vital signs: temperature, heart rate, systolic and diastolic blood pressure.
  - AEs assessment.
  - Listing of concomitant medication if applicable.

Four days after the end of study drug administration (+/- 1 day): the Investigator or the Study Nurse will call the patient in order to collect information about the possible occurrence of AEs after the patient has left the hospital.

8.2.5. Visit 7: Week 12 (+/- 7 days)

The following study procedures will be carried out:

- Before study drug course (within 24 hours before study drug course)
  - Clinical examination focused on arterial or venous thromboembolic signs.
  - Biometric information: weight.
  - Vital signs: temperature, heart rate, systolic and diastolic blood pressure.
  - Neurological status assessment:
    - INCAT disability score (adjusted INCAT disability score will be deduced from reported values).
    - Patient and Investigator CGI-S, CGI-E and CGI-I.
    - MRC sum score.

- Rasch-modified MRC sum score.
- R-ODS.
- Grip strength with Martin vigorimeter in both hands.

– Biological tests in local laboratory:
  - Haematology:
    - Complete blood count + differentials, Hb, MCV, platelets count.
    - 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).
      - Serum total IgG trough levels.
    - Urine protein reagent strip test [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 GFR in the range of 60-80 mL/min/1.73m^2]:

If urine protein reagent strip test result = Negative or Trace	Action: No further urine test required
If urine protein reagent strip test result = 1 cross (1 +) or more	Action: 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). 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) apply.

– AEs assessment.
– Listing of ongoing concomitant treatments.
– Patient diary verification. If information on the patient's diary is not clear, the Investigator will ask the patient questions. The investigator may annotate the patient's diary but must date and sign the annotations.

- <u>During the course of study drug infusion:</u>
  - Collection of infusion parameters.
  - Vital signs measured 30-45 min and 60-75 min after the beginning of the infusion: temperature, heart rate, systolic and diastolic blood pressure.
  - Listing of concomitant medication if applicable.
  - AEs assessment.
- <u>30-45 min after the end of study drug infusion:</u>
  - Vital signs: temperature, heart rate, systolic and diastolic blood pressure.
  - AEs assessment.
  - Listing of concomitant medication if applicable.

Four days after the end of study drug administration (+/- 1 day): the Investigator or the Study Nurse will call the patient in order to collect information about the possible occurrence of AEs after the patient has left the hospital.

8.2.6. Visits 8, 9 and 10: Week 15, 18 and 21 (+/- 7 days)

The following study procedures will be carried out:

- Before study drug course (within 24 hours before study drug course)
  - Clinical examination focused on arterial or venous thromboembolic signs.
  - Biometric information: weight.
  - Vital signs: temperature, heart rate, systolic and diastolic blood pressure.
- Neurological assessments:
  - INCAT disability score (adjusted INCAT disability score will be deduced from reported values).
- Biological tests in local laboratory:
  - Haematology:
    - Complete blood count + differentials, Hb, MCV, platelets count.
    - 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).
  - Serum total IgG trough levels.
  - Urine protein reagent strip test [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 GFR in the range of 60-80 mL/min/1.73m^2]:

If urine protein reagent strip test result = Negative or Trace	Action: No further urine test required
If urine protein reagent strip test result = 1 cross (1 +) or more	Action: 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). 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) apply.

- AEs assessment.
- Listing of ongoing concomitant treatments.
- Patient diary verification. If information on the patient's diary is not clear, the Investigator will ask the patient questions. The investigator may annotate the patient's diary but must date and sign the annotations.

- During the course of study drug infusion:
  - Collection of infusion parameters.
  - Vital signs measured 30-45 min and 60-75 min after the beginning of the infusion: temperature, heart rate, systolic and diastolic blood pressure.
  - Listing of concomitant medication if applicable.
  - AEs assessment.
- 30-45 min after the end of study drug infusion:
  - Vital signs: temperature, heart rate, systolic and diastolic blood pressure.
  - AEs assessment.

Four days after the end of study drug administration (+/- 1 day): the Investigator or the Study Nurse will call the patient in order to collect information about the possible occurrence of AEs after the patient has left the hospital.

8.2.7. Visit 11: Week 24 (+/- 7 days) - End of study visit

At the end of the 24-week treatment and follow-up period, patients undergo an end of study visit evaluation. This visit occurs 3 weeks after the 7th course of study drug at a dose of 1 g/kg.

In the event of premature discontinuation from the study drug or patient withdrawal from the study, an end of study visit is performed within 7 days.

The end of study assessment should be performed before any other treatment including Igs is administered.

The reason for premature study drug discontinuation / study withdrawal should be accurately assessed and entered into the eCRF.

The following study procedures will be carried out:
- Complete physical examination.
- Biometric information: weight.
- Vital signs: temperature, heart rate, systolic and diastolic blood pressure.

- Neurological status assessment:
  - INCAT disability score (adjusted INCAT disability score will be deduced from reported values).
  - Patient and Investigator CGI-S, CGI-E and CGI-I.
  - MRC sum score.
  - Rasch-modified MRC sum score.
  - R-ODS.
  - Grip strength with Martin vigorimeter in both hands.

- Biological tests in local laboratory:
  - Haematology:

        - Complete blood count + differentials, Hb, MCV, platelets count.
        - Haptoglobin.
        - Reticulocytes, direct Coombs test
    - 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, ALP, γGT.
        - Total serum protein level.
        - C3 and C4 antigens.
        - Serum total IgG trough levels.
    - HBs Ag, anti HBs & anti HBc Ab, HIV, HCV tests.
    - Serum reference sample for long term storage.
    - Urine protein reagent strip test [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 GFR in the range of 60-80 mL/min/1.73m^2]:

If urine protein reagent strip test result = Negative or Trace	Action: No further urine test required
If urine protein reagent strip test result = 1 cross (1 +) or more	Action: 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).

        - Urine Pregnancy test for female patients of child bearing potential.

- Analysis at centralised laboratory:
    - BAFF.
    - CH50.
    - Anti-CNTN1 and anti-NF155 antibodies.

- Ultrasonography coupled to neurophysiology (for Italian sites only).

- AEs assessment.
- Listing of concomitant treatments.
- Patient diary verification. If information on the patient's diary is not clear, the Investigator will ask the patient questions. The investigator may annotate the patient's diary but must date and sign the annotations.

8.3. <u>At any course</u>

In case of suspected clinical venous thrombosis: D-Dimers testing will be performed.

In case of suspected haemolysis based on biological tests (Hb, haptoglobin, LDH, total and free bilirubin levels (total bilirubin in all patients; if total bilirubin > ULN, free bilirubin will be assessed from the same blood sample, as total bilirubin)): Reticulocytes and direct Coombs test will be performed.

8.4. Central biological handling sampling

Details for blood sampling performed for the biomarkers (anti-CNTN1 and anti-NF155 antibodies, BAFF, CH50, FcγRIIB), storage and shipment to the central laboratory are described in the laboratory manual.

8.5. Ultrasonography (for Italian site only)

Details for ultrasonography coupled to neurophysiology examination are described in the ultrasonography manual.

8.6. Compliance with the study plan

The Investigator should make every effort to comply with the study plan. If the Investigator encounters difficulties in complying with the study plan, e.g. with regard to the schedule of visits or the required procedures, he/she must alert the Sponsor. The Sponsor may consider it relevant to generate an amendment.

The Investigator should make every effort to avoid the occurrence of deviations from the study plan. If deviations occur or if the Investigator knows that a deviation will occur, he/she must promptly inform the Sponsor to determine how to manage the deviation.

9. SAFETY

9.1. Reference Safety Information Document

The current version of the Investigator Brochure of I10E, will be the Reference Safety Information document to assess the expectedness of AEs.

9.2. Benefit / Risk Information

9.2.1. Potential risk(s) related to the study drug

Common and important adverse reactions associated with IVIg administration are described in the European Guideline EMA/CHMP/BPWP/94038/2007 rev.4 of IVIg [14].

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally with IVIg.

Rarely human normal Ig may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic reaction, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses have been described.

Important potential risks that could be anticipated with I10E administration are those known with IVIg preparations:

Hypersensitivity
True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.
Rarely, human normal immunoglobulins can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulins.
To minimize risk of anaphylactic reactions, patients with IgA deficiency will be excluded, except if the absence of anti-IgA antibodies is documented [37] [38]. The patients with a known hypersensitivity to the active substance or to any of the excipients of I10E will be excluded.

Thromboembolism
There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses. Such an association is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulins in at-risk patients.
To minimize the risk of thromboembolic events, patients with a history of venous thromboembolic disease, myocardial infarction or cerebrovascular accident will be excluded. As well, patients with uncontrolled cardiac arrhythmia and patients with unstable ischemic heart disease will not be allowed to participate to the study.

Acute renal failure
Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified. These included pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products and age over 65.
To minimize the risk of acute renal failure, patients with a chronic kidney disease (CKD) defined as abnormalities of kidney structure or function, present for >3 months, with implications for health, i.e. patients with persistent albuminuria category A3 and/or GFR <60 mL/min/1.73m^2 (measured according to the MDRD calculation) will be excluded [39].
The use of loop diuretics is also not allowed if used within 24 hours prior to study drug administration.

Aseptic meningitis syndrome (AMS)
Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment.
Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. AMS may occur more frequently in association with high-dose of IVIgs.

Haemolytic anaemia
IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration.
Haptoglobin and LDH levels in patients will be assessed at every visit.

Interference with serological testing
After injection of immunoglobulin the transitory rise of various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT), direct Coombs' test.

Interaction with other medicinal products
I10E may impair the efficacy of live attenuated virus vaccines for a period of up to 3 months. In the case of measles, this impairment may persist for up to 1 year.

Transmissible agents
Despite dedicated effective measures to prevent infections resulting from the use of plasma-derived products including selection of donors, screening of individual donations and plasma pools, as well as effective manufacturing steps for the inactivation/removal of viruses, the risk of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
Patient serum reference samples will be drawn at the beginning and at the end of the study, and will be kept for long term storage.

9.2.2. Potential risks related to the study procedures

Blood sampling will be performed during this study in order to monitor the safety. Although this procedure represents an inconvenience for the patient, it does not constitute an additional significant risk.

There is a minor risk of haematoma from intravenous infusion of the study drug and from drawing blood. Slight pain at the injection site, feeling light-headed, bruising and, exceptionally, infection as well as bleeding from the site of the puncture may occur.

9.3. Risk minimisation actions throughout the protocol

Some adverse drug reactions may be related to the infusion flow rate. Patients will be closely monitored and carefully observed for any symptoms throughout the infusion periods. In the case of AE, the infusion rate may be reduced or even stopped. Standard medical care should be implemented as necessary.

Potential complications will be avoided by ensuring that patients:
- have an adequate hydration status prior to infusions of the study drug;
- are not sensitive to human normal Ig by initially infusing the product slowly, starting at 0.5 mL/kg/h during the first 30 minutes;
- are carefully monitored for any symptoms throughout the infusion period and 30-45 minutes after the end of each infusion. An additional phone call at 4 days (+/- 1 day) from the Investigator or the Study Nurse to the patient is planned to ask if AEs or TAAEs are reported within 72 hours (+/- 1 day) after the end of each course;
- Close Monitoring (vital signs, biological tests, haematological tests, physical examinations planed for each course to minimise these risks);
- Haematology (96h after the end of the first course): complete blood count + differentials, platelets count, MCV and haptoglobin;

- Biochemical (96h after the end of the first course): creatinine, glomerular filtration rate according to MDRD formula, total and free bilirubin tests (total bilirubin in all patients; if total bilirubin > ULN, free bilirubin will be assessed from the same blood sample, as total bilirubin);
- D-Dimers, in case of suspected thrombus;
- Reticulocytes and Direct Coombs test, in case of haemolysis based on biological tests (Hb, haptoglobin, LDH, total and free bilirubin levels (total bilirubin in all patients; if total bilirubin > ULN, free bilirubin will be assessed from the same blood sample, as total bilirubin).

9.3.1. Benefit/Risk Balance

I10E have been developed by LFB and manufactured from plasma pools which are EMA certified.

Marketing Authorization Application (MAA) was submitted in Intravenous Immunoglobulin (IVIg) Core Summary of Product Characteristics (SPC) indications through the Decentralized Procedure (DCP) in the following European Union Member States: Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Italy, Luxembourg, the Netherlands, Spain, Slovakia, Sweden, and the United Kingdom. The first marketing authorization was granted in the United Kingdom in August 2015, then in Denmark, Germany, Hungary, Belgium and Finland.

This study is designed according to the currently accepted scheme of the standard of care of CIDP, based on the clinical guideline (EFNS/PNS CIDP Guideline 2010, First revision) which is in line with European countries' recommendations and the recommendations of EMA.

IVIg are used in CIDP patients and have shown a favorable benefit/risk balance.

I10E has already been assessed in two pivotal studies: I10E-0718 and I10E-0719, respectively in PID and ITP, in 100 patients. Both studies concluded to a comparable safety profile with IVIg preparation. The I10E doses recommended in this protocol will not exceed those used in current medical practice in this indication, in the before-mentioned clinical trials. Participation in the study is not expected to induce significant additional risk for patients.

9.4. Alternative therapeutic management - handling emergencies

- If allergic or anaphylactic-type reactions occur, the infusion must be stopped immediately and standard medical treatment must be implemented.
- In case of misuse and/or overdose, appropriate corrective actions should be promptly undertaken when possible. The patient should be followed-up until the assurance that no AE occurs is obtained.

9.5. Definition and reporting of (serious) adverse events

9.5.1. Definition of Adverse Event and Serious Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject to whom a medicinal product is administered. The occurrence does not have necessarily a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), any symptom or disease, whether new or exacerbated, temporally associated with the use of a medicinal product, whether or not related to the investigational drug product.

An AE, whether or not considered to be causally related to the investigational drug product, may be:

- The deterioration of a pre-existing chronic disease or aggravation of a symptom or disease that was present at inclusion of the patient in the study.
- A symptom or disease discovered after the start of the study even if it was probably present prior to the patient's inclusion.
- Abnormal laboratory findings when they are considered as clinically significant by the Investigator.

In case a vital sign shows a clinically significant abnormality, an AE should be reported (or the abnormal vital sign should be linked to an already reported AE). A serious AE is an AE that, at any time, fulfils one or more of the following criteria:

- results in death,
- is life threatening (the patient was at risk of death at the time of the event; it does NOT refer to an event which hypothetically might have caused death if it were more severe),
- requires in-patient hospitalisation or prolongation of existing hospitalisation - hospitalisation required by the study will not be considered as an AE,
- results in persistent or significant disability/incapacity (substantial disruption of a person's ability to carry out normal life functions),
- is a congenital anomaly/birth defect,
- is any important medical event that may not be immediately life threatening or result in death or hospitalisation but, based upon appropriate medical judgment, may endanger the patient or may require intervention to prevent one of the other outcomes listed in the definition above, and should also be reported in the same way as an SAE. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Distinction should be made between serious and severe AEs. Severity is a measure of intensity whereas seriousness is based on the outcome or the action criteria described above, for example, nausea that persists for several hours may be considered as severe, but not as an SAE. On the contrary, a cardiovascular event that causes limited degree of disability may be considered as not severe but would be recorded as an SAE.

- Events initially reported as an AE may become serious. For example, diarrhoea may become debilitating and require hospitalisation or prolongation of hospitalisation and is then reported as an SAE.
- Surgical intervention is not to be considered as a SAE but the medical condition requiring the surgery is to be reported as such.
- If a medical condition known before the start of study treatment requires hospitalisation for planned surgical measures, it should not be considered as an AE. However, the medical condition should be reported in the medical history.
- Occurrence of study drug misuse/abuse, overdose or drug dependency, whether or not associated to an adverse event, must be recorded, reported immediately to the Sponsor.

9.5.2. Definition of specific events in the study (if applicable)

A worsening of the CIDP will not be regarded as an AE (or a SAE) and will be recorded in specific eCRF forms. These data will be analysed as part as the efficacy assessment.

9.5.3. Adverse Event recording and reporting

Period of (Serious) Adverse Event Data Collection:

In order to ensure complete safety data collection, recording and reporting, all (S)AEs occurring during the study, i.e. after signature of the Informed Consent, must be recorded, even if no study drug was administered. These include all AEs occurring, recurring, or worsening after the signature of the informed consent. The period of observation for the study is from the screening visit to the end of study visit.

If the Investigator becomes aware, after that period, of any unusual safety information or any safety information that appears to be drug related involving a patient who had participated in the study, even after the patient completes the study, he/she should contact the sponsor to determine how it should be documented and reported.

Recording and Description of (Serious) Adverse Event:

All AEs occurring after signature of the informed consent until the end of study visit will be recorded in the appropriate pages of eCRF, including AEs occurring during the screening period and before the first administration of study drug, other than baseline findings which will be recorded as medical history.

Each individual AE is to be listed as a separate entry on the eCRF AE form. The Investigator will provide information on dates of onset and resolution, seriousness, severity, frequency, action(s) taken with regard to corrective therapy or to the study drug, outcome and relationship to the study drug. The Investigator must report to the Sponsor or its designee all AEs that occur during the study from the time the written informed consent is given until the EOS visit or premature termination, regardless of their relationship to the study drug. Apart from AEs clinically observed by the Investigator, the patient will be given the opportunity to report AEs spontaneously. A general prompt will also be given to detect AEs, e.g. “Did you experience any illness or unusual symptom since your last visit?”

Follow-up of Adverse Events:

All AEs and SAEs assessed as not related to study medication, including clinically significant laboratory tests or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

AEs or SAEs assessed as related to study drug will be followed for as long as necessary to adequately evaluate the subject’s safety, or until the event stabilizes, or the subject is lost to follow up. If resolved, a resolution date should be provided.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional clinical laboratory testing or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

If a patient is withdrawn from study due to safety reasons, he/she should be followed until the event disappears, is otherwise explained or the patient's condition has stabilised.

Any patient who voluntarily withdraws from the study should be carefully questioned for the possible occurrence of an adverse event. Whenever possible, a patient should be followed through the last scheduled visit.

If no follow-up information can be provided after all efforts and attempts, the Investigator must document the outcome as "unknown" and provide a justification.

9.5.4. Procedures for reporting Serious Adverse Events, Pregnancy and overdose/abuse/misuse.

9.5.4. 1. SAE

The Sponsor or its representative must be informed immediately, and no later than 24 hours, of receipt of the SAE information by the site.

If one or more seriousness criteria is fulfilled, the Investigator must promptly forward to the Sponsor or its representative a duly completed "SERIOUS ADVERSE EVENT NOTIFICATION FORM" provided by the Sponsor, even if the data are incomplete or if it is obvious that more data will be needed in order to draw any conclusions, but as soon as the minimum of following information is present:

- identification of the notifying person,
- identification of the clinical study,
- identification of a patient (patient number and/or initials),
- description of the SAE and relationship to the study drug.

After the initial SAE report, the Investigator is required to proactively follow each patient and to provide further information on the patient's condition. The Investigator will ensure that follow-up includes any further investigations as may be indicated to elucidate the nature or the causality of the SAE.

Supporting documentation (discharge summaries, all examinations carried out, etc.) will not be sent systematically, as all relevant information must appear and be summarized in the narrative of the SAE report. However, if judged important, the Investigator could send these documents or LFB could request them (all documents must be blinded with respect to the subject's name). Any follow-up information must be reported within the same timelines.

TIMEFRAME

"Initial" SAE form	**"Follow-up" SAE** form
IMMEDIATELY **and no later than 24 hours** as of awareness of the SAE	**IMMEDIATELY** **and no later than 24 hours** as of availability of essential follow-up information

FAX TRANSMISSION

The SAE reports should be faxed to the following fax number: [redacted] The sites in Tunisia can use the e-mail address: [redacted].

In rare circumstances, when fax transmission is not possible, reporting by telephone is acceptable, but this should be followed with a completed "SERIOUS ADVERSE EVENT FORM" signed and faxed by the Investigator as soon as possible.

9.5.4. 2. Suspected Unexpected Serious Adverse Reactions (SUSARs) reporting

The Sponsor will ensure that all relevant information about SUSARs are reported to the competent authorities and to relevant ehtics commitees in compliance to the European Directive 2001/20/EC or the national regulatory requirements in all the participating countries.

9.5.4. 3. Pregnancy

If a female patient becomes pregnant during the study, she must be withdrawn from study drug administration as soon as pregnancy is known and intake of the study drug must be discontinued immediately.

The Investigator should:

- collect the name and the contact of the physician/obstetrician following the patient during pregnancy
- complete the "PREGNANCY FORM" provided by the Sponsor
- and fax it to the latter as soon as possible.

FAX TRANSMISSION

The PREGNANCY FORM should be faxed immediately and no later than 24 hours to the following number: [redacted] the sites in Tunisia can use the e-mail address: [redacted] The progression of the pregnancy will be followed up by the Sponsor in collaboration with the Investigator or the patient physician and/or obstetrician.

The pregnancy must be followed up to determine outcome, including spontaneous abortion or voluntary termination, details of birth and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

9.5.4. 4. Overdose/abuse/misuse

Occurence of misuse, overdose or any medication error, whether or not associated to an adverse event, must be reported to the sponsor via the adverse event page of the eCRF.These special situations should be reported as SAEs only when fulfilling SAE criteria or associated with an SAE.

9.5.5. LFB BIOTECHNOLOGIES Medical Contacts

For urgent medical matters or questions, the Investigator may contact:

EXECUTIVE VP, GLOBAL MEDICAL AND CLINICAL DEVELOPMENT	[redacted]
Phone number	[redacted]
[redacted]	[redacted]
Location	**LFB BIOTECHNOLOGIES** 3, avenue des Tropiques, BP 40305 91958 Coutaboeuf Cedex FRANCE
Clinical Research Physician	[redacted]
Phone number	[redacted]
E-mail address	[redacted]
Clinical Research Physician	[redacted]
Phone number	[redacted]
E-mail address	[redacted]
Location	**LFB BIOTECHNOLOGIES** 3, avenue des Tropiques, BP 40305 91958 Courtaboeuf Cedex FRANCE

10. ASSESSMENT OF EFFICACY AND SAFETY

10.1. Assessment of Efficacy

10.1.1. Primary Assessment

The INCAT disability score will be assessed by the Investigator at screening, before each study drug course throughout the study and at the end of study assessment. The adjusted INCAT disability score will be deduced from the reported values.

The INCAT disability score measures the disability of both upper and lower limbs, each with a score from 0 (normal) to 5 (maximal disability) [32]. The total score may vary from 0 to 10. The adjusted and original INCAT disability scales are presented in Appendices 20.1.1 and 20.1.2.

10.1.2. Secondary efficacy assessments

Secondary assessments are:

- 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) and Rasch-modified MRC (0 to 3).

Analyses and time of assessments are described in Section 12.9 Efficacy analysis.

10.2. Assessment of Safety

The Investigator will ensure that all the AEs occurring during the study are identified and documented in the eCRF. The identification of AEs may come from various sources:

- The Investigator or nurse may clinically observe an AE in the patient at hospital.
- The patient may spontaneously report an AE to Investigator or Nurse.
- From baseline to EOS, the patient will have to document on a patient diary any AE that occurs outside the hospital. This diary will be verified at each visit by the investigator. The patient will be sensibilised to report carefully day and time of TAAEs.
- At each visit the patient will be given a general prompt, e.g. “Did you experience any illness or unusual sign or symptom since your last visit?” in order to ensure that no AE has been forgotten.
- Vitals signs, including systolic and diastolic blood pressures (mmHg), heart rate (beats/minute), and body temperature (°C) will be measured before each infusion, during infusion (30-45 min and 60-75 min after the infusion start) and 30-45 minutes after the end of infusion and will be recorded in the eCRF. Weight will also be recorded before each study drug course, as it is used to calculate the quantity of study drug to be infused.
- Biological tests will be performed at the screening, before each study drug course, 4 days after the first study drug course and at the end of study assessment. Clinically significant abnormality in physical examination or biological tests performed at the screening as per study protocol will be regarded as a medical history.
- The Investigator or a Study Nurse will call the patient 4 days after each treatment course in order to collect information about the possible occurrence of an AE after the patient has left the hospital. The purpose of this phone call is to ensure that all the temporally associated AEs (TAAEs) are tracked.
- If a TAAE is reported by the patient during the phone call, the Investigator will ask the patient additional information at the next visit. If relevant; the Investigator will report the TAAE in the eCRF.

It is the responsibility of the Investigator to collect all the relevant information regarding identified AEs.

11. DATA MANAGEMENT

11.1. eCRF completion guidelines

The following is a general description of the eCRF completion guidelines for this study. For complete details please refer to the eCRF completion guidelines included in the eCRF.

11.1.1. Introduction

All of the information required to be reported to the Sponsor as per protocol will be transcribed in the eCRFs for each study patient. The eCRFs will be completed by the Investigator or any study centre staff designated by the Investigator. The access to the data at the clinical site will be restricted and monitored through the system software with its required log-in security procedures. The Investigator will be responsible for ensuring that data recorded in the eCRFs are complete, accurate and legible. All eCRFs should be filled in before review by the Monitor.

11.1.2. General instructions

11.1.2. 1. Overview

eCRFs should be completed in English.

All data will be recorded in the eCRFs. The eCRF is a web based application linked to a computerized system that allows creating, modifying, maintaining, archiving, retrieving, or transmitting data.

Access to the eCRF must be limited to authorised individuals. In this way, each Investigator and each person, authorised to have access to the eCRF, will receive an individual user login and a unique password before the study start and after having completed a specific training. Different accesses will be limited according to individual profiles. Therefore individuals must only work under their own logins and passwords, and must not share these with others. The attributed password should be changed at the first log in.

Individual training:

It will be the responsibility of the Sponsor to organize an individual training and certification for all persons who will use the computerised system. In order to have their login and password, each person should perform this training.

All data in the eCRFs must come from and be consistent with the source documents - i.e. patient's file or medical records - except the neurological scales which are performed for the specific purpose of the study and for which source data worsheets will be provided as source documents.

Source documents may therefore be:

- The patient's medical file
- The nurse's sheets
- Laboratories results sheets
- Specific worksheets provided for neurological scales assessment
- Any other document issued in the routine practice of healthcare and providing information on the medical status of the patient.

Any discrepancy between data in the eCRF and those in the source documents should be documented by the Investigator through a query.

11.1.2. 2.Patient identification

Patients will be identified on each page of the eCRF by their patient number: patient number will be composed of 4 digit numbers (see Section 8.1.3 Patient allocation). Patients with screening failure will have an eCRF completed.

11.1.2. 3.Confidentiality

Patient identity must be kept confidential and should not appear on any eCRF form or study-specific documents.

11.1.2. 4. eCRF Completion

The Investigators should complete the eCRF as soon as possible (within 5 days) after each patient's visit. The Investigator or the delegated study site staff will complete all applicable forms in the eCRF. All data should be completed and missing data will be documented.

Specific instructions for completing the eCRF will be detailed in a specific guide.

11.1.2. 5. eCRF Completion in case of screening failure or premature withdrawal

In case of a screening failure, the Investigator will complete the relevant forms of the eCRF, including AE page and concomitant medication page if applicable.

In case of a premature withdrawal after the first study drug course, all study data available up to the point of withdrawal must be recorded on the eCRF, as well as any new AE or modifications to existing AEs and/or concomitant medications. The end of study assessment will also be completed.

11.1.2. 6. eCRF corrections

To ensure and to protect the authenticity, the integrity and the confidentiality of electronic records an audit trail will be integrated to the eCRF. All entries and all changes will be tracked in an audit trail. The audit trail is a secure, computer-generated, time-stamped system which independently records the date and time of operator entries and actions that create, modify or delete electronic records.

11.2. eCRF and Data Handling

Data management will be carried out by a Contract Research Organisation (CRO) from electronic-based CRF and in accordance with Good Clinical Practices (GCP see ICH-E6).

Throughout the study, the data will be stored in servers located in the United States of America. All transfers will be validated.

Helpdesk services for all investigators and staff will be available 16/24 hours and 5/7 days. Training will be provided to the investigators and staff.

The data handling documents, e.g. annotated eCRF, database structure, data entry manual, coding rules and computerized validation system, are defined in a Data Management Plan.

The database and data entry screens will be created in software specifically designed for clinical data management in compliance with ICH-E6 requirements.

The tracking of the eCRF will be integrated to the computerized system. As soon as a patient has signed his informed consent, the Investigator will create the patient in the e-CRF and will complete the appropriate form(s).

The consistency of data will be checked by computerised programs and related queries will be generated for resolution by the Investigator. In case of abnormality, Electronic Data Clarification Forms (DCFs) will be generated through the eCRF platform for resolution by the Investigator.

Medical coding will be done using Medical Dictionary of Regulatory Activities (MedDRA) for all medical terms (medical history, AEs) and World Health Organisation (WHO) drug for all drug names (prior and concomitant medications).

Quality controls to ensure the overall quality and consistency of the database and reconciliation of SAE reports with the Pharmacovigilance database will also be carried out.

At the end of the data handling process, a final data review meeting will be held in order to prepare the database lock. After database lock, data will be transferred into SAS format for the production of statistical analyses.

Data processing, from data capture through database lock, will be carried out in accordance with GCP-ICH-E6.

12. STATISTICS

12.1. Trial Objectives and Design

The main objective of this study is to assess the efficacy and the safety of I10E in CIDP patients. The design is a phase III, international, multicentre, single arm, open-label prospective study.

12.2. Statistical Analysis Plan

This section is the basis for the Statistical Analysis Plan (SAP) of the study.

The detailed technical aspects of the statistical analyses will be provided in the SAP. The SAP will possibly take protocol amendments into account and adapt to unexpected issues raised by the study running and/or data that affect planned analyses in the protocol.

Any changes from the protocol will be discussed in the clinical study report.

Prior to locking the database, a data review meeting will be planned in order to review individual data and validate the SAP.

12.3. Sample Size Determination

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 [10]. 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 a 10% non-evaluable patients, 42 patients will be included in the study (around one third of all patients will be either Ig-naïve or relapsing Ig-pretreated).

12.4. Randomization

Not applicable

12.5. Protocol Deviations and Analysis Sets

All deviations from protocol definitions will be listed and defined as major or minor deviations in the SAP.

The definition of analysis sets is as follows:

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

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.

12.6. General rules for handling of missing or inconsistent data

No general rules for the replacement of missing data are planned. Every effort should be made to collect the study parameters over the study period.

12.7. Demographic and baseline characteristics

All baseline characteristics and baseline efficacy variables will be summarised using descriptive statistics on relapsing Ig-pretreated patients, Ig-naive patients and overall. All summary tables will describe the variables according to their nature:

- Categorical variables (binary, nominal and ordinal) will be summarised by contingency tables (frequencies and percentage),
- Quantitative variables will be summarised by their mean, standard deviation, median, minimum and maximum values.

12.7.1. Previous Treatments

All previous treatments will be classified using the ATC codes and summarised.

12.8. Study drug and concomitant treatments

All variables will be summarised for the subgroups of relapsing Ig-pretreated patients and Ig-naïve patients as well as overall.

12.8.1. Extent of Exposure

The duration of treatment exposure will be assessed as from the first day of study drug administration to the EOS assessment.

The number of infusions, cumulative dose (g and g/kg), volume infused, duration of infusion, infusion rate (initial rate and maximum rate) will be described using descriptive statistics. The treatment exposure will also be listed for each patient.

12.8.2. Treatment Compliance

The following compliance criteria will be described:

- Prescribed course dosage included in the ranges allowed by the protocol
- Course frequency included in the ranges allowed by the protocol
- Courses administered at each visit.
- Ratio administered dose / prescribed dose within 20%.

12.8.3. Concomitant Treatment

All concomitant treatments as defined in Section 7.2 Concomitant medication will be classified using the ATC codes and summarised.

12.9. Efficacy Analysis

All efficacy endpoints will be analysed overall and by subgroups of relapsing Ig-pretreated patients and Ig-naive patients.

12.9.1. Primary Efficacy Variable(s)

12.9.1. 1. Description of the primary efficacy variable(s)

The primary efficacy endpoint will be the responder rate at EOS visit.

Responder patients are defined as patients with a decrease of at least 1 point in the adjusted INCAT disability score between baseline and the EOS visit.

If a patient is treated with a not-allowed treatment during the study period, then all efficacy variables measured after the intake of these not-allowed treatments will be censored for the efficacy analyses.

12.9.1. 2. Hypothesis Test and Primary Analysis Model

The responder rate will be tested against the historical responder rate of 33.3% with a one-sided Clopper-Pearson test (exact binomial test) at the nominal level of significance of 2.5%.

The null and alternative hypotheses are as follows:

H0: $\pi_{(I10E)} \leq 33.3\%$

Ha: $\pi_{I10E)} > 33.3\%$

The proportion of responders and the associated 95% confidence interval will be estimated using a Clopper-Pearson method. The primary analysis will be performed on the FAS.

12.9.1. 3. Handling of Missing Data

The primary analysis of the primary criterion will be done using the baseline and last available assessment of the adjusted INCAT disability score after the first study drug administration. 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. Other imputation methods might be defined in the SAP for the purpose of sensitivity analyses.

12.9.1. 4. Prognostic factors and covariates

No prognostic factors will be used in the statistical model.

12.9.1. 5.Other analyses for the primary variable

The analysis of the primary criterion will be repeated on the PPS as sensitivity analyse.

Other sensitivity analyses might be defined in the SAP.

12.9.2.Secondary efficacy variables

12.9.2. 1.Description of secondary efficacy variables

- Responder rate at 12 weeks.
- Time to response.
- Percentage of patients at 12 weeks and EOS visit with no change in CIDP treatment.
- 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) and Rasch-modified MRC (0 to 3).

12.9.2. 2.Analysis of secondary efficacy variables

All parameters as well as the change from baseline will be summarised using Hodges-Lehmann point estimates and corresponding confidence intervals. Time to response will be analysed using a Kaplan-Meier method.

If a patient is treated with a not-allowed treatment during the study period (Plasma exchange, blood products or derivatives other than the study drug, immunomodulatory/immunosuppressant agents, corticotherapy, if administred with an increasing dosage or introduced orally or systematically at a dose higher than 10 mg daily prednisolone or equivalent), then all adjusted INCAT disability scores measured after the intake of these not-allowed treatments will be censored for the efficacy analyses.

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.

The 12-week and the EOS visit values will be compared to the baseline value using appropriate statistical tests. A significance level of 5% (two-sided) will be applied.

The adjusted INCAT disability score will additionally be presented graphically over the patients' follow-up during the study.

12.10. <u>Safety Analysis</u>

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

12.10.1. Adverse events

All AE will be classified using MedDRA including Lowest Level Terms (LLT), Preferred Terms (PT) and System Organ Class (SOC).

TEAEs defined as AEs occurring after the start of the 1st study drug administration will be analysed. Other AEs will only be listed.

The absolute number of TEAEs as well as the number of patients with at least one TEAE will be tabulated by SOC and PT. Patients with SAEs, drug-related AEs will be analysed by SOC and PT.

The duration of the TEAE and the time between the last administration of study drug and the onset of the TEAE will be calculated.

TAAEs will be analysed by patients and infusions.

12.10.2. Vital signs

Vitals signs, including body temperature (in °C), heart rate (in beats/minute) and systolic and diastolic blood pressures (in mmHg), will be measured before each infusion, during infusion (30-45 min and 60-75 min after the beginning of infusion) and 30-45 minutes after the end of infusion for all visits. Descriptive statistics will be performed.

All abnormalities in vital signs, clinically significant or not, will be listed.

12.10.3. Laboratory data

Laboratory data will be assessed at screening, before each study drug course, after the 1st study drug course, and at the EOS visit. Shift tables will be produced by study drug courses and baseline. Descriptive statistics will be performed. All abnormalities, clinically significant or not will be listed.

12.11. Exploratory Analysis

The following exploratory endpoints will be analysed:

- Anti-CNTN1 and anti-NF155 antibodies titers at screening and 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 study drug administration.
- Change from baseline to EOS visit in nerve conduction velocities, distal latencies, amplitude of the negative phase of compound muscle action potentials and F wave for the following peripheral nerves: median nerve, ulnar nerve and deep fibular nerve (F wave assessed on ulnar nerve only).
- Change from baseline to EOS visit in nerve maximal/minimal cross section area (CSA), intra-nerve and inter-nerve variability and ultrasound (USG) immune-related classification (see Section 1.4.4 Peripheral nerve ultrasonography) in the following peripheral nerves: median nerve, ulnar nerve, fibular nerve and sural nerve.

All exploratory variables will be described in summary tables. The relationship between these variables and clinical response will be explored and detailed in the SAP.

13. STUDY REPORT

A clinical study report will be prepared in accordance with the ICH-E3 guidelines by the Sponsor.

Within 1 year after the end of the study, the Sponsor will provide the Health Authorities with the full study report or summary. Only the Sponsor is entitled to make the study report available to the Authorities.

Neither the complete report nor any part of the study report should be used without the approval of the Sponsor.

14. CONFIDENTIALITY AND PUBLICATION

14.1. Patient confidentiality

Patient data will be kept strictly confidential and patient anonymity will be protected by using number codes.

The Sponsor or its representative(s) and the Health Authorities are obligated to respect medical secrecy and to refrain from divulging any personal patient information they might fortuitously be aware of.

14.2. Use of information

The Investigator shall not divulge unpublished data or information related to the study provided by the Sponsor, including but not limited to the study protocol, eCRFs, assay methods and scientific data, to any third party without written approval from the Sponsor.

In addition, any new information that may become available during the course of the study shall be considered as confidential and shall not be used for any purpose other than the performance of the clinical study.

The study data are the property of the Sponsor. The Investigator and any of the research staff shall obtain written approval from the Sponsor prior to the publication/communication of the results of any work carried out during or in relation to the study.

Publication and/or communication of the results of the clinical study will be of a cooperative nature involving authors representing the Sponsor, the Investigators and the scientific committee.

The Sponsor reserves the right to request modification of the content and/or timing of any publication or presentation if a patent application, an existing patent or other proprietary rights may be jeopardized.

Authorship of any publication related to the study and the order of presentation of the authors' names shall be approved by the Sponsor. The Sponsor shall not use an Investigator's name in any publication without his/her written permission and vice versa.

15. ARCHIVING

The Investigators should retain all essential study-related documents, i.e. documents which permit evaluation of the conduct of a study and the quality of the data produced, in accordance with the applicable regulatory requirements of his/her country. These essential documents include but are not limited to signed protocol, eCRFs, medical records, laboratory reports, informed consent forms, drug disposition records, safety reports, information regarding participants who discontinued, and other relevant documents and data.

The study-related documents should be kept together in the Investigator site file provided to the Investigator by the Sponsor.

Sufficient information about the identity of all study patients, e.g. name, medical records number, patient number and study number, should be retained by the Investigator so that any Sponsor representatives, auditors or inspectors may access this information when required.

The investigator must retain all records until at least 2 years after the last approval of a marketing application in an ICH region for the Study Drug for the indication which is being investigated, or 40 years after the database locked, whichever is longer, or longer if required by specific local requirements.

The Investigator will contact the Sponsor for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any of them.

The Investigator will also notify the Sponsor should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

All records should be kept in a secure area. However, in the cases of audit or inspection, they should be rapidly made available.

16. RESPONSIBILITIES OF PARTICIPANTS

16.1. Responsibilities of the Investigator(s)

The Investigators will conduct the study in accordance with Good Clinical Practices, all applicable laws in the country where the study is conducted and in accordance with this study protocol.

The responsibilities of the Investigators are summarised below but not limited to:

- **Patient information and consent**

  Prior to undertaking any study-related procedure, it is the responsibility of the Investigator, or a formal designee, to provide each patient and/or a legal representative/witness, with relevant, comprehensive, verbal and written information, including the written information which received approval or a favourable opinion from the IEC/IRB and the Health Authorities.

  Signed informed consent must be obtained prior to undertaking any study-related procedure. Obtaining of consent and how it was obtained must be described and documented in the patient's file.

- **Information on the overall results of the study**

  Pursuant to the French "Patient's rights" law adopted on 9 August 2004, the Investigator must provide any patient who so requests it with the overall results of the study, once it is completed. The Sponsor will provide the Investigator with the overall results beforehand.

  The Investigator should document in the patient's file the fact that the information has been provided.

- **Information to other practitioners (if relevant)**

  In agreement with the patient, the Investigator will formally inform other practitioners of the patient's participation in the study, to avoid any interference or bias in the conduct of the study.

- **Independent Ethics Committee (IEC)**
  In accordance with local regulations, the Investigator may be required to interface with the IRB/IEC.

- **Adverse events**

  The investigator is responsible for ensuring adequate safety monitoring and follow-up of the study patients.

  The Investigator must report and handle any serious and non-serious adverse event, whether clinically observed or spontaneously reported by the patient, using concise medical terminology in accordance with Section 9 of the protocol.

- **Data recording**

  It is the Investigator's responsibility to ensure, on an on-going basis, completion and validation of all case report forms as well as study-related supportive data. eCRFs must be signed by the Investigator. If the Investigator formally delegates completion of the eCRFs, the Investigator nevertheless has the final responsibility for signing the eCRFs to certify the accuracy and reliability of the data recorded therein.

- **Record retention**

  To enable inspections and audits from Health Authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients, i.e. sufficient information to link records, all original signed informed consent forms and detailed records of treatment disposition. An electronic copy of eCRFs will be provided by the Sponsor to be retained and archived at site. The Investigator should maintain a site file with all essential documents.

  See also Section 15 Archiving

- **Use of study-related information**

  The Investigator is obligated to provide the Sponsor with complete test results and all data derived from the study.

  Only the Sponsor may make information available to physicians, Health Authorities and/or patients enrolled in the study, except as required by local regulations.

- **Study drug**

  Responsibility for study drug accountability at the study centre rests with the Investigator or with the institution, depending on local regulations.

- **Quality control**

  The Investigator and the relevant personnel should be available during monitoring visits and possible audits or inspections and ensure that sufficient time is devoted to the process.

  The Investigator guarantees the Sponsor or its representative and appropriate Health Authorities direct access to source documents.

- **Study discontinuation**

  Should the Health Authorities or the Sponsor decide to discontinue the study prematurely for any reason, the Investigator must promptly, contact all participating patients so they can be appropriately followed-up. All study supplies must be collected and all electronic case report forms must be completed as fully as possible.

- **Liability and insurance**

  Liability and insurance provisions for this study are set out in separate agreements.

- **Delegation of Investigator duties**

  The Investigator can delegate tasks to the research team but he/she remains responsible for coordinating and informing his/her staff about the protocol and the possible changes made to it.

  The Investigator should ensure that all persons assisting with the study are adequately qualified, and are informed about the study protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions.

  The Investigator should maintain a list of appropriately qualified persons to whom significant study-related duties will be delegated. The list is to be kept up-to-date.

  The Investigator should supply a dated and signed, up-to-date curriculum vitae (CV) in English, together with a list of his/her collaborators responsible for the operational conduct of the study. These collaborators should also provide a recent dated and signed English version of their CVs.

- **Study agreement discontinuation**

  During the study, if events such as retirement, promotion or relocation prevent the Investigator from conducting the study as agreed, the Investigator should appropriately transfer his/her responsibilities, knowledge and documents to another willing individual, with the agreement of the Sponsor. Study specific contracts must be signed between the Sponsor and the newly assigned person.

16.2. Responsibilities of the monitor

Instructions for monitoring will be developed in a monitoring plan.

The responsibilities of the study Monitor are defined in ICH-E6, Chapter 5. The Monitor, who is mandated by the Sponsor, must ensure that the study is conducted in accordance with Good Clinical Practice guidelines and all applicable local laws, and that the rights, the security and the well-being of the patients are respected.

During the conduct of the study, the Monitor reports any deviations or persistent poor compliance with the study requirements and the Sponsor makes decisions about appropriate corrective actions.

- **Communication**

  The Monitor is the main line of communication between the Investigator and the Sponsor.

- **Training**

  The Monitor must present the protocol and all procedures related to the study during the study set-up visit and provide the Investigator with case report form completion guidelines.

- **Compliance**

  During periodic monitoring visits at mutually convenient times, the Monitor has the responsibility of assessing the progress of the study, of checking that the informed consent forms have been signed, of ensuring adhesion to and compliance with the study protocol and other study-related documents, and of ensuring the accuracy and completeness of the eCRFs. Inconsistencies in the study records are to be resolved.

- **Source data verification**

  The Monitor will perform source document verification and validation and request clarification to ensure the accuracy, completeness and reliability of data.

- **Study drug**

  The Monitor must ensure that study drug handling is properly carried out and documented.
  He/she must ensure that the investigator file is up-to-date with regard to essential documents.

16.3. Responsibilities of the data manager

The LFB Data Manager is responsible for the management of clinical data from data entry to database lock.

17. ETHICS AND REGULATORY CONSIDERATIONS

The current study is to be conducted in accordance with globally accepted standards of Good Clinical Practice (ICH-E6), European Directive 2001/20/EC, and the revised version of the Declaration of Helsinki set out in the European Directive, as well as with applicable local requirements.

In France, this study will be conducted in accordance with the Code de la Santé Publique CSP.

The protocol will be submitted to the Health Authorities and a properly constituted Ethics Committee (EC) for formal approval of the study conduct in accordance with local regulations.

The study may not begin until the protocol has received written approval from the Health Authorities in accordance with local requirements.

In accordance with specific local requirements, the Investigator may be responsible for submitting the protocol and any amendments to the local EC. A copy of the decision letter, a list and versions of documents submitted, the list of EC members and their affiliation should be provided by the Investigator to the Sponsor.

During the study, the Sponsor should promptly notify the Investigators, Health Authorities and EC of any relevant information that could affect the safety of patients and could impact on the conduct of the study.

- **Personal Data Protection**

For biomedical research in France: The Sponsor attests his conformity regarding the Personal Data Protection French requirements ("Méthodologie de Réference MR001" updated in October 2010).

- **Insurance**

The Sponsor certifies substracting a contract of public liability insurance to provide patients with compensation for any injury, including the consequences of administration of the investigational product and of the study procedures.

In case of injury or disability resulting from participation in the study, the patient is requested to promptly inform the Investigator responsible for the study.

- **Indemnity**

Participation in this study will not entail any financial compensation to patient.

- **Changes to the protocol**

The Sponsor will not assume any responsibility or liability resulting from implementation of unapproved deviations or changes.

The only circumstance in which an amendment may be initiated prior to approval by the Health Authorities is where the change is necessary to eliminate apparent immediate hazards to the patients. In this event, the Investigator must notify the Sponsor and if applicable the EC, in writing within 5 working days after implementation.

18. AUDIT AND INSPECTION

An audit/inspection may be carried out by qualified Sponsor staff, by subcontracted auditors or by representatives of national or foreign Health 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.

Participation in this study implies acceptance to cooperate in any potential audit/inspection.

The audit/inspection may consist of an inspection of the premises and equipment together with verification of the study documents and data.

The investigational team must be available for inspection or audit.

When the Sponsor or the Investigator is informed that an inspection is to be performed, the other party must be informed immediately.

Audits/inspection may take place after the end of the study.

19. REFERENCES

1 Lunn MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. J Neurol Neurosurg Psychiatry. 1999; 66(5):677-80.

2 Laughlin RS, Dyck PJ, Melton LJ 3rd, Leibson C, Ransom J, Dyck PJ. Incidence and prevalence of CIDP and the association of diabetes mellitus. Neurology. 2009; 73(1):39-45.

3 Gaebel K, Blackhouse G, Campbell K, Robertson D, Xie F, Assasi N, Chalk C, Levine M, Goeree R. Intravenous immunoglobulin for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy: A systemic review and meta-analysis. Open Medicine. 2010; 4(3):154-166.

4 European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculopathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First revision. J Peripher Nerv Syst. 2010; 15:1-9.

5 Van den Bergh PY, Piéret F. Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve. 2004; 29(4):565-74.

6 Hughes R. Chronic inflammatory demyelinating polyradiculoneuropathy. J Clin Immunol. 2010 Apr 15.

7 Vlam L, van der Pol WL, Cats EA, Straver DC, Piepers S, Franssen H, van den Berg LH. Multifocal motor neuropathy: diagnosis, pathogenesis and treatment strategies. Nat Rev Neurol. 2011 Nov 22; 8(1):48-58.

8 Austin JH. Recurrent polyneuropathies and their corticosteroid treatment; with five-year observations of a placebo-controlled case treated with corticotrophin, cortisone, and prednisone. Brain. 1958; 81(2):157-92.

9 Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: Intravenous immunoglobulin in the treatment of neuromuscular disorders. Neurology 2012; 78:1009-1015.

10 Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev. 2009; 21(1):CD001797.

11 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.

12 Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med. 2001; 345:747-755.

13 Tackenberg B, Jelcic I, Baerenwaldt A, Oertel WH, Sommer N, Nimmerjahn F, Lünemann JD. Impaired inhibitory Fcgamma receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc Natl Acad Sci U S A. 2009 Mar 24; 106(12):4788-92.

14 EMA/CHMP/BPWP/94038/2007 rev.4. Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). July 2010.

15 Querol, L., G.Nogales-Gadea, R.Rojas-Garcia, E.Martinez-Hernandez, J.Diaz-Manera, X.Suarez-Calvet, M.Navas, J.Araque, E.Gallardo, and I.Illa. 2013. Antibodies to contactin-1 in chronic inflammatory demyelinating polyneuropathy. Ann.Neurol. 73:370-380.

16 Nimmerjahn, F. and J.V.Ravetch. 2008. Fcgamma receptors as regulators of immune responses. Nat.Rev.Immunol. 8:34-47).

17 Nimmerjahn, F. and J.D.Lunemann. 2011. Expression and function of the inhibitory Fcgamma-receptor in CIDP. J.Peripher.Nerv.Syst. 16 Suppl 1:41-44.

18 Tackenberg, B., I.Jelcic, A.Baerenwaldt, W.H.Oertel, N.Sommer, F.Nimmerjahn, and J.D.Lunemann. 2009. Impaired inhibitory FcRIIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc.Natl.Acad.Sci.U.S.A 106:4788-4792.| UA $

19 Tackenberg B., F.Nimmerjahn, and J.D.Lunemann. 2010. Mechanisms of IVIg efficacy in chronic inflammatory demyelinating polyneuropathy. J.Clin.Immunol. 30 Suppl 1:S65-S69.

20 Bick S., M.Tschernatsch, A.Karg, V.Fuehlhuber, T.E.Trenczek, K.Faltermeier, H.Hackstein, M.Kaps, and F.Blaes. 2013. Intravenous immunoglobulin inhibits BAFF production in chronic inflammatory demyelinating polyneuropathy - a new mechanism of action? J.Neuroimmunol. 256:84-90.

21 Jacob S. and Y.A.Rajabally. 2009. Current proposed mechanisms of action of intravenous immunoglobulins in inflammatory neuropathies. Curr.Neuropharmacol. 7:337-342.

22 Durandy A. et al, Intravenous immunoglobulins – understanding properties and mechanisms. Clin Exp Immunol. 2009 December; 158(Suppl 1): 2–13.

23 Goedee HS, Brekelmans GJ, Visser LH. Multifocal enlargement and increased vascularization of peripheral nerves detected by sonography in CIDP: A pilot study. Clin Neurophysiol 2014; 125:154–159.

24 Imamura K, Tajiri Y, Kowa H, Nakashima K. Peripheral nerve hypertrophy in chronic inflammatory demyelinating polyradiculoneuropathy detected by ultrasonography. Intern Med 2009; 48:581–582.

25 Zaidman CM, Al-Lozi M, Pestronk A. Peripheral nerve size in normals and patients with polyneuropathy: an ultrasound study Muscle Nerve. 2009 Dec;40(6):960-6; Muscle Nerve. 2012 Aug;46(2):270-5).

26 Matsuoka N, Kohriyama T, Ochi K, Nishitani M, Sueda Y, Mimori Y, Nakamura S, Matsumoto M. Detection of cervical nerve root hypertrophy by ultrasonography in chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Sci. 2004 Apr 15;219(1-2):15-21.

27 Taniguchi N, Itoh K, Wang Y, et al. Sonographic detection of diffuse peripheral nerve hypertrophy in chronic inflammatory demyelinating polyradiculoneuropathy. J Clin Ultrasound 2000; 28:488–491.

28 Padua L, Granata G, Sabatelli M, Inghilleri M, Lucchetta M, Luigetti M, Coraci D, Martinoli C, Briani C. Heterogeneity of ultrasound pattern in CIDP patients. Clin Neurophysiol. 2014 Jan; 125(1):160-5. doi: 10.1016/j.clinph.2013.07.023. Epub 2013 Oct 5.

29 Won SJ, Kim BJ, Park KS, Kim SH, Yoon JS. Measurement of cross-sectional area of cervical roots and brachial plexus trunks. Muscle Nerve; Doi: 10.1002/mus.23503. Epub 2012 Jun 22.

30 Padua L, Martinoli C, Pazzaglia C, Lucchetta M, Granata G, Erra C, Briani C. Intra- and internerve cross-sectional area variability: new ultrasound measures. Muscle Nerve. 2012 May; 45(5):730-3. Doi:10.1002/mus.23252.

31 Kersanoudis A, Klasing A, Behrendt V, Gold R, Yoon MS. Intra-and internerve cross-sectional area variability: new ultrasound measures. Muscle Nerve. 2013 Jan; 47(1):146-7. Doi: 10.1002/mus/23520. Epub 2012 Nov 21.

32 Hughes R, Bensa S, Willison H, Van den Bergh P, Comi G, Illa I, Nobile-Orazio E, van Doorn P, Dalakas M, Bojar M, Swan A; Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Randomised controlled trial of intravenous immunoglobulin versus oral Prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 2001; 50(2):195-201.

33 Van van Nes SI, Vanhoutte EK, van Doorn PA, Hermans M, Bakkers M, Kuitwaard K, Faber CG, Merkies IS, on behalf of the PeriNomS study group. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. Neurology 2011 Jan 25; 76(4):337-45.

34 Andrich D, Sheridan B, Luo G – Rasch models for measurement: RUMM2030, ed.R. Laboratory 2010, Perth.

35 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.

36 Vanhoutte EK, Latov N, Deng C, Hanna K, Hughes RA, Bril V, Dalakas MC, Donofrio P, van Doorn PA, Hartung HP, Merkies IS. vigorimeter grip strength in CIDP: A responsive tool that rapidly measure the effect of IVIg – the ICE study. Eur J Neurol.2013-may; 20(5):748-55.

[37] Anani W, Triulzi D, Yazer MH, Qu L. Relative IgA-deficient recipients have an increased risk of severe allergic transfusion reactions.Vox Sanguinis 2014; 107:389–392.

[38] Ballow M. Primary immunodeficiency disorders: Antibody deficiency. J Allergy Clin Immunol 2002;109:581-91.

[39] KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney inter, Suppl. 2012; 2:139-274.

[40] Vanhoutte EK. Faber CG, Merkies ISJ. 196th ENMC international workshop: Outcome measures in inflammatory peripheral neuropathies 8-10 February 2013, Naarden, The Netherlands. Neuromuscular Disorders 2013;23:924-933.

20. APPENDICES

20.1. Scales / score used

20.1.1. INCAT and adjusted INCAT disability score

The patient's functional disability will be measured using the INCAT disability scale, as well as the adjusted INCAT disability scale.

The INCAT disability score measures the disability of both upper and lower limbs with a score from 0 (normal) to 5 (maximal disability) [32]. The total score may vary from 0 to 10.

The adjusted score is identical to the INCAT disability score except for the exclusion of changes in upper limb function from 0 (normal) to 1 (minor symptoms) or from 1 to 0, because these changes were not judged by Health Authorities to be clinically significant in all patients. However, all other 1-point steps in either the arm or the leg scale represented clinically meaningful changes in disability [32]. Consequently, the disability of the arms is scored from 0 to 4 in the adjusted INCAT discalibity scale, instead of 0 to 5 in the original INCAT disability scale. The total score may vary from 0 to 9.

The INCAT disability scale is presented in the Table 20–1:

Table 20–1: INCAT disability scale

INCAT disability	INCAT disability scale	Adjusted INCAT

score		disability score
	Arm disability	
0	No upper limb problems	**0**
1	Symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zips *and* buttons; washing *or* brushing hair; using a knife and fork together; and handling small coins	**0**
2	Symptoms, in one arm or both arms, affecting but not preventing any of the above-mentioned functions	**1**
3	Symptoms, in one arm or both arms, preventing one or two of the above-mentioned functions	**2**
4	Symptoms, in one arm or both arms, preventing three or all of the functions listed, but some purposeful movements still possible	**3**
5	Inability to use either arm for any purposeful movement	**4**
	Leg disability	
0	Walking not affected	**0**
1	Walking affected, but walks independently outdoors	**1**
2	Usually uses unilateral support (stick, single crutch, one arm) to walk outdoors	**2**
3	Usually uses bilateral support (sticks, crutches, frame, two arms) to walk outdoors	**3**
4	Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with help	**4**
5	Restricted to wheelchair, unable to stand and walk a few steps with help	**5**
10	**Overall disability = Sum of arm and leg disability**	**9**

20.1.2. Instructions for the use of the INCAT disability scale

Encourage the patient to answer all the questions by themselves. A carer, relative or friend may help if the patient is unsure or has communication difficulties. If the patient does not understand, change the question to, "Do you have difficulty doing xxx?" If necessary ask them to demonstrate the task required.

If their condition has changed recently ask them to base their answers on the last 24 hours.

ARM GRADE

Ask:

"Do you have any tingling, numbness, pain or weakness in your hands or arms?"
Do not include symptoms not due to CIDP.

"Is your ability to do and undo all your buttons and zips affected?"
If Yes, ask: ***"Are you able to do and undo all your buttons and zips?"***
If the patient can do and undo all buttons and zips but has difficulty, they should be considered as affected. If they are not able to do and undo any of their zips and buttons, the activity is prevented. If button hooks or adapted zips are used the task is affected.

"Is your ability to wash or brush your hair affected?"

If Yes, ask: ***"Are you able to wash and brush your hair?"***
If they cannot either wash or brush their hair the task is prevented. If they do not usually wash or brush their hair, they should be asked if they think they could, if required. If there is doubt, ask them to mime the tasks.

"Is your ability to use a knife and fork (or spoon) together affected?"
If Yes, ask: **"*Are you able to use a knife and fork (or spoon) together?"***
If patients do not use a knife and fork, ask about their usual eating implements (e.g. spoon, chopsticks).The task is considered as affected if the patient can use cutlery to eat their food but has difficulty. The activity is prevented if the patient cannot use their cutlery to eat. If adapted cutlery is used the task should be considered affected.

"Is your ability to handle small coins affected?"
If Yes ask: ***"Are you able to handle small coins?"***
If there is doubt, ask them to show you how they take coins out of a purse or pocket and put them back.

If all the previous activities are prevented, ask:
"Can you move either hand or arm at all?"

If necessary, ask the patient to show you the movement. Score “Yes” if any voluntary movement is observed.

LEG GRADE
Ask: ***"Do you have difficulty walking?"***
Difficulty walking may include difficulty walking long distances, fatigue or unsteadiness.

If Yes ask: ***"Do you usually walk outdoors with aid?"***
Could be the aid of another person, or the aid of stick(s), crutch(es), arm(s).

If Yes ask:
"Do you usually walk outdoors with unilateral support (stick, single crutch, one arm)?"
"Do you usually walk outdoors with bilateral support (sticks, crutches, frame, two arms)?"

If the patient does not usually walk outdoors (is chairbound), ask:
"Are you able to stand and walk a few steps with help?"
If necessary ask them to show how they stand and walk with help.

20.1.3. Medical Research Council (MRC) scale and sum score

MRS sum score is a scale that assesses motor impairment.

Table 20–2: MRC scale

The patient is investigated in sitting position and/or lying supine.

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

The muscle groups (right and left) assessed in the measurement of the MRC-sum score are the following:

Upper limbs:
- Shoulder abduction *
- Elbow flexion
- Wrist extension

Lower limbs:
- Hip flexion
- Knee extension
- Ankle dorsal flexion

For each muscle group, a standardised joint / limb position, as well as the point at which counter-force is administered will be pre-defined and taken when assessing muscle strength.

This scale yields the so-called "MRC-sum score", ranging from 0 (paralysis) to 60 (normal strength).
** For shoulder abduction 90° is considered adequate and for hip flexion 45° to qualify for a score of 3.*

20.1.4. RASCH MODIFIED MRC SUM SCORE

The Rasch-modified version of MRC sum score ranges from 0: Total paralysis to 3: Normal strength. It assesses the same muscle group (right and left) than the MRC scale.

Rasch-modified MRC grade:

- 0: Total Paralysis
- 1: Severe Weakness
- 2: Slight Weakness
- 3: Normal Strength

The sum of these scores will range from 0 to 36.

20.1.5. CIDP R-ODS

The CIDP R-ODS (Rash-built-Overall Disability Score) scale is a linearly weighted outcome measure constructed specifically to capture activity and social participation limitations in patients with CIDP. This scale was developed noting the limitations seen in most disability ordinal based outcome measures used thus far in CIDP [33].

This questionnaire comprises 24 items ranging from ability to read a book/newspaper (as the easiest item to accomplish) to ability to run (most difficult item to accompalish). The response option for each item are: 0: Impossible to perform; 1: Able to perform, but with difficulty; and 2: Able to perform, without difficulty. Raw score obtained will be translated through RUMM2030 sofware. [34].

Table 20–3: Final 24-item of CIDP R-ODS

	Are you able to:	unable to perform	able to perform, but with difficulty	able to perform without difficulty
		0	1	2
1	read a newspaper/book?			
2	eat?			
3	brush your teeth?			
4	wash upper body?			
5	go to the toilet?			
6	make a sandwich?			
7	dress upper body?			
8	wash lower body?			
9	move a chair?			
10	turn a key in a lock?			
11	go to the general practitioner?			
12	take a shower?			
13	do the dishes?			
14	do the shopping?			
15	catch an object (e.g., ball)?			
16	bend and pick up an object?			
17	walk one flight of stairs?			
18	travel by public transport?			

19	walk and avoid obstacles?			
20	walk outdoor < 1 km?			
21	carry and put down a heavy object?			
22	dance?			
23	stand for hours?			
24	run?			

20.1.6. CGI (Clinical Global Impression)

The CGI is a 3-item observer-rated scale that measures global improvement or change and therapeutic response. The CGI has proved to be a robust measure of efficacy in many clinical drug trials, and is easy and quick to administer, provided that the clinician knows the patient well (Guy W. editor). ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education and Welfare).

Severity of illness (CGI-S)	
Considering your total clinical experience with this particular population, how ill is the patient as this time?	
0	Not assessed
1	Normal, not at all ill
2	Borderline ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients

Global improvement (CGI-I)	
Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment. Compared to his condition at admission to the project, how much has he changed?	
0	Not assessed
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

Efficacy index (CGI-E)					
Rate this item on the basis of drug effect only. Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.					
Therapeutic effect		**Side effects**			
		None	**Do not significantly interfere with patient's functioning**	**Significantly interferes with patient's functioning**	**Outweighs therapeutic effect**
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16
Not assessed = 00					

20.1.7. Grip strength

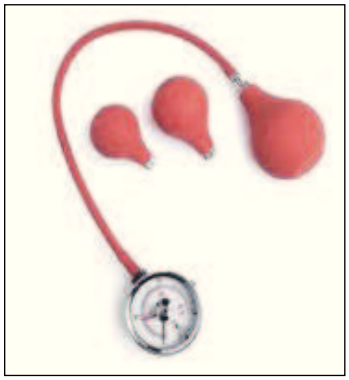
The Martin vigorimeter, a portable dynamometer have been developed to measure grip strength, although, strictly speaking, it measures the air pressure in the bulb and not the force. The pressure in the bulb is registered on a manometer via a rubber junction tube and expressed in kiloPascals (kPa). Reference values for this instrument have been provided for right-handed healthy individuals [35]. The vigorimeter has demonstrated good responsiveness, even as early as at 3 weeks of IVIg therapies in patient with CIDP [35] [36].

Grip strength measure with the Martin Vigorimeter in both hands will be used to assess the efficacy of I10E.

Grip strength reflecting distal strength and upper limb function, is a prognostic indicator of clinical and functional recovery and is useful in monitoring the effect of treatment.

The medium size bulb will be used. Three tests will be performed and the best of the three recorded.

Figure 20–1: Martin vigorimeter



Grip strength will be assessed 3 times in alternating order for both dominant and non-dominant hands.