PROTOCOL CIDP01 AMENDMENT 2

A MULTICENTER, RANDOMIZED, SUBJECT-BLIND, INVESTIGATOR-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF ROZANOLIXIZUMAB IN SUBJECTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

PHASE 2A

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[redacted]	[redacted]
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure
CDMS	clinical data management system
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
C_{max}	maximum concentration
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report form
EFNS	European Federation of Neurological Societies
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FcRn	Fc receptor
FV	Final Visit
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody test

HCAb	hepatitis C antibody
HIV	human immunodeficiency virus
HIV1	human immunodeficiency virus antibody 1
HIV2	human immunodeficiency virus antibody 2
hsCRP	high sensitivity C-Reactive protein
IA	immunoabsorption
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon gamma release assay
IMP	investigational medicinal product
INCAT	Inflammatory Neuropathy Cause and Treatment
IND	Investigational New Drug
IRB	Institutional Review Board
iRODS	inflammatory Rasch-built Overall Disability Scale
IRT	interactive response technology
ITP	immune thrombocytopenia
iv	intravenous(ly)
IVIg	intravenous immunoglobulin
LLOQ	lower limit of quantification
LOCF	last observation carried forward
logit	log odds unit
LTB	latent tuberculosis
LTBI	latent tuberculosis infection
MG	myasthenia gravis
MHC	major histocompatibility complex
MCID-SE	minimum clinically important differences-standard error

miRNA	microRNA
MMRM	mixed model repeated measures
MRC	Medical Research Council
mRNA	messenger RNA
NTMB	nontuberculosis mycobacterium
NTMBI	nontuberculosis mycobacterium infection
NF-L	neurofilament light chain
OLE	Open-Label Extension
ONLS	Overall Neuropathy Limitation scale
PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per-Protocol Set
PDS	Protocol Deviation Specification
PEOT	premature end of treatment
PGIC	Patient Global Impressions of Change
PGIS	Patient Global Impressions of Severity
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PLEX	plasma exchange
PNS	Peripheral Nerve Society
PPS	Per-Protocol Set
PRO	patient-reported outcome
PS	Patient Safety
QTc	QT-interval corrected for heart rate
RNA	ribonucleic acid
RT-MRC	Rasch-built, modified interval Medical Research Council scale
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SCIg	subcutaneous immunoglobulin
SD	standard deviation

SOC	standard of care
SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

1 SUMMARY

CIDP01 is a Phase 2A, multicenter, randomized, subject-blind, investigator-blind, placebo-controlled, parallel-group study with the primary objective of evaluating the clinical efficacy of rozanolixizumab (UCB7665) as a treatment for subjects with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Secondary objectives include evaluating the safety and tolerability of rozanolixizumab subcutaneous (sc) infusion in subjects with CIDP, and assessing the effect of rozanolixizumab as measured by the total immunoglobulin G (IgG) concentrations in serum. Eligible subjects will be adults who have a confirmed diagnosis of definite or probable CIDP according to the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for CIDP, have been shown to be immunoglobulin (Ig)-dependent within 18 months before Screening and who have remained on a stable dosage and fixed interval of immunoglobulin therapy for at least 4 months prior to Screening.

Subjects will be randomized to 1 of 2 treatment arms: rozanolixizumab [redacted] sc or placebo sc in a ratio of 1:1. For exact doses to be administered, refer to Section 7.2. Subjects will receive 12 weekly doses of investigational medicinal product (IMP). The maximum duration of the study per subject is approximately 28 weeks (up to maximum 40 weeks), consisting of a Screening Period of between 2 and 5 weeks duration, an 11-week Treatment Period, and an Observation Period of 12 weeks (up to 24 weeks). The study is planned to be conducted in approximately 24 sites globally. Approximately 34 subjects will be randomized to ensure at least 30 subjects are evaluable for the primary efficacy analysis.

All subjects completing the Treatment Period (ie, all visits performed without relapse) will be offered the possibility to enter in the Open-Label Extension (OLE) study, CIDP04, and be treated with rozanolixizumab. If they enter in the OLE, Visit 17 will be the last study visit in CIDP01. If the subjects wish to test whether they still need treatment, they will continue the Observation Period without standard of care (SOC) treatment (ie, Ig treatment; subcutaneous immunoglobulin [SCIg] and intravenous immunoglobulin [IVIg]). The subjects have also the opportunity to return immediately to SOC for the duration of the Observation Period.

If the subject relapses during the Treatment Period or Observation Period (according to the medical judgement of the investigator supported by eg, subject' score on inflammatory Rasch-built Overall Disability Scale (iRODS), Inflammatory Neuropathy Cause and Treatment (INCAT), or maximum grip strength (assessed by site personnel), the subject will return to the SOC as rescue medication at the time of relapse and will be stabilized over a period of 2 weeks up to maximum 12 weeks starting from relapse visit, ie, premature end of treatment (PEOT) or later visit. During the stabilization, visits should be performed every 1 to 3 weeks at the discretion of the investigator until the subject is stabilized.

At the end of the stabilization, a subject who completed the Treatment Period without a CIDP relapse will be offered the possibility to enter the OLE (CIDP04) and be treated with open-label rozanolixizumab from that moment onwards. The subject will complete the Final Visit (FV) (V21) and enter the OLE on the same day. If a subject does not wish to enter the OLE, the subject will continue their SOC treatment after stabilization. They will continue the stabilization visit schedule (every 1 to 3 weeks) until they have a follow-up of 12 weeks after last IMP dose.

Subjects who relapsed during the Treatment Period will only be able to enter the OLE once all subjects have completed the study, the study is unblinded and it is confirmed they were on the placebo arm in CIDP01. At the end of stabilization, they will continue their SOC treatment after stabilization. They will continue the stabilization visit schedule (every 1 to 3 weeks) until they have a follow-up of 12 weeks after last IMP dose.

The primary efficacy variable is the change from Baseline to Week 13 (Day 85) in iRODS score.

Other efficacy variables will include:

- Subject experienced CIDP relapse (iRODS) up to Week 13 (Day 85) after first treatment and time to CIDP relapse (iRODS) at each scheduled assessment during the Treatment Period, where CIDP relapse (iRODS) is defined as a clinically important deterioration from Baseline in iRODS score, ie, a minimum clinically important differences-standard error (MCID-SE) of ≤-1.96. Values and change from Baseline in iRODS scores at each scheduled assessment during the Treatment and Observation Periods will be assessed.
- Subject experienced CIDP relapse up to Week 13 (Day 85) after first treatment and time to CIDP relapse during the Treatment Period will be determined using the adjusted INCAT disability score where CIDP relapse is defined as an increase from Baseline of at least 1 point in the adjusted INCAT score. Values and change from Baseline in adjusted INCAT score at each scheduled assessment during the Treatment and Observation Periods will be assessed.
- Subject experienced CIDP relapse up to Week 13 (Day 85) after first treatment and time to CIDP relapse during the Treatment Period will be determined using maximum grip strength assessed by the site personnel, where CIDP relapse is defined as a clinically important deterioration from Baseline in grip strength, ie, a decline of >14kPa.
- Further variables include values and change from Baseline in maximum grip strength score recorded by site personnel at each scheduled assessment during the Treatment and Observation Periods; values and change from Baseline in daily maximum grip strength score recorded by the subject each day during the Treatment and Observation Periods; additional patient-reported outcomes (PROs); values and change from Baseline in Rasch-built, modified interval Medical Research Council scale (RT-MRC) sum score at each scheduled assessment during the Treatment and Observation Periods; and subjects receiving rescue medication and time to rescue medication administration.

Other and exploratory variables include: safety and tolerability variables, pharmacokinetic (PK), pharmacodynamic (PD), immunologic variables, exploratory pharmacogenetics variables, and exploratory ribonucleic acid (RNA), proteins, and metabolites biomarkers. Plasma concentration of rozanolixizumab over time will be assessed as the PK variable. The PD variables are minimum and maximum decrease from Baseline in total IgG concentration during the study; value and change from Baseline in IgG concentrations at each scheduled assessment during Treatment and Observation Periods; value and change from Baseline in IgG subclass concentrations at each scheduled assessment during Treatment and Observation Periods; and value and change from Baseline in neurofilament light chain (NF-L) levels at each scheduled assessment during Treatment and Observation Periods. Immunological variables will also be assessed.

Safety and tolerability variables will include occurrence of treatment-emergent adverse events (TEAEs); TEAEs leading to withdrawal of IMP; vital sign values and changes from Baseline (systolic and diastolic blood pressure [BP], temperature, pulse rate, and body weight) at each scheduled assessment during Treatment and Observation Periods; 12-lead electrocardiogram (ECG) parameters and change from Baseline at each scheduled assessment during Treatment and Observation Periods; laboratory values and changes from Baseline at each scheduled assessment during Treatment and Observation Periods (hematology, clinical chemistry, and urinalysis); tuberculosis (TB) evaluation; and values and change from Baseline in concentrations of total protein, albumin, α- and β-globulins at each scheduled assessment during the Treatment and Observation Periods.

Exploratory analyses of deoxyribonucleic acid (DNA), RNA, proteins, and metabolites biomarkers may be performed to understand the cause, progression, and appropriate treatment of CIDP.

A Data Monitoring Committee (DMC) will be established for the study.

2 INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy is a rare disorder of the peripheral nerves characterized by chronic and progressive onset of weakness, loss of sensation, reflexes, reduction or partial block in motor nerve conduction, and often pain and imbalance. Worldwide, the prevalence of CIDP ranges from approximately 1 to 9 cases per 100,000 (Mathey et al, 2015). For many patients, CIDP results in substantial disability, limiting their activities resulting in an overall negative impact on quality of life across multiple dimensions. Progressive disease and/or relapses can result in difficulty moving arms, hands, legs, and feet, a loss in the ability to walk independently or confinement to wheelchairs and reliance on caregivers (Mahdi-Rogers et al, 2014). Healthcare costs for CIDP are substantial (Guptill et al, 2014; Mahdi-Rogers et al, 2014; Olesen et al, 2012).

Cellular and humoral immune mechanisms are thought to be involved in the pathogenesis of CIDP resulting in inflammatory lesions in the spinal roots, proximal nerve trunks and along the peripheral nerves. The essential role of the autoimmune antibodies in mediating this pathology is supported by the improvement seen after plasma exchange (PLEX) and immunoabsorption (IA). Identification of the specific antigenic target(s) of the autoimmune antibodies in CIDP is expanding with recent immunological techniques.

Although the prognosis of CIDP has markedly improved over the last decades, significant disability remains. High dose steroids, PLEX, IA, and IVIg and SCIg have all been shown to be effective treatments for CIDP. However, comorbid diseases including hypertension, diabetes, and psychiatric diseases limit the use of high dose steroids. While PLEX is effective, the procedure is burdensome for patients. Immunoglobulin treatment (IVIg and SCIg) is often used as first line treatment but there remains a medical need for improved therapeutic options.

The neonatal major histocompatibility complex (MHC)-class-I-like Fc receptor (FcRn) recycles IgG and albumin from most cells and transports it bi-directionally across epithelial barriers to affect systemic and mucosal immunity. It has been shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling it from the sorting endosome to the cell surface (Anderson et al, 2006). Immunoglobulin G has a half-life of approximately

3 weeks in man. This is achieved by interaction of IgG with the receptor, FcRn. Thus, in effect FcRn salvages IgG, and blockade of FcRn accelerates removal of endogenous IgG.

Rozanolixizumab is a humanized anti-FcRn monoclonal antibody that has been specifically designed to inhibit IgG binding to FcRn without inhibiting albumin binding to FcRn. Rozanolixizumab is being developed as an inhibitor of FcRn activity with the aim to reduce the concentration of pathogenic IgG in patients with IgG auto-antibody mediated diseases. Rozanolixizumab was derived from a rat antibody with specificity for human FcRn. To date, rozanolixizumab has been administered to healthy subjects in a completed, first-in-human study (UP0018), a completed Phase 2 study in subjects with primary immune thrombocytopenia (ITP) (TP0001, evaluating [redacted] by sc route across 5 cohorts), and a completed Phase 2 study in subjects with myasthenia gravis (MG) (MG0002, evaluating [redacted] by sc route). See summaries below for UP0018, TP0001, and MG0002.

UP0018 is a completed, first-in-human study conducted in 49 healthy subjects. The study evaluated the safety, tolerability, PK, and the PD effect on total IgG levels of single ascending doses of intravenous (iv) and sc rozanolixizumab. Doses of rozanolixizumab [redacted] were administered by both iv and sc routes in 3 cohorts, respectively, as a [redacted]. The information from the study is summarized below.

There were no deaths or serious adverse events (SAEs) reported during UP0018, and no subjects discontinued the study due to TEAEs. Rozanolixizumab was tolerated with an acceptable safety profile after the single administration of [redacted] iv and [redacted] sc doses. Four TEAEs with a maximum intensity of severe were reported in this study: headache (3 subjects [50.0%]) and back pain (1 subject [16.7%]); all of which were reported in the rozanolixizumab [redacted] iv group. For sc administration of rozanolixizumab, the most frequently reported TEAEs were headache (5 subjects [27.8%]), and back pain and diarrhea (each reported by 3 subjects [16.7%]). No severe adverse events (AEs) were reported following sc administration. Further details on both iv and sc administration may be found in the current version of the Investigator's Brochure (IB). The peak and total exposure of rozanolixizumab showed nonlinear increases consistent with target-mediated drug disposition. Dose-dependent statistically significant reductions in levels of total IgG and dose-dependent reductions in levels of IgG subclasses (IgG 1 to 4) were observed after rozanolixizumab was administered by iv or sc routes.

TP0001 is a completed, Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of rozanolixizumab administered as sc doses of [redacted] in 66 subjects ≥18 years of age with persistent or chronic ITP.

There were no treatment-emergent deaths reported during TP0001, and no subjects discontinued from the study or IMP due to TEAEs. There were no treatment-related SAEs reported from the study. All TEAEs considered by the investigator to be related to rozanolixizumab were mild to moderate in intensity and resolved without clinical sequelae. The majority of the related TEAEs did not require treatment. The most common TEAEs were headache (26 subjects [39.4%]), diarrhea (8 subjects [12.1%]), and vomiting (6 subjects [9.1%]). Treatment with rozanolixizumab was generally [redacted] and well tolerated with an acceptable safety profile across the treatment groups.

MG0002 is a completed, multicenter, randomized, investigator-and subject-blind, placebo-controlled, treatment sequence study evaluating the safety, tolerability, and efficacy of rozanolixizumab in 43 subjects with moderate to severe MG. [redacted]

There were no deaths reported during MG0002. One subject (2.3%) discontinued from the study due to an AE (MG crisis). In addition, 3 subjects experienced TEAEs (headache) that led to discontinuation of IMP, but the subjects remained in the study. Six subjects (14.0%) reported a total of 7 serious TEAEs. One subject in the Placebo-Rozanolixizumab [redacted] Group experienced a serious TEAE of headache that was considered by the investigator to be related to the IMP. With the exception of 1 serious TEAE of ulna fracture, all other serious TEAEs were in the System Organ Class of Nervous system disorders. Three subjects (7.0%) reported serious TEAEs of MG (the studied indication), and 1 subject (2.3%) reported a serious TEAE of MG crisis. The most common TEAEs were headache (23 subjects [53.5%]), diarrhea (11 subjects [25.6%]), and nausea (6 subjects [14.0%]). Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] and [redacted] were generally [redacted] and well tolerated, with an acceptable safety profile.

The underlying hypothesis of the current study is that reducing the concentration of pathogenic IgG in patients with CIDP will improve the symptoms of CIDP and prevent long-term progression. Thus, rozanolixizumab may provide an important novel therapeutic approach to address the need for effective treatment of CIDP.

The current study, CIDP01, will assess the effectiveness of treatment with a weekly dosing regimen of rozanolixizumab for 12 weeks (dosing at Visits 2, 4, 6, and Visits 8 through 16) in subjects with active CIDP who have been maintained on an immunoglobulin-dependent regimen. In addition, this study will assess the safety and tolerability of multiple dosing with rozanolixizumab including the development of [redacted] and potential to impact clinical response, and will provide information on the PK and PD of rozanolixizumab in subjects with active CIDP.

Additional information on the development of rozanolixizumab can be found in the current version of the IB for rozanolixizumab.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of the study is:

- To evaluate the clinical efficacy of rozanolixizumab as a treatment for subjects with CIDP

3.2 Secondary objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of rozanolixizumab sc infusion in subjects with CIDP

- To assess the PD effect of rozanolixizumab as measured by the total IgG concentrations in serum

3.3 Exploratory objectives

Exploratory objectives are:

- To evaluate the effects of rozanolixizumab on the concentration of total protein, albumin, α- and β-globulins, IgG subclasses, IgM, IgA, and IgE, serum and plasma complement levels
- To evaluate the incidence and emergence of [redacted]) with respect to immunogenicity and PK and PD
- To evaluate the effect of rozanolixizumab on complement and cytokines
- To assess the plasma concentrations of rozanolixizumab administered by sc infusion
- To assess the PD effect of rozanolixizumab as measured by NF-L in serum
- To assess the effect of rozanolixizumab on gene and protein expression, and explore the relationship between DNA, RNA, protein, and metabolite biomarkers and cause, progression, and appropriate treatment of CIDP
- To assess the effect of rozanolixizumab on CIDP-specific auto-antibody levels
- To assess the effect of rozanolixizumab on vaccine antibody levels ([redacted])

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable is the:

- Change from Baseline to Week 13 (Day 85) in iRODS score

4.1.2 Other efficacy variables

Preliminary definitions linked to assessment of relapse:

- **CIDP relapse (iRODS)** is defined as a clinically important deterioration from Baseline in iRODS score, ie, a MCID-SE of ≤-1.96
- **CIDP relapse (adjusted INCAT)** is defined as an increase from Baseline of at least 1 point in the adjusted INCAT score. 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
- **CIDP relapse (maximum grip strength as assessed by site personnel)** is defined as a clinically important deterioration from Baseline in grip strength as measured by site personnel, ie, a decline of >14kPa

Other efficacy variables will include:

- Subject experienced **CIDP relapse (iRODS)** up to Week 13 (Day 85) after first treatment

- Time to **CIDP relapse (iRODS)** during the Treatment Period
- Values and change from Baseline in iRODS scores at each scheduled assessment during the Treatment and Observation Periods
- Subject experienced **CIDP relapse (adjusted INCAT)** up to Week 13 (Day 85) after first treatment
- Time to **CIDP relapse (adjusted INCAT)** during the Treatment Period
- Values and change from Baseline in adjusted INCAT score at each scheduled assessment during the Treatment and Observation Periods
- Subject experienced **CIDP relapse (maximum grip strength as assessed by site personnel)** up to Week 13 (Day 85) after first treatment
- Time to **CIDP relapse (maximum grip strength as assessed by site personnel)** during the Treatment Period
- Values and change from Baseline in maximum grip strength score (maximum of 3 assessments) taken by site personnel at each scheduled assessment during the Treatment and Observation Periods
- Values and change from Baseline in daily maximum grip strength score (maximum of 3 assessments) taken by the subject at the same time each day during the Treatment and Observation Periods
- Values and change from Baseline in RT-MRC sum score at each scheduled assessment during the Treatment and Observation Periods
- Values and change from Baseline in fatigue at each scheduled assessment during the Treatment and Observation Periods
- Values and change from Baseline in CIDP PRO instrument at each scheduled assessment during the Treatment and Observation Periods
- Values and change from Baseline in Patient Global Impressions of Severity (PGIS) at each scheduled assessment during the Treatment and Observation Periods
- Patient Global Impressions of Change (PGIC) at each scheduled assessment during the Treatment and Observations Periods
- Subjects receiving rescue medication during Treatment Period
- Time to rescue medication administration during Treatment Period

4.2 Other variables

4.2.1 Pharmacokinetic variable

The PK variable is:

- Plasma concentration of rozanolixizumab at each scheduled assessment during the Treatment Period

4.2.2 Pharmacodynamic variables

The PD variables are:

- Minimum value and maximum decrease (absolute and percentage) from Baseline in total serum IgG concentration during the study
- Value and change (absolute and percentage) from Baseline in total serum IgG concentrations at each scheduled assessment during Treatment and Observation Periods
- Value and change (absolute and percentage) from Baseline in serum IgG subclass concentrations at each scheduled assessment during Treatment and Observation Periods
- Value and change (absolute and percentage) from Baseline in NF-L levels at each scheduled assessment during Treatment and Observation Periods

4.2.3 Exploratory pharmacogenetics variables

The exploratory pharmacogenetics variables are:

- Genetic and epigenetic changes that may be measured to understand the cause, progression, and appropriate treatment of CIDP

4.2.4 Exploratory RNA, proteins, and metabolites variables

The exploratory RNA, proteins, and metabolites variables are:

- RNA, proteins, and metabolites changes that may be measured to understand the cause, progression, and appropriate treatment of CIDP
- Exploratory biomarkers such as but not limited [redacted]
- Change from Baseline relating to mechanism of action, disease activity, treatment response, and clinical outcome at each scheduled assessment during the Treatment and Observation Periods

4.2.5 Immunological variables

The immunological variables are:

- Values and change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) at each scheduled assessment during Treatment and Observation Periods
- Values and change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during Treatment Period
- [redacted] status (negative or confirmed positive) and the confirmed positive titer at each scheduled assessment during Treatment and Observation Periods
- Values and change from Baseline in cytokines at each scheduled assessment during Treatment and Observation Periods

- Change in CIDP-specific auto-antibody levels in serum from Baseline during Treatment and Observation Periods
- Values and change from Baseline in [redacted] during Treatment and Observation Periods

4.2.6 Safety variables

The safety variables for the study are:

- Occurrence of TEAEs
- TEAEs leading to withdrawal of IMP
- Vital sign values and changes from Baseline (systolic and diastolic BP, temperature, pulse rate, and body weight) at each scheduled assessment during Treatment and Observation Periods
- 12-lead ECG values and change from Baseline at each scheduled assessment during Treatment and Observation Periods
- Laboratory values and changes from Baseline at each scheduled assessment during Treatment and Observation Periods (hematology, clinical chemistry, and urinalysis)
- Tuberculosis Signs and Symptoms Questionnaire at each scheduled assessment during Treatment and Observation Periods
- Values and change from Baseline in concentrations of total protein, albumin, α- and β-globulins at each scheduled assessment during Treatment and Observation Periods

5 STUDY DESIGN

5.1 Study description

This is a Phase 2A, multicenter, randomized, subject-blind, investigator-blind, placebo-controlled, parallel-group study evaluating the efficacy, safety, and tolerability of rozanolixizumab for treatment of subjects with CIDP. Eligible subjects will be adults who have a confirmed diagnosis of definite or probable CIDP according to the EFNS/PNS criteria for CIDP, have been shown to be dependent on treatment with immunoglobulin and who have remained on a stable dosing regimen of immunoglobulin therapy for at least 4 months prior to Screening.

- Treatment Arm 1: [redacted]
- Treatment Arm 2: [redacted]

See Section 7.2 for details on treatments to be administered.

Subjects will be randomized in a ratio of 1:1 to the 2 treatment arms. The randomization will take place on the day of first treatment with IMP. The randomization will be stratified according to previous route of administration for Ig treatment (ie, SCIg and IVIg).

The dose level of [redacted] may be reduced to [redacted] (or equivalent placebo) for an individual subject based on their tolerability (see Section 7.2 for details). For example, if a subject experiences a severe headache which does not respond to headache treatment (see Section 12.1.10), a decision to decrease future doses to [redacted] may be made. The decision to decrease the dose will be made following a discussion between the investigator and the UCB study physician. In addition, the decision to decrease the dose for the remainder of the subjects may be made following a DMC recommendation.

The study consists of:

- Screening Period of between 2 and 5 weeks duration. The purpose of the Screening Period is to evaluate and confirm the subject's eligibility. All subjects must have an Ig dependency that has been confirmed within 18 months before Screening. All subjects must be on a long-term immunoglobulin maintenance therapy with a stable immunoglobulin infusion regimen at consistent intervals to be considered eligible. The Screening Period will be a minimum of 2 weeks and generally should not exceed 5 weeks. During the Screening Period, the subjects will receive their last dose of immunoglobulin therapy before the randomization (see details in Section 8.2).
- The 11-week Treatment Period begins at the Randomization Visit (Visit 2) on Day 1 to review inclusion and exclusion criteria as well as concomitant medications and treatments. Subjects who remain eligible will be randomized 1:1 to receive rozanolixizumab [redacted] or placebo. All eligible subjects will receive the same treatment at weekly intervals during the full duration of the Treatment Period, ending with the last dose of IMP (Visit 16). After initial 4 IMP administrations have been performed at the clinic, the subject will have the opportunity to be treated at home at every other visit.
- The 12-week Observation Period (from 1 week up to maximum 24 weeks):
  - All subjects completing the Treatment Period (ie, all visits up to Visit 17 performed without a CIDP relapse) will be offered the possibility to enter in the OLE study, CIDP04, and be treated with rozanolixizumab. If they enter in the OLE, Visit 17 will be the last study visit. The Observation Period will be limited to 1 week for these subjects.

    In all other instances the subjects will perform Visits 18 to 21 for efficacy and for safety assessments (see Schedule of Assessments; Table 5–1). Subjects will either return to the clinic/hospital, or, if possible and agreed by both investigator and subject, have home visits conducted by certified healthcare professionals for Visits 18 and 20.
  - For subjects who complete the Treatment Period without relapse but choose not to enter the OLE directly and wish to first test whether they still need treatment, they will continue the Observation Period without SOC treatment.
  - Subjects who do not wish to enter the OLE or test whether they still need treatment after having successfully completed the Treatment Period also have the opportunity to return immediately to SOC for the duration of the Observation Period.
  - All other subjects (ie, having relapsed or withdrawn from the study during Treatment Period) will complete the Observation Period. Subjects can return to their SOC for the duration of the Observation Period.

– Stabilization: If the subject relapses during the Treatment Period or Observation Period (according to the medical judgement of the investigator supported by eg, subject's score on iRODS, INCAT, or maximum grip strength [assessed by site personnel]), the subject will return to the SOC (ie, Ig treatment) as rescue medication at the time of relapse and will be stabilized over a period ranging from 2 weeks up to maximum 12 weeks starting from relapse visit (eg, PEOT [Visit 17] or later visit).

During the stabilization, visits should be performed every 1 to 3 weeks at the discretion of the investigator until the subject is stabilized. The stabilization may extend the Observation Period duration up to a maximum of 24 weeks after the last IMP dose.

At the end of the stabilization:

1. A subject who completes the Treatment Period without a CIDP relapse will be offered the possibility to enter in the OLE (CIDP04) and be treated with rozanolixizumab from that moment onwards. The subject will complete the FV (V21) and enter the OLE on the same day.
2. A subject who completes the Treatment Period and does not wish to enter the OLE (CIDP04) will continue their SOC treatment after stabilization and the stabilization visit schedule (every 1 to 3 weeks) until they have a follow-up of 12 weeks after last IMP dose. The subject will complete the FV (V21) and enter the OLE on the same day.
3. A subject who relapses during Treatment Period will continue their SOC treatment after stabilization. They will continue the stabilization visit schedule (every 1 to 3 weeks) until they have a follow-up of 12 weeks after last IMP dose. The subject will complete the FV (V21) and end CIDP01 study participation. These subjects will be offered entry into CIDP04 only once CIDP01 study results are available, after the blind has been broken at the end of the study, and it was confirmed they received placebo.

Access to the OLE (CIDP04) is allowed for subjects completing the Treatment Period without relapse/withdrawal. Entry can occur immediately upon completion of the Treatment Period or after stabilization in case the subject relapsed during Observation Period and did not meet withdrawal criteria other than relapse. Subjects who relapse during the Treatment Period will have the opportunity to enter the OLE once all subjects have completed the study, the study is unblinded, and key results are available. In this case, only the subjects from the placebo arm will be allowed to enter the OLE study.

See Table 8–1 for details on the different options for subjects in the Observation and Stabilization Periods.

A DMC will be established to monitor safety data during the study (see Section 14.7).

5.1.1 Study duration per subject

The total duration of the study per subject is approximately 28 weeks (up to maximum 40 weeks), consisting of:

- Screening Period of a minimum of 2 to a maximum of 5 weeks starting with Screening Visit (to occur between Day -35 and Day -14, both inclusive).

- Treatment Period (11 weeks) – from first dose of IMP to last dose of IMP. The first treatment with IMP will occur at the Randomization Visit (Visit 2) and the dosing should occur as seamlessly as possible to continue the momentum of the Baseline therapy (see Section 8.2).
- Observation Period (12 weeks up to 24 weeks) starting day after last IMP dose until study end.

In case of early withdrawal, the duration of the Treatment Period may be shortened depending on the time to withdrawal. The Observation Period may be shortened to 1 week in case a subject completes the Treatment Period and enters the OLE study immediately. In case a subject relapses during the Observation Period, the subject will be stabilized over a period of minimum 2 weeks up to 12 weeks, possibly extending the Observation Period to a maximum of 24 weeks.

The end of the study is defined as the date of the last visit of the last subject in the study.

5.1.2 Planned number of subjects and sites

To ensure that at least 30 subjects are evaluable for the primary efficacy analysis, a sample size of approximately 34 randomized subjects is planned at approximately 24 sites.

It is expected that approximately 50 subjects need to be screened in order to get 34 randomized if the screening failure rate is approximately 30%.

5.1.3 Anticipated regions and countries

Anticipated regions are Europe, United States of America, and Canada, with possible extension to other regions and countries.

5.2 Schedule of study assessments

The schedule of study assessments is presented in Table 5–1.

Table 5–1: Schedule of Assessments

Assessments		Scr[a]	11-Week Treatment Period															12-Week Observation Period [s]					
	Visit No	**1**	**2**	**3[b]**	**4**	**5[b]**	**6**	**7[b]**	**8**	**9[c]**	**10**	**11[c]**	**12**	**13[c]**	**14**	**15[c]**	**16**	**17/ PEOT**	**18[c]**	**19**	**20[c]**	**21/ FV**	**Stab visit[q]**
	Visit type	**S**	**S**	**TH**	**S**	**TH**	**S**	**TH**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**S**	**H**	**S**	**H**	**S**	
	Week		**1**		**2**		**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**15**	**18**	**21**	**24**	
	Day	**-35 to -14**	**1 BL**	**2 or 3**	**8 ±2**	**9 or 10**	**15 ±2**	**16 or 17**	**22 ±2**	**29 ±2**	**36 ±2**	**43 ±2**	**50 ±2**	**57 ±2**	**64 ±2**	**71 ±2**	**78 ±2**	**85 ±2**	**99 ±3**	**120 ±3**	**141 ±3**	**162 ±3**	
Written informed consent		X																					
Demographic data		X																					
Verification of inclusion and exclusion criteria		X	X[d]																				
CIDP history (symptoms, date of onset, therapy)		X																					
Randomization			X																				
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
General medical and procedures history		X																					
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight, height [f]		X	X															X				X	
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–1: Schedule of Assessments

Assessments		Scr[a]	11-Week Treatment Period															12-Week Observation Period [s]					
	Visit No	1	2	3[b]	4	5[b]	6	7[b]	8	9[c]	10	11[c]	12	13[c]	14	15[c]	16	17/ PEOT	18[c]	19	20[c]	21/ FV	Stab visit[q]
	Visit type	S	S	TH	S	TH	S	TH	S	H	S	H	S	H	S	H	S	S	H	S	H	S	
	Week		1		2		3		4	5	6	7	8	9	10	11	12	13	15	18	21	24	
	Day	-35 to -14	1 BL	2 or 3	8 ±2	9 or 10	15 ±2	16 or 17	22 ±2	29 ±2	36 ±2	43 ±2	50 ±2	57 ±2	64 ±2	71 ±2	78 ±2	85 ±2	99 ±3	120 ±3	141 ±3	162 ±3	
Query for suicidality [g]		X	X		X		X		X		X		X		X		X	X	X	X	X	X	X
Fatigue scale			X								X				X			X				X	
CIDP PRO instrument			X								X				X			X				X	
PGIS			X								X				X			X				X	
PGIC											X				X			X				X	
Full physical examination		X																X				X	
Brief physical examination			X		X		X		X		X				X					X			X
Full neurological examination [h]		X																X				X	
Brief neurological examination			X		X		X		X		X				X					X			X
12-lead ECG		X	X		X		X		X		X		X		X		X	X				X	
Labs (hematology, chemistry, urinalysis)		X	X		X		X		X		X		X		X		X	X		X		X	X [t]
Serology for HIV, hepatitis B, and hepatitis C [i]		X																					
Serum pregnancy test		X															X						

Table 5–1: Schedule of Assessments

Assessments		Scr[a]	11-Week Treatment Period															12-Week Observation Period [s]					
	Visit No	**1**	**2**	**3 [b]**	**4**	**5 [b]**	**6**	**7 [b]**	**8**	**9[c]**	**10**	**11[c]**	**12**	**13[c]**	**14**	**15[c]**	**16**	**17/ PEOT**	**18[c]**	**19**	**20 [c]**	**21/ FV**	**Stab visit[q]**
	Visit type	**S**	**S**	**TH**	**S**	**TH**	**S**	**TH**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**S**	**H**	**S**	**H**	**S**	
	Week		**1**		**2**		**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**15**	**18**	**21**	**24**	
	Day	**-35 to -14**	**1 BL**	**2 or 3**	**8 ±2**	**9 or 10**	**15 ±2**	**16 or 17**	**22 ±2**	**29 ±2**	**36 ±2**	**43 ±2**	**50 ±2**	**57 ±2**	**64 ±2**	**71 ±2**	**78 ±2**	**85 ±2**	**99 ±3**	**120 ±3**	**141 ±3**	**162 ±3**	
Urine pregnancy test [j]			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGRA tuberculosis test [k]		X																					
Tuberculosis Signs and Symptoms questionnaire		X																X				X	
Chest x-ray [p]		X																					
Contact IRT		X	X		X		X		X	X	X	X	X	X	X	X	X	X				X	
Administration of IMP			X		X		X		X	X	X	X	X	X	X	X	X						
Blood sampling for PK of rozanolixizumab [l]			X	X	X	X	X	X	X		X		X		X		X	X					
Blood sampling for DNA analysis			X															X					
Blood sampling for RNA analysis			X		X		X				X							X					
[redacted]		X	X		X		X		X		X		X		X		X	X				X	
Serum complement (C3, C4) and plasma complement (C3a, C5a) [m]			X		X				X				X				X						

Table 5–1: Schedule of Assessments

Assessments		Scr[a]	11-Week Treatment Period															12-Week Observation Period [s]					
	Visit No	1	2	3[b]	4	5[b]	6	7[b]	8	9[c]	10	11[c]	12	13[c]	14	15[c]	16	17/ PEOT	18[c]	19	20[c]	21/ FV	Stab visit[q]
	Visit type	S	S	TH	S	TH	S	TH	S	H	S	H	S	H	S	H	S	S	H	S	H	S	
	Week		1		2		3		4	5	6	7	8	9	10	11	12	13	15	18	21	24	
	Day	-35 to -14	1 BL	2 or 3	8 ±2	9 or 10	15 ±2	16 or 17	22 ±2	29 ±2	36 ±2	43 ±2	50 ±2	57 ±2	64 ±2	71 ±2	78 ±2	85 ±2	99 ±3	120 ±3	141 ±3	162 ±3	
Serum cytokines [m]			X		X				X				X				X						
Vaccination-specific antibody titers ([redacted])		X							X						X							X	
Immunoglobulins (total IgG and IgG subclasses)		X	X		X		X	X[c]	X	X	X	X	X	X	X	X	X	X				X	
NF-L			X				X										X					X	
IgA, IgE, IgM			X		X		X		X		X		X		X		X	X				X	
CIDP-specific auto-antibodies			X		X		X		X				X				X	X					
Blood sampling for exploratory biomarker analysis [n]			X		X				X				X				X						
iRODS assessment [o]		X	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INCAT assessment		X	X		X		X		X		X		X		X		X	X	X	X	X	X	X
Site personnel assessment of grip strength		X	X		X		X		X		X		X		X		X	X		X		X	X

Table 5–1: Schedule of Assessments

Assessments		Scr[a]	11-Week Treatment Period															12-Week Observation Period [s]					
	Visit No	1	2	3[b]	4	5[b]	6	7[b]	8	9[c]	10	11[c]	12	13[c]	14	15[c]	16	17/ PEOT	18[c]	19	20[c]	21/ FV	Stab visit[q]
	Visit type	S	S	TH	S	TH	S	TH	S	H	S	H	S	H	S	H	S	S	H	S	H	S	
	Week		1		2		3		4	5	6	7	8	9	10	11	12	13	15	18	21	24	
	Day	-35 to -14	1 BL	2 or 3	8 ±2	9 or 10	15 ±2	16 or 17	22 ±2	29 ±2	36 ±2	43 ±2	50 ±2	57 ±2	64 ±2	71 ±2	78 ±2	85 ±2	99 ±3	120 ±3	141 ±3	162 ±3	
Issue subject e-diary for recording of daily grip strength		X																					
Review subject e-diary for daily assessment of grip strength			X		X		X		X		X		X		X		X	X	X	X	X	X	X
RT-MRC assessment		X	X		X		X		X		X		X		X		X	X				X	
Collect subject e-diary																						X	
Subject exit interview																		X[r]				X	

AE=adverse event; BL=Baseline (predose); C3=complement component 3; C3a=complement component 3a; C4=complement component 4; C5a=complement component 5a; CIDP=chronic inflammatory demyelinating polyradiculoneuropathy; C-SSRS=Columbia Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FV=Final Visit; H=Home visit; HIV=human immunodeficiency virus; ICF=informed consent form; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IgM=immunoglobulin M; IGRA=interferon gamma release assay; IMP=investigational medicinal product; INCAT=Inflammatory Neuropathy Cause and Treatment; iRODS=inflammatory Rasch-built Overall Disability Scale; IRT=interactive response technology; NF-L=neurofilament light chain; OLE=Open-Label Extension; PEOT=premature end of treatment; PGIC=Patient Global Impressions of Change; PGIS=Patient Global Impressions of Severity; PK=pharmacokinetic; PRO=patient-reported outcome; RNA=ribonucleic acid; RT-MRC=Rasch-built, modified-interval Medical Research Council scale; S=site visit; Scr=Screening; Stab=stabilization; TH=telephone call and home visit.

Note: All assessments are to be completed in order specified in Section 8 if possible. The ICF should be completed before any assessment. PROs should be conducted in the order specified in Section 9.5 immediately after ICF (where applicable). The laboratory manual will provide further guidance on the order of sample collection.

[a] Screening Visit will be performed between Day -35 and -14, the Screening Period continues until Day -1.

[b] One or two days after the subject's first 3 doses of IMP, the subject will be telephoned, and a healthcare professional will visit the subject at home to collect PK samples and immunoglobulins (total IgG and IgG subclasses) (only at Visit 7). Alternately, the visit can be conducted at the site as deemed necessary by site personnel and/or the subject.

[c] The following visits (9, 11, 13, 15, 18, and 20) will be performed by a healthcare professional visiting the subject at his/her home. Alternately, the visits can be conducted at the site as deemed necessary by site and/or subject. Feasibility of IMP dosing in a home setting will have to be confirmed before the visit is conducted (see Section 8.2).

[d] For eligibility criteria the lab data from Screening will be used. However, the urine pregnancy test at Visit 2 also must be negative for eligibility.

[e] On dosing visits prior to Visit 9 vital signs will be measured prior to IMP administration, at the end of the infusion, at 2 and 4 hours after the end of the infusion. From Visit 9, vital signs will be measured predose, at the end of the infusion and 2 hours after the end of the infusion only. At nondosing visits, vital signs need only be taken once during the visit. For subjects requiring additional assessments due to AEs (see Table 5-2), additional vital sign measurements may be taken based on the timing of the assessments.

[f] Body weight at screening will be used for calculation of the dose. Height will be assessed only at Screening.

[g] A full C-SSRS assessment will be performed only when subject has a positive response to the suicidal ideation query. If a subject has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C-SSRS assessments, the subject will be excluded or withdrawn from the study and immediately referred to a Mental Healthcare Professional.

[h] See requirements in Table 5-2 in case the subject experiences severe headache.

[i] Serology includes hepatitis C virus (HCV)-antibodies (Ab)+, hepatitis B virus antibodies (HBsAg and HBcAb), human immunodeficiency virus antibodies (HIV1 and HIV2).

[j] The pregnancy test must be negative before dosing. Note that the final urinary pregnancy test of the study should be no longer than 90 days after the final dose of IMP.

[k] The IGRA test will be performed in a central laboratory. Subject should not be dosed until IGRA result is available and negative.

[l] At Visits 2, 4, 6, 8, and 10, PK samples should be taken predose and 4 hours postdose for all subjects. At Visits 12, 14, and 16 a predose sample only should be taken. At Visits 3, 5, 7 and 17, samples to be taken once during the visit.

[m] Serum complement (C3, C4), plasma complement (C3a, C5a), and serum cytokines should be taken predose at Visit 2 for all subjects. Samples should be taken predose and 4 hours postdose at Visits 4, 8, 12, and 16 for all subjects. See Table 5-2 for sampling in case of infusion reactions (with the exception of local site infusion reactions).

[n] At Visits 2, 4, 8, 12 and 16, samples for exploratory biomarkers should be taken predose. See Table 5-2 for sampling in case of AE of interest.

[o] Assessment to be performed before all other assessments at each visit (including the Screening Visit, where possible) except ICF.

[p] If a subject has had a recent radiograph of the chest within 3 months prior to the Screening Visit, it may be used as the Screening chest x-ray.

[q] Stabilization visits should take place in case of the subject relapse. Visits should be performed every 1 to 3 weeks at the discretion of the investigator until subject is stabilized. Stabilization may last from 2 weeks up to 12 weeks. At the end of stabilization, subjects who completed the Treatment Period without a CIDP relapse can enter the OLE study (CIDP04) immediately; the other subjects continue SOC. Time of required follow-up from last IMP dose to the FV is 12 weeks minimum. The stabilization visit schedule still applies (every 1 to 3 weeks).

[r] For subject entering in OLE immediately after completion of the Treatment Period.

[s] Observation Period starts the day after Visit 16.

[t] Laboratory samples during stabilization should be scheduled every 4 to 6 weeks.

5.2.1 Additional study assessments

In addition to those detailed in Table 5–1, the assessments in Table 5-2 may be required in case of infusion reactions or AEs of interest (severe headache, moderate to severe diarrhea, moderate to severe abdominal pain, or moderate to severe vomiting). Note that additional vital sign measurements may be taken based on the timing of the assessments.

Table 5-2: Additional study assessments

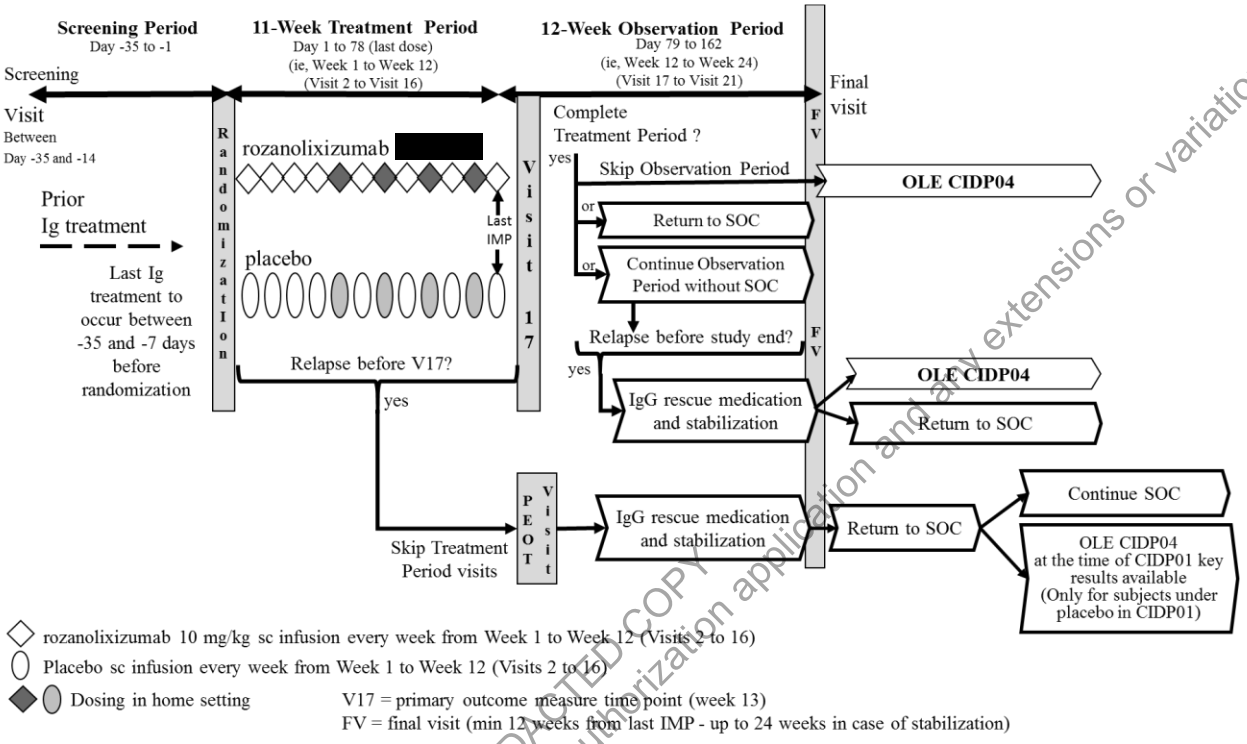
Assessment	When applicable
For subjects who experience infusion reactions (excluding local injection site reactions):	
Complements and cytokines	Samples required for all subjects are detailed in the schedule of study assessments (Table 5–1). In subjects who experience an infusion reaction within the first 2 hours at Visits 4, 8, 12, and 16, samples should also be taken 2 hours postdose (see Section 12.1.9 and Section 18.1). In subjects who experience an infusion reaction at Visits 2, 6, 10, and 14, samples should be taken 2 hours postdose and 4 hours postdose (see Section 12.1.9 and Section 18.1).
For subjects who experience an AE of interest, including severe headache, moderate to severe diarrhea, moderate to severe abdominal pain, or moderate to severe vomiting: If the AE is initially reported at a home visit or during a telephone call, the subject should be reviewed at the study site as soon as is practically possible for further investigation.	
Exploratory biomarkers	Samples required for all subjects are detailed in the schedule of study assessments (Table 5–1). In subjects who experience an AE of interest (as defined in Section 12.1.1.4) at Visits 8, 12 and 16, samples should also be taken 4 hours postdose.
For subjects who experience severe headache:	
Headache Questionnaire	In subjects who report severe headache, this assessment will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply) (see Section 12.1.10).
Full neurological examination	Assessments required for all subjects are detailed in the schedule of study assessments (Table 5–1). In subjects who report severe headache at the clinic visit, a full neurological examination (including fundoscopy) should be performed (see Section 12.1.10). In subjects who report a severe headache whilst at home a visit to the site for the full neurological examination should be arranged for as soon as is practically possible.
Other	In subjects who report severe headache, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection are to be performed if indicated at the discretion of the investigator (see Section 12.1.10).
For subjects who experience moderate or severe diarrhea:	
Stool sample assessment	In subjects who report moderate or severe diarrhea, stool collection and analysis will be performed. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally (see Section 12.1.11). If the moderate or severe diarrhea is initially reported at a home visit or during a telephone call, the subject should be reviewed at the study site as soon as practically possible.

AE=adverse event; CSF=cerebral spinal fluid; CT=computed tomography; LP=lumbar puncture; MRI=magnetic resonance imaging.

5.3 Schematic diagram

A study schematic is presented in Figure 5-1.

Figure 5-1: Schematic diagram



FV=Final Visit; Ig=immunoglobulin; OLE=open-label extension; PEOT=premature end of treatment; sc=subcutaneous; SOC=standard of care; V=Visit

See Table 8–1 for details on the management of the Observation and Stabilization Periods.

5.4 Rationale for study design and selection of dose

5.4.1 Pathophysiology of CIDP

Production of pathogenic auto-antibodies is a major feature of a number of autoimmune diseases often associated with a specific pathomechanism. Cellular and humoral immune mechanisms are thought to be involved in the pathogenesis of CIDP resulting in inflammatory lesions in the spinal roots, proximal nerve trunks, and along the peripheral nerves. The essential role of the autoimmune antibodies in mediating this pathology is supported by the improvement seen after PLEX and IA. Identification of the specific antigenic target(s) of the autoimmune antibodies in CIDP is expanding with recent immunological techniques. Treatments aimed at reducing the quantity of circulating IgG auto-antibodies are being used for primary and secondary therapy of autoimmune diseases, particularly where corticosteroid-based immune suppression is not or no longer effective. The therapeutic approach of these treatments is based on lowering levels of pathogenic auto-antibodies, which represents rational and effective treatment modalities of autoimmune diseases.

5.4.2 Mechanism of action of rozanolixizumab

Rozanolixizumab is a humanized IgG4 monoclonal antibody that is being developed as an inhibitor of the activity of FcRn. The FcRn recycles IgG and albumin and transports it bidirectionally across epithelial barriers. Recent studies have shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling it from the sorting endosome to the cell surface (Anderson et al, 2006). Rozanolixizumab has been specifically designed to block IgG binding to FcRn without blocking the binding and recycling of albumin. By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of IgG antibodies, including IgG auto-antibodies. The aim is to reduce the concentration of pathogenic IgG in patients with autoimmune diseases mediated by the action of IgG auto-antibodies.

5.4.3 Choice of study design and endpoints

The primary objective of the study is to evaluate the clinical efficacy of rozanolixizumab as a treatment for subjects with CIDP. This 2-arm parallel design study will compare the change from Baseline to Week 13 (Day 85) in iRODS score in the rozanolixizumab compared to placebo treatment groups as the primary efficacy variable. In addition, the study will evaluate efficacy using CIDP relapse up to Week 13 (Day 85) after treatment start according to the iRODS, adjusted INCAT scores, and maximum grip strength as assessed by site personnel, as well as treatment comparison versus placebo for the rozanolixizumab group. Both the iRODS and INCAT are measures of disability in CIDP. The INCAT scale was used in the registration study for IGIV-C (Gamunex-C; Hughes et al, 2008). The iRODS has demonstrated significantly higher responsiveness to the ordinal-based INCAT-Overall Neuropathy Limitation scale (INCAT-ONLS) and the modified INCAT sensory scale when using the minimum clinically important differences using the obtained individual standard error (MCID-SE) method for defining a relapse (MCID-SE ≤-1.96) (Vanhoutte et al, 2015; Draak et al, 2014). The randomized, placebo-controlled study design is widely accepted as optimal for assessing efficacy. Grip strength was assessed in the CIDP ICE (Merkies et al, 2010) and the PATH trials (van Schaik et al, 2017) and 14kPa was evaluated to be the MCID for determining a relapse.

A treatment duration of 11 weeks was judged to be sufficiently long to evaluate a difference between rozanolixizumab [redacted] treatment and placebo (Nobile-Orazio et al, 2015; Hughes et al, 2008).

5.4.4 Rationale for dose selection

The dose and regimen of IMP to be used in the current study (rozanolixizumab [redacted] sc) was selected based on the results from first-in-human study UP0018, alongside the emerging safety data from the MG and ITP studies (MG0002 and TP0001).

UP0018 was a randomized, subject-blind, investigator-blind, placebo-controlled, single dose-escalating study to evaluate the safety and PK and to explore the PD of rozanolixizumab doses of [redacted] in 49 healthy male and female subjects. Data indicate that mean absolute decreases in IgG and mean percent change from Baseline IgG were greater in the active dose groups (n=6 each) compared to the pooled iv and sc placebo group (n=12) with maximum decreases of 49.3% (range: 44.6% to 55.9%) observed on Day 6 for a rozanolixizumab [redacted] iv dose and 42.8% (range: 39.6% to 48.6%) on Day 9 for a rozanolixizumab [redacted] sc dose. Rozanolixizumab was tolerated with an acceptable

safety profile after the single administration of a [redacted] sc dose, and all subject-reported TEAEs had a maximum intensity of mild or moderate.

MG0002 is a completed, Phase 2, multicenter, randomized, investigator- and subject-blind, placebo-controlled, 2-arm repeat dose, treatment sequence study evaluating the safety and efficacy of rozanolixizumab sc [redacted] in 43 subjects with generalized MG.

[redacted] Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] sc were generally [redacted] and well tolerated, with an acceptable safety profile. No new safety concerns were identified; a summary of results is included in the IB.

TP0001 is a completed, Phase 2, multicenter, open-label, multiple-arm study to evaluate the safety, tolerability, and efficacy of rozanolixizumab in subjects with primary persistent or chronic ITP. The following dose arms were used in the study:

- Dose Arm 1 (15 subjects): rozanolixizumab [redacted]
- Dose Arm 2 (15 subjects): rozanolixizumab [redacted]
- Dose Arm 3 (12 subjects): rozanolixizumab [redacted]
- Dose Arm 4 (12 subjects): rozanolixizumab [redacted]
- Dose Arm 5 (12 subjects): rozanolixizumab [redacted]

[redacted] dose was well-tolerated, and a summary of the safety results is included in the IB. However, it should be noted that the exposure of rozanolixizumab was lower in subjects with ITP than subjects with MG when dosed with the same dose level.

The dose-exposure-response relationship, with total IgG as the primary endpoint, was determined using non-linear mixed effects modeling of the data from UP0018. The derived population PK-PD (structural PK-PD model based on that of Lowe [Lowe et al, 2010]) was then used to guide, through simulation, the selection of appropriate repeat dose regimens that would mimic decreases achieved by plasmapheresis paradigms and result in an IgG reduction of 70% or greater. The model-based simulations demonstrate that the chosen dose regimen of [redacted] sc administered weekly for a total of 12 doses are expected to produce maximum mean IgG reductions of >70% over the Treatment Period. Based on simulations, it is expected that these IgG reductions will be reached rapidly and maintained consistently with the selected dosing regimen.

This study will utilize the same liquid formulation at [redacted] as was used in the first in human study. In the first in human study, individual dose was achieved by diluting the formulation prior to administration. Based on the heaviest subject (81kg) at the highest sc dose [redacted]), the maximum concentration given was [redacted]. This change in concentration is not predicted to have an impact on local tolerability, however to allow this to be fully assessed

the first two infusions in each subject will be given at a slower rate of approximately [redacted]. If no tolerability concerns are identified subsequent infusions may be given at rates up to [redacted].

5.4.5 Justification for additional genomic analysis

CIDP is a significantly disabling disorder. However, evidence for genetic predisposition to disease or to response to therapy is limited. No genome wide association studies have been completed and unusually for an immune mediated disease, no clear human leukocyte antigen association demonstrated. Although reports of genetic findings associated with disease or response to therapy are scarce, the role of undiscovered gene variants in pathways relating to immune system biology or peripheral nerve function cannot be ruled out. As genome wide analysis of CIDP patients becomes feasible and affordable, a clearer understanding of the role of genetic and genomic factors in CIDP biology is likely to be forthcoming.

Through the collection of whole blood, DNA analysis will help facilitate identification and characterization of genetic and/or epigenetic components of CIDP and will lead to important clues into the pathogenesis of disease and possibly advance understanding of drug response phenotypes.

Gene transcription signatures associated with CIDP biology and response of CIDP patients to IVIg therapy have been generated from whole blood messenger RNA (mRNA) microarray analysis. Such profiles may provide molecular insight into disease biology and activity and can facilitate patient stratification via gene expression panels predictive of therapeutic response and clinical outcomes.

MicroRNAs (miRNAs) are short (19-25 nucleotides) evolutionarily conserved single-stranded RNA molecules that regulate the expression of genes involved in diverse biological processes. The effect of miRNA on mRNA is mediated through the binding of the miRNA to the target mRNA ribonucleoprotein complex resulting in altered expression and decreased protein translation.

Collection of blood for analysis of RNA, proteins, and metabolites will facilitate insight into the molecular etiology of CIDP at the genomic level and may enable identification of candidate markers for treatment effect and safety, and assessment of the feasibility of patient stratification.

In summary, the DNA, RNA, proteins, and metabolites elements of CIDP require further elucidation to understand the cause, progression, and appropriate treatment of CIDP. Through the collection of blood DNA, RNA, serum, and plasma samples, these analyses will help enable further investigation of this complex disease.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject.
2. The subject is considered reliable and capable of adhering to the protocol visit schedule, or medication intake according to the judgment of the investigator.
3. Subject is ≥18 years of age at Visit 1 (Screening).

4. Subject has a documented definite or probable diagnosis of CIDP according to the EFNS/PNS criteria 2010.
5. Subject has an Ig-dependency confirmed by clinical examination during therapy or upon interruption or reduction of therapy within 18 months prior to Screening and documented in medical history (ie, that a decrease or withdrawal of immunoglobulin was attempted that resulted in a clinically relevant decrease in function).
6. Subject is on a stable dosage (not more than ±20% deviation) for SCIg or IVIg and a fixed interval for at least 4 months of either treatment, eg, once weekly ±2 days for SCIg or every 2 to 6 weeks ±5 days IVIg, respectively, for stability in functioning between dosing.
7. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of IMP at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period of 3 months after their final dose of IMP. Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. According to the International Council for Harmonisation (ICH) M3 R2, highly effective methods of birth control include:

   – Combined (estrogen- and progesterone-containing) hormonal contraception (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study).
   – Progesterone-only hormonal contraceptives (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study).
   – Progesterone-releasing intrauterine systems or the TCu 380A intrauterine device.
   – Vasectomized partner (provided sole partner and partner has medical proof of surgical success).
   – True heterosexual sexual abstinence is an acceptable form of contraception when this is in line with the preferred and usual lifestyle of the person. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.

   Women not agreeing to use birth control must be of nonchildbearing potential, defined as being:

   – Postmenopausal (for at least 2 years before the Screening Visit), verified by serum follicle-stimulating hormone level >40mIU/mL at the Screening Visit, or
   – Permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or
   – Congenitally sterile

8. Male subjects with a partner of childbearing potential must be willing to use a condom when sexually active during the study and for 3 months after the final administration of IMP. In addition, the female partner of childbearing potential of a male subject must be willing to use a highly effective method of contraception (as above), during the study period and for 3 months after the final administration of IMP. Sperm donation is not permitted during the study and for 3 months after final administration of IMP.

6.2 Exclusion criteria

6.2.1 Exclusion criteria related to study participation

Subjects are not permitted to enroll in the study if any of the following criteria are met:

1. Subject has previously received treatment in this study or subject has previously been exposed to rozanolixizumab.
2. Subject has participated in another study of an IMP (or a medical device) within the previous 30 days of Screening Visit or is currently participating in another study of an IMP (or a medical device). For experimental biological agents refer to Exclusion Criterion 26.

6.2.2 Exclusion criteria related to CIDP diagnosis

3. Subject has a current diagnosis or has a history of Type 1 or Type 2 diabetes mellitus and/or hemoglobin A1c level >6.0%.
4. Subject with IgM paraproteinemia.
5. Subjects with known IgM-mediated neuropathy (eg, multifocal motor neuropathy).
6. Clinical or known evidence of associated systemic diseases that might cause neuropathy, including but not limited to connective tissue disease, Lyme disease, Castleman's disease and systemic lupus erythematosus, malignant plasma cell dysplasia, or treatment with agents that might lead to neuropathy (eg, amiodarone therapy).
7. Subjects on an average dose less than 0.4g IgG/kg/month over the past 4 months.

6.2.3 Exclusion criteria related to health status/safety of the subject

8. Female subject who is pregnant or lactating.
9. Subject has any medical (acute or chronic illness) or psychiatric condition that, in the opinion of the investigator, could harm the subject or would compromise the subject's ability to participate in this study.
10. Subject has 12-lead ECG with abnormalities considered to be clinically significant upon medical review.
11. Subject has renal impairment, defined as:

– Serum creatinine level of ≥1.4mg/dL for females and ≥1.5mg/dL for males at Screening Visit.

12. Subject has an absolute neutrophil count <1500/mm3 (1.5x109/L).

13. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

    If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.

14. Subject has a history of alcohol use disorder or other substance use disorder (as per Diagnostic and Statistical Manual of Mental Disorders-5 [American Psychiatric Association, 2013]) within 12 months of Screening Visit.

15. Subject has a history of clinically relevant ongoing chronic infections including but not limited to human immunodeficiency virus (HIV), hepatitis B, hepatitis C, or is tested positive for HIV (anti-HIV1 or anti-HIV2 antibodies), hepatitis B (HBsAg positive or HBcAb positive without positive HBsAb), or hepatitis C antibody (HCAb) at the Screening Visit.

16. Subjects with known TB infection, at high risk of acquiring TB infection, or latent tuberculosis infection (LTBI), or current/history of nontuberculosis mycobacteria (NTMB) are excluded.

a. Known TB infection whether present or past is defined as:

    – Active TB infection or clinical signs and symptoms suggestive of TB (pulmonary or extrapulmonary).

    – History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection.

    – Any historical evidence by radiography or other imaging modalities consistent with previously active TB infection.

b. High risk of acquiring TB infection is defined as:

    – Known exposure to another person with active TB infection within the 3 months prior to Screening.

    – Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. LTBI (see Section 12.3 for further details and instructions).

d. NTMB is defined as a group of lung infections caused by mycobacteria different from mycobacterium tuberculosis infections.

17. Subject has a family history of primary immunodeficiency.
18. Subject has a clinically relevant active infection (eg, sepsis, pneumonia, abscess) or has had a serious infection (resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to the first dose of IMP.
19. Subject has active neoplastic disease or history of neoplastic disease within 5 years of Screening Visit (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix which has been definitively treated with SOC approaches).
20. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a "yes" answer to numbers 4 or 5 on the screening Columbia Suicide Severity Rating Scale (C-SSRS).
21. Subject has any planned elective surgery due to occur during the study dosing period which in the opinion of the investigator could interfere with study procedures.
22. Subject has a history of known inflammatory bowel disease, active diverticular disease, or a history of confirmed duodenal, gastric, or esophageal ulceration in the past 6 months.

6.2.4 Exclusion criteria related to the IMP/concomitant medications/procedures

23. Subject has a known hypersensitivity to any components of the IMP.
24. Subject has a history of hyperprolinemia, since L-proline is a constituent of rozanolixizumab.
25. Subject has received a live vaccination within 8 weeks prior to the Baseline Visit; or intends to have a live vaccination during the course of the study or within 7 weeks following the final dose of IMP.
26. Subject has received any experimental biological agent within or outside of a clinical study in the past 3 months or within 5 half-lives prior to Baseline (whichever is longer) (refer to Table 6-1).
27. Subject has had prior treatment with rituximab, ofatumumab, or ocrelizumab in the 6 months prior to the Baseline Visit or subject has had prior treatment with rituximab, ofatumumab, or ocrelizumab in the 12 months prior to Baseline and B cells are not within the normal range.
28. Subject has been treated with immunosuppressants, biologics, and other therapies in the recent timeframe as detailed in Table 6-1 OR has been on permitted medications detailed in Table 7-3, but has not been on stable dosing regimens of those medications as detailed in Table 7-3.

Table 6-1: Time restrictions required prior to Randomization Visit (Visit 2) for immunosuppressants, biologics and other therapies

Generic name	Time restrictions required prior to Randomization Visit (regardless of route)
Immunosuppressants	
Cyclophosphamide	[redacted]
Pimecrolimus	
Vinca alkaloids (vincristine, vinblastine)	
Biologics (mabs and fusion proteins)	
Abatacept (CTLA 4-Ig)	
Belimumab	
Golimumab	
Natalizumab	
Ofatumumab	
Rituximab	
Ocrelizumab	
Atacicept (TACI-Ig)	
Veltuzumab	
Other biologics	
Others	
Rigerimod	
PLEX	

CTLA 4-Ig=cytotoxic T lymphocyte-associated molecule-4 immunoglobulin; mabs=monocolonal antibodies; PLEX=plasma exchange; TACI-Ig=transmembrane activator and calcium modulator and cyclophilin ligand interactor-immunoglobulin

Note: For other immunotherapies not included in the table, consult with Medical Monitor prior to enrollment.

6.3 Rescreening of subjects

For subjects, otherwise fully eligible but not able to be randomized as planned for nonclinical reasons, rescreening may be allowed at the discretion of the investigator, following discussion with the sponsor's Medical Monitor and/or Study Physician.

If a subject has 1 isolated test result in the exclusionary range which is deemed not being clinically significant by the investigator, retesting may be allowed at the discretion of the investigator, following discussion with the sponsor's Medical Monitor and/or Study Physician. If the normalization of the test result occurs within the Screening Period, then no other screening procedures need to be repeated.

6.4 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects ***MUST be withdrawn from the study*** if any of the following events occur:

1. Subject withdraws his/her consent.
2. Subject becomes pregnant during the study, as confirmed by a positive pregnancy test.

Subjects ***must discontinue IMP*** if any of the following events occur:

1. Subject develops an illness that would interfere with his/her continued participation.

- Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy (including but not limited to bacteremia or sepsis, bacterial meningitis, osteomyelitis or septic arthritis, bacterial pneumonia, or visceral abscess).
- Subject has an AE of severe infusion reaction requiring corticosteroid and/or epinephrine therapy (see Section 12.1.9).
- Subject has an AE of severe anaphylactic reaction requiring corticosteroid and/or epinephrine therapy.
- Subject has a TB test that is confirmed positive or any further evidence suggestive of potential TB infection (eg, exposure) and further examinations result in a diagnosis of active TB or LTBI (refer to Section 12.3.7 for further details and instructions).
- If a nontuberculosis mycobacterium infection (NTMBI) is identified during a study, the same withdrawal procedures as those used for an active TB infection identified during the study should be followed.

2. Subject has active suicidal ideation as indicated by a positive response (Yes) to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional.
3. The sponsor or a regulatory agency requests withdrawal of the subject.
4. Subject needs or takes PLEX, dexamethasone or rituximab.
5. Subject is treated with rescue medication and/or relapses during the Treatment Period (refer to Section 7.7.3).

Subjects ***may be discontinued from IMP*** at the discretion of the investigator, Medical Monitor, and Study Physician if any of the following events occur:

1. Subject takes prohibited concomitant medications during the Treatment Period as defined in this protocol (refer to Section 7.7.2).
2. Subject experiences a severe AE of headache which is considered related to the IMP in the opinion of the investigator (see Section 12.1.10). Following an event of a severe headache, a subject may continue participation in the study if the subject is willing to do so and the investigator, Medical Monitor, and Study Physician agree that the subject's continuation in

the study poses no significant risk for the subject. The use of symptomatic headache treatment is allowed at the discretion of the investigator. The IMP dose can be reduced to [redacted] (or its placebo equivalent) if the headache persists despite symptomatic treatment (refer to Section 12.1.10 for details on the medical management of headaches and Section 7.2 for treatment to be administered).

3. Subject experiences severe AE of gastrointestinal disturbance which is considered related to the IMP in the opinion of the investigator. Following an event of a severe gastrointestinal disturbance, a subject may continue in the study if they are willing to do so and the investigator and Medical Monitor agree that the subject's continuation in the study poses no significant risk

Subjects ***may be withdrawn from the study*** at the discretion of the investigator, Medical Monitor, and Study Physician if any of the following events occur:

1. Subject is noncompliant with the study procedures or medications in the opinion of the investigator.
2. In case of intake of prohibited concomitant medication other than IVIg, SCIg, PLEX, dexamethasone or rituximab, the investigator will (where possible) discuss with the Medical Monitor and/or Sponsor Study Physician and a *decision will be made whether the subject should discontinue IMP*.

Subjects who withdraw from the study or discontinue IMP during the Treatment Period should complete the assessments outlined for Visit 17/PEOT (see Table 5–1 and Section 8.4). Subjects who withdraw from the study and who are not entering the OLE will be encouraged to return to the clinic for all visits during the Observation Period (which should occur every 2 or 3 weeks (±3 days) following their final dose of IMP) and the Final Visit (scheduled 12 weeks after final dose of IMP). The subjects can return to their SOC during the Observation Period.

Investigators should attempt to obtain information on subjects in the case of withdrawal.

For subjects considered as lost to follow up, the investigator should try (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation, plus whether or not the blind was broken, with the reason and date for withdrawal, discontinuation, and/or unblinding.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

Subjects who withdraw from the study will not be replaced.

6.4.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require ***immediate and permanent*** discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 12.2.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 12.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

[redacted] for sc administration is supplied from a commercial source.

Details of the IMPs and their specifications are provided in the IMP Handling Manual.

7.2 Treatments to be administered

Eligible subjects will be randomized 1:1 to receive rozanolixizumab [redacted] or placebo [redacted]) by sc infusion as follows:

- Subjects in Treatment Arm 1 will receive 1 sc dose of rozanolixizumab [redacted] (see Table 7-1) weekly for 12 weeks (Visits 2, 4, and 6, and Visit 8 through Visit 16).
- Subjects in Treatment Arm 2 will receive 1 sc dose of placebo weekly for 12 weeks (Visits 2, 4, and 6, and Visit 8 through Visit 16).

The interval between 2 consecutive dosing should at least 5 days.

Table 7-1: IMP doses to be administered (equivalent to approximately [redacted] by body weight

Body weight ranges	IMP doses to be administered (equivalent to approximately [redacted][a])	IMP volume to be administered
≥40 to <49kg	[redacted]	3mL
≥49 to <63kg		4mL
≥63 to <77kg		5mL
≥77 to <91kg		6mL
≥91 to <105kg		7mL
≥105 to <119kg		8mL
≥119 to <133kg		9mL
≥133 to <147kg		10mL
≥147 to <161kg		11mL
≥161 to 170kg		12mL

IMP= investigational medicinal product
[a] Doses administered will be ±10% of the intended dose, except for subjects with a body weight of 47 to 50kg and 63kg.

In case of tolerability issues (eg, severe headache) and if symptomatic headache medication (eg, acetylsalicylic acid 1000mg) is not sufficient, the dose of IMP could be lowered to [redacted] (see Table 7-2) (or equivalent placebo) during the next visit when the investigator, Medical Monitor, and Study Physician agree that the dose reduction poses no significant risk for the subject (see Section 12.1.10).

Table 7-2: IMP doses to be administered (equivalent to approximately [redacted] by body weight

Body weight ranges	IMP doses to be administered (equivalent to approximately [redacted])	IMP volume to be administered
≥40 to <49kg	[redacted]	2mL
≥49 to <69kg		3mL
≥69 to <89kg		4mL
≥89 to <109kg		5mL
≥109 to <129kg		6mL

Table 7-2: IMP doses to be administered (equivalent to approximately 7mg/kg) by body weight

Body weight ranges	IMP doses to be administered (equivalent to approximately [redacted]	IMP volume to be administered
≥129 to <149kg	[redacted]	7mL
≥149 to <169kg	[redacted]	8mL
≥169 to 170kg	[redacted]	9mL

IMP= investigational medicinal product

The IMP will be administered at the clinic or in a home setting (Visits 9, 11, 13, and 15) (see Table 5–1). Home administration is subject to a set of conditions (see Section 8.2) to ensure subject safety.

The IMP will be administered as a sc infusion using a syringe pump.

- For the first 2 doses, [redacted].
- For the subsequent doses, [redacted]

[redacted]. The chronology of all infusion related events should be recorded accurately in the source data and eCRF.

The subject's body weight at Screening Visit will be used for the dose calculation. The dose will be constant for a subject throughout the duration of the study, and will not be adjusted during the treatment.

The exact procedure for dose preparation according to treatment arm and body weight will be provided in the IMP Handling Manual.

7.3 Labeling

Clinical drug supplies will be labeled in accordance with the current ICH guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

7.4 Handling and storage requirements

The investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (ie, every workday), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

In case of home dosing, the IMP will be transferred to the subject's home. The related process will also be described in the IMP Handling Manual.

7.5 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed (all details are provided in the IMP Handling Manual).

The investigator may assign some of the investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures (SOPs) or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.6 Procedures for monitoring subject compliance

Subject compliance will be ensured by the administration of IMP by sc infusion by designated site personnel. Drug accountability must be recorded on the Drug Accountability form.

7.7 Concomitant medications/treatments

7.7.1 Permitted concomitant treatments (medications and therapies)

Concomitant treatments/medications permitted at a stable dose during the course of the study are detailed in Table 7-3.

Table 7-3: Permitted concomitant treatments

Permitted medications	Dose	Comment
Oral corticosteroids (prednisolone)	≤30mg/day	[redacted]
Methotrexate	≤30mg/week	
Mycophenolate mofetil	≤3g/day	
Cyclosporin [a]	≤5mg/kg/day for unmodified ≤4mg/kg/day for modified (microemulsion)	
Azathioprine	≤3mg/kg/day	
Tacrolimus [b]	≤5mg/day	

[a] Doses higher than listed are permissible if plasma trough level is ≤300ng/L.
[b] If the total daily weight-based dose is >5mg, then a plasma trough level should be checked to ensure subject is not above the recommended therapeutic range.

The use of cannabidiols and medicinal marijuana (prescribed by a physician) is also permitted. When applicable, the subject must be on a stable dose of cannabidiols and/or medicinal marijuana for [redacted].

7.7.2 Prohibited concomitant treatments (medications and therapies)

The following medications are prohibited during the Treatment Period:

- IVIg and SCIg (refer to Section 7.7.3)
- All biologics including rituximab
- Cyclophosphamide
- Pimecrolimus
- IPP-201101 (Lupuzor™)
- PLEX
- IA
- Systemic dexamethasone

If a subject requires or takes IVIg, SCIg, PLEX, dexamethasone, or rituximab they *must be discontinued from IMP*. In all other cases of intake of prohibited concomitant medication, the investigator will (where possible) discuss with the Medical Monitor and/or Sponsor Study Physician and a *decision will be made whether the subject should discontinue IMP* (see Section 6.4).

If a subject is discontinued from IMP they should be encouraged to complete Visit 17/PEOT and complete the Observation Period (see Table 5–1 and Section 6.4).

7.7.3 Rescue medication

If, at any time during the Treatment and Observation Period, the subject relapses according to the predefined criteria for relapse as specified in Section 4.1.2 using the subject's score on iRODS, INCAT, or maximum grip strength (assessed by site personnel), and supported by the medical judgement of the investigator, then rescue medication must be considered and the subject will be withdrawn from IMP (see Section 6.4). The subject will return to the SOC Ig treatment (eg, IVIg of 2g/kg) as rescue medication at the time of relapse at the discretion of the investigator. The subject will have the opportunity to be stabilized over a period of 2 weeks to maximum 12 weeks starting from the relapse visit (ie, PEOT or later visit; see Section 8.3). Once stabilized, the subject who completed the Treatment Period with no CIDP relapse, will be offered the possibility to enter in the OLE (CIDP04) and be treated with rozanolixizumab from that moment onward. The subject will complete the FV (V21) and enter the OLE on the same day. If a subject relapses during Treatment Period or does not wish to enter the OLE, the subject will continue their SOC treatment after stabilization. They will continue the stabilization visit schedule (every 1 to 3 weeks) until they have a follow-up of 12 weeks after last IMP dose.

7.8 Blinding

7.8.1 Procedures for maintaining and breaking the treatment blind

7.8.1.1 Maintenance of study treatment blind

[redacted]

All subject treatment details, ie, rozanolixizumab [redacted] sc or placebo, will be allocated and maintained by the interactive response technology (IRT) system.

Study site pharmacists or other suitably qualified site personnel who are responsible for preparation of IMP treatments and any necessary assistants will have access to treatment allocations for individual subjects via the IRT. The unblinded pharmacy monitors from the contract research organization (CRO), and the Clinical Supply Manager will also have access to the treatment allocations and to the drug accountability records, if applicable.

Laboratory results that could unblind the site personnel will not be disclosed to sites and will be reviewed accredited unblinded study team.

The following individuals will, as necessary, have access to the randomization code as indicated:

- Sponsor Drug Safety staff as needed for reporting SAEs to regulatory authorities.
- Sponsor and/or CRO staff supporting preparation of the data outputs for the DMC review and/or any interim efficacy analyses.
- The laboratories involved in the detection of PK, PD, and immunological variables.
- A Quantitative Clinical Pharmacologist/Modeling and Simulation Scientist.

7.8.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the subject has been allocated by contacting the IRT. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible. The study blind should not be broken except in a medical emergency, where knowledge of the IMP received would affect the treatment of the emergency.

The Clinical Project Manager (CPM) will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the investigator must be recorded in the source documents and on the Study Termination eCRF page.

7.9 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule which will be produced by the IRT vendor. The randomization will be stratified according to previous route of administration for Ig treatment (ie, SCIg and IVIg). The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

To enroll a subject (Visit 1), the investigator or designee will contact the IRT and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at Screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To randomize a subject, the investigator or designee will contact the IRT and provide brief details about the subject to be randomized. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study. Randomization numbers will be automatically transferred from the IRT to the clinical database.

The randomization window is described in Section 8.2.

8 STUDY PROCEDURES BY VISIT

Study visits should preferably be conducted at the same time of the day throughout the study. Details of the study assessments to be performed at specific time points prior to and after IMP administration are provided in Table 5–1. An outline of all assessments performed is provided in the following sections. All assessments are to be completed in the recommended order if possible. The Informed Consent form (ICF) should be completed before any assessment. The PROs should be conducted in the order specified in Section 9.5 immediately after ICF (where applicable). The laboratory manual will provide further guidance on the order of sample collection. Additional assessments which may be required in case of infusion reactions or AEs of interest (severe headache, moderate to severe diarrhea, moderate to severe abdominal pain, or moderate to severe vomiting) are provided in Table 5-2; these assessments are not included in the by-visit study procedures within Section 8.

8.1 Screening Period (Day -35 to Day -1)

The Screening Period will be a minimum of 2 weeks and generally should not exceed 5 weeks. The purpose of the Screening Period is to evaluate and confirm the subject's eligibility. All subjects must have an Ig dependency that has been confirmed within 18 months before Screening. All subjects must be established on a long-term immunoglobulin maintenance therapy with a stable immunoglobulin infusion regimen at consistent intervals to be considered eligible. Stable dose regimen is defined as subjects remaining on the same dose (not more than ±20% deviation), and fixed treatment interval for at least 4 months, eg, receiving treatment once weekly (±2 days) or every 2 to 6 weeks (±5 days) for SCIg or IVIg, respectively, for stability in functioning between dosing.

The subject's diagnosis, disability, impairment, and past treatments including documentation of dependency on immunoglobulin treatment, current treatment with immunoglobulin at a consistent dosage regimen, and other previous and concomitant medications and treatments will be evaluated at the Screening Visit.

8.1.1 Screening Visit 1 (Day -35 to Day -14)

The following procedures will be performed at the Screening Visit (or as close as possible to the Screening date):

- Informed consent process including obtaining written informed consent from the subject
- iRODS assessment – to be performed before any other assessment after the consenting process
- Query for suicidality (C-SSRS)
- Tuberculosis Signs and Symptoms questionnaire
- Obtain a chest radiograph, unless one has been obtained 3 months prior to the Screening Visit
- Record subject demographics
- Verify (to the extent possible with available Screening Visit 1 information) that subject fulfills all the inclusion criteria and none of the exclusion criteria
- General medical and procedures history
- Prior medication
- Concomitant medical procedures
- CIDP history (symptoms, date of onset, therapy)
- Vital signs (taken once during the visit)
- Body weight (Screening weight will be used for calculation of the dose) and height
- 12-lead ECG
- Full physical examination
- Full neurological examination
- Recording of AEs

- Contact IRT
- Blood sample (the laboratory manual will provide guidance on the order of sample collection) for:
  - Clinical laboratory tests (ie, hematology, clinical chemistry, serology [including hepatitis C and hepatitis B virus-antibodies, human immunodeficiency virus 1 (HIV1) and human immunodeficiency virus 2 antibodies (HIV2)], and interferon gamma release assay [IGRA] for active and latent tuberculosis [LTB])
  - Serum pregnancy test for women of childbearing potential
  - Immunoglobulins (total IgG, IgG subclasses)
  - Vaccination-specific antibody titers ([redacted]
  - [redacted]
- Urine sample for urinalysis
- INCAT assessment
- RT-MRC assessment
- Assessment of grip strength by the site personnel
- Issue subject e-diary for daily record of grip strength
- Provide an appointment to the next visits (see Section 8.2 for details related to scheduling of the next visit)

At the end of the Screening Visit, subjects will be issued a subject e-diary in which they will record daily grip strength from the Screening Visit until the end of study participation. Subjects should be reminded to bring their diaries with them to each clinic visit and to have them available at home nursing visits.

8.2 Treatment Period Visits 2 to 16 (Day 1 to Day 78)

The 11-week Treatment Period begins at the Randomization Visit (Visit 2) on Day 1 to review inclusion and exclusion criteria as well as concomitant medications and treatments. Subjects who remain eligible will be randomized 1:1 to receive rozanolixizumab [redacted] or placebo. All eligible subjects will receive the same treatment allocation for the duration of the study.

- For subjects on an IVIg 3- to 6-week regimen, randomization should occur 1 week before the next planned IVIg dose (according to the baseline IVIg regimen). However, if that specific date is not possible, the Randomization Visit could be conducted up to the date of the next planned IVIg dose (ie, 1 week after the preferred date).
- Subjects on a 2-week IVIg treatment regimen will continue on their regular schedule for 1 further IVIg treatment until randomization. Randomization will occur 1 week before the planned IVIg dose. However, if that specific date is not possible, the Randomization Visit could be conducted up to the date of the next planned IVIg dose (ie, 1 week after the preferred date).

- Subjects on a weekly SCIg treatment regimen will continue on their regular schedule for at least 1 further SCIg treatment until randomization. Randomization should occur on the day of a planned dose (according to the baseline SCIg regimen). However, if that specific date is not possible, the Randomization Visit should be within a window ±2 days of that date.

This will ensure continuation of treatment so that subjects do not relapse prior to start of study treatment.

For the 11-week Treatment Period, visits will occur weekly from Visit 2 to Visit 16. Three additional visits (Visits 3, 5, and 7) will be performed 1 or 2 days after each of the first 3 IMP administrations to monitor safety and collect samples for PK/PD.

At the Randomization Visit (Visit 2), and at Visit 4, Visit 6, and Visit 8 through Visit 16, subjects will receive IMP by a sc infusion. Other study-related assessments and procedures will be conducted as described in the following sections. For site Visits 2, 4, 6, 8, 10, 12 and 16, subjects will be required to remain in the clinic for at least 4 hours following the end of the sc infusion to monitor the safety of the subject and collect appropriate blood samples. Subjects may leave the clinic thereafter provided the investigator has no safety concerns. For all other visits, the visit length should be limited to 2 hours post dose if the investigator has no safety concerns. Visit duration may be extended in case of safety concerns (see Table 5-2).

Visits 3, 5, and 7 are nondosing, safety monitoring visits in which the subject will be telephoned by the site personnel at home. Samples for PK sampling (Visits 3, 5, and 7) and Igs (Visit 7) will be performed as part of the home nursing visits (ie, a healthcare professional visiting the subject at his/her home). Alternately, Visits 3, 5, and 7 can be conducted at the site as deemed necessary by site personnel and/or the subject.

Dosing Visits 9, 11, 13, and 15 are home nursing visits to be conducted by fully trained healthcare professionals (one unblinded for IMP preparation and one blinded for the other assessments) visiting the subject at his/her home. Alternatively, these visits can be conducted at the site as deemed necessary by site personnel and/or subject. Where dosing is done at home the same safety monitoring schedule will be followed as if in clinic. The home nurse will be present during the full duration of the visit. Home visits can be conducted in case the following conditions are met:

- The subject is willing to be dosed and monitored at home over a 2-hour period by a home nurse.
- The subject has shown good acute tolerability to previous administrations of IMP (namely they must have had no moderate or severe infusion reactions, or other AEs which the investigator considers could increase the risk of home administration).
- The subject does not require specific medical supervision based on their medical history/condition.
- The team delivering the home dose must be trained in the identification and management of infusion reactions and hypersensitivity and must have access to immediate treatments (eg, an EpiPen).

- The subject's home allows rapid access to emergency treatment if required (ie, the subject must not live so remotely that a reasonable arrival time of an ambulance could not be predicted).
- The investigator is contactable to support the health care provider (HCP) if needed.
- UCB has not requested to limit the possibility to perform home visits (eg, based on DMC recommendation).

The investigator will be asked to complete a checklist confirming all criteria have been fully evaluated. This checklist will be shared with the UCB study physician and reviewed before IMP administration in a home setting can take place.

If at any time during the Treatment Period, the subject relapses according to the predefined criteria for relapse as specified in Section 4.1.2 using the subject's score on iRODS, INCAT, or maximum grip strength (assessed by site personnel), and supported by the medical judgement of the investigator, then rescue medication must be considered and the subject must be withdrawn from IMP (see Section 6.4 and Section 7.7.3). The subject will return to the SOC (ie, Ig treatment) as rescue medication at the time of relapse and will be stabilized over a period of 2 weeks to maximum 12 weeks starting from PEOT (Visit 17). At the end of the stabilization, the subject will continue SOC. The time required for follow-up since last IMP dose is 12 weeks. The stabilization visit schedule still applies (every 1 to 3 weeks) if the subject has not reached 12 weeks after the last IMP dose at the end of stabilization. The subjects in the placebo arm will be offered the possibility to enter in the OLE and be treated with rozanolixizumab once all subjects have completed the CIDP01 study, the study is unblinded, and key results are available.

8.2.1 Visit 2 (Day 1, Baseline)

The following procedures and assessments will be performed at Visit 2 (Day 1, Baseline):

- PROs should be conducted as the first assessments in the study in the following order:
  - iRODS assessment – to be performed before any other assessment
  - CIDP PRO instrument
  - Fatigue scale
  - PGIS
  - Query for suicidality (predose)
- Verification of inclusion/exclusion criteria (including results of laboratory samples, ECG, chest x-ray performed since Visit 1).
- Assessment of withdrawal criteria (see Section 6.4)
- Prior and concomitant medication
- Concomitant medical procedures
- Vital signs (taken predose, at the end of the infusion, at 2 hours and at 4 hours after the end of the infusion)
- Body weight (predose)

- 12-lead ECG (predose)
- Recording of AEs
- Brief physical examination (predose)
- Brief neurological examination (predose)
- Contact IRT and randomize the subject (upon confirmation of eligibility)
- Administration of IMP
- Urine sample for urinalysis (predose)
- Urine pregnancy test for women of childbearing potential (which must be confirmed negative prior to subject dosing)
- Blood sample (all samples should be taken predose unless otherwise specified; the laboratory manual will provide guidance on the order of sample collection) for:
  - Serum complement (C3, C4) and plasma complement (C3a, C5a)
  - Clinical laboratory tests (ie, hematology, clinical chemistry)
  - Serum cytokines
  - Immunoglobulins (total IgG, IgG subclasses)
  - Neurofilament light chain
  - Exploratory biomarker samples
  - RNA samples
  - CIDP-specific auto-antibodies
  - IgA, IgM, IgE
  - Whole blood for exploratory genetic (DNA)
  - PK of rozanolixizumab (predose and 4 hours postdose)
  - [redacted]
- INCAT assessment (predose)
- RT-MRC assessment (predose)
- Assessment of grip strength by site personnel (predose)
- Review subject e-diary for daily assessment of grip strength

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

8.2.2 Visit 3 Telephone Call and Home Visit (Day 3)

Visit 3 consists of a telephone call from the site personnel and a home nursing visit performed after 1 or 2 days of the previous IMP administration. The home nursing visit will be conducted

by a healthcare professional visiting the subject at his/her home. Alternately, this visit can be conducted at the site as deemed necessary by site personnel and/or subject.

The subject will be telephoned at home and the following assessments performed:

- Subjects will be assessed to see if they meet any of the study withdrawal criteria
- Prior and concomitant medication
- Concomitant medical procedures
- Recording of AEs

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

At home, the following assessments will be performed:

- Vital signs (taken once during the visit)
- Blood sample for:
  - PK of rozanolixizumab

8.2.3 Visit 4 (Day 8)

At Visit 4 the following assessments will be performed:

- iRODS assessment– to be performed before any other assessment
- Query for suicidality (predose)
- Subjects will be assessed to see if they meet any of the study withdrawal criteria
- Prior and concomitant medication
- Concomitant medical procedures
- Vital signs (taken predose, at the end of the infusion, at 2 hours and at 4 hours after the end of the infusion)
- 12-lead ECG
- Recording of AEs
- Brief physical examination
- Brief neurological examination
- Contact IRT
- Administration of IMP
- Urine sample for urinalysis (predose)
- Urine pregnancy test for women of childbearing potential (which must be confirmed negative prior to subject dosing)

- Blood sample (all samples should be taken predose unless otherwise specified; the laboratory manual will provide guidance on the order of sample collection) for:
  - Serum complement (C3, C4) and plasma complement (C3a, C5a) (predose and 4 hours postdose)
  - Clinical laboratory tests (ie, hematology, clinical chemistry)
  - Serum cytokines (predose and 4 hours postdose)
  - Immunoglobulins (total IgG, IgG subclasses)
  - Exploratory biomarker analysis
  - CIDP-specific auto-antibodies
  - IgA, IgM, IgE
  - RNA samples
  - PK of rozanolixizumab (predose and 4 hours postdose)
  - [redacted]
- INCAT assessment (predose)
- RT-MRC assessment (predose)
- Assessment of grip strength by the site personnel (predose)
- Review subject e-diary for daily assessment of grip strength

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

8.2.4 Visit 5 Telephone Call and Home Visit (Day 10)

Visit 5 is a telephone call from the site with a home nursing visit performed after 1 or 2 days of the previous IMP administration. The home nursing visit will be conducted by a healthcare professional visiting the subject at his/her home. Alternately, this visit can be conducted at the site as deemed necessary by site personnel and/or subject.

The subject will be telephoned at home and the following assessments performed:

- Subjects will be assessed to see if they meet any of the study withdrawal criteria
- Prior and concomitant medication
- Concomitant medical procedures
- Recording of AEs

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

At home, the following assessments will be performed:

- Vital signs (taken once during the visit)
- Blood sample for:
  - PK of rozanolixizumab

8.2.5 Visit 6 (Day 15)

At Visit 6 the following assessments will be performed:

- iRODS assessment– to be performed before any other assessment
- Query for suicidality (predose)
- Assessment of study withdrawal criteria
- Prior and concomitant medication
- Concomitant medical procedures
- Vital signs (taken predose, at the end of the infusion, at 2 hours and at 4 hours after the end of the infusion)
- 12-lead ECG
- Recording of AEs
- Brief physical examination
- Brief neurological examination
- Contact IRT
- Administration of IMP
- Urine sample for urinalysis (predose)
- Urine pregnancy test for women of childbearing potential (which must be confirmed negative prior to subject dosing)
- Blood sample (all samples should be taken predose unless otherwise specified; the laboratory manual will provide guidance on the order of sample collection) for:
  - Clinical laboratory tests (ie, hematology, clinical chemistry)
  - Immunoglobulins (total IgG, IgG subclasses)
  - Neurofilament light chain
  - CIDP-specific auto-antibodies
  - IgA, IgM, IgE
  - RNA samples
  - PK of rozanolixizumab (predose and 4 hours postdose)
  - [redacted]

- INCAT assessment (predose)
- RT-MRC assessment (predose)
- Assessment of grip strength by the site personnel (predose)
- Review subject e-diary for daily assessment of grip strength

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

8.2.6 Visit 7 Telephone Call and Home Visit (Day 17)

Visit 7 is a telephone call from the site with a home nursing visit performed after 1 or 2 days of the previous IMP administration. The home nursing visit will be conducted by a healthcare professional visiting the subject at his/her home. Alternately, this visit can be conducted at the site as deemed necessary by site personnel and/or subject.

The subject will be telephoned at home and the following assessments performed:

- Subjects will be assessed to see if they meet any of the study withdrawal criteria
- Prior and concomitant medication
- Concomitant medical procedures
- Recording of AEs

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

At home, the following assessments will be performed:

- Vital signs (taken once during the visit)
- Blood sample for:
  - Immunoglobulins (total IgG, IgG subclasses)
  - PK of rozanolixizumab

8.2.7 Visits 8 (Day 22) through 16 (Day 78) inclusive

All visits and IMP administrations (during the Treatment Period) are performed at 1-week intervals. For site Visits 8, 10, 12 and 16, subjects will be required to remain in the clinic for at least 4 hours following the end of the sc infusion to monitor the safety of the subject and collect appropriate blood samples. Subjects may leave the clinic thereafter provided the investigator has no safety concerns. For all other visits, the visit length should be limited to 2 hours post dose if the investigator has no safety concerns. Visit duration may be extended in case of safety concerns (see Table 5-2). Dosing Visits 9, 11, 13, and 15 are home nursing visits to be conducted by a healthcare professional visiting the subject at his/her home; these visits can be conducted at the site as deemed necessary by site personnel and/or subject. Home dosing will only be undertaken if no tolerability issues have been identified on previous dosing occasions in that subject (see full details in Section 8.2).

The following assessments and procedures will be performed at each visit (unless specified otherwise):

- PROs should be conducted as the first assessments in the study in the following order:
  - iRODS assessment– to be performed before any other assessment
  - CIDP PRO instrument (Visits 10 and 14 only)
  - Fatigue scale (Visits 10 and 14 only)
  - PGIS (Visits 10 and 14 only)
  - PGIC (Visits 10 and 14 only)
- Query for suicidality (predose) (Visits 8, 10, 12, 14, and 16 only)
- Subjects will be assessed to see if they meet any of the study withdrawal criteria
- Prior and concomitant medication
- Concomitant medical procedures
- Vital signs (taken predose, at the end of infusion, at 2 hours after infusion end)
- Vital signs (at 4 hours after infusion end) (Visit 8 only)
- 12-lead ECG (Visits 8, 10, 12, 14, and 16 only)
- Recording of AEs
- Brief physical examination (Visits 8, 10, and 14 only)
- Brief neurological examination (Visits 8, 10, and 14 only)
- Contact IRT
- Administration of IMP
- Urine sample for urinalysis (predose) (Visits 8, 10, 12, 14, and 16 only)
- Urine pregnancy test for women of childbearing potential (which must be confirmed negative prior to subject dosing)

- Blood sample (all samples should be taken predose unless otherwise specified; the laboratory manual will provide guidance on the order of sample collection) for:
  - Serum complement (C3, C4) and plasma complement (C3a, C5a) (predose and 4 hours postdose) (Visits 8, 12, and 16 only)
  - Clinical laboratory tests (ie, hematology, clinical chemistry) (Visits 8, 10, 12, 14, and 16 only)
  - Serum cytokines (predose and 4 hours postdose) (Visits 8, 12, and 16 only)
  - Immunoglobulins (total IgG, IgG subclasses)
  - Neurofilament light chain (Visit 16 only)
  - Exploratory biomarker analysis (Visits 8, 12, and 16 only)
  - CIDP-specific auto-antibodies (Visits 8, 12, and 16 only)
  - IgA, IgM, IgE (Visits 8, 10, 12, 14, and 16 only)
  - RNA samples (Visit 10 only)
  - PK of rozanolixizumab (predose and 4 hours postdose) (Visits 8 and 10 only)
  - PK of rozanolixizumab (predose) (Visits 12, 14, and 16 only)
  - Vaccination-specific antibody titers ([redacted]) (Visits 8 and 14 only)
  - [redacted] (Visits 8, 10, 12, 14, and 16 only)
  - Serum pregnancy test for women of childbearing potential (Visit 16 only)
- INCAT assessment (predose) (Visits 8, 10, 12, 14, and 16 only)
- RT-MRC assessment (predose) (Visits 8, 10, 12, 14, and 16 only)
- Assessment of grip strength by the site personnel (predose) (Visits 8, 10, 12, 14, and 16 only)
- Review subject e-diary for daily assessment of grip strength (Visits 8, 10, 12, 14, and 16 only)

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

8.3 12-Week Observation Period Visits 17 to 21 (Day 85 to Day 162)

Following the final dose of rozanolixizumab or placebo at Day 78 (Visit 16), 5 subsequent visits will be scheduled over 12 weeks (Visit 17 through Visit 21) to collect safety and efficacy data for study related outcome measures and procedures. Visit 18 and Visit 20 are home nursing visits to be conducted by a healthcare professional visiting the subject at his/her home; these visits can be conducted at the site as deemed necessary by site personnel and/or subject.

Visit 17 will be the last study visit for the subjects entering immediately in the OLE study upon completing all visits in the Treatment Period.

All subjects not entering the OLE immediately should perform all visits of the Observation Period, including the Final Visit (scheduled 12 weeks after the final dose of IMP).

If at any time during the Observation Period, the subject relapses according to the predefined criteria for relapse as specified in Section 4.1.2 using the subject's score on iRODS, INCAT, or maximum grip strength (assessed by site personnel), and supported by the medical judgement of the investigator, then rescue medication must be considered. The subject will return to the SOC (ie, Ig treatment) as rescue medication at the time of relapse and will be stabilized over a period ranging from 2 weeks to maximum 12 weeks starting from time of relapse. During the stabilization, visits should be performed every 1 to 3 weeks at the discretion of the investigator until the subject is stabilized. The stabilization may extend the Observation Period duration up to a maximum of 24 weeks after last IMP dose. At the end of the stabilization, the subjects who complete the Treatment Period without a CIDP relapse will be offered the possibility to enter in the OLE immediately and be treated with rozanolixizumab. Their last visit in the study will be the FV, scheduled at the end of stabilization and enter the OLE on the same day. Assessments performed at the FV will not be repeated in the OLE.

If the subject does not wish to/cannot enter the OLE, the subject will continue treatment with SOC. The time required for follow-up since last IMP dose is 12 weeks. The stabilization visit schedule still applies (every 1 to 3 weeks) if the subject has not reached 12 weeks post last IMP dose at the end of stabilization.

Table 8–1 summarizes the options for the subject to proceed in the Observation Period.

Table 8–1: Management of Observation and Stabilization Periods

Subject status	Stabilization with rescue medication?	Ability to enter OLE?	End of study CIDP01
Subject completes Treatment Period without CIDP relapse (all visits performed until Visit 17)	NA	yes	• Last Visit=Visit 17=Entry visit in OLE (CIDP04)
	NA	no	If the subject wants to return immediately to SOC: • Subject returns to treatment with SOC (eg, IVIG or SCIG) during Observation Period. • Time of required follow-up since last IMP dose is 12 weeks. • Subject attends Visit 17 to Visit 21 (FV=last visit).

Table 8–1: Management of Observation and Stabilization Periods

Subject status	Stabilization with rescue medication?	Ability to enter OLE?	End of study CIDP01
	NA	Maybe later	If the subject wants to test whether he/she still needs treatment: • Subject continues Observation Period without SOC until maximum of 12 weeks post last IMP dose. Subject attends Visit 17 to Visit 21 (FV). • If the subject relapses and wants to enter the OLE, please refer to line **
Subject relapses during Treatment Period (before Visit 17)	yes	Maybe later	• Subject attends PEOT Visit. • IMP is stopped. • Conduct stabilization for a minimum of 2 weeks and a maximum of 12 weeks with rescue medication. Visits are scheduled every 1 to 3 weeks. • Subject continues SOC after stabilization. Time of required follow-up since last IMP administration is 12 weeks. The stabilization visit schedule still applies (every 1 to 3 weeks). • FV (V21)=Last visit after stabilization visits. • Entry in OLE (CIDP04) for subjects from the placebo arm once all subjects have completed the study, unblinding is performed, and key results are available.
	yes	no	• Subject attends PEOT Visit. • IMP is stopped. • Conduct stabilization for a minimum of 2 weeks and a maximum of 12 weeks with rescue medication. Visits are scheduled every 1 to 3 weeks. • Subject continues SOC after stabilization. Time of required follow-up since last IMP dose is 12 weeks. The stabilization visit schedule still applies (every 1 to 3 weeks). • FV (V21)= Last visit after stabilization visits.

Table 8–1: Management of Observation and Stabilization Periods

Subject status	Stabilization with rescue medication?	Ability to enter OLE?	End of study CIDP01
** CIDP relapse during Observation Period (after Visit 17) for subjects who completed Treatment Period	yes	yes	• Subject starts stabilization for minimum of 2 weeks and maximum 12 weeks with rescue medication. Visits are scheduled every 1 to 3 weeks. • If relapse happens towards the end of the 12-week Observation Period, overall timeframe (ie, since PEOT, including IMP free and stabilization period) until entry in OLE can be up to 24 weeks from last IMP dose. • FV (V21)=Last visit after stabilization visits=Entry visit in OLE (CIDP04).
	yes	no	• Subject starts stabilization for a minimum of 2 weeks and a maximum of 12 weeks with rescue medication. Visits are scheduled every 1 to 3 weeks. • Subject continues SOC after stabilization. Time of required follow-up since last IMP dose is 12 weeks. Stabilization visit schedule still applies (every 1 to 3 weeks). • FV (V21)=Last visit after stabilization visits.
Withdrawal for other reasons than CIDP relapse (before Visit 17)	no	no	• Subject attends PEOT Visit • IMP is stopped • Subject returns to treatment with SOC (eg, IVIg or SCIg) during Observation Period • Time of required follow-up since last IMP dose is 12 weeks • Subject attends Visit 17 to Visit 21 (FV=Final Visit)

CIDP=chronic inflammatory demyelinating polyradiculoneuropathy; FV=Final Visit; ICF=informed consent form; IMP=investigational medicinal product; IVIg=intravenous immunoglobulin; OLE=Open-Label Extension; PEOT=premature end of treatment; SCIg=subcutaneous immunoglobulin; SOC=standard of care

8.3.1 Visits 17 (Day 85) through 20 (Day 141) inclusive

The following assessments and procedures will be performed at each visit of the Observation Period (unless specified otherwise):

- PROs should be conducted as the first assessments in the study in the following order:
  - iRODS assessment– to be performed before any other assessment
  - CIDP PRO instrument (Visit 17 only)
  - Fatigue scale (Visit 17 only)
  - PGIS (Visit 17 only)
  - PGIC (Visit 17 only)
- Query for suicidality
- Assessment of the study withdrawal criteria
- Tuberculosis Signs and Symptoms questionnaire (Visit 17 only)
- Prior and concomitant medication
- Concomitant medical procedures
- Vital signs (taken once during each visit)
- Body weight (Visit 17 only)
- 12-lead ECG (Visit 17 only)
- Recording of AEs
- Brief physical examination (Visit 19 only)
- Full neurological examination (Visit 17 only)
- Brief neurological examination (Visit 19 only)
- Full physical examination (Visit 17 only)
- Contact IRT (Visit 17 only)
- Urine sample for urinalysis (Visits 17 and 19 only)
- Urine pregnancy test
- Blood sample (the laboratory manual will provide guidance on the order of sample collection) for:
  - Clinical laboratory tests (ie, hematology, clinical chemistry) (Visits 17 and 19 only)
  - Immunoglobulins (total IgG, IgG subclasses) (Visit 17 only)
  - CIDP-specific auto-antibodies (Visit 17 only)
  - IgA, IgM, IgE (Visit 17 only)
  - Whole blood for exploratory genetic (DNA) (Visit 17 only)

  - RNA samples (Visit 17 only)
  - PK of rozanolixizumab (Visit 17 only)
  - [redacted] (Visit 17 only)

- INCAT assessment
- RT-MRC assessment (Visit 17 only)
- Assessment of grip strength by site personnel (Visit 17 and Visit 19 only)
- Review subject e-diary for daily assessment of grip strength
- Subject exit interview (Visit 17 only for subjects entering in OLE on completion of Treatment Period)

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

8.3.2 Visit 21 (Day 162) Final Visit

The following assessments and procedures will be performed at the Final Visit (Visit 21):

- PROs should be conducted as the first assessments in the study in the following order:
  - iRODS assessment – to be performed before any other assessment
  - CIDP PRO instrument
  - Fatigue scale
  - PGIS
  - PGIC
- Query for suicidality
- Tuberculosis Signs and Symptoms questionnaire
- Prior and concomitant medication
- Concomitant medical procedures
- Vital signs (taken once during the visit)
- Body weight
- 12-lead ECG
- Recording of AEs
- Full physical examination
- Full neurological examination
- Contact IRT
- Urine sample for urinalysis

- Urine pregnancy test
- Blood sample (the laboratory manual will provide guidance on the order of sample collection) for:
  - Immunoglobulins (total IgG, IgG subclasses)
  - Neurofilament light chain
  - IGA, IgM, IgE
  - Clinical laboratory tests (ie, hematology, clinical chemistry)
  - [redacted]
  - Vaccination-specific antibody titers ([redacted]
- INCAT assessment
- RT-MRC assessment
- Assessment of grip strength by site personnel
- Review subject e-diary for daily assessment of grip strength
- Collect subject's daily grip strength e-diary
- Subject exit interview

8.3.3 Stabilization Visits

During the stabilization, visits should be performed every 1 to 3 weeks at the discretion of the investigator until the subject is stabilized.

The following assessments and procedures will be performed at each visit of the Observation Period (unless specified otherwise):

- PROs should be conducted as the first assessments in the study in the following order:
  - iRODS assessment– to be performed before any other assessment
- Query for suicidality
- Assessment of the study withdrawal criteria
- Prior and concomitant medication
- Concomitant medical procedures
- Vital signs (taken once during each visit)
- Recording of AEs
- Brief physical examination
- Brief neurological examination
- Urine sample for urinalysis

- Urine pregnancy test
- Blood sample (every 4 to 6 weeks only) (the laboratory manual will provide guidance on the order of sample collection) for:
  - Clinical laboratory tests (ie, hematology, clinical chemistry)
- INCAT assessment
- Assessment of grip strength by site personnel
- Review subject e-diary for daily assessment of grip strength

Subjects should be reminded to continue to record daily grip strength in their diaries and to bring their e-diary with them to their next study visit.

8.4 PEOT and Final Visit

All subjects who withdraw early from the Treatment Period should attend a PEOT Visit which will be scheduled as close as possible to the date of the decision for the study or treatment withdrawal.

Subjects are encouraged to complete all visits of the Observation Period following the PEOT Visit by either coming to the clinic or as home nursing visits, if appropriate.

In case a subject is not willing to attend the visits in the Observation Period, the subject should still be strongly encouraged to attend at least the PEOT Visit and the FV.

The FV should be scheduled 12 weeks after their final dose of IMP.

The assessments to be done at the PEOT Visit and the FV are the same as those at Visit 17 and Visit 21, respectively.

In the event a subject enters the OLE immediately after Visit 17, Visit 17 will be the final study visit and there will be no FV.

In the event a subject experiences a relapse, the subject will be stabilized; stabilization visits will be conducted from the time of relapse. Stabilization duration may range from 2 weeks to 12 weeks after the time of relapse. Once stabilized, the subject will continue SOC onwards. Subjects not entering the OLE following stabilization should perform the FV after minimum 12 weeks or maximum 24 weeks post last IMP dose. Management of the stabilization period is summarized in Table 8–1.

After the end of the study, the subjects not entering the OLE study should resume treatment according to their standard care as per the recommendation of their physician.

8.5 Unscheduled Visit/Telephone call

At any time, a subject may have an unscheduled study visit/telephone call if the investigator and/or the subject deem it necessary. An unscheduled visit may be conducted due to safety or efficacy reasons and appropriate assessments will be conducted in relation to the reason for the visit. All information, including reason for visit/telephone call, any information on AEs, etc, should be collected in the source documents and recorded in the appropriate section of the eCRF.

8.6 Open-label extension study

Subjects from this study have the option of taking rozanolixizumab during an OLE study (CIDP04) provided they have completed the Treatment Period without a CIDP relapse. The last study visit in CIDP01 will be either Visit 17 (immediate entry on completion of the Treatment Period) or FV (for subjects who continued the Observation Period, relapsed during this period and were then stabilized before entry in the OLE).

Subjects from the placebo arm who relapsed during the Treatment Period will have the option to enter the OLE at the study completion, ie, when all subjects have completed study CIDP01, the study is unblinded, and key results are available.

The decision to enter the OLE study must be made by the subject in consultation with the investigator. This decision must consider the potential risks of long-term exposure to rozanolixizumab and the potential benefits and risks of other treatment options available.

9 ASSESSMENT OF EFFICACY

9.1 iRODS

The iRODS questionnaire should be completed by the subject prior to dosing and before any discussion of their current health status with the treating physician or any other study assessments. Subjects will complete the iRODS questionnaire at the time points detailed in the schedule of study assessments (Table 5–1). The questionnaire will be given to the subject to complete and will then be recollected and checked, for completeness only, by study personnel other than the treating physician. Subjects should complete the questionnaires themselves, unaided, in a quiet location.

The iRODS is a linearly weighted patient-reported outcome measure (questionnaire) that specifically captures activity and social participation limitations in patients with CIDP. The iRODS scale was constructed based on the World Health Organization (WHO) International Classification of Functioning, Disability and Health, literature search, and patient interviews (van Nes et al, 2011). All 24 items of iRODS meet Rasch model expectations. The questionnaire consists of 24 items (including eating, taking a shower, walking a flight of stairs, standing for hours, etc.) and assesses a patient's perception of their ability to perform daily and social activities. Patients have 3 response options: 0=impossible to perform; 1=performed with difficulty; and 2=easily performed, performed without difficulty (van Nes et al, 2011). The raw sum scores of iRODS (range 0 to 48) will be translated to log odds units (logits), placing patients' estimates on the same logit scale. For easier interpretation the person locations can be translated to values changing from 0 (most severe activity and social participation restrictions) to 100 (no activity and social participation limitations).

Subjects will be asked to complete the iRODS questionnaire at every study visit except for nondosing Visits 3, 5, and 7.

In addition to the primary efficacy variable in which subjects will be assessed for the change from Baseline to Week 13 (Day 85) in their iRODS score, subjects will also be assessed for change from Baseline in iRODS scores at each scheduled assessment during the Treatment and Observation Periods. Other efficacy variables will also include subject experienced CIDP relapse (iRODS), defined as a clinically important deterioration, ie, an MCID-SE ≤-1.96, and time to CIDP relapse (iRODS) during the Treatment Period.

9.2 INCAT

The INCAT disability scale is a 10-point clinician-reported ordinal measure capturing problems in daily arm and leg activities and mobility. The measure captures daily activities such as dressing the upper part of the body, doing and undoing buttons and zips, washing and brushing hair, and handling coins. Each item is scored as being "not affected", "affected but not prevented", or "prevented". The leg scale measures problems with walking, taking into account the use of aids. The INCAT scale ranges from 0 (no signs of disability) to 10 (most severe disability score) (Breiner et al, 2014; Léger et al, 2013; Hughes et al, 2008). For the purposes of the present study, the adjusted INCAT disability score will be used. 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.

The investigator (or qualified personnel) will record the subjects' adjusted INCAT score at every study visit according to schedule of assessments (see Table 5–1). It is recommended that the rater of the scale remains the same throughout the duration of the study to ensure consistency of the rating.

Subject experienced CIDP relapse (adjusted INCAT) (defined as an increase from Baseline of at least 1 point in their adjusted INCAT score) up to Week 13 (Day 85) after first treatment and time to CIDP relapse (adjusted INCAT) during the Treatment Period will be assessed together with the change from Baseline in adjusted INCAT score at each scheduled assessment during the Treatment and Observation Periods.

9.3 Grip strength reported by site personnel

Grip strength will be assessed by qualified site personnel according to the schedule of study assessments (Table 5–1). Qualified site personnel will be trained regarding obtaining and recording measurements. At each scheduled visit, the grip strength, generated by the subject, and measured using a standardized tool, will be evaluated 3 times in the dominant hand. All 3 assessments will be recorded in the eCRF. For analyses, UCB will utilize the maximum of the 3 assessments. Efficacy will be assessed as change from Baseline in maximum grip strength score at each scheduled assessment during the Treatment and Observation Periods.

Subject experienced CIDP relapse (maximum grip strength) (defined as a clinically important deterioration from Baseline in grip strength, ie, a decline of >14kPa) up to Week 13 (Day 85) after first treatment and time to CIDP relapse (maximum grip strength) during the Treatment Period will be assessed together with the change from Baseline in maximum grip strength score at each scheduled assessment during the Treatment and Observation Periods.

9.4 Patient-reported grip strength

During the study, subjects will keep e-diaries to record daily grip strength from the Screening Visit until the end of study participation. Subjects should be reminded to bring their diaries with them to each clinic visit and to have them available at home nursing visits. Subjects will be trained by the site personnel and receive a manual describing how to assess grip strength using a standardized tool. At approximately the same time every day, the maximum grip strength, the peak pressure generated by the subject, will be assessed 3 times, with at least 30sec between measurements, using the dominant hand. Subjects will be asked to complete their diaries each day and record the values for each of the 3 assessments.

For variable derivation, see Section 9.3.

9.5 Patient-reported outcomes

The PRO assessments should be administered in the following order: iRODS, CIDP PRO instrument, Fatigue, PGIS, PGIC, and exit interview (Final Visit). Refer to Section 9.1 for detail on iRODS.

Subjects will complete PROs and participate in a subject exit interview at the time points detailed in the schedule of study assessments (Table 5–1). Study personnel other than the treating physician should administer the PROs. The PROs should be completed by the subject themselves in a quiet place.

9.5.1 CIDP PRO instrument

Neuropathic Symptoms will be assessed at the time points detailed in the schedule of study assessments (Table 5–1). The CIDP PRO instrument consists of 2 domain scales; (1) Pain Severity numeric rating scale and (2) Neuropathy scale. Pain Severity consisting of 4 items assessing pain severity in the past 7 days and at the time of completion of the instrument, using 0-10 numeric rating scales. Summed total raw score will range between 0 to 40 with higher scores reflecting higher levels of pain severity. The Neuropathy scale consists of 17 items rated within a 7-day recall period on a 6-point Likert severity scale ranging from “none” to “very severe”. The summed total raw score will range from 17 to 102 with higher scores reflecting higher levels of pain and physical sensations severity. Following psychometric evaluation and refinement (eg, reduction in items) of these domains scales by using data generated in CIDP01, transformed interval 0-100 scoring will be provided for both domain scores with higher score reflecting higher severity.

9.5.2 Fatigue

Fatigue will be assessed at the time points detailed in the schedule of study assessments (Table 5–1). The Fatigue instrument consists of 3 domain scales; Physical Fatigue comprising 16 items; Mental Fatigue comprising 18 items and Fatigability comprising 21 items. All 55 items across the 3 domain scales are rated within a 7-day recall period on a 5-point Likert frequency scale ranging from “none of the time” to “all of the time”. The summed total raw scores for each of the 3 scales will range between 16 and 80; 18 to 90 and 21 to 105 points for the Physical, Mental, and Fatigability, scales respectively with a potential for an exploratory total overall score ranging from 55 to 275. Higher scores reflect higher levels of fatigue across all domain scale scores. Following psychometric evaluation and refinement (eg, reduction in number of items) of these domain scales by using data generated in CIDP01, transformed interval 0-100 scoring will be provided for each domain score with higher scores reflecting higher levels of fatigue.

9.5.3 Patient Global Impressions

Patient global impressions will be assessed at the time points detailed in the schedule of study assessments (Table 5–1).

Subjects will rate their global impression of CIDP symptom severity and fatigue severity respectively, on a 5-point Likert severity scale ranging from “none” to “very severe”.

Subjects will rate their global impression of change (if at all) in CIDP symptom and fatigue respectively, on a 7-point Likert severity scale ranging from "very much improved" to "very much worse" from Baseline/start of clinical study treatment to the scheduled visits.

9.6 RT-MRC

The RT-MRC will be assessed by qualified site personnel according to the schedule of study assessments (Table 5–1).

The RT-MRC sum score is a summation of the RT-MRC grades in integers of the following muscles on each side: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsal flexors.

The RT-MRC sum score was developed based on a Rasch analysis of the original MRC grading system (Merkies et al, 2010; Merkies et al, 2002; Vanhoutte et al, 2012). The MRC grades were rescored from 6 to 4 response options (0, paralysis; 1, severe weakness; 2, slight weakness; 3, normal strength) for the RT-MRC in order to acceptably fulfill Rasch model expectations. Sum scores range from 36 "normal" to 0 "quadriplegic".

Efficacy will be assessed as a change from Baseline in RT-MRC sum score at each scheduled assessment during the Treatment and Observation Periods.

9.7 Subject exit interview

At the Final Visit, qualitative interviews will be conducted by a study nurse/study personnel using a semi-structured interview guide. The aim of the interview is to collect the subject's experience with CIDP in terms of fatigue, pain, and physical sensations symptoms and impact, and the perceived changes during the course of the study. The extent to which the exploratory fatigue, pain, and physical sensation items and scales used fully captured their experience will also be assessed. The interviews will be audio-recorded. If a subject leaves the study prematurely, he/she will also be invited to participate in an exit interview at the Final Visit.

10 ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC AND PHARMACOGENOMIC VARIABLES

10.1 Pharmacokinetic variables

The plasma concentration of rozanolixizumab will be characterized. Blood samples will be drawn by qualified personnel according to the schedule in Table 10-1. All blood samples collected before dosing with rozanolixizumab at the dosing visits will be drawn at the same time as the sampling for standard clinical laboratory tests. The time and date of collection will be recorded in the eCRF.

Table 10-1: Serial blood sampling for rozanolixizumab concentration

Matrix	Time after start of sc infusion
Plasma	Predose and postdose at 4 hours after finishing the infusion on Visits 2, 4, 6, 8, and 10
	Predose on Visits 12, 14, and 16
	Nondosing Visits 3, 5, 7, and 17: samples to be taken once during the visit

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

10.2 Pharmacodynamic variables

Pharmacodynamic variables are defined in Section 4.2.2. Neurofilament light chain levels are a marker of neuronal cell damage.

For all PD assessments blood samples will be collected predose (at dosing visits) by qualified site personnel at the same time that samples are collected for standard clinical laboratory assessments. Blood samples for PD analyses will be drawn according to the schedule of study assessments (Table 5–1). The time and date of collection will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

10.3 Exploratory pharmacogenomic variables

Collection of these samples will occur according to the schedule of study assessments (Table 5–1). Blood samples will be drawn prior to dosing (on dosing visits) at the same time as the sampling for clinical laboratory tests. Exploratory samples may be collected 4 hours postdose in case of AE of interest (Table 5-2). The time and date of collection will be recorded in the eCRF.

For RNA, blood samples will be collected at Baseline (Visit 2) and Visits 4, 6, 10, and Visit 17/PEOT. For each RNA blood sample, a volume of 2.5mL whole blood is needed.

For protein and metabolite exploratory biomarkers, blood samples will be collected at Baseline (Visit 2) and Visits 4, 8, 12, and 16. For each protein and metabolite exploratory biomarker blood sample, a volume of 8mL of whole blood is needed (4mL for serum and 4mL for plasma).

If not used immediately, these samples will be stored at -80°C for up to 20 years for later exploratory analyses. Any exploratory biomarker or genomic analysis will only ever be related to the exploration of the underlying causes of CIDP in patients, related biology, and drug response. Justification for additional genomic analyses is detailed in Section 5.4.5. The nature and format of these tentative additional analyses will be determined at a later time.

Details on the collection, storage, preparation, and shipping of samples will be presented in the laboratory manual provided separately.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Detailed information on sample analyses will be provided in a bioanalytical report.

11 ASSESSMENT OF IMMUNOLOGICAL VARIABLES

The following immunological assessments will be performed according to the schedule of study assessments (Table 5–1). For all immunological assessments, blood samples will be collected predose by qualified site personnel at the same time that samples are collected for standard clinical laboratory. Serum complement (C3, C4), plasma complement (C3a, C5a), and serum cytokine will also be taken 4 hours postdose at Visits 4, 8, 12 and 16. Additional samples may be collected in case of infusion reactions (see Table 5-2). The time and date of the blood draws will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

- Serum immunoglobulin concentration over time
  - IgA
  - IgE
  - IgM
- Serum complement levels over time
  - C3
  - C4
- Plasma complement levels over time
  - C3a
  - C5a
- Plasma [redacted]
- Serum cytokines

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definitions

12.1.1.1 Adverse event

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

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the investigator from the subject's history or the Baseline Period.

12.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening
- (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious
- (Important medical events may include, but are not limited to, potential Hy's Law [see Section 12.2], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization
- (A subject admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].
- Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

12.1.1.2.1 Anticipated serious adverse events

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 12.1.2.3.

Table 12-1: Anticipated serious adverse events for CIDP population

Neurologic diseases [a]:	muscle weakness, numbness and pain in the extremities, impaired balance, difficulty walking

[a] The investigator should report these adverse events as serious adverse events only if they meet criteria for seriousness (see Section 12.1.1.2).

12.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

12.1.1.4 Adverse events of interest

For rozanolixizumab, AEs of interest that require immediate reporting to UCB are:

- Severe headache
- Moderate to severe diarrhea
- Moderate to severe abdominal pain
- Moderate to severe vomiting

These events should be reported to UCB within 24 hours, regardless of seriousness, using the fax and email details for AEs of interest and independent of SAE reporting.

Additional assessments which may be required in case of AEs of interest are presented in Table 5-2.

12.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the investigator should review any self-assessment procedures (eg, e-diary) employed in the study.

12.1.2.1 Description of adverse events

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words

on his/her own records and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

For recording an AE, Common Terminology Criteria for Adverse Events (CTCAE) will be used, and only if it is impossible to assess severity using CTCAE, then AE intensity will be assessed using a scale of mild, moderate, or severe.

12.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

12.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An investigator SAE report form will be provided to the investigator. The investigator SAE Report form must be completed in English.

It is important for the investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the investigator SAE report form.

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the IB.

12.1.2.4 Immediate reporting of adverse events

The following AEs must be reported immediately using the SAE Report Form according to the procedure in Section 12.1.2.3:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 12.1.1.3)
- AE of interest (see Section 12.1.1.4)
- Confirmed LTBI, active TB, and NTMBI (see Section 12.3.7)

12.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 12.2.1.4.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the investigator must provide a justification. The follow up will usually be continued for 12 weeks after the subject has discontinued his/her IMP.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

12.1.4 Pregnancy

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see SAE reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for a PEOT Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the PEOT Visit.
- A Final Visit should be scheduled 12 weeks after the subject has discontinued her IMP.

The investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to

follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the investigator site file. In case of questions about the consent process, the investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see SAE reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes a SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the investigator SAE Report form.

12.1.5 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

12.1.6 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose ie, >10% above [redacted]) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

12.1.7 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible. A DMC will be responsible for monitoring safety data during the study. Further details are provided in Section 14.7.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

12.1.8 Suicidality

At Screening, the investigator will query each subject if he/she has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) or suicidal ideation in the past 6 months. A full C-SSRS "Lifetime recent" assessment will be performed only when the subject has a positive response to this query. This scale will be assessed by trained study personnel. When suicide attempt or suicidal ideation is confirmed by a positive response (Yes) to either Question 4 or Question 5 of the C-SSRS, the subject must be excluded and immediately referred to a Mental Healthcare Professional.

At each clinical visit, the investigator must query the suicidal ideation since the last visit. A full C-SSRS "Since last visit" assessment will be performed only when the subject has a positive response to this query. When suicide attempt or suicidal ideation is confirmed by a positive response (Yes) to either Question 4 or Question 5 of the C-SSRS, the subject must be withdrawn and immediately referred to a Mental Healthcare Professional. Details of case must be documented by the investigator (PI or investigator physician, not site staff conducting the C-SSRS) and provided to UCB via the SAE reporting process.

12.1.9 Hypersensitivity and adverse reactions

The grading for infusion-related reactions according to the NCI Common Terminology Criteria for Adverse Events version 4.03 (Jun 2010) (Doessegger and Banholzer, 2015) is provided in Table 12-2. In the event of a severe or life-threatening (ie, Grade 3 or 4) infusion reaction, the subject must permanently discontinue IMP (see Section 6.4) and be managed as described in Section 18.1.

Table 12-2: Infusion-related reaction grading according to the NCI Common Terminology Criteria for adverse events version 4.03 (Jun 2013)

Grading	Infusion-related reaction
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Moderate: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours
3	Severe: Prolonged; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; urgent intervention indicated
5	Death

IV=intravenous; NCI=National Cancer Institute; NSAIDs= non-steroidal anti-inflammatory drugs
Data source: Doessegger et al, 2015

In case of occurrence of a hypersensitivity reaction (except for local injection site reaction) and depending upon its severity, appropriate countermeasures will immediately be taken by the investigator. In the event the infusion reaction occurs during a home visit, the home nurse will be trained to follow all steps as detailed in the study manual and will liaise with the investigator for the proper handling of the case. Serum complement (C3, C4), plasma complement (C3a, C5a), and serum cytokine samples must be collected from subjects experiencing infusion reactions (Table 5-2).

If the investigator does not initially choose to discontinue the infusion of IMP and symptoms persist or escalate during continued infusion, the infusion should be stopped. In case of any severe infusion reaction(s), the infusion of IMP must be stopped immediately and appropriate treatment initiated, as necessary, at the discretion of the investigator and in accordance with the SOC. When infusion reactions occurred while the IMP has not been stopped, the investigator should closely assess the adequacy of home administrations (refer to Section 8.2) and consult with UCB Study physician before considering home administration after the infusion reactions.

Suspected anaphylactic reactions should be diagnosed using Sampson's Criteria (Sampson et al, 2006) as described in Section 18.2. In the event of an anaphylactic reaction meeting Sampson criterion 1 or 2, the infusion must be discontinued immediately and emergency resuscitation measures implemented.

12.1.10 Management of headache

Treatment of headaches should be as per national guidelines and take medical history of previous headaches, concomitant medication, and co-morbidities (eg, asthma) in consideration. In case of continued tolerance issues, and if symptomatic headache medication is not sufficient, a further step can be to reduce dose of IMP to [redacted] (see Section 7.2).

Severe headache is defined as severe pain limiting self-care activities of daily living (ADL) or new/prolonged hospitalization for management of headache or life-threatening consequences requiring urgent medical intervention. Self-care ADL refer to bathing, dressing and undressing,

feeding self, using the toilet, taking medications. Treatment of headache will be provided as clinically indicated according to the national guidelines.

Subjects experiencing severe headache will complete the Headache Questionnaire daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply). At the clinic visit when the severe headache is reported, the Headache Questionnaire will be followed by a neurological assessment (including fundoscopy). If the severe headache is initially reported at a home visit or during a telephone call, the subject should be reviewed at the study site as soon as is practically possible for further investigations. Further workup will be performed at the discretion of the investigator and may include, eg, a computed tomography scan, magnetic resonance imaging and/or a lumbar puncture for cerebral spinal fluid collection. In addition, samples for exploratory biomarkers should be taken for subjects experiencing severe headache (Table 5-2). These investigations will be performed to further understand the mechanism of headache in these subjects.

Details of neurological examination to be performed are provided in Section 12.3.5. The Headache Questionnaire will be provided in the study procedures manual.

12.1.11 Management of moderate or severe diarrhea

Moderate or severe diarrhea is defined as an increase of ≥4 stools per day over Baseline or incontinence due to urgency of diarrhea or new/prolonged hospitalization for management of diarrhea or limiting self-care ADL or life-threatening consequences requiring urgent medical intervention.

Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally. In addition, collection of blood samples for assessment of exploratory biomarkers is required for subjects with moderate to severe gastrointestinal disturbances including diarrhea (Table 5-2).

Treatment of diarrhea will be provided as clinically indicated according to the local guidelines.

12.2 Laboratory measurements

Blood and urine specimens for routine assay of hematology, clinical chemistry, and urinalysis testing, as well as pregnancy testing and serology testing will be performed according to the schedule of assessments (Table 5–1) to monitor the safety of subjects. All parameters will be assessed by the designated central laboratory with the exception of the urine pregnancy test prior to each dose. Specific details regarding the handling and processing of serum chemistry, hematology, and urinalysis samples are provided in the study laboratory manual.

The following laboratory parameters will be measured as detailed in Table 12-3.

Table 12-3: Laboratory measurements

Hematology	Chemistry	Urinalysis [a]
Hemoglobin	ALP	pH
Hematocrit	ALT	Protein
RBC	AST	Glucose
WBC (including differential)	GGT	Ketone
Platelet count	Total bilirubin [b]	Urobilinogen
	LDH	Bilirubin
	Creatine kinase	Blood
Serology [c]	Total protein	Nitrite
HBsAg, HBcAb	Albumin	Leukocytes
HCV Ab	Alpha- and beta–globulins	
HIV (anti-HIV1 or anti-HIV2 antibodies)	Urea-nitrogen	
Tuberculosis	Creatinine	Albumin
	Triglycerides	Creatinine
	Total-cholesterol	
	LDL cholesterol	**Pregnancy test**
	HDL cholesterol	Serum HCG [d]
	Electrolytes (calcium, phosphate, sodium, potassium, chloride, and magnesium)	Urine HCG [e]
	Amylase	
	hsCRP	
	Procalcitonin	
	HBA1c [f]	

Ab=antibody; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase; HBcAb= hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HCV=hepatitis C virus; HDL=high density lipoprotein; HIV=human immunodeficiency virus; hsCRP=high sensitivity C-reactive protein; IGRA=interferon gamma release assay; IMP=investigational medicinal product; LDH=lactate dehydrogenase; LDL=low density lipoprotein; RBC=red blood cell; WBC=white blood cell

[a] Urine microscopy will be performed if urine is positive for protein, blood, nitrite, or leukocytes.

[b] Direct bilirubin will also be measured when total bilirubin is elevated.

[c] Serology performed at Screening only. An IGRA should be performed for active or latent tuberculosis testing.

[d] Serum pregnancy test performed at Screening and Visit 16 only for women of childbearing potential.

[e] Urine pregnancy test (dipstick) for women of childbearing potential performed prior to dosing (and confirmed negative) at dosing visits and each visit of the Observation Period. Note that the final urinary pregnancy test of the study should be no longer than 90 days after the final dose of IMP.

[f] Performed at Screening only.

12.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.4.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest, and, if applicable, also reported as an SAE (see Section 12.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 12-4 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 12.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 12.2.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.4.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 12.2.1.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Table 12-4 summarizes the approach to investigate PDILI.

Table 12-4: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms [a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN [b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 12.2.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Hepatology consult required if ALT or AST ≥8xULN.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.2.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 12.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 12.2.1.3) and SAE report (if applicable).

12.2.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.4.1 and Table 12-4 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

12.2.1.2.1 IMP restart/rechallenge (if applicable)

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.4.1 and Table 12-4), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 12.2.1.3 and Section 12.2.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the investigator-recommended monitoring plan.

12.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 12-5 (laboratory measurements) and Table 12-6 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 12-5: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR [a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 12-6: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

12.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 12-4. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.3 Other safety measurements

12.3.1 Pregnancy testing

Pregnancy testing will consist of serum testing at the Screening Visit and Visit 16 and urine testing at dosing visits during the Treatment Period and each visit during the Observation Period as indicated in the schedule of study assessments (Table 5–1). The Screening Visit serum pregnancy testing results must be negative and should be confirmed by a negative urine pregnancy test prior to first dose of IMP. The urine pregnancy test will be performed locally. A negative urine pregnancy test result should be obtained prior to each dose of IMP. A positive urine pregnancy test must be confirmed using a serum pregnancy test. Pregnancy tests should be

administered to all female subjects of childbearing potential, regardless of their use of birth control.

12.3.2 Vital signs

Vital signs will be measured at all visits as indicated in the schedule of study assessments (Table 5–1).

Vital signs to be assessed are as follows:

- PR
- Systolic/diastolic BP
- Temperature (oral preferred, ear or axillary allowed)

Subjects should be sitting for 5 minutes prior and during the collection of BP and PR measurements. On dosing days prior to Visit 9, vital signs will be measured prior to IMP administration, at the end of the infusion, at 2 hours and 4 hours after the end of the infusion. From Visit 9, vital signs will be measured predose, at the end of the infusion and at 2 hours after the end of infusion only. The same schedule of vital signs monitoring will be used even if IMP is administered at home.

At nondosing visits, vital signs need only be taken once during the visit.

For subjects requiring additional assessments due to AEs (see Table 5-2), additional vital sign measurements may be taken based on the timing of the assessments.

12.3.3 Body weight and height

The subject's body weight will be determined at Screening, Visit 2, Visit 17/PEOT, and at Final Visit (Visit 21). Body weight at Screening will be used for calculating the dose for administration. Height is measured at Screening only.

12.3.4 Physical examination

12.3.4.1 Full physical examination

A physical examination will be performed at the visits specified in the schedule of study assessments (Table 5–1) and findings will be recorded in the eCRF. A full physical examination will be performed at Screening, Visit 17/PEOT, and Final Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

Clinically important abnormal changes in subsequent physical examinations will be recorded as AEs. Physical examinations must be documented in source documentation.

The following body systems will be examined as a part of the complete physical examination:

- General appearance
- Ear, nose, and throat
- Eyes
- Hair and skin
- Respiratory

- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Hepatic
- Neurological examination (see also Section 12.3.5)
- Mental status

12.3.4.2 Brief physical examination

The following body systems will be examined as a part of the brief physical examination at the visits outlined in the schedule of assessments (Table 5–1):

- General appearance
- Ear, nose, and throat
- Eyes
- Skin
- Respiratory
- Gastrointestinal
- Neurological (focused assessment of sensitivity and power)

12.3.5 Neurological examination

A full neurological examination should be performed at Screening Visit, Visit 17/PEOT and Final Visit. In addition, full neurological examination should be performed for any subject who experiences severe headache (see Section 12.1.10 and Table 5-2). A full neurological assessment will include: (1) General appearance, including posture, motor activity and meningeal signs and, if indicated, the following assessments to be done; (2) Cranial nerves examination; (3) Motor system examination, including muscle tone and power and sensory system examination – light touch; (4) Reflexes, including deep tendon reflexes; (5) Coordination, gait (if possible); and (6) Fundoscopy.

A brief neurological examination will include a selected assessment of the following: cognition, general, reflexes, muscle strength, and coordination/cerebellar function.

12.3.6 12-lead ECG

A standard 12-lead ECG will be performed at the visits specified in the schedule of study assessments (Table 5–1). Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position in a controlled, calm environment for at least 15 minutes prior to the recording and should be motionless during the recording. The ECG will be performed in triplicate prior to blood collection for assessment of laboratory parameters.

The ECGs will be read at a central site. The PR, RR, QRS, QT, and corrected QT (QTc) intervals and heart rate will be recorded. All ECG readings from an individual subject should be read by the same reader, if possible. Findings will be recorded in the eCRF.

For the QTc, the following correction formula will be applied:

Fridericia's correction: $QTc = QT/RR^{0.33}$

12.3.7 Assessment and management of TB and TB risk factors

With the currently available data, TB is not considered as an important potential or identified risk for treatment with rozanolixizumab. As immunomodulation may carry risk of new or activation of LTBI, UCB has conservatively developed TB detection and management procedures considering the most current recommendations of international guidelines (2010 WHO) and most recent literature, covering any infection by the mycobacteria TB complex.

Appropriate rigorous precautions are being taken within this protocol to monitor the risk of TB infection in this study (see Section 6.2.3 Exclusion Criterion 16 and Section 6.4 Withdrawal Criteria). The following are the key considerations of these procedures:

TB tests at Screening

The IGRA, chest x-ray, and TB questionnaire are required as indicated in schedule of assessments (Table 5–1).

- TB screening is mandatory both before study entry and during the conduct of the study. The preferred screening test is the IGRA performed at a central laboratory.
  - The IGRA result must be negative for subjects to enroll in this study.
  - Subjects who test positive for IGRA test should be excluded from the study and referred for appropriate medical evaluation according to the local medical practice guidelines.
  - If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to IMP and, if already randomized, must undergo appropriate study specified withdrawal procedures. The retest must be done during the protocol-defined Screening window.
- Subjects will be evaluated for signs and symptoms of latent or active TB infection and for risk factors of exposure to TB, using the TB questionnaire, at Screening. Subjects with known TB, at a high risk of acquiring TB or with LTBI should be excluded from this study as described in Exclusion Criteria (Section 6.2.3).
- A plain posteroanterior chest x-ray must be performed in the Screening Period unless one has been performed within 3 months prior to the Screening Visit. The chest x-ray (or, if done, computed axial tomography of the chest) must be clear of signs of TB infection (previous or current) before first IMP dose.

Monitoring for TB during the study

Subjects will be monitored for signs/symptoms of TB using routine pharmacovigilance measures for AEs. Subjects reporting AEs related to signs/symptoms of TB will be evaluated for LTB and active TB according to the local medical practice guidelines.

Subjects with confirmed LTB or active TB or NTMB infection will be immediately withdrawn from the study as described in Section 6.4 Withdrawal Criteria. Confirmed LTB, active TB, and

NTMB must be reported to the Sponsor immediately regardless of seriousness using the SAE Report Form. Additional information received by the investigator should be provided to the Sponsor within 24 hours of awareness.

Once withdrawn from study treatment, subjects should return for the PEOT, complete all early withdrawal assessments, and complete the follow-up visits.

TB tests at Final Visit

Subjects will be evaluated for signs and symptoms of latent or active TB infection and for risk factors of exposure to TB, using the TB questionnaire, at the Final/PEOT Visit. See the "TB signs and symptoms questionnaire" section for further instructions on using the questionnaire.

Signs and symptoms of TB

The investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the subject's history.

Common symptoms with which the subject may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking inflammatory bowel disease, frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

Chest x-ray for TB

A plain posteroanterior chest x-ray must be performed in the Screening Period unless one has been performed within 3 months prior to the Screening Visit. The chest x-ray (or, if done, computed axial tomography of the chest) must be clear of signs of TB infection (previous or current) before first IMP administration. All chest imaging (particularly x-rays) should be available for review by the investigator before randomization of the subject. The chest x-ray should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential lung TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest imaging must be negative for any old or recent TB infection as determined by a qualified radiologist and/or pulmonary physician. Any new clinically significant findings post Baseline on chest x-ray must be documented in the source documents and the eCRF as an AE.

TB signs and symptoms questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question "[redacted]" at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has

latent or active TB (see Section 6.2.3, Exclusion Criterion 16). A "Yes" response to any of the questions at the end of the study should trigger further assessments as per local medical guidelines to determine if the subject has either LTB or active TB infection.

LTB infection, active TB or other NTBM identified during study

During the study, subjects who develop evidence of LTB infection or active TB or NMTB must immediately stop further administration of IMP and will be referred to an appropriate medical specialist for further evaluation.

Confirmed LTB or active TB or NTMB must be reported to the Sponsor immediately as described above.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the investigator must notify the CPM of the sponsor within 24 hours and follow any local regulatory requirements.

13.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring SOPs, ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the subject's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

13.2.1.1 Apps

The data recorded in myUCB 4me is not intended to be used to influence the treatment decisions of subjects during the conduct of this study. Rather, the data will be analyzed at the end of the study as part of the efficacy measurements (see Section 9).

Furthermore, this app is designed to only record data associated with the subject's disease state, and therefore it is neither designed nor intended to be used to collect or report safety-related information about the subject. See Section 12 that describes the procedures for handling safety-related information.

To ensure the confidence in the reliability, quality, and integrity of the data, several security measures have been put in place. myUCB 4me itself is protected by a Personal Identification Number (PIN) that is known only to the subject participating in CIDP01.

All data entered by the subject is fully encrypted within myUCB 4me and its transmission to the database.

13.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 13.2.1.

13.3 Data handling

13.3.1 Case Report form completion

The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the investigator's review and approval (by means of a password/electronic signature) will be reapproved by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

13.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database using independent, double-data entry, except for comment fields, which are verified by a second person. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

13.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The investigator will keep a Subject Identification Code list. This list remains with the investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

13.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

13.5 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained

for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's trial master file.

13.6 Audit and inspection

The investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform UCB (or designee).

13.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

14 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP), which will be finalized prior to unblinding.

14.1 Definition of analysis sets

Seven analysis sets will be defined for this study: the Enrolled Set (ES), the Randomized Set (RS), the Safety Set (SS), the Full Analysis Set (FAS), the Per-Protocol Set (PPS), the Pharmacokinetic Per-Protocol Set (PK-PPS), and the Pharmacodynamic-Per Protocol Set (PD-PPS).

14.1.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent.

14.1.2 Randomized Set

The Randomized Set (RS) will consist of all subjects randomized into the study.

14.1.3 Safety Set

The Safety Set (SS) will consist of all subjects in the RS, who have received at least 1 dose of IMP.

Safety variables will be analyzed using the SS.

It is expected that subjects will receive treatment as randomized and hence safety analyses will be based on the randomized treatment group. However, if after unblinding it is determined that a subject has received treatment different to the treatment they were randomized to, then for safety analyses the subject will be allocated to the actual treatment they received.

14.1.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the SS, who have a Baseline and least 1 post-Baseline iRODS measurement.

The FAS is the primary analysis set for efficacy analyses. Even in the case of mistreatment, subjects will be analyzed as treated. As for the SS, in the case of mistreatment subjects will be primarily analyzed as treated. However, if applicable, sensitivity analyses will also be performed according to the randomized treatment group.

14.1.5 Per-Protocol Set

The Per-Protocol Set (PPS) is a subset of the FAS, consisting of those subjects who had no important protocol deviation affecting the primary efficacy variable, as confirmed during a preanalysis data review meeting conducted prior to study unblinding. Post-Baseline deviations will not necessarily lead to total exclusion of a subject from the PPS but may lead to exclusion of specific data.

Analysis of the primary efficacy variable will be repeated using the PPS.

14.1.6 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) is a subset of the SS, consisting of those subjects who had no important protocol deviation affecting the plasma concentration of rozanolixizumab. Post-Baseline deviations will not necessarily lead to total exclusion of a subject from the PK-PPS but may lead to exclusion of specific data.

14.1.7 Pharmacodynamic Per-Protocol Set

The Pharmacodynamic Per-Protocol Set (PD-PPS) is a subset of the FAS, consisting of those subjects who had no important protocol deviation affecting the serum concentrations of total IgG, IgG subclasses, or neurofilament light chain. Post-Baseline deviations will not necessarily lead to total exclusion of a subject from the PD-PPS but may lead to exclusion of specific data.

14.2 General statistical considerations

All analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, USA). Continuous variables will be summarized by treatment group (Placebo and rozanolixizumab) and visit (where applicable) with the statistics mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by treatment group and visit (where applicable) with frequency counts and percentages.

Unless stated otherwise, all statistical tests will be 1-sided and conducted at 0.05 alpha levels.

Data listings containing all documented data and all calculated data will be generated.

Baseline will be the last nonmissing data collected prior to the first dose of IMP, and measurement-specific Baseline values will be defined in the SAP.

14.3 Planned efficacy analyses

14.3.1 Analysis of the primary efficacy variable

The primary efficacy variable is the change from Baseline to Week 13 (Day 85) in the iRODS score.

The primary analysis of the primary variable will be based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) that includes terms for treatment group, the Baseline iRODS score, the prior Ig therapy, and the interaction between treatment group and week. The model will define subject as a random effect and utilize an unstructured covariance pattern.

An estimate for the placebo-adjusted treatment effect with a 2-sided 90% confidence interval (CI) will be produced.

For subjects who prematurely withdraw for any reason before Week 13 (Day 85), data collected during the PEOT Visit will be used to impute iRODS at the next visit. Since the analysis is based on the MMRM approach, visits beyond the PEOT Visit will not be imputed.

Different sensitivity analyses to evaluate the effect of missing observations on the primary analysis findings will be done. The first sensitivity analysis will be performed in the same way as the primary analysis, however for the PPS. A further analysis will utilize the last observation carried forward (LOCF) approach; missing values will be replaced by the last observed post-Baseline value of the variable and the analysis will be performed on the resulting dataset. An additional sensitivity analysis will be performed excluding any subject who received a mean dose more than ±10% from the intended dose.

14.3.2 Other efficacy analyses

For the CIDP relapse (Yes/No) up to Week 13 (Day 85) after first treatment according to iRODS, adjusted INCAT, and maximum grip strength assessed by the site personnel scores, treatment comparison versus placebo for the rozanolixizumab group (differences in CIDP relapse rates) will be performed using a standard 1-sided Wald asymptotic test with a 5% alpha level. The corresponding 2-sided 90% CI for the difference will be constructed using the asymptotic standard error (asymptotic Wald confidence limits). Sensitivity analyses for relapse will be performed and described in the SAP.

For the analysis, subjects who withdraw for any reason before Week 13 (Day 85) or who have missing data at Week 13 (Day 85) will be considered as relapsed. The same is true for subjects administered an Ig infusion rescue medication during this time interval.

Kaplan-Meier estimates and log-rank tests will be used to compare the treatment difference for the time to CIDP relapse (according to iRODS, adjusted INCAT scores, and maximum grip strength assessed by site personnel).

The statistical methods applied for the variables derived from rescue medication (subject received rescue medication [Yes/No] and time to rescue medication administration) will be the same as those for the CIDP relapse and time to CIDP relapse.

For the change from Baseline at each scheduled assessment during the Treatment and Observation Period, iRODS score, adjusted INCAT score, maximum grip strength assessed by the site personnel score, and RT-MRC sum score, treatment differences will be compared by

ANCOVAs adjusted for Baseline measurement and prior Ig therapy. Analyses will be performed for the FAS utilizing the observed cases.

The results of the newly developed PROs (CIDP PRO instrument and fatigue scale) will be listed and frequency tables will be provided at an item level. A psychometric analysis plan will be created, which will detail all the exploratory and correlation analyses between the newly developed PROs and clinical variables. The PROs will also be subject to a Rasch analysis. The results of the psychometric analyses will be reported separately from the clinical study report (CSR).

14.4 Other analyses

14.4.1 Safety analyses

The incidence of subjects with TEAEs will be determined by treatment group. Furthermore, the absolute and relative frequencies for subjects with a given TEAE with respect to the preferred term according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®), will be determined within each treatment group and system organ class. Additional tables will summarize TEAEs by maximum severity and causal relationship with rozanolixizumab, as judged by the investigator, per treatment group. Adverse events will be categorized by severity according to the National Institutes for Health (CTCAE) version 4.03 grading (National Institutes for Health, 2009). In case the CTCAE grading is not available, the intensity (mild/moderate/severe) will be utilized. The TEAEs leading to discontinuation of IMP and the serious TEAEs will also be summarized by treatment group. The action taken, time of onset relative to dosing, actual dose received, and duration of each AE will be listed only.

For the continuous laboratory variables, the values and changes from Baseline will be descriptively summarized by treatment group at each time point. For categorized values according to the reference range, shift tables from Baseline to each post-Baseline time point will be presented for selected variables to be defined in the SAP. Values outside the reference range will be flagged in the data listings.

Descriptive statistics will be presented for ECG value and changes from Baseline by treatment group and over time based on the mean of the triplicate assessments at each time point. Categorical analyses for QTc, eg, QTc increase >60msec, will also be performed.

Descriptive statistics will be reported for all vital sign measurements (including BP, PR, temperature, and body weight). Measured values and changes from Baseline will be summarized by treatment group and by time point.

Physical and neurological examination findings and the results of any pregnancy testing will be presented in listings only. Results will be listed for any subjects who complete a headache questionnaire, undergo stool sampling, or lumbar puncture, etc.

14.4.2 PK analyses

Pharmacokinetic variables of rozanolixizumab like AUC (area under the curve), C_{max} (maximum concentration) cannot be derived, since blood sampling will be performed at 1 time point post-dosing per visit only. Thus, PK is restricted to concentration data.

In contrast to the general descriptive display, concentration data will be summarized by treatment group, actual dose received, and time point using the number of available observations, mean,

median, SD, minimum, maximum, geometric mean (and associated 95% confidence intervals), and geometric coefficient of variation (assuming log-normally distributed data). Values below the lower limit of quantification (LLOQ) will be reported with a clear sign indicating that they were below the LLOQ. Descriptive statistics of concentrations will be calculated if at least two-thirds of the individual data points are quantifiable (≥LLOQ). Individual concentrations of rozanolixizumab will also be displayed graphically.

14.4.3 PD analyses

For all PD variables, descriptive statistics for the value, change from Baseline, and/or percentage change from Baseline will be tabulated by treatment group, actual dose received, and time point.

The PD variables will include serum IgG, IgG subclass, and neurofilament light chain concentrations.

Population PK analyses and PK/PD analyses may be conducted for the PD variables of interest. All such PK and PK/PD analyses will be described in a separate Data Analysis Plan (DAP) however results will not be reported in the CSR.

14.4.4 Immunological analyses

All immunologic variables including concentrations of immunoglobulins (IgA, IgE, and IgM), and serum (C3 and C4) and plasma (C3a and C5a) complement levels, and serum cytokines will be summarized by treatment group and visit using descriptive statistics.

The [redacted] status (negative or confirmed positive) and the changes in confirmed positive titer at each scheduled assessment during Treatment and Observation Periods will be summarized by treatment group and visit to inform on incidence and emergence of [redacted] figures will also be presented.

Further details will be provided in the SAP.

14.4.5 Subject exit interview

The anonymous audio recordings will be analyzed by a third party and reported outside the clinical study report.

14.5 Handling of protocol deviations

Important protocol deviations are identified as part of the data cleaning process in the Protocol Deviation Specification (PDS). Ongoing data cleaning meetings will be held throughout the duration of the study. Objectives of these meetings include to review and update (if necessary) the important protocol deviations in the PDS and discuss criteria for exclusion of subjects from analysis populations. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting. Through this ongoing data cleaning and evaluation process, all decisions regarding important protocol deviations and exclusions from analysis populations are made on an ongoing basis and will be finalized before database lock.

14.6 Handling of dropouts or missing data

For subjects who prematurely withdraw for any reason before Week 13 (Day 85), data collected during the PEOT Visit will be used to impute iRODS at the next visit. Since the primary analysis of the primary variable is based on the MMRM approach, visits beyond the PEOT Visit will not be imputed. Missing data in-between visits will be covered by the MMRM approach.

All imputation of missing or partial dates for safety assessments, as well as detailed handling of missing efficacy data, will be detailed in the SAP.

14.7 Planned interim analysis and data monitoring

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible (see safety signal detection in Section 12.1.7).

At least 4 interim analyses will be performed.

The first interim analysis will be conducted after 8 subjects have received their first 4 sc infusions and have attended the next visit (Visit 9). The second interim analysis will be conducted after 8 subjects (receiving 12 sc infusions) have attended the first visit of the Observation Period (ie, Visit 17, the visit 1 week after last dosing). The third interim analysis will take place after data from 8 additional subjects are available, ie, after 16 subjects have attended the first visit of the Observation Period. Each time, the DMC will assess the safety of rozanolixizumab based on an unblinded data analysis. The safety and PD variables to be used and decision rules will be specified in the DMC charter. During these reviews recruitment will not be stopped. If the observed safety or PD of the data from of interim analyses 1 and 2 is not as expected, the DMC may recommend to either lower or increase the dose. The implementation of such changes would be handled via a substantial protocol amendment.

The analyses will be described in a separate Interim Statistical Analysis Plan. The first 3 interim analyses will utilize all safety, PK and PD data available at the time of the cut off (eg, possibly additional visits and/or subjects). For all interim analyses, the data to be analyzed should be as clean as possible; however, the database will not be locked and a snapshot will be taken.

The fourth and final interim analysis will be performed once all subjects have attended Visit 17, the first visit of the Observation Period (ie, Day 85). This interim analysis will provide, at a minimum, the results for the primary variable “Change from Baseline to Week 13 (Day 85) in iRODS score”.

If needed, subsequent DMC meetings will take place. The timing of further interim analyses and reviews of the data by the DMC will be decided by the DMC. Ad hoc DMC meetings can be held for reasons determined appropriate by the sponsor.

The deliberations and decisions of the DMC will be formally documented.

A detailed description of the DMC composition, processes, and responsibilities will be provided in a separate DMC charter.

14.8 Determination of sample size

Due to the pilot character of the study, the sample size is mainly chosen based on the practical limitations (eg, to recruit sufficient subjects in a reasonable time). In addition, currently no data of results is available in the literature for the primary variable. Thus, the sample size considerations are only based on assumptions for the effect size index (difference in group means/SD). When the sample size in each group is [redacted] a 1-sided 5.0% t-test for the comparison of rozanolixizumab and placebo will provide 80% power to detect a statistically significant difference in case there is a large effect of rozanolixizumab with an effect size index of [redacted] In

case of a medium index ([redacted]) the power already decreases to 40%. It will be assumed that [redacted] of the randomized subjects cannot be utilized for the efficacy analysis; hence 34 subjects will be randomized.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Informed consent

Subject's informed consents must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the investigator.

Prior to participation in the study, the Informed Consent form(s) should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent form is amended during the study, the investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

Any data already generated on the samples will be retained and used, but no further laboratory analysis will occur.

15.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The investigator will fill in the subject identifying information and medical emergency contact information. The investigator will instruct the subject to keep the card with him/her at all times.

15.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, Informed Consent form, IB, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the investigator or the sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the sponsor (or its representative) with evidence of such IRB/IEC notification.

15.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

15.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

16 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the investigator and/or CRO agreements, as applicable.

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18 APPENDICES

18.1 Suggested management guidelines for infusion reactions

Table 18-1: Suggested management guidelines for infusion reactions

Type of reaction	Sponsor recommendations for management
Acute – Mild eg, flushing, dizziness, headache, sweating, palpitations, nausea	Slow infusion rate to [redacted]. [redacted] Administer antihistamine iv/im. Administer paracetamol 1g orally. Monitor vital signs every 10 minutes until back to Baseline. [redacted] as tolerated until intended dose has been given.
Acute – Moderate eg, flushing, chest tightness, dyspnea, hypo/hypertension (change >20mmHg in systolic blood pressure), raised temperature, palpitations, urticaria	Stop infusion. Infuse [redacted]. Administer antihistamine iv/im. Administer paracetamol 1g orally. Monitor vital signs every 5 minutes until back to Baseline. Wait 20 minutes. [redacted] following this suggested regimen: [redacted] as tolerated until intended dose has been given.
Acute – Severe eg, hypo/hypertension (change >40mmHg in systolic blood pressure), raised temperature with rigors, chest tightness, dyspnea with wheezing, stridor	Stop infusion definitively. Alert crash team. Maintain airway, ensure oxygen is available. If wheezing, give epinephrine 0.5mg im (0.5mL 1:1000 epinephrine). Administer antihistamine iv/im. Administer corticosteroids iv. Monitor vital signs every 2 minutes until back to Baseline.

im=intramuscular; iv=intravenous

18.2 Diagnosis of anaphylactic reactions

Anaphylaxis is highly likely when any of the following 3 criteria is fulfilled (Sampson et al, 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b. Reduced blood pressure [BP] or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours): Systolic BP of less than 90mmHg or greater than 30% decrease from the subject's Baseline systolic BP value.

18.3 Protocol amendment 1

Rationale for the amendment

The CIDP01 protocol was originally finalized by UCB in Mar 2017, but was not submitted to any regulatory authorities nor IRBs/IECs. The current protocol has been amended to incorporate changes to the study's conduct and analysis to better align with the current understanding of available data from completed and ongoing studies with rozanolixizumab. Given that the protocol has been updated subsequent to original protocol finalization at UCB, the current protocol is considered an amendment per UCB policy. A summary of changes section is not included since the original protocol was not previously submitted to any regulatory authorities.

18.4 Protocol amendment 1.1

Rationale for the amendment

This is a local amendment for France. The changes implemented in this amendment (modifying the timeframe for use of contraception post study completion and the final urinary pregnancy test) have been incorporated into and are detailed in global Protocol Amendment 2 below.

18.5 Protocol amendment 2

Rationale for the amendment

The purpose of this substantial protocol amendment is to provide clarification on the dose of investigational product administered (including an allowance of ±10% compared to the [redacted] target dose arm), as well as a flexible infusion rate. Sensitivity analyses were introduced to account for deviation outside the ±10% target dosage and the descriptive analyses will inform about actual doses administered to the subjects. Updates to the status of the other

rozanolixizumab studies have been included. The visit windows and the scheduling of the randomization visit in view of the Ig treatment at study start have been clarified. The predominance of objective criteria over the investigator's judgement has been confirmed for the assessment of CIDP relapse. The timeframe of expected use of contraception post-study completion has been extended to 90 days in view of the probable half-life of rozanolixizumab. Exclusion criterion #3 has been extended to prediabetic condition. The expectation with regards to the use of cannabidiols and medicinal marijuana has been clarified in the concomitant medication section. The protocol amendment confirms the expectation of a single rater for the INCAT assessment to ensure consistency of the rating during the course of the study.

In addition, some administrative changes have been made.

Modifications and changes

Specific changes

Change #1

Section 1 Summary, second paragraph

Subjects will be randomized to 1 of 2 treatment arms: rozanolixizumab [redacted] sc or placebo sc in a ratio of 1:1. Subjects will receive 12 weekly doses of investigational medicinal product (IMP). The maximum duration of the study per subject is approximately 28 weeks (up to maximum 40 weeks), consisting of a Screening Period of between 2 and 5 weeks duration, an 11-week Treatment Period, and an Observation Period of 12 weeks (up to 24 weeks). The study is planned to be conducted in approximately 24 sites globally. Approximately 34 subjects will be randomized to ensure at least 30 subjects are evaluable for the primary efficacy analysis.

Has been changed to:

Subjects will be randomized to 1 of 2 treatment arms: rozanolixizumab [redacted] sc or placebo sc in a ratio of 1:1. **For exact doses to be administered, refer to Section 7.2.** Subjects will receive 12 weekly doses of investigational medicinal product (IMP). The maximum duration of the study per subject is approximately 28 weeks (up to maximum 40 weeks), consisting of a Screening Period of between 2 and 5 weeks duration, an 11-week Treatment Period, and an Observation Period of 12 weeks (up to 24 weeks). The study is planned to be conducted in approximately 24 sites globally. Approximately 34 subjects will be randomized to ensure at least 30 subjects are evaluable for the primary efficacy analysis.

Change #2

Section 2 Introduction, fifth paragraph, final sentence

To date, rozanolixizumab has been administered to healthy subjects in a completed, first in-human study (UP0018, detailed below), an ongoing Phase 2 study in subjects with primary immune thrombocytopenia (ITP) (TP0001, evaluating [redacted] by sc route across 5 cohorts), and an ongoing Phase 2 study in subjects with myasthenia gravis (MG) (MG0002, evaluating [redacted] by sc route).

Has been changed to:

To date, rozanolixizumab has been administered to healthy subjects in a completed, first-in-human study (UP0018~~, detailed below~~), a **completed** Phase 2 study in subjects with primary immune thrombocytopenia (ITP) (TP0001, evaluating [redacted] by sc route across 5 cohorts), and a **completed** Phase 2 study in subjects with myasthenia gravis (MG) (MG0002, evaluating [redacted] by sc route). **See summaries below for UP0018, TP0001, and MG0002.**

Change #3

Section 2 Introduction

The following text has been added:

TP0001 is a completed, Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of rozanolixizumab administered as sc doses of [redacted], in 66 subjects ≥18 years of age with persistent or chronic ITP.

There were no treatment-emergent deaths reported during TP0001, and no subjects discontinued from the study or IMP due to TEAEs. There were no treatment-related SAEs reported from the study. All TEAEs considered by the investigator to be related to rozanolixizumab were mild to moderate in intensity and resolved without clinical sequelae. The majority of the related TEAEs did not require treatment. The most common TEAEs were headache (26 subjects [39.4%]), diarrhea (8 subjects [12.1%]), and vomiting (6 subjects [9.1%]). Treatment with rozanolixizumab was generally [redacted] and well tolerated with an acceptable safety profile across the treatment groups.

MG0002 is a completed, multicenter, randomized, investigator-and subject-blind, placebo-controlled, treatment sequence study evaluating the safety, tolerability, and efficacy of rozanolixizumab in 43 subjects with moderate to severe MG. [redacted]

There were no deaths reported during MG0002. One subject (2.3%) discontinued from the study due to an AE (MG crisis). In addition, 3 subjects experienced TEAEs (headache) that led to discontinuation of IMP, but the subjects remained in the study. Six subjects (14.0%) reported a total of 7 serious TEAEs. One subject in the Placebo-Rozanolixizumab [redacted] Group experienced a serious TEAE of headache that was considered by the investigator to be related to the IMP. With the exception of 1 serious TEAE of ulna fracture, all other serious TEAEs were in the System Organ Class of Nervous system disorders. Three subjects (7.0%) reported serious TEAEs of MG (the studied indication), and 1 subject (2.3%) reported a serious TEAE of MG crisis. The most common TEAEs were headache (23 subjects [53.5%]), diarrhea (11 subjects [25.6%]), and nausea (6 subjects [14.0%]). Overall, repeated administrations of rozanolixizumab at dose levels of

[redacted] sc were generally [redacted] and well tolerated, with an acceptable safety profile.

Change #4

Section 2 Introduction, final paragraph

Additional information on the development of rozanolixizumab, including data from the ongoing clinical studies in ITP subjects (TP0001) and MG subjects (MG0002), can be found in the current version of the IB for rozanolixizumab.

Has been changed to:

Additional information on the development of rozanolixizumab, ~~including data from the ongoing clinical studies in ITP subjects (TP0001) and MG subjects (MG0002),~~ can be found in the current version of the IB for rozanolixizumab.

Change #5

Section 5.1 Study description

The following text has been added:

See Section 7.2 for details on treatments to be administered.

Change #6

Section 5.1 Study description, third paragraph

The dose level of [redacted] may be reduced to [redacted] (or equivalent placebo) for an individual subject based on their tolerability. For example, if a subject experiences a severe headache which does not respond to headache treatment (see Section 12.1.10), a decision to decrease future doses to 7mg/kg may be made. The decision to decrease the dose will be made following a discussion between the investigator and the UCB study physician. In addition, the decision to decrease the dose for the remainder of the subjects may be made following a DMC recommendation.

Has been changed to:

The dose level of [redacted] may be reduced to [redacted] (or equivalent placebo) for an individual subject based on their tolerability **(see Section 7.2 for details)**. For example, if a subject experiences a severe headache which does not respond to headache treatment (see Section 12.1.10), a decision to decrease future doses to [redacted] may be made. The decision to decrease the dose will be made following a discussion between the investigator and the UCB study physician. In addition, the decision to decrease the dose for the remainder of the subjects may be made following a DMC recommendation.

Change #7

Table 5-1 Schedule of Assessments, Days 3, 10, and 17 column headings

Visit No	1	2	3 [b]	4	5 [b]	6	7 [b]	8	9 [c]	…
Visit type	S	S	TH	S	TH	S	TH	S	H	…
Week		1		2		3		4	5	…

Day	-35 to -14	1 BL	3	8 ±2	10	15 ±2	17	22 ±2	29 ±2	…

Have been changed to:

Visit No	1	2	3 [b]	4	5 [b]	6	7 [b]	8	9 [c]	…
Visit type	S	S	TH	S	TH	S	TH	S	H	…
Week		1		2		3		4	5	…
Day	-35 to -14	1 BL	**2 or** 3	8 ±2	**9 or** 10	15 ±2	**16 or** 17	22 ±2	29 ±2	…

Change #8

Table 5-1 Schedule of Assessments, footnotes b and j

[b] Two days after the subject's first 3 doses of IMP, the subject will be telephoned and a healthcare professional will visit the subject at home to collect PK samples and immunoglobulins (total IgG and IgG subclasses) (only at Visit 7). Alternately, the visit can be conducted at the site as deemed necessary by site personnel and/or the subject.

[j] The pregnancy test must be negative before dosing. Note that the final urinary pregnancy test of the study should be no longer than 60 days after the final dose of IMP.

Have been changed to:

[b] **One or** two days after the subject's first 3 doses of IMP, the subject will be telephoned**,** and a healthcare professional will visit the subject at home to collect PK samples and immunoglobulins (total IgG and IgG subclasses) (only at Visit 7). Alternately, the visit can be conducted at the site as deemed necessary by site personnel and/or the subject.

[j] The pregnancy test must be negative before dosing. Note that the final urinary pregnancy test of the study should be no longer than **90** days after the final dose of IMP.

Change #9

Section 5.4.4 Rationale for dose selection, paragraphs 3 through 5

MG0002 is an ongoing, Phase 2, multicenter, randomized, investigator- and subject-blind, placebo-controlled, 2-arm repeat dose, treatment sequence study evaluating the safety and efficacy of rozanolixizumab sc [redacted]) in 43 subjects with generalized MG.

[redacted]

Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] sc have been generally [redacted] and well tolerated, with an acceptable safety profile. No new safety concerns have been identified to date; a summary of results is included in the IB.

TP0001 is an ongoing, Phase 2, multicenter, open-label, multiple-arm study to evaluate the safety, tolerability, and efficacy of rozanolixizumab in subjects with primary persistent or chronic ITP. The following dose arms are being used in the study:

- Dose Arm 1 (15 subjects): rozanolixizumab [redacted] sc ([redacted])
- Dose Arm 2 (15 subjects): rozanolixizumab [redacted] sc [redacted])

- Dose Arm 3 (6 to 12 subjects): rozanolixizumab [redacted] sc ([redacted])
- Dose Arm 4 (6 to 12 subjects): rozanolixizumab [redacted] sc ([redacted])
- Dose Arm 5 (6 to 12 subjects): rozanolixizumab [redacted] g sc ([redacted])

[redacted]. Based on an interim analysis of 55 subjects, the [redacted] dose was well-tolerated according to data available to date and a summary of the safety results is included in the IB. However, it should be noted that the exposure of rozanolixizumab was lower in subjects with ITP than subjects with MG when dosed with the same dose level.

Have been changed to:

MG0002 is **a completed**, Phase 2, multicenter, randomized, investigator- and subject-blind, placebo-controlled, 2-arm repeat dose, treatment sequence study evaluating the safety and efficacy of rozanolixizumab sc ([redacted] in 43 subjects with generalized MG.

[redacted] Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] sc **were** generally [redacted] and well tolerated, with an acceptable safety profile. No new safety concerns **were** identified; a summary of results is included in the IB.

TP0001 is a **completed**, Phase 2, multicenter, open-label, multiple-arm study to evaluate the safety, tolerability, and efficacy of rozanolixizumab in subjects with primary persistent or chronic ITP. The following dose arms **were** used in the study:

- Dose Arm 1 (15 subjects): rozanolixizumab [redacted] sc ([redacted])
- Dose Arm 2 (15 subjects): rozanolixizumab [redacted] sc ([redacted])
- Dose Arm 3 (~~6 to~~ 12 subjects): rozanolixizumab [redacted] g sc ([redacted])
- Dose Arm 4 (~~6 to~~ 12 subjects): rozanolixizumab [redacted] sc [redacted]
- Dose Arm 5 (~~6 to~~ 12 subjects): rozanolixizumab [redacted] sc [redacted]

[redacted]s. ~~Based on an interim analysis of 55 subjects,~~ **T**he [redacted] dose was well-tolerated, ~~according to data available to date~~ and a summary of the safety results is included in the IB. However, it should be noted that the exposure of rozanolixizumab was lower in subjects with ITP than subjects with MG when dosed with the same dose level.

Change #10

Section 5.4.4 Rationale for dose selection, final paragraph, final 2 sentences

This change in concentration is not predicted to have an impact on local tolerability, however to allow this to be fully assessed the first two infusions in each subject will be given at a slower rate [redacted]). If no tolerability concerns are identified subsequent infusions may be given at [redacted].

Have been changed to:

This change in concentration is not predicted to have an impact on local tolerability, however to allow this to be fully assessed the first two infusions in each subject will be given at a slower rate **of approximately** [redacted]. If no tolerability concerns are identified subsequent infusions may be given at **rates up to** [redacted].

Change #11

Section 6.1 Inclusion criteria, criterion 7, second paragraph, first sentence

Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period of 2 months after their final dose of IMP.

Has been changed to:

Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period of **3** months after their final dose of IMP.

Change #12

Section 6.2.2 Exclusion criteria related to CIDP diagnosis, criterion 3

Subject has a current diagnosis or has a history of Type 1 or Type 2 diabetes mellitus.

Has been changed to:

Subject has a current diagnosis or has a history of Type 1 or Type 2 diabetes mellitus **and/or hemoglobin A1c level >6.0%**.

Change #13

Section 6.2.3 Exclusion criteria related to health status/safety of the subject, criterion 14

Subject has a history of alcohol use disorder or other substance use disorder within 12 months of Screening Visit.

Has been changed to:

Subject has a history of alcohol use disorder or other substance use disorder **(as per Diagnostic and Statistical Manual of Mental Disorders-5 [American Psychiatric Association, 2013])** within 12 months of Screening Visit.

Change #14

Section 6.4 Withdrawal criteria, Subject may be discontinued from IMP section, criterion 2

Subject experiences a severe AE of headache which is considered related to the IMP in the opinion of the investigator (Table 5-2). Following an event of a severe headache, a subject may

continue participation in the study if the subject is willing to do so and the investigator, Medical Monitor, and Study Physician agree that the subject's continuation in the study poses no significant risk for the subject. The use of symptomatic headache treatment is allowed at the discretion of the investigator. The IMP dose can be reduced to [redacted] (or its placebo equivalent) if the headache persists despite symptomatic treatment (refer to Section 12.1.10 for details on the medical management of headaches).

Has been changed to:

Subject experiences a severe AE of headache which is considered related to the IMP in the opinion of the investigator (**see Section 12.1.10**). Following an event of a severe headache, a subject may continue participation in the study if the subject is willing to do so and the investigator, Medical Monitor, and Study Physician agree that the subject's continuation in the study poses no significant risk for the subject. The use of symptomatic headache treatment is allowed at the discretion of the investigator. The IMP dose can be reduced to [redacted] (or its placebo equivalent) if the headache persists despite symptomatic treatment (refer to Section 12.1.10 for details on the medical management of headaches **and Section 7.2 for treatment to be administered**).

Change #15

Section 7.2 Treatments to be administered, first paragraph, first bullet

- Subjects in Treatment Arm 2 will receive 1 sc dose of placebo weekly for 12 weeks (Visits 2, 4, and 6, and Visit 8 through Visit 16).

Has been changed to:

- Subjects in Treatment Arm 1 will receive 1 sc dose of rozanolixizumab [redacted] **(see Table 7-1)** weekly for 12 weeks (Visits 2, 4, and 6, and Visit 8 through Visit 16).

Change #16

Section 7.2 Treatments to be administered

The following table has been added:

Table 7-1: IMP doses to be administered (equivalent to approximately 10mg/kg) by body weight

Body weight ranges	IMP doses to be administered (equivalent to approximately [redacted])	IMP volume to be administered
≥40 to <49kg	[redacted]	3mL
≥49 to <63kg		4mL
≥63 to <77kg		5mL
≥77 to <91kg		6mL
≥91 to <105kg		7mL
≥105 to <119kg		8mL
≥119 to <133kg		9mL

Table 7-1: IMP doses to be administered (equivalent to approximately 10mg/kg) by body weight

Body weight ranges	IMP doses to be administered (equivalent to approximately [redacted])	IMP volume to be administered
≥133 to <147kg	[redacted]	10mL
≥147 to <161kg		11mL
≥161 to 170kg		12mL

IMP= investigational medicinal product
[a] Doses administered will be ±10% of the intended dose, except for subjects with a body weight of 47 to 50kg and 63kg.

Change #17

Section 7.2 Treatments to be administered, third paragraph

In case of tolerability issues (eg, severe headache) and if symptomatic headache medication (eg, acetylsalicylic acid 1000mg) is not sufficient, the dose of IMP could be lowered to [redacted] (or equivalent placebo) during the next visit when the investigator, Medical Monitor and Study Physician agree that the dose reduction poses no significant risk for the subject (see Section 12.1.10).

Has been changed to:

In case of tolerability issues (eg, severe headache) and if symptomatic headache medication (eg, acetylsalicylic acid 1000mg) is not sufficient, the dose of IMP could be lowered to [redacted] **(see Table 7-2)** (or equivalent placebo) during the next visit when the investigator, Medical Monitor, and Study Physician agree that the dose reduction poses no significant risk for the subject (see Section 12.1.10).

Change #18

Section 7.2 Treatments to be administered

The following table has been added:

Table 7-2: IMP doses to be administered (equivalent to approximately 7mg/kg) by body weight

Body weight ranges	IMP doses to be administered (equivalent to approximately [redacted])	IMP volume to be administered
≥40 to <49kg	[redacted]	2mL
≥49 to <69kg		3mL
≥69 to <89kg		4mL
≥89 to <109kg		5mL
≥109 to <129kg		6mL
≥129 to <149kg		7mL

Table 7-2: IMP doses to be administered (equivalent to approximately [redacted] by body weight

Body weight ranges	IMP doses to be administered (equivalent to approximately [redacted])	IMP volume to be administered
≥149 to <169kg	[redacted]	8mL
≥169 to 170kg		9mL

IMP= investigational medicinal product

Change #19

Section 7.2 Treatments to be administered, fifth paragraph

The IMP will be administered as a sc infusion using a syringe pump.

- For the first 2 doses, [redacted]
- For the subsequent doses, [redacted]

Has been changed to:

The IMP will be administered as a sc infusion using a syringe pump.

- For the first 2 doses, [redacted]
- For the subsequent doses, [redacted]

Change #20

Section 7.7.1 Permitted concomitant treatments (medications and therapies)

The following text has been added:

The use of cannabidiols and medicinal marijuana (prescribed by a physician) is also permitted. When applicable, the subject must be on a stable dose of cannabidiols and/or medicinal marijuana for [redacted].

Change #21

Section 7.7.3 Rescue medication, first sentence

If, at any time during the Treatment and Observation Period, the subject relapses according to the medical judgement of the investigator supported by eg, subject's score on iRODS, INCAT, or maximum grip strength (assessed by site personnel), then rescue medication must be considered and the subject will be withdrawn from IMP (see Section 6.4).

Has been changed to:

If, at any time during the Treatment and Observation Period, the subject relapses according to the **predefined criteria for relapse as specified in Section 4.1.2 using the** subject's score on iRODS, INCAT, or maximum grip strength (assessed by site personnel), **and supported by the medical judgement of the investigator**, then rescue medication must be considered and the subject will be withdrawn from IMP (see Section 6.4).

Change #22

Section 8.1.1 Screening Visit 1 (Day -35 to Day -14), first sentence

The following procedures will be performed at the Screening Visit:

Has been changed to:

The following procedures will be performed at the Screening Visit **(or as close as possible to the Screening date)**:

Change #23

Section 8.2 Treatment Period Visits 2 to 16 (Day 1 to Day 78), first paragraph, first 2 bullets

- For subjects on an IVIg 3- to 6-week regimen, randomization should occur 1 week before the next planned IVIg dose (according to the baseline IVIg regimen). However, if that specific date is not possible, the Randomization Visit could be up to 1 week after that date.
- Subjects on a 2-week IVIg treatment regimen will continue on their regular schedule for 1 further IVIg treatment until randomization. Randomization will occur 1 week before the planned IVIg dose. However, if that specific date is not possible, the Randomization Visit could be up to 1 week after that date.

Has been changed to:

- For subjects on an IVIg 3- to 6-week regimen, randomization should occur 1 week before the next planned IVIg dose (according to the baseline IVIg regimen). However, if that specific date is not possible, the Randomization Visit could be **conducted** up **to the date of the next planned IVIg dose (ie,** 1 week after **the preferred** date**)**.
- Subjects on a 2-week IVIg treatment regimen will continue on their regular schedule for 1 further IVIg treatment until randomization. Randomization will occur 1 week before the planned IVIg dose. However, if that specific date is not possible, the Randomization Visit could be **conducted** up to **the date of the next planned IVIg dose (ie,** 1 week **after the preferred** date**)**.

Change #24

Section 8.2 Treatment Period Visits 2 to 16 (Day 1 to Day 78), third paragraph

For the 11-week Treatment Period, visits will occur weekly from Visit 2 to Visit 16.
Three additional visits (Visits 3, 5 and 7) will be performed 1 day after each of the first 3 IMP administrations to monitor safety and collect samples for PK/PD.

Has been changed to:

For the 11-week Treatment Period, visits will occur weekly from Visit 2 to Visit 16.
Three additional visits (Visits 3, 5, and 7) will be performed 1 **or 2** day**s** after each of the first 3 IMP administrations to monitor safety and collect samples for PK/PD.

Change #25

Section 8.2 Treatment Period Visits 2 to 16 (Day 1 to Day 78), final paragraph, first sentence

If at any time during the Treatment Period the subject relapses according to the medical judgement of the investigator supported by, eg, subject's score on iRODS, INCAT, or maximum grip strength (assessed by site personnel), then rescue medication must be considered and the subject must be withdrawn from IMP (see Section 6.4 and Section 7.7.3).

Has been changed to:

If at any time during the Treatment Period, the subject relapses according to the **predefined criteria for relapse as specified in Section 4.1.2 using the** subject's score on iRODS, INCAT, or maximum grip strength (assessed by site personnel), **and supported by the medical judgement of the investigator,** then rescue medication must be considered and the subject must be withdrawn from IMP (see Section 6.4 and Section 7.7.3).

Change #26

Section 8.2.2 Visit 3 Telephone Call and Home Visit (Day 3), first paragraph, first sentence

Visit 3 consists of a telephone call from the site personnel and a home nursing visit performed within 2 days of the previous IMP administration.

Has been changed to:

Visit 3 consists of a telephone call from the site personnel and a home nursing visit performed **after 1 or** 2 days of the previous IMP administration.

Change #27

Section 8.2.4 Visit 5 Telephone Call and Home Visit (Day 10), first paragraph, first sentence

Visit 5 is a telephone call from the site with a home nursing visit performed within 2 days of the previous IMP administration.

Has been changed to:

Visit 5 is a telephone call from the site with a home nursing visit performed **after 1 or** 2 days of the previous IMP administration.

Change #28

Section 8.2.6 Visit 7 Telephone Call and Home Visit (Day 17), first paragraph, first sentence

Visit 7 is a telephone call from the site with a home nursing visit performed within 2 days of the previous IMP administration.

Has been changed to:

Visit 7 is a telephone call from the site with a home nursing visit performed **after 1 or** 2 days of the previous IMP administration.

Change #29

Section 8.3 12-Week Observation Period Visits 17 to 21 (Day 85 to Day 162), fourth paragraph, first sentence

If at any time during the Observation Period the subject relapses (according to the medical judgement of the investigator supported by eg, subject's score on iRODS, INCAT, or maximum grip strength [assessed by site personnel]), then rescue medication must be considered.

Has been changed to:

If at any time during the Observation Period, the subject relapses according to the **predefined criteria for relapse as specified in Section 4.1.2 using the** subject's score on iRODS, INCAT, or maximum grip strength (assessed by site personnel), **and supported by the medical judgement of the investigator,** then rescue medication must be considered.

Change #30

Section 9.2 INCAT, second paragraph

The investigator (or qualified personnel) will record the subjects' adjusted INCAT score at every study visit according to schedule of assessments (see Table 5–1).

Has been changed to:

The investigator (or qualified personnel) will record the subjects' adjusted INCAT score at every study visit according to schedule of assessments (see Table 5–1). **It is recommended that the rater of the scale remains the same throughout the duration of the study to ensure consistency of the rating.**

Change #31

Section 12.1.6 Overdose of investigational medicinal product, first sentence

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF.

Has been changed to:

Excessive dosing (beyond that prescribed in the protocol and including overdose **ie,** [redacted] should be recorded in the eCRF.

Change #32

Table 12-3 Laboratory measurements, footnote e

[e] Urine pregnancy test (dipstick) for women of childbearing potential performed prior to dosing (and confirmed negative) at dosing visits and each visit of the Observation Period. Note that the final urinary pregnancy test of the study should be no longer than 60 days after the final dose of IMP.

Has been changed to:

[e] Urine pregnancy test (dipstick) for women of childbearing potential performed prior to dosing (and confirmed negative) at dosing visits and each visit of the Observation Period. Note that the final urinary pregnancy test of the study should be no longer than **90** days after the final dose of IMP.

Change #33

Section 14.3.1 Analysis of the primary efficacy variable, fifth paragraph

Different sensitivity analyses to evaluate the effect of missing observations on the primary analysis findings will be done. The first sensitivity analysis will be performed in the same way as the primary analysis, however for the PPS. A further analysis will utilize the last observation carried forward (LOCF) approach; missing values will be replaced by the last observed post-Baseline value of the variable and the analysis will be performed on the resulting dataset.

Has been changed to:

Different sensitivity analyses to evaluate the effect of missing observations on the primary analysis findings will be done. The first sensitivity analysis will be performed in the same way as the primary analysis, however for the PPS. A further analysis will utilize the last observation carried forward (LOCF) approach; missing values will be replaced by the last observed post-Baseline value of the variable and the analysis will be performed on the resulting dataset. **An additional sensitivity analysis will be performed excluding any subject who received a mean dose more than ±10% from the intended dose.**

Change #34

Section 14.4.1 Safety analyses, first paragraph, final sentence

The action taken, time of onset relative to dosing, and duration of each AE will be listed only.

Has been changed to:

The action taken, time of onset relative to dosing, **actual dose received,** and duration of each AE will be listed only.

Change #35

Section 14.4.2 PK analyses, second paragraph, first sentence

In contrast to the general descriptive display, concentration data will be summarized by treatment group and time point using the number of available observations, mean, median, SD, minimum, maximum, geometric mean (and associated 95% confidence intervals), and geometric coefficient of variation (assuming log-normally distributed data).

Has been changed to:

In contrast to the general descriptive display, concentration data will be summarized by treatment group, **actual dose received,** and time point using the number of available observations, mean,

median, SD, minimum, maximum, geometric mean (and associated 95% confidence intervals), and geometric coefficient of variation (assuming log-normally distributed data).

Change #36

Section 14.4.3 PD analyses, first paragraph

For all PD variables, descriptive statistics for the value, change from Baseline, and/or percentage change from Baseline will be tabulated by treatment group and time point.

Has been changed to:

For all PD variables, descriptive statistics for the value, change from Baseline, and/or percentage change from Baseline will be tabulated by treatment group, **actual dose received,** and time point.

Change #37

Section 14.5 Handling of protocol deviations, first 3 sentences

Important protocol deviations are identified as part of the data cleaning process in the Data Cleaning Plan (DCP). Ongoing data cleaning meetings will be held throughout the duration of the study. Objectives of these meetings include to review and update (if necessary) the important protocol deviations in the DCP and discuss criteria for exclusion of subjects from analysis populations.

Has been changed to:

Important protocol deviations are identified as part of the data cleaning process in the **Protocol Deviation Specification (PDS)**. Ongoing data cleaning meetings will be held throughout the duration of the study. Objectives of these meetings include to review and update (if necessary) the important protocol deviations in the **PDS** and discuss criteria for exclusion of subjects from analysis populations.

Change #38

Section 17 References

The following reference has been added:

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

Change #39

Table 18-1 Suggested management guidelines for infusion reactions, first 2 reactions

Type of reaction	Sponsor recommendations for management
Acute – Mild eg, flushing, dizziness, headache, sweating, palpitations, nausea	Slow infusion rate to [redacted] Infuse [redacted] Administer antihistamine iv/im. Administer paracetamol 1g orally. Monitor vital signs every 10 minutes until back to Baseline. [redacted]

Type of reaction	Sponsor recommendations for management
	[redacted], as tolerated until intended dose has been given.
Acute – Moderate eg, flushing, chest tightness, dyspnea, hypo/hypertension (change >20mmHg in systolic blood pressure), raised temperature, palpitations, urticaria	Stop infusion. Infuse [redacted] Administer antihistamine iv/im. Administer paracetamol 1g orally. Monitor vital signs every 5 minutes until back to Baseline. Wait 20 minutes. [redacted] following this suggested regimen: Restart infusion at [redacted]. [redacted], as tolerated until intended dose has been given.

Have been changed to:

Type of reaction	Sponsor recommendations for management
Acute – Mild eg, flushing, dizziness, headache, sweating, palpitations, nausea	Slow infusion rate to [redacted] Infuse [redacted]. Administer antihistamine iv/im. Administer paracetamol 1g orally. Monitor vital signs every 10 minutes until back to Baseline. [redacted] as tolerated until intended dose has been given.
Acute – Moderate eg, flushing, chest tightness, dyspnea, hypo/hypertension (change >20mmHg in systolic blood pressure), raised temperature, palpitations, urticaria	Stop infusion. Infuse [redacted] Administer antihistamine iv/im. Administer paracetamol 1g orally. Monitor vital signs every 5 minutes until back to Baseline. Wait 20 minutes. [redacted] following this suggested regimen: Restart infusion [redacted]**, as tolerated until intended dose has been given**. [redacted] ~~as tolerated until intended dose has been given~~.

19 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

20 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: CIDP01-protocol-amendment-2

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Document Approvals	
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