A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PHASE 2A, PROOF-OF-CONCEPT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ROZANOLIXIZUMAB TO TREAT ADULT STUDY PARTICIPANTS WITH SEVERE FIBROMYALGIA SYNDROME

PROTOCOL AMENDMENT 3 FM0001

PHASE 2A

SHORT TITLE:

A Phase 2A proof-of-concept study to evaluate the efficacy and safety of rozanolixizumab to treat adult study participants with severe fibromyalgia syndrome

Sponsor:
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Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 3	14 Apr 2023	Substantial
Protocol Amendment 2	29 Nov 2022	Substantial
Protocol Amendment 1	24 Oct 2022	Substantial
Original Protocol	23 Jun 2022	Not applicable

Amendment 3 (14 Apr 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The main reason for this amendment is to adjust the inclusion/exclusion criteria in order to better reflect the characteristics of the population with fibromyalgia syndrome (FMS). Additional changes have been made to update and simplify the protocol based on safety knowledge gained from the rozanolixizumab program and to adjust the wording of the statistical section with the current version of the Statistical Analysis Plan (SAP).

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of activities 3. Objectives and endpoints 9.4.1 Safety analyses	Change from Baseline in electrocardiogram (ECG) results was removed from the exploratory endpoints, as ECG will be performed only before dosing (screening and Visit 3). Electrocardiograms at Visit 15, 27, and End of Treatment (EOT)/Early Withdrawal (EW) were removed. A footnote was added to specify that a 12-lead ECG can be performed any time during the study at the investigator's discretion. Change from Baseline in ECG was removed from the analyses. Exclusion criterion #33, related to QT interval, was removed.	Monoclonal antibodies do not directly gain access to the cell cytosol and are too large to bind to the potassium channel encoded by the human ether-a-go-go related gene (hERG) known to play a key role in repolarization of the ventricular cardiac action potential. Rozanolixizumab is, therefore, not expected to induce a prolongation of the action potential duration leading to prolongation of the QT interval and cardiac arrhythmia, and no cardiac events are expected adverse drug reactions from review of data across the program. Twelve-lead ECG will still be performed at screening and may be performed at any time if deemed necessary by the investigator.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of activities 3. Objectives and endpoints 8.9.2 Immunology 9.4.2.4 Immunological analyses 10.2 Appendix 2: Clinical laboratory tests	The objective 'to assess the effects of rozanolixizumab on immunoglobulin (Ig)A, IgE, and IgM levels', the associated endpoint, and scheduled activities as well as related text were removed throughout the document.	As no impact on serum levels of IgA, IgE, and IgM are expected based on the pharmacology of rozanolixizumab and no clinically meaningful changes in IgA, IgE and IgM levels following the administration of rozanolixizumab or any other neonatal Fc receptor (FcRn) inhibitor have been observed in any clinical study of rozanolixizumab to date, assessments of these immunoglobulin classes are no longer deemed necessary for the safety monitoring of the study participants.
1.1 Synopsis 4.1 Overall design	In the overall design description, the number of study centers was increased from 6 to 8.	To allow the inclusion of additional study centers.
1.1 Synopsis 7.2.1 Study withdrawal criteria 8.3.5 Pregnancy	Description of the safety follow-up period was slightly reworded. The procedures to be completed if a study participant withdraws was adapted as follows: "*SFU or EOS Visit should be scheduled 6 weeks after the study participant has discontinued his/her IMP ~~in the Run-out Period~~.*"	Clarification.
2.1 Study rationale 4.1 Overall design 5.1 Inclusion criteria	In the study rationale, text was added to provide newly published evidence demonstrating that fibromyalgia patients with elevated levels of anti-satellite glia cell (SGC) IgG antibodies present with higher levels of self-reported pain. In the overall study design description, study population was updated (pain intensity change from ≥5 to ≥6, removal of Revised Fibromyalgia Impact Questionnaire (FIQR) score ≥64 and Fatigue numeric rating scale (NRS) score ≥5). Inclusion criterion #3a (now 3b) was updated to remove completion of pain management program of at	To better reflect the recently published findings on fibromyalgia and the current clinical practices in term of pain management in the population of patients with severe fibromyalgia, as well as reduce protocol complexities.

Section # and Name	Description of Change	Brief Rationale
	least 36 hours duration performed >6 months before study entry date, FIQR score≥64 and fatigue NRS score≥5. Range for mean daily average 24h pain intensity was updated (from ≥5 and <10 to ≥6 and <10).	
1.3 Schedule of activities 6.5.1 Permitted concomitant treatments	In the Schedule of activities, completion of pain management program was added as part of the information to be collected as general medical/procedure history. Pain management programs were added to the treatments permitted during the study, providing they are considered acceptable in the judgment of the investigator and in discussion with the medical monitor.	As a pain management program is no longer part of the eligibility criteria, information related to pain management program are collected along with medical history for exploratory purposes.
1.3 Schedule of activities 5.1 Inclusion criteria 5.4 Screen failures 7.1.4 Temporary discontinuation	Coronavirus disease 2019 (COVID-19) vaccination status and testing was removed from the Schedule of Activities table. Inclusion criterion #8, related to COVID-19 vaccination, was removed. Text related to COVID-19 was removed in the Screen failures section. Text related to temporary discontinuation in the event of COVID-19 was removed.	To update and simplify the protocol based on safety knowledge gained from the rozanolixizumab program during and after the COVID-19 pandemic.
1.3 Schedule of activities 5.2 Exclusion criteria 7.1.2 Other permanent discontinuation criteria 7.2.1 Study withdrawal criteria 8.2.6 Assessment and management of tuberculosis and tuberculosis risk factors 8.2.7 Suicidal risk monitoring	In Schedule of Activities, Section 8.2.6, and Section 10.12, tuberculosis (TB) signs and symptoms questionnaire was removed and replaced by focused medical history. In Schedule of Activities and Section 10.12, interferon gamma release assay (IGRA) test was modified from mandatory to optional. Related footnotes in the schedule of activities were updated accordingly. The footnote for physical examination was updated	To clarify and simplify text related to diagnosis, assessment and management of TB. The prior focus on TB within the protocol was standard text for UCB protocols for immunomodulator drugs but gave undue prominence to the topic considering the mechanism of action of rozanolixizumab. Rozanolixizumab is not expected to inhibit the generation of an immune response or have effects on the B-cell repertoire (eg, on plasma cells or memory B cells), or to interfere

Section # and Name	Description of Change	Brief Rationale
10.12 Appendix 12: Assessment and management of tuberculosis and tuberculosis risk factors	to include an assessment of potential signs and symptoms of TB and risk factors for exposure to TB. Exclusion criterion #13 (Study participant has positive TB test at the Screening Visit) was removed. Exclusion criterion #14 (now 14a), requirements for latent tuberculosis infection (LTBI) and nontuberculous mycobacterial (NTM) infection, were updated. Treatment for LTBI was reduced from 4 weeks to 1 week and "*current NTM infection or history of NTM infection unless proven to be fully recovered*" was removed. Text related to NTM infection was removed as covered by exclusion criterion #9a. Text on the assessment and management of TB was moved from Section 8.2.6 to Section 10.12 Appendix 12. In addition, new text on safety reporting requirements related to TB was added. Consequently, Section 8.2.7 Suicidal risk monitoring was renumbered to Section 8.2.6.	with other cells of the innate and adaptive immune systems or complement. Because of its discrete mechanism of action, FcRn inhibition is less likely to be associated with increased risk of infection compared with other immunomodulators and unlikely to lead to opportunistic infections with intracellular pathogens, particularly those requiring granulomatous inflammation for control (eg, mycobacteria, fungi) (Peter et al, 2020).
1.3 Schedule of activities 8.1.3 Pressure pain threshold	In the Schedule of activities, footnote was added on pressure pain threshold assessment to clarify assessment should be done predose. This was also specified in the description of study procedures.	Clarification.
1.3 Schedule of activities 8.2.3 Vital signs	Reduction in the number of vital sign assessment (blood pressure, pulse rate and temperature) during the treatment period.	The considered study population has a chronic pain condition characterized by widespread pain and increased pain sensitivity to mechanical pressure; thus, blood pressure monitoring can be very painful. The study protocol was consequently adapted based on the recent safety knowledge gained from the rozanolixizumab program and feedback from a FMS clinical expert.

Section # and Name	Description of Change	Brief Rationale
4.1 Overall study design 5.1 Inclusion criteria 8.1.2 Pain NRS	Clarification that, during the Screening Period, 1) the assessment of the pain intensity at Screening should be performed over a 10-day period within the Screening Period. 2) Study participants require a minimum of 7 out of 10 daily Pain NRS assessments to be eligible for randomization.	Clarification.
5.1 Inclusion criteria	Inclusion Criterion #5a (now 5b) Males was added to clarify that both males and females can be enrolled in the study.	Clarification.
5.2 Exclusion criteria	Exclusion criterion #7 (related to clinically significant finding in 12-lead ECG) was removed as it was covered under exclusion criterion #3. Exclusion criterion #25 (now 25a), time since last vaccination with a live vaccine, was reduced from 8 weeks to 4 weeks (changes were also made in Table 6-2: Prohibited concomitant medications).	To update the exclusion criteria based on gained safety knowledge on rozanolixizumab, to align with current therapeutic practices, and to remove redundancies, as some provisions are adequately captured by other eligibility criteria.
5.2 Exclusion criteria	Exclusion criterion #9 (now 9a) has been modified to limit the exclusion of a participant due to a current active infection, an unresolved, or an inadequately treated infection. Exclusion criterion #20, related to IgA deficiency was removed.	Infection exclusion criterion language simplified but intent to exclude clinically relevant infection retained. No impact on serum levels of IgA, IgE, and IgM are expected based on the pharmacology of rozanolixizumab and no clinically meaningful changes in IgA, IgE and IgM levels following the administration of rozanolixizumab or any other FcRn inhibitor have been observed in any clinical study of rozanolixizumab to date.
5.2 Exclusion criteria	Exclusion criterion #15 (study participant has any of the following active gastrointestinal (GI) disorders: inflammatory bowel disease, GI ulceration, or diverticulitis) was removed.	The accumulated safety data on rozanolixizumab led to an update of the adverse events of special monitoring (AESM) (ie, previous removal of the former AESM of severe GI disorders) and reconsideration of study exclusion criteria with corresponding removal

Section # and Name	Description of Change	Brief Rationale
		of the exclusion criterion relating to active GI disorders.
5.2 Exclusion criteria 8.2.6 Suicidal risk monitoring	Exclusion criterion #21 (now 21a) was updated to shorten from 5 to 2 years the period of time before screening visit which the study participants had a suicide attempt.	With a chronic pain disorder, fibromyalgia patients suffer from high rates of comorbid anxiety and depression, which are risk factors for suicidal behaviors. Study participants at serious or active suicide risk will be excluded from the study with recommended referral for appropriate intervention as assessed by the investigator's clinical judgment, the participant's history of suicide attempt(s), and/or responses to the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire administered at Screening.
6.5.1 Permitted concomitant treatments (medications and therapies)	Dose and class of concomitant medications permitted during the study duration have been clarified.	To better reflect the current practices in term of pain management in the population of patients with severe fibromyalgia.
8 Study assessments and procedures	The paragraph related to procedures conducted as part of participant's routine clinical management that may be utilized for Screening/Baseline purposes have has been removed.	Correction as all data obtained before signing of the ICF will be considered as historical data and will not be utilized for Screening or Baseline purpose.
8.3 Adverse events and serious adverse events	The following sentence was added: "*For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment-emergent SAEs will be published*".	Clarification.
9.1 Definition of analysis sets	Clarification that the Safety Set-as randomized (SS-r) will be utilized for the analyses of demographics and immunogenicity. Clarification that the Safety Set-as treated (SS-t) will be utilized for the tabulation of AEs by treatment. Full Analysis Set definition was clarified. Clarification that the Pharmacodynamic Set will be identified after database lock.	To align with the current SAP.

Section # and Name	Description of Change	Brief Rationale
10.4 Appendix 4 Contraceptive guidance and collection of pregnancy information	Procedure for collection of pregnancy information on any male participant's female partner who becomes pregnant was added back in the protocol.	Correction.
10.14 Appendix 14: Management of infections and hypogammaglobulinemia	Update of the cutoff level of serum total IgG for temporary investigational medicinal product (IMP) discontinuation in case of a hypogammaglobulinemia event.	Correction.
Global	Minor administrative, consistency, formatting, and typographical changes have been made. Lists of abbreviations (general and tables), list of references, and footnotes have been updated in line with other changes made throughout the document.	Updated to provide clarity and be consistent with remainder of protocol.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21
Email	**Global:** DS_ICT@ucb.com (for interventional clinical studies)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: A randomized, double-blind, placebo-controlled, multicenter, Phase 2a, proof-of-concept study to evaluate the efficacy and safety of rozanolixizumab to treat adult study participants with severe fibromyalgia syndrome

Short title: A Phase 2a proof-of-concept study to evaluate the efficacy and safety of rozanolixizumab to treat adult study participants with severe fibromyalgia syndrome

Rationale: Recently there is increasing scientific evidence in the pathobiology of severe fibromyalgia syndrome (FMS) suggesting it may be an autoimmune condition that is mediated by immunoglobulin (Ig)G. Research has shown that the transfer of IgG from patients with severe FMS, but not IgG from healthy volunteers, to rodents transfers the clinical features of severe FMS (Goebel et al, 2021). Features transferred included allodynia, thermal hypersensitivity, reduced grip strength, and small fiber neuropathy. IgG derived from patients with severe FMS was also found to bind cells in the dorsal root ganglia (DRG) in rodents as well as to cells in human DRG sections. These findings suggest that there are pathogenic IgG present in patients with severe FMS that contribute to their clinical symptoms. These novel scientific insights support the hypothesis that the reduction of IgG in patients with severe FMS is a potential therapeutic treatment approach. The aim of this study is to reduce IgG levels in patients with severe FMS with rozanolixizumab and assess its safety and efficacy in these patients.

Objectives and endpoints

Objectives	Endpoints/Estimands
Primary	
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	Primary estimand (efficacy): • Treatment: rozanolixizumab 560mg once weekly (QW) or Placebo QW • Target Population: study participants with severe FMS • Endpoint: Brief Pain Inventory-short form (BPI-SF) average interference score after 12 weeks of double-blind treatment. • Intercurrent event (ICE) handling: – The ICE discontinuation of treatment will be handled using a hypothetical strategy assuming that the study participants did not experience the events, with data following discontinuation excluded from analysis.

Objectives	Endpoints/Estimands
	• Population level summary: mean difference in average BPI-SF interference score between the two treatments
Secondary	
• To assess the safety and tolerability of rozanolixizumab in study participants with severe FMS	• Occurrence of treatment-emergent adverse events (TEAEs) during the study • TEAEs leading to withdrawal of investigational medicinal product (IMP)
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	• BPI-SF average interference score after 24 weeks of treatment • Revised Fibromyalgia Impact Questionnaire (FIQR) score after 10 weeks of treatment • Mean 7-day average daily pain score (Pain numeric rating scale [NRS]) after 10 weeks of treatment • Mean 7-day fatigue score (Fatigue NRS) after 10 weeks of treatment
Exploratory	
• To assess the pharmacokinetics (PK) of rozanolixizumab in study participants with severe FMS	• Plasma concentration of rozanolixizumab prior to dosing on Week 13 and Week 25
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	• Pressure pain threshold as measured by pressure algesiometry
• To assess the safety and tolerability of rozanolixizumab in study participants with severe FMS	• Change from Baseline in vital signs and laboratory results at scheduled assessments during the Treatment Period through the Run-out Period
• To evaluate the incidence and emergence of antidrug antibody (ADA) of rozanolixizumab in study participants with severe FMS	• Antidrug antibody incidence at scheduled assessments during the Treatment Period

Objectives	Endpoints/Estimands
• To assess the pharmacodynamic (PD) effect of rozanolixizumab in study participants with severe FMS	• Value (absolute) and change from Baseline (absolute and percentage) in serum total IgG and IgG subclasses at scheduled assessments during the Treatment Period
• To assess the effect of rozanolixizumab on exploratory biomarkers in study participants with severe FMS	• Assessment of IgG binding in in vitro cell assay at scheduled assessments during the Treatment Period and the Run-out Period • Assess genetic variation for potential effects on disease progression and/or drug response and also any changes in epigenetics • Exploratory biomarkers may be measured to evaluate changes from Baseline in response to rozanolixizumab

Overall design

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, proof-of-concept study to evaluate the efficacy, safety, PK, and PD of rozanolixizumab for the treatment of severe FMS. The primary endpoint is the average BPI-SF interference score after 12 weeks of double-blind treatment.

The study will consist of Screening Period of up to 28 days, a 2-week, single-blind Run-in Period, 2 subsequent 12-week, double-blind Treatment Periods, followed by a 2-week, single-blind Run-out Period, and a 5-week Safety Follow-Up (SFU) Period.

Study participants will be randomized in a 1:1:1 ratio to 1 of 3 sequences. The study participants in each sequence will receive the following treatment regimen during the double-blind Treatment Periods (see Figure 1-1):

- Sequence 1: Rozanolixizumab 560mg subcutaneously (sc) QW for 24 weeks (12 + 12 weeks Treatment Period) (N=20, Group 1)
- Sequence 2: Placebo sc QW for 12 weeks, followed by rozanolixizumab 560mg sc QW for 12 weeks (N=20, Group 2)
- Sequence 3: Placebo sc QW for 24 weeks (N=20, Group 3)

The initial 2-week Run-in Period and the final 2-week Run-out Period will be study participant-blind, with study participants not informed that they are receiving placebo, to limit the impact of any start-of-study or end-of-study induced placebo effects. The two 12-week Treatment Periods will be study participant-, investigator-, and sponsor-blind. It is important that study participants do not know when their treatment changes, whether it is going from Run-in to Period 1, Period 1 to Period 2, or Period 2 to Run-out.

After approximatively 30 study participants have been randomized and these study participants have completed their 2 double-blind Treatment Periods, an interim analysis may be conducted with the possibility of stopping for efficacy or futility.

An internal Safety Monitoring Committee (SMC) will regularly review (approximately every 3 months, with the option to adapt the frequency based on recruitment rates) the available blinded safety data.

In addition, a Program Independent data monitoring committee (PiDMC) is in place to evaluate data over the entire rozanolixizumab clinical development program as this molecule is being investigated in several indications.

Number of study participants

In total and allowing for a dropout rate of 25%, approximately 60 study participants are planned to be enrolled and randomized in the study at up to 8 centers from the UK, with a target of 48 evaluable study participants completing the study. Evaluable study participants are those with BPI-SF scores at Baseline, Visit 15, and Visit 27 (see also Section 9.3).

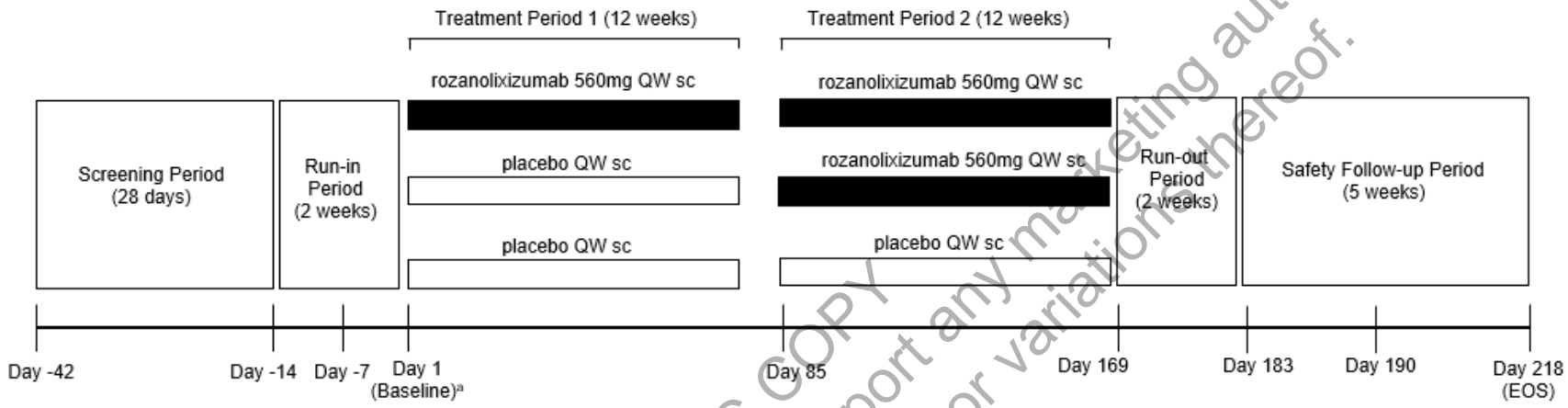
Treatment groups and duration

The maximum study duration per study participant will be 37 weeks.

- Screening Period: Eligibility will be assessed during the Screening Period of up to 28 days.
- Run-in Period: Study participants who have been confirmed eligible to participate in the study will be randomized 1:1:1 to receive rozanolixizumab 560mg sc QW or placebo sc QW, as described in the study design section above. During the 2-week Run-in Period, all study participants will receive placebo sc QW and will be blinded to this treatment.
- Treatment Period: As shown in Section 1.2, study participants will receive rozanolixizumab 560mg sc QW for two 12-week Treatment Periods, placebo sc QW for the first 12-week Treatment Period followed by rozanolixizumab 560mg sc QW for the second 12-week Treatment Period, or placebo sc QW for two 12-week Treatment Periods.
- Run-out Period: At the end of both 12-week Treatment Periods, all study participants will receive placebo sc QW during a 2-week Run-out Period and will be blinded to this treatment.
- Safety Follow-up Period: Study participants who complete both Treatment Periods and Run-out Period will enter the 5-week SFU Period. These participants will attend the EOT visit 2 weeks after the last dose in the Run-out Period and the SFU/EOS visit 4 weeks later (6 weeks after the last dose in the Run-out Period). Study participants who permanently discontinue IMP are encouraged to complete the EOT/EW Visit and the SFU/End of Study (EOS) Visit.

1.2 Schema

Figure 1-1: Study Schematic



[a] The baseline for each variable will be taken as the value measured prior to, but closest to, the treatment on Day 1. This may be measured on Day 1 prior to treatment or during Weeks -1 or -2 depending on the endpoint.

EOS=end of study; QW=once weekly; sc=subcutaneous.
Note: All study participants receive placebo in a single-blind manner during the Run-in and Run-out Periods.

1.3 Schedule of activities

The Schedules of Activities are provided in Table 1-1 (through Treatment Period 1) and in Table 1-2 (Treatment Period 2 through EOS). Additional study assessments are outlined in Section 1.3.1.

Table 1-1: Schedule of Activities (through Period 1)

Procedure	Screen	Run-in	Run-in	12-week Treatment Period: 1											
Visit number	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Visit window	up to 28 days	-	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d
Week	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12
Day	-42	-14	-7	1	8	15	22	29	36	43	50	57	64	71	78
Informed consent	X														
Verification of inclusion/exclusion criteria	X	X													
Demography	X														
Randomization		X													
General medical/ procedure history (including headache history and pain management program)[a]	X														
C-SSRS[b]	X			X											
Serum pregnancy test	X														
Urine pregnancy test		X		X				X				X			
Serology (Hepatitis B, Hepatitis C, and HIV)	X														
IGRA TB test (optional)[c]	X														
Laboratory assessments (full hematology, chemistry, urinalysis)	X	X		X				X				X			
Urine drug screen[d]	X														

Table 1-1: Schedule of Activities (through Period 1)

Procedure	Screen	Run-in	Run-in	12-week Treatment Period: 1											
Visit number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit window	**up to 28 days**	**-**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**
Week	**-6**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Day	**-42**	**-14**	**-7**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**
12-lead ECG[e]	X			X											
Vital signs (blood pressure, pulse, and temperature)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination[g]	X														
Brief physical examination[g]		X		X											
Full neurological examination[h]	X														
Pain NRS	X[i]	X[i]	X[i]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[i]	X[i]
BPI-SF	X			X				X				X			
FIQR	X		X			X				X				X	
Fatigue NRS	X[j]	X[i]	X[i]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[i]	X[i]
Pressure pain threshold[k]			X												
IMP discontinuation/study withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration		X(pb)	X(pb)	X	X	X	X	X	X	X	X	X	X	X	X
PK[m]		X		X	X							X			
ADA[m]		X		X	X							X			
IgG (total, subclasses) [m]	X[n]	X		X	X			X				X			

Table 1-1: Schedule of Activities (through Period 1)

Procedure	Screen	Run-in	Run-in	12-week Treatment Period: 1											
Visit number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit window	**up to 28 days**	**-**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**
Week	**-6**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Day	**-42**	**-14**	**-7**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**
IgG binding, in vitro assay				X[o]											
Blood sampling for DNA and RNA analysis		X													
Serum complement (C3, C4) and plasma complement (C3a, C5a)[pq]				X											
Exploratory biomarkers		X[m,q]		X[m,q]											

ADA=anti-rozanolixizumab antibodies; BPI-SF=brief pain inventory-short form; C-SSRS=Columbia Suicidality Severity Rating Scale; d=day; ECG=electrocardiogram; FIQR=Revised Fibromyalgia Impact Questionnaire; HBV=Hepatitis B virus; HIV=Human Immunodeficiency Virus; Ig=immunoglobulin; IGRA=interferon gamma release assay; IMP=investigational medicinal product; NRS=numeric rating scale; pb=placebo; PK=pharmacokinetics; PRN=pro re nata; TB=tuberculosis

Note: Assessments in the weekly columns are meant to be performed at the start of that Week prior to dosing, unless otherwise specified.

Note: The BPI-SF should be completed by the study participants in a quiet place prior to other patient-reported outcomes or protocol-specified assessments at each visit.

Note: The Baseline for each variable will be taken as the value measured prior to, but closest to, the treatment on Day 1. This may be measured on Day 1 prior to treatment or during Weeks -1 or -2 depending on the endpoint.

[a] History of the completion of a pain management program should be collected when available.

[b] A full C-SSRS assessment will be performed only when the study participant has a positive response to the suicidal ideation query. If a study participant has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C-SSRS assessments, the study participant will be excluded or withdrawn from the study and immediately referred to a mental healthcare professional. A C-SSRS assessment may be conducted at other visits at the discretion of the investigator.

[c] The IGRA test is optional and may be performed at the investigator's discretion, based on an individual risk assessment for the study participant, including, but not limited to, the following considerations: medical history, potential prior exposure to other individuals with known TB, local prevalence of TB, clinical practice, and applicable local guidelines. Management of an IGRA test result will be done as outlined in Section 10.12.

[d] Urine drug screen for drug abuse includes amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opiates. This test can be performed at other visits at the discretion of the investigator.

[e] 12-lead ECG can be performed any time during the study at the investigator's discretion.

Table 1-1: Schedule of Activities (through Period 1)

Procedure	Screen	Run-in	Run-in	12-week Treatment Period: 1											
Visit number	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Visit window	up to 28 days	-	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d
Week	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12
Day	-42	-14	-7	1	8	15	22	29	36	43	50	57	64	71	78

[f] Vital signs comprise systolic and diastolic blood pressure, pulse rate, and temperature. At Visit 1, 2, 3, and 4, vital signs will be measured prior to IMP administration, at the end of the infusion (+5 min), and at 2 hours after the end of infusion (±15 min). At Visit 5, 6, and 7, vital signs will be measured prior to IMP administration and 1 hour after the end of infusion (±15 min). From Visit 8 through Visit 14, the vital signs will be measured approximately 15 minutes prior to IMP administration. At Screening, vital signs will be taken only once during the visit.

[g] A brief physical examination can also be performed on the occurrence of an adverse event. Brief and full physical examinations should include evaluation for medical history, for signs and symptoms of latent or active TB, and for risk factors for exposure to TB. An IGRA test can be performed any time, at the investigator's discretion.

[h] A full neurological examination should also be performed for any study participant who experiences severe and/or serious headache and for study participants who experience suspected aseptic meningitis. For details of the assessments included in these examinations see Section 8.2.1 (description of full and brief physical examination), and Section 8.2.2 (description of full and brief neurological examination).

[i] Daily 24-hr pain and fatigue assessments to be collected every day for a week. Within the Screening Period, the daily average pain over the previous 24 hours will be captured using the Pain NRS through a diary over a 10-day period. Study participants require a minimum of 7 out of the 10 daily Pain NRS assessments over this 10-day period to be eligible for randomization.

[j] The 24-hr pain and fatigue assessments to be collected for that day only.

[k] To be performed before IMP dosing.

[l] Study participants to provide their usual range doses of analgesics PRN.

[m] On dosing days, PK, ADA, and IgG will be taken pre-dose.

[n] Total IgG only.

[o] 80mL at Visit 3.

[p] Samples for serum complement (C3, C4) and plasma complement (C3a, C5a) are collected predose at Visit 3 (Day 1) for all study participants. In study participants who experience an infusion reaction or hypersensitivity reaction at site, samples should also be taken 2 hours and 4 hours after the onset of the event, or otherwise as soon as possible but prior to the next dose.

[q] 10mL at Visit 1 and Visit 3. In study participants who experience severe and/or serious headaches or suspected aseptic meningitis, exploratory biomarker samples should also be taken 4 hours after the onset of the event, or otherwise as soon as possible within 72 hours after the onset of the event.

Table 1-2: Schedule of Activities (Period 2 through End of Study)

Procedure	12-week Treatment Period: 2												Run-out	Run-out	EOT/ EW	SFU/ EOS
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**-**	**-**
Visit window	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±7d**	**±7d**
Week	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**28**	**32**
Day	**85**	**92**	**99**	**106**	**113**	**120**	**127**	**134**	**141**	**148**	**155**	**162**	**169**	**176**	**190**	**218**
C-SSRS[a]	X												X		X	X
Urine pregnancy test	X				X				X				X		X	X
Laboratory assessments (full hematology, chemistry, urinalysis)	X				X				X				X		X	
Vital signs (blood pressure, pulse and temperature at every visit)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination[c]															X	X
Brief physical examination[c]	X												X			
Full neurological examination[d]															X	X
Pain NRS	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[f]	X[f]	X[f]		X[e]	X[e]
BPI-SF	X				X				X				X		X	X
FIQR			X				X				X			X	X	X
Fatigue NRS	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[f]	X[f]	X[f]		X[e]	X[e]
Pressure pain threshold[g]	X												X		X	X
IMP discontinuation/study withdrawal criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1-2: Schedule of Activities (Period 2 through End of Study)

Procedure	12-week Treatment Period: 2												Run-out	Run-out	EOT/ EW	SFU/ EOS
Visit number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**-**	**-**
Visit window	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±7d**	**±7d**
Week	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**28**	**32**
Day	**85**	**92**	**99**	**106**	**113**	**120**	**127**	**134**	**141**	**148**	**155**	**162**	**169**	**176**	**190**	**218**
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X	X(pb)	X(pb)		
PK[h]	X	X							X				X			
ADA[h]	X	X							X				X		X	X
IgG (total, subclasses)[h]	X	X			X				X				X		X	X
IgG binding, in vitro assay[h,i]	X												X			X
Blood sampling for DNA and RNA analysis															X	
Exploratory biomarkers	X[f,g]												X[f,g]			X[g]

ADA=anti-rozanolixizumab antibodies; BPI-SF=brief pain inventory-short form; C-SSRS=Columbia Suicidality Severity Rating Scale; d=day; EOS=End of Study; EOT=End of Treatment; EW=Early Withdrawal; FIQR=Revised Fibromyalgia Impact Questionnaire; Ig=immunoglobulin; IGRA=interferon gamma release assay; IMP=investigational medicinal product; NRS=numeric rating scale; pb=placebo; PK=pharmacokinetics; SFU=Safety Follow-up; TB=tuberculosis

Note: Assessments in the weekly columns are meant to be performed at the start of that Week prior to dosing, unless otherwise specified.

Note: The BPI-SF should be completed by the study participants in a quiet place prior to other patient-reported outcomes or protocol-specified assessments at each visit.

[a] A full C-SSRS assessment will be performed only when the study participant has a positive response to the suicidal ideation query. If a study participant has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C-SSRS assessments, the study participant will be excluded or withdrawn from the study and immediately referred to a mental healthcare professional. A C-SSRS assessment may be conducted at other visits at the discretion of the investigator.

[b] Vital signs comprise systolic and diastolic BP, pulse rate, and temperature. At Visit 15 and Visit 16, vital signs will be measured prior to IMP administration, at the end of the infusion (+5 min) and at 2 hours after the end of infusion (±15 min). At Visit 17, 18, and 19, vital signs will be measured prior to IMP

Table 1-2: Schedule of Activities (Period 2 through End of Study)

Procedure	12-week Treatment Period: 2												Run-out	Run-out	EOT/ EW	SFU/ EOS
Visit number	15	16	17	18	19	20	21	22	23	24	25	26	27	28	-	-
Visit window	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d
Week	13	14	15	16	17	18	19	20	21	22	23	24	25	26	28	32
Day	85	92	99	106	113	120	127	134	141	148	155	162	169	176	190	218

administration and 1 hour after the end of infusion (±15 min). From Visit 20 through Visit 28, the vital signs will be measured approximately 15 minutes prior to IMP administration. At EOT/EW and SFU/EOS Visits, vital signs will be taken only once during the visit.

[c] A brief physical examination can also be performed on the occurrence of an adverse event. Brief and full physical examinations should include evaluation for medical history, for signs and symptoms of latent or active TB, and for risk factors for exposure to TB. An IGRA test can be performed any time, at the investigator's discretion.

[d] In addition to the EOT/EW and SFU/EOS Visits, a full neurological examination should be performed for any study participant who experiences severe and/or serious headache and/or suspected aseptic meningitis (see Section 10.13).

[e] The 24-hr pain and fatigue assessments to be collected for that day only.

[f] Daily 24-hr pain and fatigue assessments to be collected every day for a week.

[g] To be performed before IMP dosing.

[h] On dosing days, PK, ADA, IgG will be taken pre-dose.

[i] 10mL at Visit 15, 27, and SFU/EOS.

1.3.1 Additional study assessments

In addition to those detailed in Table 1-1 and Table 1-2, the assessments in Table 1-3 may be required in case of adverse events of special monitoring (AESMs) (severe and/or serious headache and suspected aseptic meningitis, see Section 8.3.7). Note that additional vital sign measurements and/or additional investigations may be taken at the discretion of the investigator.

Table 1-3: Additional study assessments

Assessment	When applicable
For study participants who experience a severe and/or serious headache[a] and for study participants with suspected aseptic meningitis:	
Headache or Suspected aseptic meningitis follow-up questionnaire	Headache follow-up questionnaire which sites will receive after reporting AESM of severe and/or serious headache should be completed promptly and returned to the Sponsor via the SAE reporting process. Suspected aseptic meningitis follow-up questionnaire which sites will receive after reporting AESM of suspected aseptic meningitis should be completed promptly and returned to the Sponsor via the SAE reporting process.
Full neurological examination	In study participants who report severe and/or serious headache or with suspected aseptic meningitis at the clinic visit, a full neurological examination (including fundoscopy) should be performed (see Section 10.13). In study participants who report a severe and/or serious headache or features suggestive of aseptic meningitis while at home, a visit to the site for the full neurological examination should be arranged for as soon as is practically possible.
Blood analysis	Blood sample collection for exploratory analysis.
Other	In study participants who report severe and/or serious 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.
For study participants who experience suspected aseptic meningitis:	
Lumbar puncture	In study participants who reported signs and/or symptoms of meningitis which required a lumbar puncture, results of the CSF analysis should be recorded and preliminary data should be included on the SAE form used for reporting the event as an AESM within 24 hours (ie, preliminary data reported on the first reporting may not have CSF results yet but the reporting should occur as soon as there is a suspected diagnosis. Full results should be communicated in subsequent exchanges with UCB).
Additional analysis	Results of all investigations should be recorded and preliminary data should be included on the SAE form used for reporting the event as an AESM. Please include details on all investigations results including but not limited to blood or CSF cultures and analysis/ PCR test (including list of microorganisms tested) / MRI scans +/- gadolinium.

AESM=adverse event under special monitoring; CSF=cerebrospinal fluid; CT=computed tomography; eCRF=electronic case report form; LP=lumbar puncture; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; SAE=serious adverse event

[a] For these assessments, the term headache includes migraine.

The frequency of the collection of samples for exploratory biomarker sample collection after severe and/or serious headache or suspected aseptic meningitis are described in Section 1.3.

2 INTRODUCTION

Rozanolixizumab is a humanized IgG4 monoclonal antibody that is being developed as an inhibitor of the activity of the neonatal Fc receptor (FcRn) for IgG. By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of IgG antibodies, including IgG pathogenic autoantibodies. The aim is to reduce the concentration of pathogenic IgG in patients with autoimmune diseases mediated by the action of IgG autoantibodies.

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 (Roopenian and Akilesh, 2007). Neonatal Fc receptor may also mediate transcytosis of IgG to facilitate its distribution within tissues. Rozanolixizumab has been specifically designed to block IgG binding to FcRn without blocking the binding and recycling of albumin.

Production of pathogenic IgG autoantibodies is the major pathophysiology leading to a number of autoimmune diseases, which include myasthenia gravis (MG), pemphigus vulgaris (PV), immune thrombocytopenia (ITP), Goodpasture's syndrome, neuromyelitis optica, and Guillain-Barré Syndrome. Recently there is increasing scientific evidence regarding the pathobiology of FMS that suggests it may also be an IgG-mediated condition, as detailed in Section 2.1. Therefore, the removal of IgG by FcRn blockade may provide an effective therapeutic option for FMS.

Nonclinical and clinical data generated on rozanolixizumab support the sc administration of rozanolixizumab in study participants with IgG autoantibody-mediated conditions, including primary ITP and generalized MG (ie, gMG). Recently, a Phase 3 UCB study in patients with gMG met all primary and secondary endpoints with statistical significance and showed rozanolixizumab was well tolerated with no new safety concerns. Overall, data from the rozanolixizumab clinical development program showed that repeated administrations of rozanolixizumab at a dose approximating 7mg/kg and 10mg/kg sc are generally well tolerated, with an acceptable safety profile in completed studies. The TEAEs were most frequently reported in the SOC of nervous system disorders. The most frequently reported TEAEs in rozanolixizumab-treated study participants in MG0003, a completed phase 3 study evaluating the efficacy and safety of rozanolixizumab in patients with gMG and upon repeated cyclic treatment were headache, diarrhoea, pyrexia, nausea, and arthralgia. Therefore, rozanolixizumab represents an innovative, subcutaneous anti-FcRn monoclonal antibody that may provide a novel and specific therapeutic approach for the treatment of patients with severe FMS.

Detailed information regarding the nonclinical and clinical development programs for rozanolixizumab, including all completed and ongoing studies, can be found in the latest version of the Investigator's Brochure (IB).

2.1 Study rationale

Recently there is increasing scientific evidence suggesting severe FMS may be an autoimmune condition that is mediated by IgG. A consortium of UK and Swedish investigators has reported research findings indicating that serum IgG contributes to the pathogenesis of severe FMS

(Goebel et al, 2021). The team transferred both single and pooled serum IgG from patients with severe FMS to rodents and identified typical features of clinical FMS in the rodents, including allodynia, thermal hypersensitivity, reduced grip strength, and small fiber pathology when compared with the transfer of serum IgG from healthy volunteers (Goebel et al, 2021). IgG derived from patients with severe FMS was also found to bind cells in the DRG in rodents as well as to cells in human DRG sections. These findings suggest that there are pathogenic IgG present in patients with severe FMS that contribute to their clinical symptoms. Recently, additional research quantified anti-satellite glia cells (SGCs) IgG levels using an indirect immunofluorescence murine cell culture assay, showed elevated anti-SGC IgG levels in fibromyalgia cohorts compared with control group, and suggested elevated anti-SGC IgG was associated with higher levels of self-reported pain (Krock et al, 2023).

These novel scientific insights support the hypothesis that the reduction of IgG in patients with severe FMS is a potential therapeutic treatment approach. The aim of this study is to reduce IgG levels in patients with severe FMS with rozanolixizumab and assess its safety and efficacy in these patients.

2.2 Background

Fibromyalgia is a highly prevalent (2 to 3% of adult population) and complex syndrome primarily characterized by the presence of chronic widespread pain, but which also incorporates a wide range of other symptoms adversely impacting on function and quality of life such as severe fatigue, cognitive dysfunction, and sleep disturbances (Häuser et al, 2015). This can impair working ability, leading to reduced productivity and high healthcare costs (White et al, 2008). The direct and indirect costs related to FMS are higher among patients with more severe disease (Chandran et al, 2012).

Pain throughout the body is generally considered the most debilitating of the symptoms experienced by patients with fibromyalgia (Mease et al, 2011). The scales used to measure and monitor pain levels vary and include visual analog scales (VAS) for pain, the McGill Pain Questionnaire, the Fibromyalgia Impact Questionnaire pain item, various numerical rating scales (often recorded in diaries), and the BPI-SF. The BPI-SF interference score measures the impact of pain across seven domains of daily life experience and was considered as being suitable for measuring the effect of a treatment that may improve the experience of pain and the functional interference experienced by patients.

Challenges surround the diagnosis of FMS as there is no confirmatory laboratory test, and, consequently, it often takes >2 years for patients to obtain a diagnosis, often involving multiple consultations with different physicians. An absence of specific disease biomarkers also hinders patient stratification and impacts on all areas of research into FMS. Current clinical practice recommendations and guidelines for FMS include non-pharmacologic and pharmacologic strategies, with focus towards reduction of symptoms and improvement of function. Pharmacological agents include tricyclic antidepressants, anti-epileptic drugs, selective serotonin reuptake inhibitors, and norepinephrine/serotonin reuptake inhibitors. While the US Food and Drug Administration has approved pregabalin, duloxetine, and milnacipran for treatment of fibromyalgia in adults, the modest efficacy of available therapies in many patients underlines the unmet clinical need for this patient population. Severe patients are distinguished by their higher scores on pain and other scales, as well as significant differences in disability and depression

(Chandran et al, 2012). Patients with severe FMS have an unmet need due to the limited efficacious treatment options available.

2.3 Benefit/risk assessment

Though available drug and non-drug treatments can reduce FMS symptoms and their impact on a patient's life, the modest efficacy of these therapies in most patients leaves a significant unmet clinical need (Macfarlane et al, 2017; Mascarenhas et al, 2021), particularly in the clinical setting of severe FMS. Novel scientific insights support the hypothesis that the reduction of IgG in patients with severe FMS is a potential therapeutic treatment approach. In removal of IgG autoantibodies by FcRn blockade and preventing their functional consequences, rozanolixizumab has the potential to alleviate the signs and symptoms of severe FMS that are not adequately addressed by available standard of care (SoC) treatments. The potential for this effective treatment approach could result in meaningful improvements to quality of life, reduction in long-term disability, and decreased utilization of concomitant medication (eg, gabapentinoids, nonsteroidal anti-inflammatory drugs, opioids, paracetamol, antiepileptics) in this patient population.

The aim of this study is to reduce IgG levels in patients with severe FMS with rozanolixizumab, given the recent evidence that severe FMS may be an autoimmune condition that is mediated by IgG. A rozanolixizumab-induced IgG lowering of about 70% from Baseline is similar to that achieved with other FcRn antagonists and alternative strategies such as plasma exchange (PLEX), and falls within the range associated with clinical benefit in various autoimmune indications. For FMS, indication-specific targets for IgG lowering are not yet established; however, the current assumption is that the desired level of IgG reduction would be similar to gMG and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (~70%) (see Section 4.3.1) and of clinical benefit to patients with FMS.

Rozanolixizumab represents an innovative, anti-FcRn monoclonal antibody that may provide a novel and specific therapeutic approach for the treatment of patients with severe FMS. While not previously evaluated in severe FMS, data show that rozanolixizumab markedly lowers serum IgG and IgG autoantibody levels in patients with gMG.

In MG0003, a Phase 3 study evaluating efficacy and safety of sc rozanolixizumab in adult patients with gMG [redacted] clinical efficacy of rozanolixizumab was demonstrated by improvements vs placebo in all efficacy endpoints tested in the study. There were clinically meaningful and statistically significant reductions from baseline in the primary endpoint, MG activities of daily living (ADL) score, at Day 43 for both rozanolixizumab dose groups versus placebo.

The identified adverse drug reactions associated with sc administration of rozanolixizumab are headaches, diarrhoea, pyrexia, nausea, upper respiratory tract infections, arthralgia, rash, injection site reactions, vomiting, myalgia, and herpes simplex infections.

Headache is the most commonly reported ADR, and these were mostly mild to moderate and easily managed with over-the-counter medications. Important potential risks are serious hypersensitivity reactions and serious infections. Other safety topics of interest include effects on vaccination response, effects on the kidney, reductions in albumin and plasma proteins, drug-induced aseptic meningitis, and decreased platelet counts. These risks can be mitigated by careful monitoring, exclusion of at-risk study participants, and appropriate protocol withdrawal

and stopping criteria. Additionally, protocol guidance for management of hypogammaglobulinemia/infection and infusion and hypersensitivity reactions is provided in Appendix 14 (Section 10.14) and Appendix 15 (Section 10.15), respectively. The management of and expedited reporting requirements of the AESMs (severe and/or serious headaches and suspected aseptic meningitis) to UCB are specified in Appendix 13 (Section 10.13).

Restrictions on use of live vaccines have been defined in the exclusion criterion 25a. If vaccination with non-live vaccines (including coronavirus disease 2019 [COVID-19] vaccines) is considered necessary once a study participant has started therapy with IMP, then the degree of protection afforded with a vaccine may be compromised while the participant is being treated with IMP.

Given the clinical evidence to date, the overall risk to the participants in this study is deemed to be low and the benefit-risk balance for study participants is anticipated to be favorable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of rozanolixizumab may be found in the current version of the IB.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints/Estimands
Primary	
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	Primary estimand (efficacy): • Treatment: rozanolixizumab 560mg QW or Placebo QW • Target Population: study participants with severe FMS • Endpoint: BPI-SF average interference score after 12 weeks of double-blind treatment. • Intercurrent event handling: – The ICE discontinuation of treatment will be handled using a hypothetical strategy assuming that the study participants did not experience the events, with data following discontinuation excluded from analysis. • Population level summary: mean difference in average BPI-SF interference score between the two treatments
Secondary	
• To assess the safety and tolerability of rozanolixizumab in study participants with severe FMS	• Occurrence of TEAEs during the study • TEAEs leading to withdrawal of IMP

Objectives	Endpoints/Estimands
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	• BPI-SF average interference score after 24 weeks of treatment • FIQR score after 10 weeks of treatment • Mean 7-day average daily pain score (Pain NRS) after 10 weeks of treatment • Mean 7-day fatigue score (Fatigue NRS) after 10 weeks of treatment
Exploratory	
• To assess the PK of rozanolixizumab in study participants with severe FMS	• Plasma concentration of rozanolixizumab prior to dosing on Week 13 and Week 25
• To evaluate the efficacy of rozanolixizumab for treatment of study participants with severe FMS	• Pressure pain threshold as measured by pressure algesiometry
• To assess the safety and tolerability of rozanolixizumab in study participants with severe FMS	• Change from Baseline in vital signs and laboratory results at scheduled assessments during the Treatment Period through the Run-out Period
• To evaluate the incidence and emergence of ADA of rozanolixizumab in study participants with severe FMS	• Antidrug antibody incidence at scheduled assessments during the Treatment Period
• To assess the PD effect of rozanolixizumab in study participants with severe FMS	• Value (absolute) and change from Baseline (absolute and percentage) in serum total IgG and IgG subclasses at scheduled assessments during the Treatment Period
• To assess the effect of rozanolixizumab on exploratory biomarkers in study participants with severe FMS	• Assessment of IgG binding in in vitro cell assay at scheduled assessments during the Treatment Period and the Run-out Period • Assess genetic variation for potential effects on disease progression and/or drug response and also any changes in epigenetics • Exploratory biomarkers may be measured to evaluate changes from Baseline in response to rozanolixizumab

4 STUDY DESIGN

4.1 Overall design

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, proof-of-concept study to evaluate the efficacy, safety, PK, and PD of rozanolixizumab for the treatment of severe FMS. Study participants who have a confirmed diagnosis of FMS, with pain intensity ≥6 and <10 on Pain NRS and a BPI-SF interference score ≥6 will be enrolled into the study.

In total and allowing for a dropout rate of 25%, approximately 60 study participants are planned to be enrolled and randomized in the study at up to 8 centers from the UK, with a target of 48 study participants completing the study.

The study will consist of a 28-day Screening Period, a 2-week, single-blind Run-in Period, 2 subsequent 12-week, double-blind Treatment Periods, followed by a 2-week, single-blind Run-out Period and a 5-week SFU Period.

Study participants will be randomized in a 1:1:1 ratio to 1 of 3 sequences. The study participants in each sequence will receive the following treatment regimen during the double-blind Treatment Periods (see Figure 1-1):

- Sequence 1: Rozanolixizumab 560mg sc QW for 24 weeks (12 + 12 weeks Treatment Period) (N=20, Group 1)
- Sequence 2: Placebo sc QW for 12 weeks, followed by rozanolixizumab 560mg sc QW for 12 weeks (N=20, Group 2)
- Sequence 3: Placebo sc QW for 24 weeks (N=20, Group 3).

The two 12-week period design allows for both intra- and inter-study participant comparisons. Sequence 2 allows for intra-study participant comparison of 12 weeks receiving placebo and 12 weeks receiving rozanolixizumab. Sequence 3, which has placebo throughout, enables adjustments for any period effects, and Sequence 1 Period 1 allows for inter-study participant comparisons with both Sequence 2 (Period 1) and Sequence 3 (Period 1 and Period 2).

In addition, comparing treatment effects after 24 weeks of treatment is possible through comparing the 24-week assessments from Sequence 1 and Sequence 3.

The initial 2-week Run-in Period and the final 2-week Run-out Period will be study participant-blind, with study participants not informed that they are receiving placebo, to limit the impact of any start-of-study or end-of-study induced placebo effects. The two 12-week Treatment Periods will be study participant-, investigator-, and sponsor-blind. It is important that study participants do not know when their treatment changes, whether it is going from Run-in to Period 1, Period 1 to Period 2, or Period 2 to Run-out.

The Baseline for each variable will be taken as the value measured prior to, but closest to, the treatment on Day 1. This may be measured on Day 1 prior to treatment or during Weeks -1 or -2 depending on the endpoint.

After approximatively 30 study participants have been randomized and these study participants have completed their 2 double-blind Treatment Periods, an interim analysis may be conducted with the possibility of stopping for efficacy or futility or continuing recruiting the remaining study participants.

The daily average pain over the previous 24 hours will be captured using the Pain NRS through a diary over a 10-day period within the Screening Period. Study participants require a minimum of 7 out of the 10 daily Pain NRS assessments over this 10-day period to be eligible for randomization. All recorded Pain NRS scores over the 10-day period within the Screening Period will be used to calculate the Mean daily average 24 hours pain intensity ≥6 and <10 for Inclusion (for example, if 10 daily scores are available take the mean of the 10 days; if 9 daily scores are available take the mean of the 9 days and so on).

During the Run-in Period and at the end of the Treatment Periods, the Pain NRS will be collected daily for 7 consecutive days following the assessment visit as described in the Schedule of Activities. For all other visits, the average pain for the preceding 24 hours prior to the visit will be captured by the Pain NRS for that day only. The timings of these assessments are described in the Schedule of Activities (Section 1.3).

4.2 Scientific rationale for study design

The choice of the study population (study participants with severe FMS) is based on recent research findings (Goebel et al, 2021) suggesting that in patients with severe FMS 1) pathogenic IgG contribute to their clinical symptoms and 2) reduction of IgG is a potential therapeutic treatment approach. Nonclinical and clinical data generated on rozanolixizumab support the sc administration of rozanolixizumab in study participants with IgG autoantibody-mediated conditions. Patients with severe FMS have an unmet need due to the limited efficacious treatment options available. There is a burden of disease in patients with high levels of pain that impact overall function.

The semi-crossover, three treatment-sequence design was chosen to allow for comparisons of the same study participant across different treatment periods in addition to comparisons between study participants, which leads to a substantially smaller sample size than a parallel-group design. An overview of estimates of variability and treatment effects from previous fibromyalgia and pain studies indicated that the variability between study participants is greater than that between the same study participant over time, which implies that a cross-over design is more efficient than a parallel-group design. However, a classic cross-over design is not appropriate, because if rozanolixizumab was followed by placebo any washout period is not feasible, as it would take too long for the IgG levels to return close to their Baseline levels. The third placebo-only sequence was included to ensure a placebo control in the second period.

The study includes single-blind, placebo-only Run-in and Run-out Periods before the start of Treatment Period 1 and after Treatment Period 2. The Run-in Period is included to allow any initial start-of-study placebo effect to stabilize, while the Run-out Period is included to limit the impact of shifts in endpoints that may be associated with the participants knowing that they have reached the end of study.

4.3 Justification for dose

A rozanolixizumab dose of 560mg given weekly via sc infusion for at least 12 weeks is proposed in this study. Such a duration of dosing will ensure that sustained reduced IgG levels within the target range of ~70% to 80% reduction from Baseline will be maintained for a 6-week period once the PD steady state is achieved (after 6 weeks). Different treatment durations are being explored in this study (12 or 24 weeks on active treatment).

The planned dose of rozanolixizumab for this study is 560mg QW by sc infusion. As outlined below, this dose is justified by:

- Clinical data from two Phase 2 studies showing a meaningful improvement at repeated doses of 7mg/kg in gMG and 10mg/kg in ITP.
- Pharmacodynamic data showing a desired reduction in IgG levels of 70% from Baseline after repeated doses of 7mg/kg and 10mg/kg.
- Simulations from a population PK-PD analysis showing comparable exposure and IgG response for the 560mg fixed dose and weight-tiered doses approximating 7mg/kg and 10mg/kg doses.

Rozanolixizumab has been studied in two Phase 2 studies in gMG and ITP with body weight normalized dosing (mg/kg). Repeated doses up to 10mg/kg and single doses up to 20mg/kg were generally well tolerated with an acceptable safety profile in these Phase 2 studies. In participants with gMG, clinically relevant improvements in day-to-day functioning were observed following treatment with rozanolixizumab 7mg/kg compared with placebo. In participants with ITP, rozanolixizumab produced clinically meaningful responses across the treatment groups (rozanolixizumab 4mg/kg to 20mg/kg at varying administration frequency), in all of the response variables defined by platelet counts.

Phase 3 studies are being conducted to evaluate the efficacy and safety of rozanolixizumab in participants with gMG and ITP. The dose regimens being evaluated in the gMG studies are weight-tiered doses approximating 7mg/kg and 10mg/kg QW. For ITP, a weight-tiered loading dose approximating 15mg/kg followed by an initial weight-tiered maintenance dose approximating 10mg/kg Q2W or the exclusion of a loading dose is being evaluated; an initial weight-tiered maintenance dose approximating 10mg/kg every 1 week is also being evaluated.

The proposed 560mg fixed dose of rozanolixizumab is selected to achieve a comparable range of exposures and IgG reductions as the weight-tiered doses that are being evaluated in the ongoing Phase 3 pivotal study in gMG.

A population PK-PD model was developed based on observed PK and IgG data from the two Phase 2 studies (TP0001, MG0002) and two Phase 1 studies (UP0018 and UP0060). Rozanolixizumab exposure and IgG response to rozanolixizumab were comparable between healthy participants and the gMG and ITP populations. In addition, ethnicity was not found to affect PK or IgG response. Therefore, there are no anticipated changes in exposure or IgG responses, where the Baseline IgG levels are similar, between different indicated populations or ethnicities.

Simulations performed using the population PK-PD model show that the planned dose of 560mg QW should:

- Produce PK variability similar to that with weight-tiered dosing.
- Achieve rozanolixizumab exposures that are consistent with those obtained with weight-tiered doses of 7mg/kg and 10mg/kg QW as used in the currently ongoing Phase 3 studies.
- Achieve and maintain a desired IgG reduction of 70% from Baseline, irrespective of body weight.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for investigators and participants and to reduce the potential for dosing errors. Thus, a dose regimen of 560mg QW is planned for investigation in this study.

4.3.1 Rationale of targeted 70% IgG reduction

Rozanolixizumab administration resulted in a rapid clearance of serum IgG levels in both healthy volunteers (UP0018 and UP0060) and participants with gMG (MG0002) or ITP (TP0001). Serum IgG levels decreased on average by 69% from Baseline levels after 2x3 weekly administrations of 7mg/kg in participants with gMG. The reduction in IgG was mirrored by a reduction in anti-acetylcholine receptor (AChR) autoantibodies in participants with gMG and was also associated with clinically meaningful improvements in clinical outcome scales (myasthenia gravis-activities of daily living [MG-ADL]) compared with placebo.

A rozanolixizumab-induced IgG lowering of about 70% from Baseline is similar to that achieved with other FcRn antagonists and alternative strategies such as PLEX, and falls within the range associated with clinical benefit in various autoimmune indications.

- A single PLEX reduces plasma IgG by about 30%; a minimum of 3 but commonly 5 to 6 cycles are required to decrease specific IgGs by about 70% to 80%, which is the maximum reduction seen due primarily to the fact that IgG is constantly being synthesized at a high rate (Williams and Balogun, 2014; Kaplan, 2013).
- Data in participants with CIDP treated with PLEX for 3 weeks showed decreases in IgG of 60% to 75%. These decreases were associated with improvement in neurologic-disability scores, in scores on the weakness and reflex subsets of the neurologic-disability score, and in nerve conduction (Dyck et al, 1986).
- Five to 6 PLEX cycles for a 70% to 80% reduction in total IgG is consistent with studies that have investigated the effect of PLEX on IgG autoantibody levels. An average of 5 to 6 cycles of PLEX are needed to get a clinical benefit, and this is typically associated with an approximately 70% reduction in the level of anti-AChR autoantibodies in gMG (Guptill et al, 2016), antithyroid peroxidase autoantibodies in Hashimoto's encephalopathy (Cook et al, 2015), or autoantibodies in PV (Turner et al, 2000).
- Phase 3 data for the FcRn antagonist efgartigimod showed that a reduction of total IgGs and anti-AChR autoantibodies was correlated to clinically meaningful improvements in MG disease scores (Vyvgart Prescribing Information, 2021).

For FMS, indication-specific targets for IgG lowering are not yet established. The current assumption is that the desired level of IgG reduction would be similar to gMG and CIDP (~70%).

4.4 End of study definition

A study participant is considered to have completed the study if he/she has completed all phases of the study, including the SFU Period. Study participants will have an EOT/EW Visit performed 2 weeks after the Run-out Period or upon discontinuation of the study, followed by an SFU/EOS 5 weeks after the Run-out Period.

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Study participant must be ≥18 years and ≤70 years of age at the time of signing the informed consent form (ICF).

Type of participant and disease characteristics

2a. Study participant alone or with assistance of the caregiver is considered reliable and capable of adhering to the protocol visit schedule or medication intake according to the judgment of the investigator.

3b. Study participant with a diagnosis of fibromyalgia as defined by the 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria (American College of Rheumatology Preliminary Diagnostic Criteria) plus the following characteristics during the Screening Period:

At the Screening Visit, confirm:

a. BPI-SF interference score ≥6

b. Criterion removed

c. Criterion removed

d. Criterion removed

e. Study participant has been diagnosed with FMS for at least 6 months

f. Study participant has been having FMS symptomatology for at least 2 years before enrollment.

Prior to randomization, confirm:

a. Mean daily average 24 hours pain intensity ≥6 and <10 assessed by Pain NRS. This will be assessed over a 10-day period within the Screening Period. Study participants require a minimum of 7 out of 10 assessments over this 10-day period within the Screening Period.

b. Pain NRS scores should be ≥4 at all completed assessments within this 10-day period.

Rescreening can be allowed as described in Section 5.4.

Weight

4. Body weight of at least 35 kg.

Sex

5b. Males or females

Note: A female study participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 4

  OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the Treatment Period and for at least 90 days after the final dose of IMP.

Informed consent

6. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this study protocol.

Other

7. Criterion removed.

8. Criterion removed.

5.2 Exclusion criteria

Study participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Study participant has been diagnosed with FMS for ≥15 years.
2. Study participant has any systemic autoimmune inflammatory disease (eg, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory arthritis [including ankylosing spondylitis, psoriatic arthritis]).
3. Study participant has any medical or psychiatric or separate chronic pain condition (pain from traumatic injury or structural disease, regional pain syndromes, multiple surgeries or failed back syndrome, or any other chronic pain not related to FMS) that, in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study or the ability to assess FMS-related pain.
4. Study participant has a current history of alcohol or drug use disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders V, within the previous 12 months prior to the Screening Visit.
5. Study participant has a known hypersensitivity to any components of the study medication or any other anti-FcRn medications. This includes a known history of hyperprolinemia, since L-proline is a constituent of the rozanolixizumab formulation.
6. Study participant has active neoplastic disease or a history of neoplastic disease within 5 years of study entry (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix which has been definitely treated with SoC approaches).
7. Criterion removed

8a. Study participant has severe renal impairment, defined as estimated glomerular filtration rate <30mL/min/1.73m^2 (calculated using Modification of Diet in Renal Disease [MDRD] study equation), at Screening visit.

9a. Study participant has a clinically important active infection (including unresolved or not adequately treated infection) as assessed by the investigator.

10. Study participant has chronic inflammatory demyelinating polyneuropathy.

11. Study participant has current unstable liver or biliary disease, per investigator assessment, defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note an exception is stable chronic hepatobiliary conditions (including Gilbert's syndrome, asymptomatic gallstones).

12. Study participant has a current or medical history of primary immunodeficiency.

13. Criterion removed.

14a. Study participants meet any of the following TB exclusion criteria:

- Known active TB disease
- History of active TB involving any organ system unless adequately treated according to World Health Organization/US Center for Disease Control therapeutic guidance and proven to be fully recovered upon consult with a TB specialist
- Latent tuberculosis infection (LTBI) (unless appropriate prophylaxis is initiated at least 1 week prior to IMP dosing and will be continued to completion of prophylaxis). Prophylaxis should be in accordance with applicable clinical guidelines and TB specialist judgment based on the origin of infection
- High risk of exposure to TB infection, as assessed by the investigator
- Criterion removed

For further information relating to definitions of known active TB, past history of TB, LTBI, and high risk of acquiring TB infection, see Appendix 12 (Section 10.12).

15. Criterion removed

16. Study participant has a history of solid organ transplant or hematopoietic stem cell/marrow transplant.

17. Study participant has a history of chronic ongoing infections (eg, Hepatitis B or C, human immune deficiency virus [HIV], or who tests positive for HIV, Hepatitis B or C at Screening Visit.

- Presence of Hepatitis B surface antigen at the Screening Visit.
- Positive Hepatitis C antibody test result at Screening or within 3 months prior to the IMP dose. NOTE: Study participant with a positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained.

18. Study participant has undergone a splenectomy.

19. Study participant is pregnant or lactating.

20 Criterion removed.

21a. Study participant

- Has suicide attempt in the past 2 years (including an active attempt, interrupted attempt, or aborted attempt),
- OR had suicidal ideation with at least some intent to act in the past 6 months as indicated by a positive response (Yes) to either Question 4 or Question 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening or Baseline (Visit 3);
- OR is otherwise judged clinically to be at a serious suicidal risk based on the investigator's judgment.

Prior/Concomitant therapy

22. Study participant has been treated with prohibited immunosuppressive medications, biologics, or other therapies within the exclusion period (see Section 6.5.2).
23. Study participant has current treatment with prednisolone or equivalent (except for a short course to treat, for example, an episode of asthma or chronic obstructive pulmonary disease exacerbation).
24. Study participant has current treatment with morphine or equivalent of >80mg/day (>40mg/day if morphine or equivalent are taken in association with gabapentin [>1200mg/day] or pregabalin [>150mg/day]).

25a. Study participant has received a live vaccination within 4 weeks prior to Visit 1 or intends to have a live vaccination during the study or within 8 weeks following the final dose of IMP (Visit 28).

Prior/Concurrent clinical study experience

26. Study participant has previously been randomized in this study (rescreening for screen-failed participants is allowed with prior consultation and permission of the medical monitor/study physician; see Section 5.4).
27. Study participant has participated in another study of an IMP (and/or an investigational device) within the previous 30 days or 5 half-lives prior to screening (whichever is longer) or is currently participating in another study of an IMP (and/or an investigational device).

Diagnostic assessments

28. Study participant has alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) that is >2x upper limit of normal (ULN).
    - If study participant has >ULN for ALT, AST, or ALP that does not meet the exclusion limit at Screening, the tests must be repeated prior to dosing to ensure there was no further ongoing clinically relevant increase. In case of a clinically relevant increase as per the investigator's judgment, the study participant must be excluded.
    - Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit (>2xULN) may be repeated once for confirmation. This includes rescreening. If any of the repeated tests (ALT, AST, or ALP) are >2xULN, the study participant will meet the exclusion criterion #28 and the study participant must be excluded.

- For randomized study participants with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin but <1.5xULN, a Baseline diagnosis and/or the cause of any clinically meaningful elevation will have to be understood and recorded in the electronic case report form (eCRF).

29. Study participant has bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

30a. Study participant has IgG ≤5.5g/L at the Screening Visit.

31. Study participant has an absolute neutrophil count <1500 cells/mm^3 at the Screening Visit.

32. Study participant has a planned major elective surgical procedure during their participation in the study.

33. Criterion removed

5.3 Lifestyle restrictions

There are no lifestyle restrictions during this study.

5.3.1 Meals and dietary restrictions

There are no meal or dietary restrictions during this study.

5.3.2 Caffeine, alcohol, and tobacco

There are no restrictions on caffeine or tobacco during this study. Study participants are to avoid excessive alcohol consumption during the study.

5.3.3 Activity

There are no restrictions on activity during this study.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, following discussion with the sponsor's medical monitor or study physician. Rescreened study participants should be assigned a new study participant number for rescreening and repeat all Screening assessments.

If a study participant has 1 isolated test result outside the specific range which is deemed clinically nonsignificant, the abnormal value may be rechecked at the discretion of the investigator, following discussion with the sponsor's medical monitor or study physician. If the normalization of the test result occurs within the Screening Period, then no other Screening procedures need to be repeated.

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

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

Study participants will be randomized to one of three different treatment sequences at the beginning of the 2-week Run-in Period.

All study participants will receive placebo during the Run-in Period. Study participants will receive either rozanolixizumab (Sequence 1) or placebo QW (Sequence 2 and 3) for the first 12 weeks. At the end of 12 weeks, study participants who were on active (Sequence 1) will receive an additional 12 weeks of rozanolixizumab.

In the first cohort receiving placebo (Sequence 2), study participants will receive 12 weeks of rozanolixizumab, and in the second placebo cohort (Sequence 3), study participants will receive an additional 12 weeks of placebo.

At the end of the second Treatment Period, all study participants will receive placebo during a 2-week Run-out Period.

Study treatment will be administered as an sc infusion over approximately 12 minutes. The infusion duration may be increased at the discretion of the investigator.

ARM Name	Sequence 1	Sequence 2	Sequence 3
Intervention name	Placebo (Run-in and Run-out) Rozanolixizumab (Treatment Period 1+2)	Placebo (Run-in, 12-week Treatment Period 1 + Run-out) Rozanolixizumab (Treatment Period 2)	Placebo (Run-in, 24 weeks [Treatment Period 1+2], Run-out)
Type	Placebo + Biologic	Placebo + Biologic	Placebo
Dose formulation	Solution for injection	Solution for injection	Solution for injection
Unit dose strength for the Treatment Period	A glass vial containing rozanolixizumab at a concentration of 140mg/mL, formulated with 30mM L-histidine, 250 nM L-proline, 0.03% (w/v) polysorbate 80 and pH 5.6 Dose of 560mg	0.9 % w/v saline (Placebo) Or A glass vial containing rozanolixizumab at a concentration of 140mg/mL, formulated with 30mM L-histidine, 250 nM L-proline, 0.03% (w/v) polysorbate 80 and pH 5.6 Dose of 560mg	0.9 % w/v saline

Dosage levels	Placebo weekly for 2 weeks (Run-in), then rozanolixizumab 560mg weekly for 24 weeks (Treatment Period 1 + 2), followed by Placebo weekly for 2 weeks (Run-out)	Placebo weekly for 2 weeks (Run-in), then Placebo weekly for 12 weeks (Treatment Period 1), followed by rozanolixizumab 560mg weekly for 12 weeks (Treatment Period 2), followed by Placebo weekly for 2 weeks (Run-out)	Placebo weekly for 2 weeks (Run-in), then Placebo weekly for 24 weeks (Treatment Period 1 + 2), followed by Placebo weekly for 2 weeks (Run-out)
Route of administration	Subcutaneous infusion	Subcutaneous infusion	Subcutaneous infusion
Use	Experimental	Placebo comparator and Experimental (active)	Placebo comparator
IMP and NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Packaging will be described in the IMP Handling Manual. Packaging will be labelled as required per country requirement.	Packaging will be described in the IMP Handling Manual. Packaging will be labelled as required per country requirement.	Packaging will be described in the IMP Handling Manual. Packaging will be labelled as required per country requirement.
Current/Former name or alias	UCB7665	UCB7665 + not applicable for placebo	Not applicable

IMP=investigational medicinal product; NIMP=non-investigational medicinal product; w/v=weight/volume

6.2 Preparation, handling, storage, and accountability requirements

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff.

Details on the preparation of study treatment for infusion, rate of infusion, administration, appropriate records handling, and blinded and unblinded site personnel roles are provided in the IMP Handling Manual. All site personnel and healthcare professionals delegated to handle study treatment storage, preparation, and administration must be trained to IMP Handling Manual.

The investigator or delegate is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

Further guidance and information for the final disposition of unused study treatment are provided in the IMP Handling Manual.

6.2.1 Drug accountability

A Drug Accountability form will be used to record study medication dispensing and return information on a by-study participant basis and will serve as source documentation during the course of the study. Details of any study medication 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 may assign some of the investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study medication until returned or destroyed.

The investigator must ensure that the study medication 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 study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures 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.

6.3 Measures to minimize bias: randomization and blinding

Study participants will be randomized to the appropriate treatment (active or placebo) in their cohort using the Trial Supply Management system. The unblinded randomization list will be provided to pharmacies via a digital format. After informed consent is obtained, participants will be allocated a unique Screening number.

An interactive response technology (IRT) will be used for assigning eligible study participants to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The IRT will generate individual assignments for kits of study medication, as appropriate, according to the visit schedule.

To enroll a study participant (Visit 0), the investigator or designee will contact the IRT and provide brief details about the study participant to be enrolled. Each study participant will receive a 5-digit number assigned at Screening that serves as the study participant identifier throughout the study. The study participant number will be required in all communication between the investigator or designee and the IRT regarding a particular study participant. Study participant numbers and kit numbers will be tracked via the IRT.

To randomize a study participant, the investigator or designee will contact the IRT and provide brief details about the study participant to be randomized. The IRT will automatically inform the investigator or designee of the study participant's randomization number. The IRT will allocate

kit numbers to the study participant based on the study participant number during the course of the study. The randomization number must be incorporated into the eCRF.

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study treatment blind

All study participant treatment details will be allocated and maintained by IRT system.

The following individuals will receive the randomization code at the start of the study:

- Sponsor Patient Safety staff for reporting SAEs to regulatory authorities
- Designated bioanalytical staff analyzing PK samples
- IRT provider

[redacted] The unblinded pharmacy monitors from the Contract Research Organization (CRO) and the Clinical Supply Set-Up Manager/Clinical Supply Planner, and the unblinded Clinical Project Manager (CPM)(or designee) will also have access to the treatment allocations and to the drug accountability records, if applicable. Further details are provided in the IMP Handling Manual and Site Unblinded Team Management Plan.

Due to differences in presentation between rozanolixizumab and placebo, special precautions will be taken to ensure blinding. Both products have packaging differences (unblinded labels) but also physical appearance differences (packaging presentation, volumes, color, viscosity). The IMP preparation will be performed by unblinded personnel. Please note that the difference in appearance of the two IMPs can be seen in the syringe but not in the tubing. Therefore, only the syringe will be covered by blinding stickers (see IMP Handling Manual).

The IMP administration will be performed by blinded qualified site staff.

The following individuals may, as necessary, request access to the randomization code from IRT as indicated:

- Interim analysis biostatistician/statistical programmer
- Members of the SMC who participate in unblinded sessions will be given information about the IMP allocation for those study participants for whom data are provided at these sessions (see also Section 9.7.2).
- The designated unblinded statistician and supporting programmer(s) responsible for the preparation of the data outputs for the SMC review and/or any interim analyses.

Certain clinical laboratory results have the potential to unblind the investigator, site personnel, and study team. These results will not be reported to investigative sites or other blinded personnel (see Section 10.2 for a list of these clinical laboratory parameters). A medical monitor independent from the study team and unblinded to the serum IgG and albumin levels, but blinded to actual treatment assignment (an independent unblinded medical monitor) will monitor these parameters during the Treatment Period. If temporary treatment discontinuation due to low serum IgG levels or low serum albumin levels (as per Section 7.1.4) is required, the independent

unblinded medical monitor will contact the IRT system to initiate mock infusions with only placebo. This procedure will take place irrespective of the randomized IMP. Allocation of mock kit numbers will be handled via the IRT. The independent unblinded medical monitor will re-initiate the IMP via the IRT system when the serum IgG and/or albumin levels have returned to protocol-defined thresholds specified in Section 7.1.4.

Further details of maintenance of the study treatment blind are provided in the IMP Handling Manual and Site Unblinded Team Management Plan.

6.3.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm the study participant 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 CPM and medical monitor will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the study medication performed by the investigator must be recorded in the source documents and on the Study Termination eCRF page.

Inadvertent unblinding must be listed as a major protocol deviation.

6.4 Treatment compliance

Drug accountability must be recorded on the Drug Accountability form (Section 6.2.1).

6.5 Concomitant medications/treatments

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant treatments are permitted during the study:

- Medications or therapies for FMS or chronic pain
  - PRN (as needed) analgesics taken as over the counter (OTC) (eg, ibuprofen, paracetamol, codeine) and/or prescribed (eg, opioids) if initiated [redacted] before randomization.
  - Prescribed regular opioids (short or long acting) up to a total opioid equivalent dose of 80mg/day of morphine (including PRN opioids, if taken). For regular opioids, the patient must have been on the stable equivalent daily dose of morphine for [redacted] after initiation/up-titration or [redacted] after down-titration.
  - Regular antidepressants or gabapentinoids (eg, pregabalin, gabapentin) prescribed for pain and/or sleep if started [redacted] and stable for [redacted] before randomization.
  - Migraine treatment-related drugs that are not antibody-based.
  - Any other pain therapies are only permitted if deemed acceptable in the judgment of the investigator and, where appropriate, in discussion with the medical monitor.
  - Any pain management programs are only permitted if deemed acceptable in the judgment of the investigator and in discussion with the medical monitor.

6.5.2 Prohibited concomitant treatments (medications and therapies)

Prohibited medications and therapies relative to Baseline are summarized in the table below. The use of these medications is also prohibited during the study and the use of these may result in the study participant being discontinued from IMP. Investigators should contact the medical monitor where possible to discuss the discontinuation of IMP in advance.

Concomitant medications prohibited during the study are presented in Table 6-1.

Table 6-1: Concomitant medications prohibited during the study

Generic Name (commercial/trade name)	Exclusionary period relative to Visit 1 (regardless of route)
Immunosuppressive medications	
Cyclophosphamide (Cytoxan®)	6 months
Cyclosporine (Neoral®)	4 weeks
Biologics	
Monoclonal therapeutic antibodies	Used within 6 months of Visit 1 or used ≥6 months prior to Visit 1 with B-cells that have not returned to normal levels
Others	
Antineoplastics or treatments for neoplastic disease (including anti-PD1 monoclonal antibodies)	3 months
Dabigatran	2 weeks
Intravenous methylprednisolone	4 weeks
Prednisone (or other steroids equivalent)[a]	4 weeks
Intravenous or subcutaneous immunoglobulin	6 weeks
Plasma exchange or plasmapheresis	6 weeks
Immunoadsorption	6 weeks

PD1 = programmed cell death protein 1
[a] Except for a short course to treat, for example, an episode of asthma or chronic obstructive pulmonary disease exacerbation.

Table 6-2: Prohibited concomitant medications and therapies relative to the last rozanolixizumab dose

Generic Name (commercial/trade name)	Exclusionary period relative to Visit 1 (regardless of route)
Live vaccination	4 weeks
Treatment with IgG based monoclonal antibodies	8 weeks

6.5.3 Rescue medication

The use of OTC analgesics (eg, ibuprofen, paracetamol, codeine) and other medications for treatment of FMS is allowable at a stable dose during the study (see Section 6.5.1). The use of these medications is considered rescue medication if the dose is increased relative to the stable dose or if an additional medication not used at Screening is considered necessary by the investigator. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eCRF under concomitant medication (see Schedule of Activities, Section 1.3). As the rescue medication might overlap with the permitted medication, the rescue medication can be identified as a new analgesic not listed at screening or as a change in the usual dosage regimen of a permitted SoC analgesic medication.

6.6 Dose modification

Dose modification of IMP is not permitted in this study. However, temporary discontinuation of IMP may occur as detailed in Section 7.1.4.

6.7 Criteria for study hold or dosing stoppage

After approximatively 30 study participants have completed their 2 treatment periods, a planned interim analysis may be conducted (Section 9.7.1). A decision to halt the study may be taken based on this analysis, if performed.

The sponsor's decision for study hold may also be based on an SMC recommendation (see Section 9.7.2).

6.8 Treatment after the end of the study

There are no plans for the provision of rozanolixizumab after the end of the study. The study participant should discuss any alternative treatment options (if needed after the study) with their healthcare provider.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

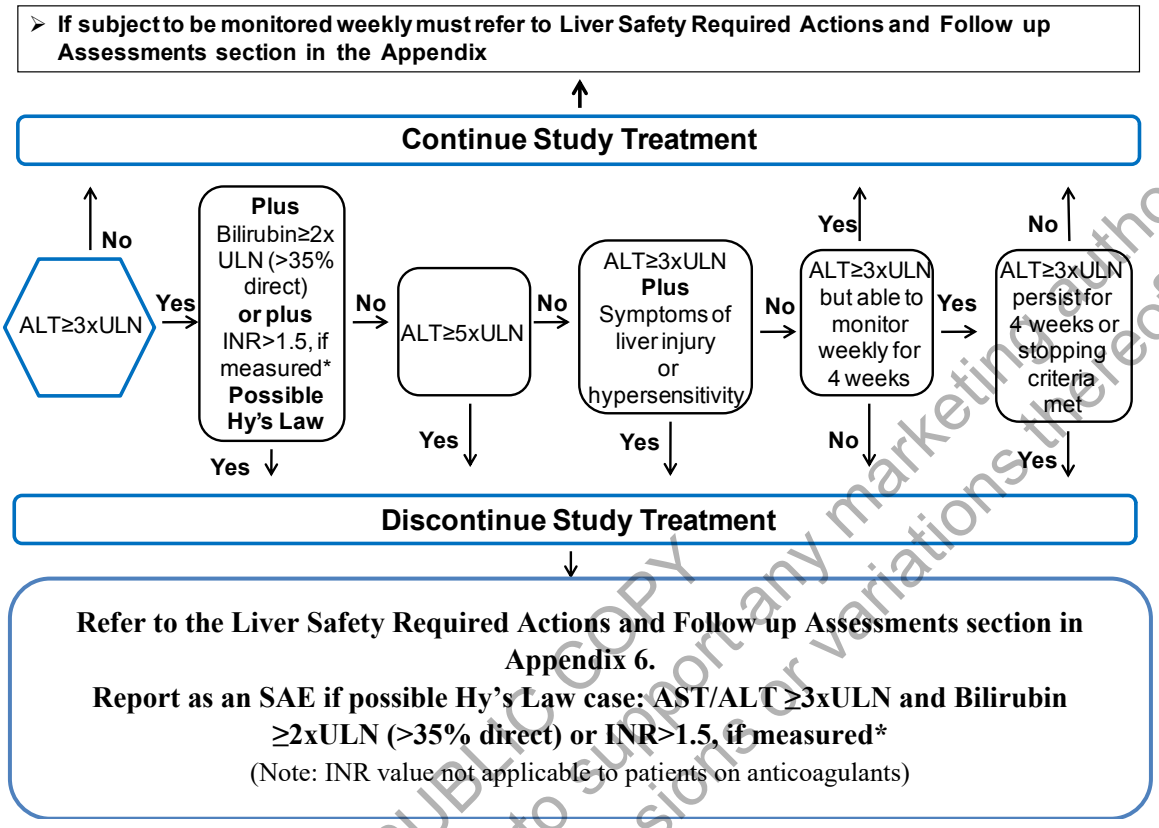
7.1 Discontinuation of study medication

In addition to algorithmic stopping criteria, management of AEs is ultimately at the investigator's discretion.

7.1.1 Liver chemistry stopping criteria

Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a study participant meets one of the conditions outlined in Figure 7-1 or if the investigator believes that it is in best interest of the study participant.

Figure 7-1: Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



AST=aspartate aminotransferase; ALT=alanine transaminase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Specific assessments and follow-up actions for potential drug-induced liver injury (PDILI) are provided in Appendix 6 (Section 10.6).

7.1.2 Other permanent discontinuation criteria

Study participants **must permanently discontinue** IMP if any of the following events occur:

1. Study participant develops an illness that would interfere with their continued participation.
2. Study participant has a significant infective episode including but not limited to bacteremia/sepsis, infectious meningitis, septic arthritis, osteomyelitis, complicated pneumonia, or visceral abscess which may or may not result in hospitalization. This list is not intended to be all inclusive, and the investigator is expected to apply their clinical judgment on continuing IMP based on the clinical situation (see Appendix 14; Section 10.14).
3. Study participant has an AE of severe or serious hypersensitivity, infusion-related reaction (Appendix 15; Section 10.15), or anaphylaxis requiring corticosteroid and/or epinephrine therapy (Sampson et al, 2006).
4. Study participant has a recurrence of aseptic meningitis (see also Appendix 13; Section 10.13).

5. Participant meets PDILI permanent discontinuation criteria (see Appendix 6, Section 10.6).
6. Study participant for whom further examinations result in a diagnosis of active TB, or if the study participant is diagnosed with LTBI with no initiation of TB preventive therapy, prematurely discontinues TB preventive therapy, or, in the opinion of the investigator or sponsor is noncompliant with TB preventive therapy. An EW visit must be scheduled as soon as possible, but not later than the next regular visit.
7. Study participant has new onset or recurrent neoplastic disease (except for superficial basal or squamous cell carcinoma of the skin not requiring targeted biological therapy, chemotherapy, or radiation).
8. Study participant 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 study participant should be referred immediately to a mental healthcare professional and must be withdrawn from the study.

7.1.3 Level of follow up to be considered when permanent discontinuation from IMP occurs

In circumstances where permanent discontinuation from IMP may occur (Section 7.1.1 and Section 7.1.2), the investigator is to discuss with the study participant the appropriate processes for discontinuation from IMP and must discuss with the study participant the options for continuation of the assessments in the Schedule of Activities (Section 1.3), including different options of follow up (eg, in person, by phone/mail, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints and AEs.

Study participants who have discontinued IMP should not be automatically removed from the study. Whenever safe and feasible, it is imperative that study participants remain on study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow up that is agreed to by the study participant, any changes to the scheduled visits and assessments, and the plan for follow up that is agreed to by the study participant. In regards to changes to scheduled visits, for the level of follow up, it is recommended the EOT/EW Visit and the SFU/EOS Visit be prioritized.

If the study participant does not want to continue the IMP and withdraws consent (refer to Section 7.2), investigators should contact the medical monitor, whenever possible, to discuss the withdrawal of a study participant in advance.

7.1.4 Temporary discontinuation

Study participants **must be temporarily discontinued** from the IMP if any of the following events occur:

1. The study participant develops an event of hypogammaglobulinemia with a serum total IgG reported below the lower limit of quantification (LLOQ) (currently 1.09g/L), irrespective of infection. Study participant may resume treatment when IgG level returns to ≥2g/L. In view of re-initiating the IMP, additional samples will be collected to monitor study participants' IgG levels during the period of temporary discontinuation. In order to preserve the blind, additional study participants will be selected at random and requested to provide additional samples.
2. Study participant develops an event of hypoalbuminemia with serum albumin level <2g/dL. When the serum albumin level returns to ≥2.5g/dL, the study participant may be allowed to resume treatment with IMP. Ad hoc assessments can be performed to monitor recovery of albumin levels. In view of re-initiating the IMP, additional samples will be collected to monitor study participants' serum albumin levels during the period of temporary discontinuation. In order to preserve the blind, additional study participants may be selected at random and requested to provide additional samples.

   If IMP treatment is resumed, the next dose should be continued as previously scheduled. No "make up" dose is permitted. The study participant should subsequently follow the visit schedule as described in the protocol and the eCRF should be completed accordingly.
3. Study participant has a suspected drug-induced aseptic meningitis. The IMP may be restarted if clinically appropriate when signs and symptoms have resolved.

Study participants **may** be temporarily discontinued from the IMP if the following event occurs:

1. Study participant develops a nonserious persisting or recurrent infection with serum total IgG level reported between the LLOQ (currently 1.09g/L) and <2g/L. Upon resolution of infection and return of IgG level to ≥2g/L, the study participant may be allowed to resume treatment.
2. Removed

If IMP treatment is resumed, continue the next dose as previously scheduled. No "make up" dose is permitted. The participant should subsequently follow the visit schedule as described in the protocol and the eCRF should be completed accordingly.

7.2 Participant discontinuation/withdrawal from the study

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

A study participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the study participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a study participant withdraws from the study, he/she may request destruction of any samples taken and not tested. The investigator must document this in the site study records, suspend further sample shipments, and inform the site monitor immediately.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Study withdrawal criteria

Study participants **must be withdrawn from the study** if any of the following events occur:

1. Study participant withdraws his/her consent.
2. There is confirmation of a pregnancy during the study, as evidenced by a positive serum pregnancy test.
3. The sponsor or a regulatory agency requests withdrawal of the study participant.
4. Removed
5. Study participant 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 study participant should be referred immediately to a mental healthcare professional and must be withdrawn from the study.

If a study participant withdraws from the study, the following procedures should be completed:

- The study participant should not receive further doses of IMP.
- The study participant should return for an EW Visit scheduled as soon as possible, but no later than the next scheduled visit.
- SFU or EOS Visit should be scheduled 6 weeks after the study participant has discontinued his/her IMP.

Study participants **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. Study participant is noncompliant with the study procedures or medications in the opinion of the investigator.
2. Study participant takes prohibited concomitant medications as defined in this protocol (Section 6.5.2).
3. Study participant develops an illness that would interfere with his/her continued participation.

Investigators should contact the medical monitor, whenever possible, to discuss the withdrawal of a study participant in advance.

For the study participants who are withdrawn from the study, the EOT Visit must be scheduled as soon as possible, but no later than the next regular visit. Study participants will be encouraged to complete the SFU Period.

Participants who are randomized but withdraw prior to dosing at Day 1 may be replaced. Replacement study participants will be assigned the same treatment that was assigned to the withdrawn study participant.

7.3 Lost to follow-up

A study participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a study participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the study participant and reschedule the missed visit as soon as possible and counsel the study participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the study participant wishes to and/or should continue in the study.
- Before a study participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the study participant (at least 1 phone call and 1 written message to the study participant), 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 study participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the study participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3). Study visits should preferably be conducted at the same time of the day throughout the study.

Some study-specific investigations may not be conducted according to the study protocol during a pandemic or other exceptional circumstance (eg, extreme weather) due to the need to implement safety measures and guidance from regulatory authorities. In such a situation, which may be accompanied by local or global containment or other measures, sites may need to prohibit access to study participants and study-related personnel. Study participants' visits to the study site may be replaced by contingency measures. These measures are primarily established to ensure the safety of study participants during the course of the study and to maintain the study participants' treatment schedules, if the investigator considers it appropriate. These measures include, but are not limited to, virtual visits or home-nursing visits replacing site visits, eg, telemedicine contacts or home-nursing visits when treatment and/or blood sampling is scheduled. The contingency measures are described in a contingency plan which will be maintained by UCB for the respective study. The contingency measures are shared with the investigator and the respective study-related personnel as soon as there are indications that it is necessary to implement any of the measures.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the study participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Screening assessments can be performed on different days throughout the Screening Period, if required. The investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

The maximum amount of blood collected from each study participant over the duration of the study, including any extra assessments that may be required, will not exceed 500mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are summarized in the Schedule of Activities (Section 1.3).

8.1.1 Brief Pain Inventory-Short Form

The BPI-SF was designed to measure multiple clinically relevant aspects of pain such as pain intensity and interference from pain in cancer populations. There are two versions; the short version is the most commonly used and is often included in the context of clinical trials (Williams and Arnold, 2011). The short form of the BPI is a self-administered questionnaire used to evaluate the severity of a study participant's pain and the impact of this pain on the study participant's daily functioning. The BPI-SF assesses for the location of pain, pain intensity, and functional interference from pain. The BPI-SF should be completed by the study participants in a quiet place prior to other PROs or protocol-specified assessments at each visit including dosing on dosing days.

The 4 BPI-SF severity items include: worst pain in last 24 hours, least pain in last 24 hours, pain on average, and pain right now. Each item is rated on a 0 (no pain) to 10 (pain as bad as you can imagine) scale with a recall period of 24 hours.

The 7 BPI-SF interference items include: general activity, mood, walking ability, normal work (including housework), relations with other people, sleep, and enjoyment of life. Each item is rated on a 0 (does not interfere) to 10 (completely interferes) scale with a recall period of 24 hours. The arithmetic mean of the 7 interference items can be used as a measure of pain interference.

8.1.2 Pain NRS

The Pain NRS is a numeric version of the VAS in which a respondent selects a whole number that best describes "How much pain have you experienced on average over the past 24 hours?" The 11-point Pain NRS ranges from 0 (no pain) to 10 (pain as bad as you can imagine).

The daily average pain over the previous 24 hours will be captured using the Pain NRS through a diary over a 10-day period within the Screening Period. Study participants require a minimum of 7 out of the 10 daily Pain NRS assessments over this 10-day period to be eligible for randomization. All recorded Pain NRS scores over the 10-day period within the Screening Period will be used to calculate the Mean daily average 24 hours pain intensity ≥6 and <10 for Inclusion (for example, if 10 daily scores are available take the mean of the 10 days; if 9 daily scores are available take the mean of the 9 days and so on).

During the Run-in Period and at the end of the Treatment Periods, the Pain NRS will be collected daily for 7 consecutive days following the assessment visit as described in the Schedule of Activities. For all other visits, the average pain for the preceding 24 hours prior to the visit will be captured by the Pain NRS for that day only.

8.1.3 Pressure pain threshold

Pressure pain threshold will be assessed by pressure algesiometry before dosing. Pressure algesiometry will be performed at 2 sites on the body: (1) the lateral forearm and (2) the contralateral anterior thigh.

8.1.4 Revised Fibromyalgia Impact Questionnaire

The FIQR is a 21-item questionnaire with a recall period of 7 days. The FIQR includes 3 domains: function, overall impact, and symptoms. Each item is based on an 11-point numeric rating scale. The FIQR will be completed by the participant during study visits.

8.1.5 Fatigue NRS

The Fatigue NRS is a numeric version of the VAS in which a respondent selects a whole number that best describes "How much fatigue have you experienced on average over the past 24 hours?" The 11-point Fatigue NRS ranges from 0 (no fatigue) to 10 (fatigue as bad as you can imagine). The Fatigue NRS will be completed by the participant at home/during study visits.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.2.1 Physical examination

For full and brief physical examinations, investigators should pay special attention to clinical signs related to previous serious illnesses, as well as signs and symptoms of infections.

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

A full physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, gastrointestinal (GI), and musculoskeletal systems. Weight and height will also be measured and recorded at Visit 0 and the SFU/EOS Visit with the study participant wearing light clothing and without wearing shoes.

A brief physical examination will include, at a minimum, assessments of the skin, respiratory system, cardiovascular system, and abdomen (liver and spleen).

8.2.2 Neurological examination

In addition to the Screening and EOT/EW Visits, a full neurological examination should be performed for any study participant who experiences severe and/or serious headache or suspected aseptic meningitis (see Section 10.13).

A full neurological examination will include: (1) General appearance, including motor activity and meningeal signs and, if indicated, the following assessments will be performed; (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 categories, including but not limited to: general (including level of consciousness, mental status, and meningeal signs), reflexes, muscle power, and coordination.

8.2.3 Vital signs

Oral, tympanic, and axillary temperature, pulse rate, and blood pressure will be assessed.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the study participant in a quiet setting without distractions (eg, television, cell phones). All measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs comprise systolic and diastolic BP, pulse rate, and temperature.

- At Visit 1, 2, 3, 4, 15, and 16, vital signs will be measured prior to IMP administration, at the end of the infusion (+5 min) and at 2 hours after the end of infusion (±15 min).
- At Visit 5, 6, 7, 17, 18, and 19, vital signs will be measured prior to IMP administration and 1 hour after the end of infusion (±15 min).
- From Visit 8 through Visit 14 and from Visit 20 through Visit 28, the vital signs will be measured approximately 15 minutes prior to IMP administration.
- At Screening, EOT/EW, and SFU/EOS Visits, vital signs will be taken only once during the visit.

8.2.4 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes before the recording.

The ECGs will be read locally. All ECG readings from an individual study participant should be read by the same reader, if possible. Findings will be recorded in the eCRF.

8.2.5 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the study participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the Schedule of Activities.

If laboratory values from non-protocol specified laboratory assessments performed at the laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the source data.

8.2.6 Suicidal risk monitoring

Study participants being treated with IMP should be monitored appropriately for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing IMP in study participants who experience signs of suicidal ideation or behavior.

Families and caregivers of study participants being treated with IMP should be instructed to monitor study participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be performed at the scheduled timepoints as described in the Schedule of Activities (Section 1.3).

8.3 Adverse events and serious adverse events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3). AEs will be reported by the study participant (or, when appropriate, by a caregiver, surrogate, or the study participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the study participant to discontinue study treatment or the study (see Section 7).

For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment-emergent SAEs will be published.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the EOS Visit at the time points specified in the Schedule of Activities (Section 1.3).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the CRF even if no study medication 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.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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 study medication), up to 30 days from the end of the study for each study participant, and to also inform study participants of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the study participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each study participant at subsequent visits/contacts. All SAEs and AESMs (as defined in Section 8.3.7) will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the study participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of study participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female study participants and, if indicated, female partners of male study participants will be collected after the start of study treatment and until 90 days after the final dose.

If a pregnancy is reported, the investigator must immediately inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

The study participant should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The study participant should not receive further doses of IMP.
- The study participant should return for an EW Visit scheduled as soon as possible, but no later than the next scheduled visit.
- The study participant must be withdrawn from the study (Section 7.2.1).
- An SFU or EOS Visit should be scheduled 6 weeks after the study participant has discontinued her study medication.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse events of special interest

An AE of special interest (AESI) 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.

For rozanolixizumab, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Hy's Law
  - Potential Hy's Law, defined as ≥3x ULN ALT or AST with coexisting ≥2xULN total bilirubin (35% direct bilirubin) in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the study participant.

This AESI will follow the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3).

8.3.7 Adverse events of special monitoring

An AE of special monitoring is a product-specific AE, adverse reaction, or safety topic requiring special monitoring by UCB.

For rozanolixizumab, AESMs that require immediate reporting (within 24 hours regardless of seriousness) to UCB are:

- Severe headache and/or serious headache

- Suspected aseptic meningitis

All AESM will follow the SAE recording and reporting procedures as indicated in Section 10.3 (Appendix 3) and the AESM recording and reporting procedures as indicated in Section 10.13 (Appendix 13).

Additionally, protocol guidance for management of hypogammaglobulinemia/infection and infusion and hypersensitivity reactions is provided in Section 10.14 (Appendix 14) and Section 10.15 (Appendix 15), respectively.

Although hypersensitivity reactions including infused-related reactions and anaphylaxis are not classified as AESM, these AEs will be monitored by the investigator. If such an event is suspected it should be managed according to the guidance provided in Section 10.15 (Appendix 15). Suspected anaphylactic reactions should be diagnosed using Sampson's Criteria (Sampson et al, 2006).

8.3.8 Anticipated serious adverse events

The anticipated SAEs in Table 8-1 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 8.3.1 and Appendix 3 (Section 10.3).

Table 8-1: Anticipated serious adverse events for FMS population

MedDRA System Organ Class	MedDRA Preferred Term
Psychiatric disorders	Abnormal behavior, anxiety, cognitive disorder, confusional state, psychotic behavior, sleep disorder and disturbances
Gastrointestinal disorders	Abdominal pain
General disorders and administration site conditions	Pain
Nervous system disorders	Headache

MedDRA=Medical Dictionary for Regulatory Activities

8.4 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 study medication so that investigators, clinical study participants, regulatory authorities, and IECs will be informed appropriately and as early as possible.

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

In addition, an SMC will be responsible for monitoring safety data during the study (Section 9.7.2). A detailed description of the SMC composition, processes, and responsibilities will be provided in a separate SMC charter.

As appropriate for the stage of development and accumulated experience with the study medication, 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.

8.5 Treatment of overdose

Any dose increase of 10% or greater from the assigned dose for each administered dose of IMP per week should be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

1. Contact the medical monitor immediately.
2. Closely monitor the study participant for any AE/SAE or laboratory abnormalities for at least 5 days.
3. Obtain a plasma sample for PK analysis and IgG (total and subclasses) within 3 days from the date of the overdose if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the study participant.

8.6 Pharmacokinetics and immunogenicity

Venous blood samples will be collected for measurement of plasma concentrations of rozanolixizumab and the detection of ADA as specified in the Schedule of Activities (Section 1.3).

A sample will be taken for the purpose of assay characterization (eg, ADA cutpoint). For study participants withdrawing from the study, a sample should be taken for ADA detection upon his/her EW Visit. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time of each sample will be recorded in the eCRF.

Samples will be used to evaluate the PK of rozanolixizumab or detection of ADA and may be used for establishing the assay parameters. Samples collected for analyses of rozanolixizumab concentration may also be used to evaluate safety and efficacy aspects related to concerns arising during or after the study.

Study participant confidentiality will be maintained. At visits during which plasma/serum samples for the determination of multiple aspects of rozanolixizumab will be taken, one sample of sufficient volume can be used.

Samples for ADA analysis may be stored for a maximum of 20 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to rozanolixizumab.

Instructions pertaining to sample collection, processing, storage, labeling and shipping are provided in the Laboratory Manual for this study. These samples will be tested by the sponsor or the sponsor's designee.

8.7 Pharmacodynamics

Venous blood samples will be collected at time points specified in the Schedule of Activities (Section 1.3) for measurement of total serum IgG and subclass IgG concentrations.

For all PD assessments, samples will be collected predose. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the Laboratory Manual.

8.8 Genetics

Venous blood samples for potential genetics analyses are part of this study and are described in Appendix 5 (Section 10.5).

8.9 Biomarkers

Venous blood samples will be collected to measure IgG binding as an exploratory endpoint; this assay is described in Section 8.9.1. Timing of these assessments is provided in the Schedule of Activities (Section 1.3).

Biomarker results will be reported separately from the CSR for this study unless stated otherwise.

Collection of samples for potential future biomarker research to address questions based upon evolving science (including companion/complementary diagnostic and general assay development/optimization and/or mechanism of action or disease exploration) forms part of the study objectives (where biomarkers investigated can include, but are not limited to, DNA, RNA, protein, metabolites, and cells). Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

The following samples will be collected from all study participants and stored to support potential future biomarker research. These samples are a required component of the protocol as specified in the Schedule of Activities (Section 1.3):

- Venous blood sample for DNA isolation for genetic/epigenetic analysis.

Additional biomarker samples:

- For exploratory biomarkers, 10mL blood samples will be collected for future research into biomarkers of some or all of the following: diagnosis, pharmacodynamic effects, disease monitoring, response prediction, prognosis, and/or safety.

If not used immediately, the samples are planned to be stored at -80°C for up to 20 years to allow for future exploratory analyses. These samples will be used to further the understanding of FMS and related disease conditions, and/or how biomarkers (including genetic variation [Section 10.5]) may affect response or safety, or be affected by treatment with rozanolixizumab

and comparators, and/or background products and concomitant medications in the treatment of FMS.

8.9.1 In vitro IgG binding assay

At Visit 3 (Day 1), 80mL of whole blood will be collected. At subsequent scheduled assessments, 10mL of whole blood will be collected for the determination of IgG binding in an exploratory in vitro cell assay. These data will be collected for an exploratory endpoint. If not used immediately, the samples are planned to be stored at -80°C for up to 20 years to allow for future exploratory analyses.

8.9.2 Immunology

Blood samples for immunological testing are required and will be collected from all study participants in this study as specified in the Schedule of Activities (Section 1.3) for measurement of:

- Serum complement (C3, C4)
- Plasma complement (C3a, C5a)

Samples for serum complement (C3, C4) and plasma complement (C3a, C5a) are collected predose at Visit 3 (Day 1) for all study participants. In study participants who experience an infusion reaction or hypersensitivity reaction at site, samples should also be taken 2 hours post event and 4 hours post event, or otherwise as soon as possible but prior to the next dosing. In study participants who experience severe and/or serious headaches or suspected aseptic meningitis, additional blood samples should also be taken 4 hours after the onset of the event; or otherwise as soon as possible within 72 hours, but prior to next dose. These samples may be tested for exploratory biomarkers such as proteins and metabolites to evaluate their association with the cause, progression, and appropriate treatment of fibromyalgia. Details on genetic analysis are described in Appendix 5 (Section 10.5).

8.10 Health economics

Health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

9.1 Definition of analysis sets

The following analysis sets have been defined for this study:

All Study Participants Set: The All-Study Participants Set (ASP) consists of all study participants that sign the informed consent form. This set includes screening failures.

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

Safety Set – as Randomized: The Safety Set as randomized (SS-r) consists of all study participants who received any study treatment, including during the run-in period. The study participants will be analyzed according to the randomized treatment groups during the specific treatment period.

The SS-r will be used for production of safety analysis by visit, as well as demographics and immunogenicity analyses.

Safety Set – as Treated: The Safety Set as treated (SS-t) consists of all study participants who received any study treatment including during the run-in period. If a participant received at least one dose of active treatment during a given treatment period, participant will be allocated to active treatment group at the given treatment period and any period thereafter in the SS-t as treated analysis set (most conservative approach). For analysis purposes, the SS-t will be used for tabulating AEs by treatment where AEs are assigned to the active treatment group based on the onset of AE relative to the first dose of active treatment.

The SS-t will be used for safety overall analysis.

Full Analysis Set: The Full Analysis Set (FAS) consists of all study participants in the SS-r who have a Baseline value and at least one post-Baseline efficacy endpoint assessment. Study participants who receive at least one dose of treatment not per randomization schedule will be excluded from the FAS.

This analysis set will be used for the summaries and analyses of primary, secondary, and exploratory efficacy variables data.

Pharmacokinetic Set: The Pharmacokinetics Set (PKS) consists of all study participants in the SS-r who have at least one dose of active IMP and at least one measurable PK concentration including below limit of quantification (BLQ). The PKS will be used for all PK summaries and analyses. If a study participant in the PKS is missing individual time points or are otherwise unobservable, they will be included in the PKS but those time points will be omitted from the PK summaries, as appropriate.

Pharmacodynamic Set: The Pharmacodynamic set (PDS) is a subset of the FAS, consisting of those study participants who had no important protocol deviations affecting the PD variables, as confirmed during a pre-analysis review of the data prior to database lock, and who had at least one valid post-Baseline measurement of serum total IgG and IgG subclasses. The final PDS will be identified after database lock to confirm availability of at least one post-Baseline valid measurement due to blinding. The PDS will be used for all PD summaries and analyses.

Participants who had important protocol deviations affecting the relevant efficacy/PK/PD variables, as confirmed during a pre-analysis review of the data prior to database lock might be excluded from relevant analyses. Such exclusions will be described in tables, figures, and listings (TFLs) and/or the CSR.

9.2 General statistical considerations

All TFLs, including statistical evaluation, will be using SAS version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). Analysis data will adhere to Clinical Data Interchange Standards Consortium (CDISC) guidance documents for Analysis Data Model (ADaM) and follow the UCB interpretation.

The Baseline for each variable will be taken as the value measured prior to, but closest to, the treatment on Day 1. This may be measured on Day 1 prior to treatment or during Weeks -1 or -2 depending on the endpoint.

Summary TFLs will be presented by sequence and by period (Period 1, Period 2 or SFU), as well as by treatment, and period. For continuous variable summaries for the study participant-level difference between Period 2 and Period 1 by sequence will also be presented. Listings will be presented by study participant and treatment sequence. In addition, summaries by visit may be presented where appropriate.

Data will also be summarized graphically by sequence, treatment, and time as appropriate. All clinical outcome data will be listed, and additional exploratory statistical analysis may be conducted.

1) Categorical Variables

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise stated, the denominator for the percentage calculations will be based on the number of study participants in the respective analysis set, treatment group, visit and timepoint (as applicable) with non-missing data

2) Continuous Variables

Summary statistics will be presented for continuous variables including number of study participants (n), mean, standard deviation (SD), median, minimum and maximum. Geometric mean (geoMean), geometric coefficient of variation (geoCV) and 95% CI for the geoMean will also be presented in the summaries of rozanolixizumab concentration data.

When reporting descriptive statistics, the following rules will apply in general:

- Mean (arithmetic and geometric), SD and median will use 1 decimal place more, or 1 significant figure more — than the original data
- Confidence intervals will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the value around which the confidence interval is constructed
- Coefficient of variation will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value
- If no study participants have data at a given time point, then only n=0 will be presented. If n<3, then only the n, minimum and maximum will be presented. If n=3, then only n, minimum, median and maximum will be presented. The other descriptive statistics will be left blank.

9.3 Planned efficacy/outcome analyses

9.3.1 Analysis of the primary efficacy/primary endpoint

The primary endpoint is the average BPI-SF interference score after 12 weeks of double-blind treatment, adjusted for Baseline score (see also Section 4.1 on Study Design).

For the purpose of analysis, there will be three treatment groups: placebo, rozanolixizumab for up to 12 weeks, or rozanolixizumab given beyond 12 weeks [Sequence 1, Period 2]. The main difference of interest is that between rozanolixizumab for up to 12 weeks and placebo.

In order to estimate the mean difference in the average BPI-SF interference scores after 12 weeks of treatment, the BPI-SF interference scores measured at Visits 7, 11, 15, 19, 23, and 27 will be modelled using a longitudinal linear mixed effect model (LMM). The pre-dose value taken at the first visit of Period 2 (Visit 15) will be used as the measure of treatment effect after 12 weeks of treatment for Period 1, while the pre-dose value taken at run-out Visit 27 will be used as the measure of treatment effect after 12 weeks of treatment for Period 2.

Treatment will be a fixed effect and the study participant ID will be included as a random effect. The following additional fixed effects will be included:

- treatment period (period 1 or period 2)
- assessment number within the period (1st, 2nd, or 3rd assessment corresponding to Visit 7, 11, and 15 for Period 1, or Visit 19, 23, or 27 for Period 2)
- an interaction of treatment by assessment number
- an interaction of treatment period by assessment number

The following covariates will also be included:

- BPI-SF interference scores at Baseline (taken at Visit 3, prior to dosing)

Other covariates may be included if considered appropriate.

The model result of interest will be the marginal estimated mean treatment difference in average BPI-SF after 12 weeks of treatment.

All study participants in the FAS with Baseline BPI-SF score and one or more post-Baseline assessments will be included in the model.

As secondary analysis strategy, each period will be analyzed separately using a mixed effect model, with study participant as random effect and treatment, assessment number, treatment by assessment number interaction, Baseline, Baseline by assessment number and site as fixed effects.

For Period 1, there will be 2 treatment groups: placebo and rozanolixizumab. For Period 2, there will be 3 as defined for the primary analysis. Additional analyses will be described in the SAP.

9.3.1.1 Estimand/ICE handling rationale and impact on the study

The primary estimand (as described in Section 3) has been chosen to best reflect the goal of identifying a treatment effect of rozanolixizumab for FMS. FMS is a highly prevalent (2 to 3% of adult population) and complex syndrome primarily characterized by the presence of chronic widespread pain, but which also incorporates a wide range of other symptoms adversely impacting on function and quality of life such as severe fatigue, cognitive dysfunction, and sleep disturbances (Häuser et al, 2015). The BPI-SF interference score measures the impact of pain across seven domains of daily life experience and was considered as being suitable for measuring the effect of a treatment and the functional interference experienced by patients.

The main ICE of interest is treatment discontinuation. The chosen Hypothetical strategy of ICE handling whereby data following discontinuation is excluded from analysis reflects the focus on demonstrating efficacy rather than effectiveness, and thus estimating the treatment effect in an ideal condition where such events would not occur.

9.3.2 Secondary efficacy analyses

Analyses of the following secondary efficacy endpoints will be conducted using an LMM in the same way as for the primary estimand analysis, using the same ICE strategies:

- FIQR score after 10 weeks of treatment
- Mean 7-day average pain score (Pain NRS) after 10 weeks of treatment
- Mean 7-day fatigue score (Fatigue NRS) after 10 weeks of treatment

However, for these endpoints, the value taken at/subsequent to Week 11 (Visit 13) will be used as the measure of treatment effect after 10 weeks of treatment for Treatment Period 1, while the value taken at/subsequent to Week 23 (Visit 25) will be used as the measure of treatment effect after 10 weeks of treatment for Treatment Period 2. The data collected at Run-in Visit 2, Week -1, will be used as Baseline values. Note that for the Pain NRS and Fatigue NRS, the subject will be asked at Visit 13 and Visit 25 to fill in their diary for that day and every day for the following 6 days, and the average of these 7 measurements will be taken as the endpoint.

For the BPI-SF interference scores and these scores, the mean scores will be plotted over time for each sequence. For the BPI-SF interference score, the values after 12 and 24 weeks from Sequence 1 and 3 will be analysed to estimate treatment effects after 24 weeks and compare this with 12 weeks. The data will be analysed using a mixed effect model with a random study participant effect and fixed effects for treatment, week and treatment by week interaction, Baseline and Baseline by week interaction. The same ICE strategies will be used as in the 12-week analysis.

9.3.3 Other efficacy/other outcome analyses

As a secondary analysis strategy, dropouts will be imputed as if they belong to the placebo group, under the conservative assumptions that dropouts are due to a lack of drug efficacy. Details on the imputation will be provided in the SAP.

Exploratory endpoints will be summarized and represented graphically where relevant. Due to the exploratory nature of this study, additional analyses may be completed to further understand any findings.

9.4 Planned safety and other analyses

9.4.1 Safety analyses

All safety variables will be analyzed by descriptive methods and presented by sequence and by period (Period 1, Period 2, or SFU) showing the treatment when the safety event occurred. In addition, events will be summarized by treatment and period. Any events in the SFU Period from sequence 1 and 2 will be tabulated under active treatment.

- Frequency and intensity of TEAEs from Baseline to SFU, and
- TEAEs leading to withdrawal of IMP

will be the safety variables analyzed in this study and will be included in the summary tables.

The overall frequency during the study period will be presented for each of the safety variables, as well as separately by System Organ Class, high level term, and preferred term (Medical Dictionary for Regulatory Activities [MedDRA®]). The data will be displayed as number of

study participants experiencing the event, percentage of study participants, and number of events. Additional tables will summarize the safety variables by maximum intensity, by intensity, and by relationship to study drug.

Laboratory evaluations and vital signs will be analyzed over time. Possibly clinically significant treatment-emergent abnormalities will be listed and summarized by visit for each treatment group.

9.4.2 Other analyses

9.4.2.1 PK analyses

Plasma concentration data of rozanolixizumab 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 geoCV (assuming log-normally distributed data). Values below the 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). However, minimum and maximum will always be reported even if <2/3 are quantifiable; minimum should be reported as value of LLOQ where it is not above this value.

9.4.2.2 Immunogenicity analyses

A tiered ADA approach will be used for this study. Samples will first be evaluated in the screening assay using a false positivity rate of 5% (reported as negative screen or positive screen), followed by analysis of screened positive samples in the confirmatory assay (which is a drug depletion assay) to confirm the true positivity of the samples (reported as negative immunodepletion or positive immunodepletion). Samples that are confirmed as positive will be evaluated in a titration assay to quantify the ADA level and will be reported as titer (reciprocal dilution factor including minimum required dilution). For ADA positive immunodepletion samples (or subset of), further characterization for neutralizing ADA potential in vitro will be performed. Results will be presented in a listing and as summary tables with full details provided in the SAP.

9.4.2.3 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 total IgG and IgG subclass concentrations.

9.4.2.4 Immunological analyses

All immunologic variables including serum (C3 and C4) and plasma (C3a and C5a) complement levels will be summarized by treatment group and visit using descriptive statistics.

9.5 Handling of protocol deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data (primary or key secondary outcomes) or that may significantly affect a subject's rights, safety, or well-being.

The criteria for identifying such protocol deviations will be defined within the IPD specifications document.

Important protocol deviations will be categorized as follows:

- Inclusion/exclusion criteria deviations
- Incorrect treatment or dose administered
- Procedural non-compliance
- Prohibited concomitant medication use
- Withdrawal criteria deviation

All IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. At least one Data Evaluation Meeting (DEM) will be performed prior to the final database lock after all data have been verified/coded/entered into the database. All protocol deviations will be discussed at the DEM and decisions made on whether they should be considered important or not. Important protocol deviations will be identified and classified by the deviation types in the IPD document.

IPDs identified at the DEM will be listed and summarized by treatment sequence and period for the SS and will include the deviation type and description.

9.6 Handling of dropouts or missing data

In general, there will be no imputation of missing data. Handling of missing or partial dates and/or times for safety assessments will be described in the SAP.

9.7 Planned interim analysis and data monitoring

9.7.1 Interim analysis

After approximatively 30 study participants have been randomized and these study participants have completed their 2 treatment periods, an interim analysis may be conducted where the primary endpoint and some of the secondary and exploratory endpoints may be analyzed. The timing of the interim analysis may be changed depending on recruitment rates to allow for an earlier analysis. It may also be decided not to perform the interim analysis. The purpose of this interim analysis is to provide results to trigger regulatory discussions, aid Phase 3 planning, and investigate some of the exploratory endpoints. The outcome of this interim analysis may lead to stopping the study for futility if there is a >75% posterior probability that the reduction in mean BPI-SF interference score is below 0.5 when treated with rozanolixizumab compared with placebo or stopping for efficacy if >90% posterior probability that the reduction in mean score is greater than 1 (using a Bayesian interpretation of the results with a non-informative prior). If a futility or efficacy decision is not reached, the study will continue. The interim decision criteria will be described in the SAP for the interim and in the interim charter.

In addition, at the interim analysis, the observed dropout rate and observed within/between variability will be evaluated, and a recommendation on whether to adjust the overall sample size may be provided.

The interim analysis will be completed by an independent, internal, Interim Analysis Group (IAG) who will be unblinded to the randomization and treatment allocation. The study team will remain blind to the treatment allocation until database lock at the end of the study. The composition of the IAG will be specified in an IAG charter.

The recommendation of the IAG will be presented to selected senior stakeholders who will make the final decision of stopping or continuing the study, and whether to adjust the sample size. The IAG charter will specify the senior stakeholders to be informed, and will also contain a communication plan setting out what information will be presented to the senior stakeholders, to the wider study team and what will be presented to other audiences.

9.7.2 Data monitoring

An internal SMC will regularly review (approximately every 3 months, with the option to adapt the frequency based on recruitment rates) the available blinded safety data. If required, a "closed session" may be instituted to allow the review of unblinded data.

If there are safety concerns during the SMC session, an ad hoc closed SMC meeting may be called if revealing treatment allocation would aid decision making. The members of closed SMC sessions will be restricted and specified in the SMC charter.

The first SMC review will be conducted approximately 2 months after randomization of the first study participant, or when 25% of the study participants are randomized, whatever comes first. The SMC will decide if the study is safe to continue.

In addition, a Program Independent Data Monitoring Committee (PiDMC) is in place to evaluate data over the entire rozanolixizumab clinical development program as this molecule is being investigated in several indications. Details of the PiDMC composition, procedures, and responsibilities are detailed in the PiDMC charter.

9.8 Determination of sample size

The operating characteristics of the design were evaluated using a simulation approach and based on estimates of variability and treatment effects from fibromyalgia studies reported in clinicaltrials.gov and other papers. BPI-SF was used consistently in duloxetine studies. A sample size of 48 completed study participants gives more than 80% probability that if the true difference of the mean BPI-SF interference score after 12 weeks of treatment on rozanolixizumab compared with placebo was 1.0 units or better, then the comparison would pass a 1-sided 10% significance test. This assumes a between-study participant standard deviation component for the BPI-SF interference score of 1.74 units, and a within-study participant SD of 1.5 units (a total between-study participant SD of 2.3 units) after accounting for the Baseline BPI-SF interference score. It is assumed that the dropout rate will be 25% also estimated for the study results. Through simulations using the design, it was estimated that 60 study participants starting the study would achieve the desired power.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IEC, as defined in local regulations, International Council for Harmonisation (ICH)-Good Clinical Practice (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 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, ICF, IB, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other study participant-related documents to be used for the study to the IEC for its review and approval.

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

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

The investigator will not make any changes in the study or study conduct without IEC approval, except where necessary to eliminate apparent immediate hazards to the study participants. 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 IEC as allowed.

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

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

10.1.3 Informed consent process

Study participant's informed consent 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 study participant in both oral and written form by the investigator (or designee). Each study participant will have the opportunity to discuss the study and its alternatives with the investigator.

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

If the ICF 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 ICF by the IEC and use of the amended form.

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

10.1.4 Data protection

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

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IEC, or representatives of regulatory authorities will be allowed to review that portion of the study participant'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 study participant's study participation, and autopsy reports for deaths occurring during the study).

The study participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the study participant.

The study participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees structure

As described in Section 9.7.2, an internal SMC will be established to regularly review available blinded safety data, and if required, a SMC "closed session" may be instituted to allow the review of unblinded data.

An internal SMC will be established and will comprise key sponsor personnel and coordinating investigator at the CRO. The SMC will operate in the setting of a PiDMC that has been established as an independent panel of external experts whose principal responsibilities are to review and evaluate on a regular basis pooled cumulative data overall across the rozanolixizumab program and by indication. The PiDMC has access to unblinded data with appropriate safeguards in place for maintaining the blind with respect to the investigators, site monitors and UCB Rozanolixizumab Program Team (including extended members and study teams). The operation of the SMC and PiDMC and the roles and responsibilities of committee members are described in their respective charters.

10.1.6 Data quality assurance

All study participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of study participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

All essential documents must be retained by the investigator for the minimum retention period mandatory under the applicable local laws and regulations. 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.

Quality tolerance limits may be established for the study using parameters related to patient safety reporting and reliability of study results. If limits are stablished, the parameters will be monitored throughout the study to identify systematic issues. Parameters used, parameter values, important deviations from the quality tolerance limits, and actions taken will be summarized in the clinical study report.

10.1.6.1 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 electronic CRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

10.1.7 Source documents

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 CRFs 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, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

The following data will be recorded directly in the electronic device and will not appear in a source document as defined above:

- Pain NRS
- BPI-SF
- FIQR
- Fatigue NRS

A list of source data will be provided in a separate document (Source data agreement).

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 study participant'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).

10.1.8 Study and site closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of study participants by the investigator
- Discontinuation of further study medication development

10.1.9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of study participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded, unless a safety alert requires a clinical review of the study participant.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	Urea	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total protein[b] Albumin[b]
	Random Glucose	Calcium	Alkaline phosphatase	
	Lactate dehydrogenase (LDH)	C-reactive protein (CRP)	Low-density lipoprotein (LDL) High-density lipoprotein (HDL) Total cholesterol Triglycerides	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in WOCBP only) • Serum human chorionic gonadotropin pregnancy test (as needed for WOCBP)			

Laboratory Assessments	Parameters
	• Serology testing for Hepatitis B surface antigen, Hepatitis C virus antibody, and human immunodeficiency virus. • IGRA TB test (if applicable, as this test is optional) All study-required laboratory assessments will be performed by a central laboratory, with the exception of: – Urine pregnancy dipstick test[c] – Urine drug screen

eCRF=electronic case report form; IEC=Independent Ethics Committee; IGRA= interferon gamma release assay INR=international normalized ratio; RBC=red blood cell; SAE=serious adverse event; TB=tuberculosis; ULN=upper limit of normal; WBC=white blood cell; WOCBP=woman of childbearing potential
The results of each test must be entered into the eCRF.
[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 10.6 (Appendix 6). All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
[b] The results of these assessments will not be reported to investigative sites or other blinded personnel until the study has been unblinded, unless a safety alert requires a clinical review of the study participant.
[c] Urine testing will be standard for the protocol unless serum testing is required by local regulation or IEC.

Investigators must document their review of each laboratory safety report.

Other protocol-required laboratory assessments

Laboratory Assessments	Parameters
Other laboratory assessments	• Blood sampling for PK of rozanolixizumab[a] • Blood sampling for DNA and RNA analysis[b] • Serum complement (C3, C4), and plasma complement (C3a, C5a)[b] • Total IgG[a] • IgG subclasses[a] • Anti-drug antibodies[a] • Blood sampling for exploratory biomarker analysis[b]

C3=complement component 3; C3a=complement component 3a; C4=complement component 4; C5a=complement component 5a; Ig=immunoglobulin; PK=pharmacokinetics
[a] The results of these assessments will not be reported to investigative sites or other blinded personnel until the study has been unblinded, unless a safety alert prompts a clinical review of the study participant.
[b] The results of these assessments will not be reported to investigative sites.

10.3 Appendix 3: Adverse events – Definitions and procedures for recording, evaluating, follow-up, and reporting

Definition of AE

AE definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the study participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the study participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical events: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the study participant's medical records to UCB in lieu of completion of the UCB/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all study participant identifiers, with the exception of the study participant number, will be redacted on the copies of the medical records before submission to UCB.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the investigator must be mild, moderate, or severe.

Assessment of causality

- The investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to UCB. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 study participant is lost to follow-up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a study participant dies during participation in the study or during a recognized follow-up period, the investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE reporting to UCB via an electronic data collection tool

- The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the UCB by telephone.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

SAE reporting to UCB via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to UCB; see SERIOUS ADVERSE EVENT REPORTING.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the study participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception guidance

Female participants

Female study participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Table 10-1: Highly effective contraceptive methods[a]

Highly effective contraceptive methods that are user dependent[b] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[c]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the study participant.
NOTES: a) In case of newly started contraception pills/IUDs, the investigator should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as when these newly started methods would become effective. b) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for study participants participating in clinical studies.

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed as specified in the Schedule of Activities (Section 1.3) and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 25mIU/mL will be performed.

Female participants who become pregnant

- Any female study participant who becomes pregnant while participating in the study will be withdrawn from the study.
- The investigator will collect pregnancy information on any female study participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a study participant's pregnancy. The study participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the study participant and the neonate and the information will be forwarded to the sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study medication by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Male Participants With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive rozanolixizumab. If the participant is later found to be on placebo, then pregnancy data collection can stop.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within one working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 Appendix 5: Genetics

Use and analysis of DNA

- Genetic variation may impact a study participant's response to study medication, susceptibility to, and severity and progression of disease. Variable response to study medication may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IEC allow, a blood sample will be collected for DNA analysis from consenting study participants.
- DNA samples will be used for research related to rozanolixizumab and/or FMS and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to rozanolixizumab /or interventions of this drug class and FMS. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers across the entire genome (as appropriate), but only as they relate to the aims of further understanding the response to rozanolixizumab and FMS.
- The samples may be analyzed as part of this study alone or as part of a multi-study assessment of genetic factors involved in FMS and the response to rozanolixizumab or study medications of this class, and to understand the disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on FMS continues but no longer than 20 years or other period as per local requirements.

10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments

Study participants with PDILI must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants 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 study medication discontinuation and/or study participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB study physician and the investigator for study participants who have ALT >3xULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal laboratory values).

Phase 2 liver chemistry stopping criteria are designed to assure study participant safety and to evaluate liver event etiology. They are presented in the tables below.

Table 10-2: Phase 2 liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria	
ALT-absolute	ALT ≥5x ULN
ALT increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[b]	ALT ≥3xULN **and** INR >1.5, if INR measured
Cannot monitor	ALT ≥3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[c]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested actions and follow-up assessments	
Actions	**Follow-up assessments**
• **Immediately** discontinue study medication. • Report the event to UCB **within 24 hours.** • Complete the liver event CRF, and complete an SAE data collection tool if the event also met the criteria for an SAE.[b] • Perform liver chemistry follow-up assessments.	• Viral hepatitis serology[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend • Obtain blood sample for PK analysis as soon as feasible after the most recent dose[e]

Table 10-2: Phase 2 liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria	
• Monitor the study participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**). • **Do not restart/rechallenge** study participant with study medication. • Permanently discontinue study medication, and continue study participant in the study for any protocol-specified follow-up assessments • Consider the need for a toxicology screening **MONITORING:** **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Repeat liver chemistry tests (include ALT, AST, ALP, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor study participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to Baseline. • A specialist or hepatology consultation is recommended. **If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, ALP, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor study participants weekly until liver chemistry abnormalities resolve, stabilize, or return to Baseline.	• Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the AE eCRF • Record use of concomitant medications (including acetaminophen [or paracetamol], herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF • Exclude pregnancy **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in study participants with definite or likely acetaminophen use in the preceding week [James et al, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRFs.

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; CRF=case report form; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PK=pharmacokinetic; SAE=serious adverse event; ULN=upper limit of normal

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study medication if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if

Table 10-2: Phase 2 liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria
serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury. [b] All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required and the stated threshold value will not apply to study participants receiving anticoagulants. [c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia). [d] Includes: hepatitis A IgM antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. [e] PK sample may not be required for study participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the dose of study medication prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the study participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the IMP Handling Manual.

Table 10-3: Phase 2 liver chemistry increased monitoring criterion with continued study medication

Liver chemistry increased monitoring criterion and follow-up	
Criterion	**Actions**
ALT ≥3x ULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the UCB medical monitor within **24 hours** of learning of the abnormality to discuss study participant safety. • Study participant can continue study medication. • Study participant must return weekly for repeat liver chemistry tests (ALT, AST, ALP, bilirubin) until the abnormalities resolve, stabilize or return to Baseline. • If at any time, the study participant meets liver chemistry stopping criteria, proceed as described in Section 7.1.1. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor study participants twice monthly until liver chemistry tests resolve, stabilize, or return to Baseline.

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal

10.7 Appendix 7: Medical device AEs, adverse device effects, SAEs, and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

AChR	anti-acetylcholine receptor
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AESM	adverse event of special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BPI-SF	Brief Pain Inventory-short form
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
COVID-19	coronavirus disease 2019
CNS	Central nervous system
CPM	Clinical Project Manager
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicidality Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DEM	Data Evaluation Meeting
DIAM	Drug-induced aseptic meningitis
DRG	dorsal root ganglia
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EW	Early Withdrawal
FAS	Full Analysis Set
FcRn	neonatal Fc receptor
FIQR	Revised Fibromyalgia Impact Questionnaire

FMS	fibromyalgia syndrome
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
geoCV	geometric CV
geoMean	geometric mean
GI	gastrointestinal
gMG	generalized myasthenia gravis
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IAG	Interim Analysis Group
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon gamma release assay
IMP	investigational medicinal product
IND	Investigational New Drug
IPD	important protocol deviation
IRT	interactive response technology
ITP	immune thrombocytopenia
LLOQ	lower limit of quantification
LMM	linear mixed effect model
LTBI	latent tuberculosis infection
MDRD	Modification of Diet in Renal Disease
MG	myasthenia gravis
MG-ADL	myasthenia gravis-activities of daily living
MOG	myelin oligodendrocyte glycoprotein antibody
NRS	numeric rating scale
NTM(B)	nontuberculosis mycobacteria
OTC	over-the-counter

PD	pharmacodynamic(s)
PD-PPS	Pharmacodynamic Per-Protocol Set
PDILI	potential drug-induced liver injury
PiDMC	Program Independent Data Monitoring Committee
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PLEX	plasma exchange
prn	(pro re nata) as needed)
PRO	patient-reported outcome
PV	pemphigus vulgaris
QTcF	QT interval corrected using Fridericia's formula
QW	once weekly
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SFU	Safety Follow-up
SMC	Safety Monitoring Committee
SoC	standard of care
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TFL	Tables, figures, and listings
ULN	upper limit of normal
VAS	visual analog scale
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol amendment history

10.11.1 Amendment 2 (29 Nov 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The reason for this amendment is to update safety information in line with the revised IB dated 06 September 2022.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities 1.3.1 Additional study assessments 2.3 Benefit/Risk Assessment 7.1.2 Other permanent discontinuation criteria 7.1.4 Temporary discontinuation 10.2 Appendix 2: Clinical Laboratory Tests 8.2.2 Neurological examination 8.3.7 Adverse events of special monitoring 8.9.2 Immunology 10.13 Appendix 13 Management of Adverse Event of Special Monitoring	Removal of the assessments related to the former AESM of severe GI disorders and opportunistic infections. Addition of assessments for the new AESM of suspected aseptic meningitis. Removal of the headache questionnaire (formerly Appendix 13) and management of severe diarrhoea (formerly Appendix 15). New Appendix 13 detailing the management of the AESM (severe/serious headache, and suspected aseptic meningitis)	The accumulated safety data on rozanolixizumab led to an update of the adverse events requiring special monitoring. As of the cut-off date of the IB (13 Jul 2022), the following SAEs Headache and Meningitis Aseptic (PT terms) suggest a possible causal relationship to rozanolixizumab; based on both their temporal association with IMP infusion (primarily initial infusion) and given the events have occurred more than once. There is a change in the headache reporting process such that severe and/or serious headache will be reported via the SAE reporting process.
1.1 Synopsis	The maximum study duration per study participant was updated to 37 weeks.	Correction.
1.3 Schedule of activities, Table 1-1	The visit window for Run-In Visit 1 was removed.	A visit window is not required as participants can enter the study once their eligibility is confirmed.
	A visit window of ±2d was added to Visit 3	To allow clinical flexibility.
	Footnote b was updated to remove reference to the local laboratory.	The CRO does not have local laboratory facilities and therefore all tests must be performed at the central laboratory.
	Footnote e was updated to include Visit 2.	Added for completeness.

Section # and Name	Description of Change	Brief Rationale
	Footnote m was added to "Serum complement (C3, C4) and plasma complement (C3a, C5a)."	Added for completeness.
2 Introduction	Updates to text describing the results of completed studies in the rozanolixizumab clinical development program.	Update in line with studies status at the time of this amendment, and to reference the most recent information on exposure to rozanolixizumab.
2.3 Benefit/Risk Assessment	Revised text on most common adverse drug reactions, potential risks, and AESM.	To update the list of most common adverse drug reactions, potential risks, and adverse events of special monitoring.
4.4 End of study definition	The SFU/EOS visit was corrected to 5 weeks after the Run-out Period.	Correction.
5.1 Inclusion criteria	Inclusion criterion #2 (now #2a) was updated to add "or with assistance of the caregiver." Inclusion criterion #7 was removed.	To improve clarity and remove redundancy across Inclusion criteria #2 and #7.
	Inclusion criterion #3 (now #3a) was modified. "Prior confirmed" related to fibromyalgia diagnosis was removed. "Score" was added after "BPI-SF interference."	The criterion has been updated to ensure the study participant meets the American College of Rheumatology 2016 diagnosis criteria at Screening. "Score" was added for clarity.
	Inclusion criterion #5 (now #5a) was updated to remove male contraception requirements.	To update male contraception requirements with current guidelines, after completion of the required reproductive toxicity studies and considering that rozanolixizumab has not genotoxic potential and potential exposure through seminal fluid is expected to be negligible.
5.2 Exclusion criteria	Exclusion criterion #8 (now #8a) was updated to add reference to the MDRD study equation for assessment of renal impairment.	To ensure consistency across study sites and as requested by the agency.
	Exclusion criterion #30 (now #30a) was updated to remove "Baseline."	Clarification.
6.5.1 Permitted concomitant treatments	The standard of care medications for FMS text was updated.	To provide clarity and align with local prescribing practices.

Section # and Name	Description of Change	Brief Rationale
(medications and therapies)		
7.1.4 Temporary discontinuation of IMP	Point #1 was updated to remove <1.0g/L and add "serum total IgG reported below the LLOQ (currently 1.09g/L)"	To accurately reflect the lower limit of quantification of the assay
	Point #1 was updated to remove <1.0g/L and add "serum total IgG reported between the LLOQ (currently 1.09g/L)"	
	Update of the temporary discontinuation in relation to COVID-19.	Update to adapt the withdrawal criteria to the evolution of the medical practices and local guidelines with regards to COVID management.
8.1 Efficacy assessments	Section 8.1.4 Patient-reported outcomes was removed. Subsequent subsections were renumbered.	Clarification.
8.1.1 Brief Pain Inventory-Short Form	Paragraph #1 was updated to add "including dosing on dosing days."	Clarification.
8.1.5 Fatigue NRS	Text was added to clarify that the Fatigue NRS can be completed by the patient at home.	Clarification.
8.2.1 Physical examination	Reference to Visit 1 was updated to Visit 0.	Clarification.
8.2.2 Neurological examination	Posture was removed.	During the time of eCRF development, posture was not available in the data standards, however, other variables included on the eCRF capture enough information.
8.2.3 Vital signs	Visit 2 was added to the vital signs bulletpoint.	Updated for consistency to schedule of activities.
8.2.5 Clinical safety laboratory assessment	Reference to local laboratory was removed.	The CRO does not have local laboratory facilities and therefore all tests must be performed at the central laboratory.
8.2.6.2 Tuberculosis signs and symptoms questionnaire	The text regarding the TB questionnaire was updated.	To clarify application of the TB questionnaire for the study in assessment and management of tuberculosis and tuberculosis risk factors.

Section # and Name	Description of Change	Brief Rationale
8.2.6.3 Tuberculosis assessment by IGRA	References to local laboratory IGRA tests were removed.	The CRO does not have local laboratory facilities and therefore all tests must be performed at the central laboratory.
8.3.3 Follow-up of AEs and SAEs	"Non-serious" was deleted.	Clarification.
8.3.8 Anticipated serious adverse events	Pain was added as an anticipated serious adverse event for FMS population.	Other (including FMS-related) pain increase and exacerbation of FMS can be a serious expected event in the FMS population.
9.1 Definition of analysis sets	The analysis sets and definitions were updated.	Analysis sets updated to match the Early Phase SSI accepted standard.
9.3.1 Analysis of the primary efficacy/primary endpoint	The covariate "site" was removed.	No longer required as site will be evaluated in a sensitivity analysis.
9.7.1 Interim analysis	A sentence about the timing of the interim analysis was added.	To allow for an earlier interim analysis if required.
10.2 Appendix 2: Clinical Laboratory Tests	Bulletpoint #2 about local laboratory results was removed and references to dipstick urinalysis and local urine testing.	The CRO does not have local laboratory facilities and therefore all tests must be performed at the central laboratory.
	Blood Urea Nitrogen was updated to Urea	To align with regional terminology.
	Glucose (non-fasting) was updated to Random Glucose.	To account for study participants who arrive to clinic in a fasted state.
	Serology testing for hepatitis A was removed.	To correct an error.
	IGRA TB test and stool samples were removed.	To correct an error as these tests are performed by a central laboratory.
	Footnote b was removed from the IgA, IgE and IgM bulletpoint.	IgA, IgE, IgM are not blinded parameters as the mechanism of action of rozanolixizumab does not affect these parameters.
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Contraception requirements for males was removed. Follow-up for pregnant partners of male study participants was removed.	To update male contraception requirements with current guidelines, after completion of the required reproductive toxicity studies and considering that rozanolixizumab has not genotoxic potential and potential exposure

Section # and Name	Description of Change	Brief Rationale
		through seminal fluid is expected to be negligible.
10.10 Appendix 10: Abbreviations and trademarks	The definitions for CNS, CSF, DIAM, MDRD abbreviations were added.	General update.
10.14 Appendix 14: Management of Infections and Hypoammaglobulinemia	Paragraph #4 was updated to remove <1.0g/L and add "serum total IgG reported between the LLOQ (currently 1.09g/L)."	To accurately reflect the parameters lower limit of quantification of the assay.
Protocol Amendment Summary of Changes Table (before the Table of Contents)	Summary of changes and table for Protocol Amendment 1 was moved to Section 10.11 Appendix 11: Protocol amendment history.	To accommodate the protocol amendment summary of changes for the most recent amendment (#2).
Global	Minor administrative, consistency, formatting and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol

10.11.2 Amendment 1 (24 Oct 2022)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The reason for this amendment was to incorporate the changes requested by the Medicines and Healthcare products Regulatory Agency to the original protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Paragraph #6 was updated to add "internal" before Safety Monitoring Committee (SMC).	To clarify the SMC is a group of experts internal to the Sponsor which monitors emerging data of the study
1.3 Schedule of activities, Table 1-1	Urine drug screen was added as a Screening assessment. A new footnote d was added to state that urine drug screen for drug abuse includes amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opiates. This test can be performed at other visits at the discretion of the investigator. Subsequent footnotes were renumbered.	The urine drug screen was added as this is a standard procedure at the Clinical Research Organization (CRO) study sites

Section # and Name	Description of Change	Brief Rationale
6.1 Treatments administered	A sentence was added to state the approximate duration of study treatment sc infusion.	To clarify the duration and route of study treatment administration
9.7.2 Data monitoring	Paragraph #1 was updated to add "internal" before SMC. A sentence was added to state that if required a "closed session" may be instituted to allow the review of unblinded data. Brief details about the closed SMC session were added.	To clarify the SMC is a group of experts internal to the Sponsor which monitors emerging data of the study
	An additional paragraph about the Program Independent Data Monitoring Committee (PiDMC) was added	To clarify the PiDMC is a group of independent experts external to the Sponsor assessing progress and safety data over the entire rozanolixizumab clinical development program
10.1.5 Committees structure	The text was updated to add "internal" before SMC. A sentence was added to state that if required a "closed session" may be instituted to allow the review of unblinded data.	To clarify the SMC is a group of experts internal to the Sponsor which monitors emerging data of the study
	An paragraph about the PiDMC was added	To clarify PiDMC is a group of independent experts external to the Sponsor assessing progress and safety data over the entire rozanolixizumab clinical development program
10.2 Clinical laboratory tests	Urine drug screen was added	The urine drug screen was added as this is a standard procedure at the CRO study sites
10.10 Abbreviations and trademarks	The definition for the PiDMC abbreviation was added	General update

10.12 Appendix 12: Assessment and Management of Tuberculosis and Tuberculosis Risk Factors

Tuberculosis is a safety topic of interest. The safety topics of interest are selected based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related mechanism of action.

For rozanolixizumab clinical studies, the safety topic of interest was selected because it is a biologic immunomodulator, although its mechanism of action is less likely to be associated with increased risk of infection compared with other immunomodulators such as glucocorticoids.

10.12.1 TB definitions

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

- Active TB disease or clinical signs and symptoms strongly suggestive of TB (pulmonary or extrapulmonary).
- History of active TB disease involving any organ system or findings in other organ systems consistent with TB, unless adequately treated and proven to be fully recovered upon consultation with an appropriate specialist.
- Any evidence by radiography or other imaging modalities consistent with previously active TB disease that is not reported in the study participant's medical history.

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

- HIV infection.
- Known close exposure (eg, sleeping in the same room) to another person with active TB disease within 3 months prior to Screening.
- Time spent within 3 months prior to Screening in a healthcare delivery setting or institution where individuals infected with TB are housed or where the risk of transmission of infection is high.

c. **LTBI** is defined as an infection by Mycobacterium tuberculosis with:

- Evidence of prior exposure (ie, a positive IGRA or TB skin test result) AND
- Chest imaging (or other imaging) negative for TB infection, AND
- Absence of signs, symptoms (eg, evidence of organ-specific involvement), or physical findings suggestive of TB infection.

d. **Tuberculosis (IGRA) test conversion** is defined as a positive or indeterminate (and confirmed indeterminate on repeat) IGRA result for the current test when previous IGRA test results were negative.

10.12.2 Screening Period

If IGRA TB testing is considered to be performed at Screening, it is recommended that is the first study procedure to be performed after signing the ICF.

10.12.3 Physical Examination

The investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the study participant's medical or social history. The most common primary focus of TB is the lung. Other sites may include gastrointestinal system, bone/joints, lymph glands, and meninges, etc. However, in immune compromised patients and/or patients treated with biologics, especially TNF inhibitors, extra-pulmonary manifestations of TB are common compared to a normal population.

In addition to a physical examination done intermittently throughout the study, study participants will be evaluated for medical history and for signs and symptoms of latent or active TB and for risk factors for exposure to TB at the following time points: Screening, Baseline, and at regular intervals (not less than 12 weeks apart, that is at Week 13 and Week 25) thereafter, including the EOT/EW and SFU/EOS. IGRA testing during the study should be performed as clinically indicated.

10.12.4 Interferon gamma release assay (IGRA)

IGRA is a whole-blood testing methodology for diagnosing Mycobacterium tuberculosis infection. It has become the gold standard but does not allow differentiating LTBI from active tuberculosis disease.

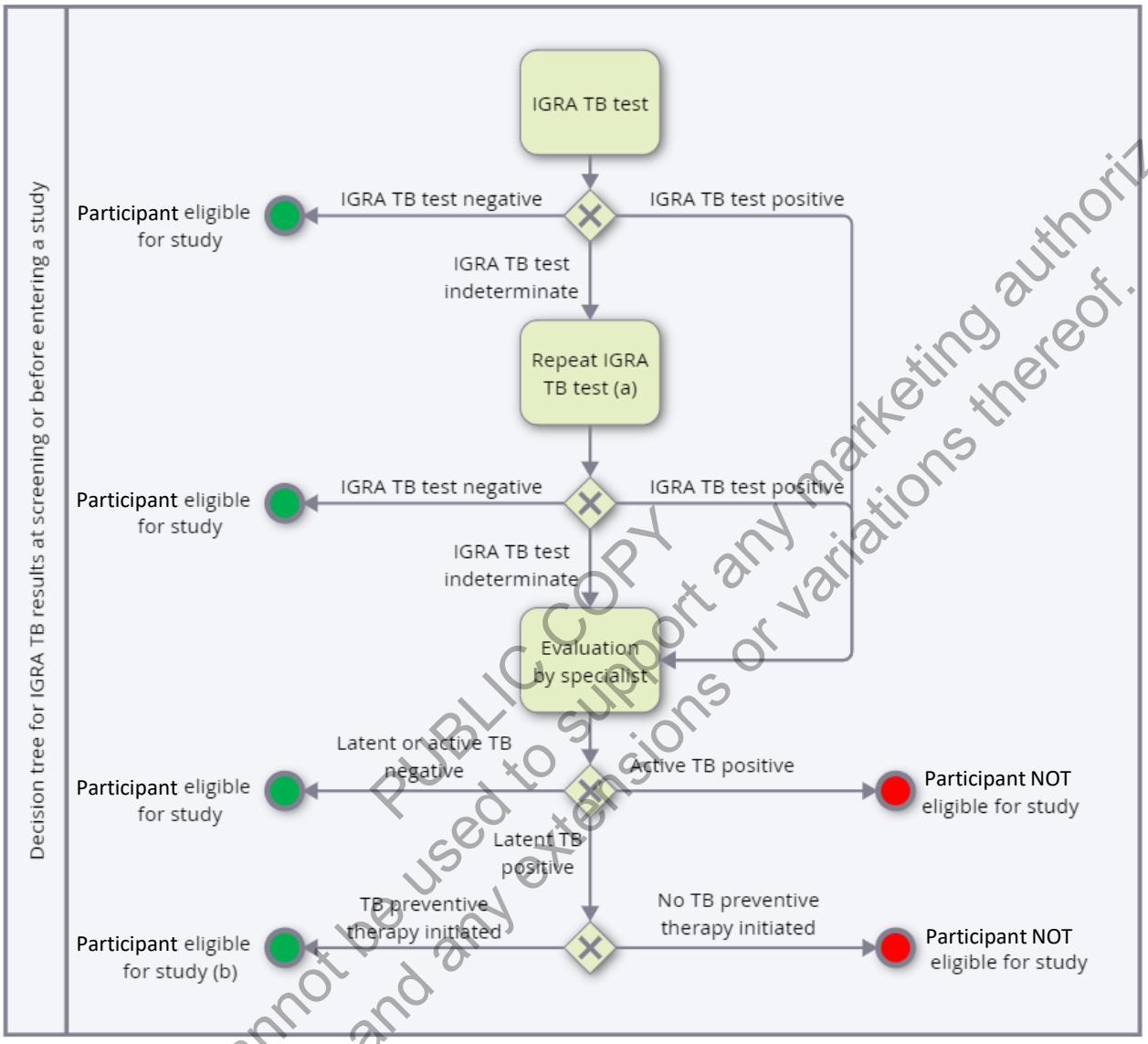
In case an IGRA test is performed in a study participant, the choice of a commercially available IGRA test should be made in accordance with current clinical practice.

The result must be recorded in the eCRF.

10.12.5 Practical steps

In case an IGRA test is required, it will be performed at Screening and the test results will be reported as positive, negative, or indeterminate. Schematic representation on IGRA testing is presented as follows:

Figure 10-1: Decision tree for IGRA TB results at Screening or before entering a study



IGRA=interferon-gamma release assay; LTBI=latent tuberculosis infection; TB=tuberculosis
[a] IGRA retest must be done during the Screening period.
[b] Study participants with LTBI may be randomized in the study only after they have completed at least 1 week of appropriate TB preventive therapy and thereafter, will continue and complete the entire preventive therapy.

If an IGRA is positive or indeterminate, the study participant must be evaluated by an appropriate specialist.

The positive IGRA may represent LTBI or active TB disease. The positive IGRA result may also reflect positivity from a prior diagnosed and adequately or inadequately treated past TB infection.

If the IGRA test result is indeterminate, the IGRA previously performed may be repeated once. The retest must be done during the Screening Period. If the test is positive or indeterminate on

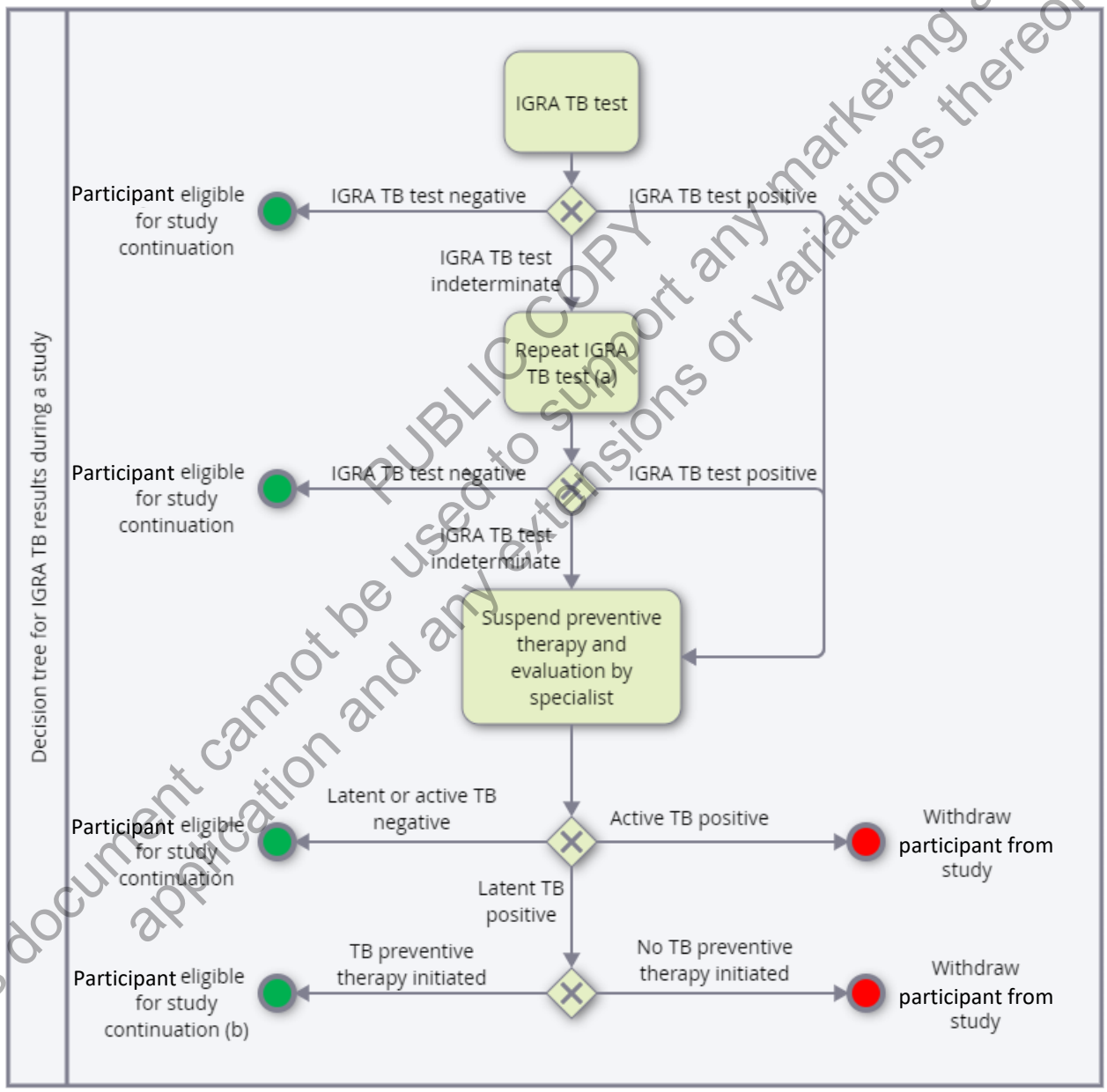
retest, the study participant must not be randomized to IMP without further evaluation by an appropriate specialist.

If upon evaluation by an appropriate specialist, active TB is diagnosed at Screening the study participant is not eligible for the study and must not be enrolled.

If upon evaluation LTBI is diagnosed at Screening, an appropriate TB preventive therapy must be initiated and the study participant can be enrolled after successful completion of at least 1 week of TB preventive therapy.

Schematic representation on IGRA testing during the study is presented below.

Figure 10-2: Decision tree for IGRA TB results during a study



ASAP=as soon as possible; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; LTBI=latent tuberculosis infection; TB=tuberculosis

[a] IGRA retest must be done ASAP and prior to the next IMP dose
[b] Study participants with LTBI may continue the study only after they have completed at least 1 week of appropriate TB preventive therapy and thereafter, will continue and complete the entire regimen.

10.12.6 IGRA Test Conversion

All study participants with positive or indeterminate IGRA test results must immediately stop IMP administration. In case of a IGRA test conversion, the study participant must be considered as having either a suspected new latent or an active TB infection and be promptly referred to an appropriate specialist (eg, pulmonologist, infectious disease specialist) for further evaluation. Additional assessments (eg, blood tests or IGRA, chest X-rays, or other imaging) should be performed where medically relevant and documented. Such conversions should be reported as AEs - see Section 10.3. The AE term would need to be updated with final diagnosis once available.

10.12.7 Latent TB

In case the evaluation by the appropriate specialist diagnoses a new LTBI, a TB preventive therapy in accordance with applicable clinical guidelines should be immediately initiated. The investigator must provide full documentation of duration, start and stop dates of TB preventive therapy (of at least 1 week duration) and discuss with the UCB study physician (or medical monitor) in an anonymized manner prior to allowing study participant to screen (if the LTBI was discovered prior to study participant Screening) or prior to receiving IMP (if LTBI was identified at Screening) or prior to re-starting the IMP (if LTBI was identified during the study). The investigator must assess that the study participant's likelihood of completing the full course of therapy is high and duly record their opinion in the study participant's record prior to randomizing the study participant or re-starting the IMP.

Evidence of treatment adherence or compliance should be recorded within the treatment timeframe and should be completed in appropriate sections of the eCRF.

If no TB preventive therapy is initiated for the newly diagnosed LTBI, the study participant must permanently stop IMP and be withdrawn from the study. Every related action should be discussed in advance with the medical monitor.

Study participants who prematurely discontinue treatment for LTBI or who, in the opinion of the investigator or sponsor, are noncompliant with TB preventive therapy must discontinue further intake of IMP and be immediately withdrawn. Once withdrawn from study treatment, study participants should return for the EOT/EW, complete all EW assessments, and complete an EOS Visit. LTBI must be reported as an AE. Follow-up reports should be completed as per protocol requirement until such time as the LTBI resolves.

Additional considerations regarding including LTBI study participants in the study

- Study participants who initiated treatment for LTBI during the Screening Period should repeat chemistry laboratory parameters (can also be done at a local laboratory), medical history and all physical examinations for signs and symptoms of TB (after completing at least 1 week of treatment for LTBI) prior to randomization in the study and must continue the full course of TB preventive treatment.

Rescreening may occur only after discussion with and approval by the study physician (or medical monitor).

10.12.8 Active TB

Study participants who develop active TB during the study must be withdrawn from the study. The study participant must be immediately permanently discontinued from study medication and an EW Visit must be scheduled as soon as possible, but no later than the next scheduled visit. The study participant should be encouraged to keep the EOS Visit as specified by the protocol. Treatment for active TB should be started immediately.

10.12.9 Safety Reporting Requirements

The reporting requirements for events relating to TB are as follows:

- IGRA test conversions defined as a positive or indeterminate (and confirmed indeterminate on repeat) should be reported as AEs. The AE term would need to be updated with final diagnosis once available.
- LTBI must be reported as an AE. It is usually reported as a non-serious AE unless it meets SAE criteria. Follow-up reports should be completed as per protocol requirement until the LTBI resolves.
- Confirmed active TB is always considered an SAE and must be reported per SAE reporting instruction. Follow-up reports should be completed as per protocol requirement until TB infection resolves.

Notes:

  - "TB Positive" is an unclear term and the study investigative site will be queried for clarification to obtain event diagnosis.
  - Suspected LTBI and suspected active TB are considered working diagnosis that should be clarified before final database lock. The study investigative site will be queried for final diagnosis.

10.13 Appendix 13: Management of Adverse Event of Special Monitoring

Management of Adverse Event of Special Monitoring

Adverse events of special monitoring are defined as product specific adverse events, adverse reactions, or safety topics requiring special monitoring by one or more regulatory authorities or by UCB. For rozanolixizumab, AESMs (defined by UCB) are:

- Severe and/or serious headache
- Suspected aseptic meningitis

Occurrence of AESM require immediate reporting (within 24h of awareness regardless of seriousness) to UCB. Upon reception of AESM by UCB a standard medical follow-up query will be sent to the site to gather extensive medical information about the AESM. See Table 1-3 for assessments that may be required in case of an AESM.

Suspected Aseptic Meningitis

Drug-induced aseptic meningitis (DIAM) is a diagnosis of exclusion after ruling out infectious causes (Jolles et al, 2000). A few cases of aseptic meningitis (drug-induced) have been reported in the rozanolixizumab program. Consequently, suspected aseptic meningitis is being managed as an adverse event of special monitoring (see Section 8.3.7).

Participants should be monitored for signs and symptoms suggestive of central nervous system (CNS) involvement and evaluated immediately if meningitis is suspected. A full neurological workup should be strongly considered including, but not limited to, imaging, (eg, CT scan, or preferably gadolinium enhanced MRI), a lumbar puncture with cerebrospinal fluid (CSF) analysis inclusive of glucose, protein, differential complete blood count, cultures, gram stain, and/or viral polymerase chain reaction (PCRs), as appropriate. Whenever possible, CSF should be stored for assessment of rozanolixizumab PK, PD, specific antibody titers, or other biomarkers. A concurrent blood sample should be collected as per local practice. The ultimate investigative procedures are at the discretion of the investigator or the treating physician. For studies where a neurologist is not the investigator, a neurological consultation is also recommended to aid in decision making and patient management. In addition, blood samples for exploratory safety biomarkers (see Section 8.9) should be collected for participants with a diagnosis of DIAM, preferably within 72 hours after onset of symptoms. These investigations will be performed to further understand the potential mechanisms of DIAM in the participants.

All procedures related to the diagnosis, treatment, and investigation of meningitis should be recorded in the eCRF and preliminary data should be included on the SAE form used for reporting the event as an AESM within 24 hours (ie, preliminary data reported on the first reporting may not have CSF results yet but the reporting should occur as soon as there is a suspected diagnosis). Full results should be communicated in subsequent exchanges with the sponsor).

Treatment must be temporarily held if a participant has a diagnosis of suspected meningitis of any cause until the diagnostic workup is complete. Based on CSF findings, negative cultures, absence of other disease causes, and relationship with IMP a diagnosis of potential DIAM can be made (given that the blinded portions of a study should remain blinded to actual treatment

assignment). If deemed appropriate by the investigator and agreed upon by the participant and the sponsor, the study treatment can resume upon the complete resolution of symptoms. The benefit and risk of the treatment should be carefully considered prior to reinitiating the IMP. If a participant experiences a second episode of similar symptoms suggestive of DIAM, then the participant must discontinue the IMP and treatment must be permanently discontinued. Participants experiencing an event of DIAM should be strongly encouraged to remain in the study regardless of IMP discontinuation. This will allow for monitoring and follow-up of the participant including a complete neurological exam on subsequent physical examinations. Longer term follow-up on any AEs related to DIAM that are ongoing may be warranted until resolution. Associated symptoms with aseptic meningitis should be managed at the investigator's discretion.

Severe and/or Serious Headache

Based on current available clinical data, headache is the most commonly reported adverse drug reaction in study participants treated with rozanolixizumab. Study participants should be well informed of this potential adverse drug reaction and should be instructed on how to manage it.

Determination of the severity of headache will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Severe headache is defined as severe pain limiting ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, and taking medications.

In the event of a headache, the investigators should take the medical history of previous headaches, concomitant medication, and co-morbidities (eg, asthma) in consideration.

Severe and/or serious headache is initially reported at a home visit or during a telephone call, the study participant should be evaluated by a healthcare professional as soon as possible for further investigations. Study participants should be monitored for signs and symptoms suggestive of CNS involvement and evaluated immediately if other causes (eg, meningitis, intracranial bleeding) are suspected (please see above). In addition, samples for exploratory safety biomarkers should be collected for study participants experiencing severe or serious headache when possible. These investigations will be performed to further understand the mechanism of headaches in the study participants.

If deemed appropriate by the investigator and agreed upon by the study participant and the sponsor, the study treatment can resume treatment upon the resolution of the severe and or serious headache event. The benefit and risk of the treatment should be carefully considered prior to reinitiating the IMP.

Headaches will be treated as clinically indicated according to national guidelines. It is recommended that the study participants have an analgesic available in case of headache with the instruction for frequency and dosage provided by a healthcare professional. The analgesic can be started at the early onset of headache. Study participants experiencing any treatment-related headache will be followed until resolution of the event.

Prophylactic treatment of headaches may be permitted for study participants who have experienced previous episodes of treatment-related headache after discussion with the medical monitor. The benefit risk of continuing treatment with IMP and chronic prophylactic with analgesics must be carefully evaluated by the investigator.

10.14 Appendix 14: Management of Infections and Hypogammaglobulinemia

Study participants who have signs or symptoms of any infection should be monitored closely and managed according to local guidelines. This may include tests for specific organisms if clinically indicated.

Study participants **MUST discontinue IMP, perform the EOT/EW Visit, AND move into the SFU Period** if the following event occurs: Study participant has a significant infective episode including but not limited to bacteremia/sepsis, infectious meningitis, septic arthritis, osteomyelitis, complicated pneumonia, or visceral abscess which may or may not result in hospitalization. This list is not intended to be all inclusive, and the investigator is expected to apply their judgment on continuing IMP based on the clinical situation (Section 7.1.2).

To maintain the study integrity, IgG level will remain blinded to the study sites and the study team (see Section 6.3.1.1 for further details on the maintenance of the study blind). During this time, serum IgG level will be monitored by an independent unblinded medical monitor external to the study team. As part of the overall safety surveillance, the unblinded medical monitor will review available safety information for study participants with low IgG levels and may query the site for supportive information. In addition, to preserve the blind, the unblinded medical monitor may request additional IgG sampling and/or supportive information for any study participants at random.

The IMP may be temporarily discontinued as requested by the independent unblinded medical monitor in case of low serum IgG levels as described in Section 7.1.4. Mock infusions will be administered to maintain the blind in case of low IgG levels.

Treatment may be temporarily discontinued for the study participant who develops a non-serious persisting or recurrent infection with a serum total IgG level reported between the LLOQ (currently 1.09g/L) and <2g/L. Upon resolution of infection and the IgG returning to the level of ≥2g/L, the study participant may be allowed to resume treatment with the IMP. Ad hoc assessments can be performed to monitor recovery of IgG levels.

Treatment must be temporarily discontinued for the study participant who develops an event of hypogammaglobulinemia with a serum total IgG of <1.09g/L irrespective of infection. When the IgG level reaches ≥2g/L, the study participant may be allowed to continue treatment with IMP.

The risks and benefits of the treatment should be carefully considered prior to reinitiating the IMP.

10.15 Appendix 15: Management of Infusion Reactions or Hypersensitivity Reactions

Study participants must be closely monitored for reactions during and after the study drug administration period. Standard precautions must be taken for the study participants with regards to potential infusion-related reactions. Suggested management guidelines for infusion-related reactions or anaphylaxis at the study site are provided in Table 10-4. Definitions of severity of the relevant events should be consistent with CTCAE version 5.0. Nurses administering the IMP at home should follow their own management guidelines, which should be reviewed and endorsed by the investigator prior to first home administration.

Table 10-4: Suggested management guidelines at site for infusion reactions or anaphylaxis

Type of reaction	Suggested action
Acute – Mild Grade 1	Monitor vital signs every 10 min. If the reaction worsens to Grade 2, follow the instruction below.
Acute – Moderate Grade 2	Interrupt/hold infusion temporarily to further assess and initiate treatment if necessary. Consider the use of iv fluid and antihistamine iv/im. Consider administering acetaminophen or NSAIDs. Monitor vital signs initially every 5 min. If the reaction improves and upon further assessment it is clear that the event is not an anaphylaxis, restart the infusion cautiously. Continue to monitor vital signs every 5 minutes. If reaction recurs or worsens to Grade 3, discontinue infusion.
Acute – Severe Grade 3 or anaphylaxis	Discontinue IMP infusion permanently. Alert crash team. Maintain airway; ensure oxygen is available. Administer: – Antihistamine iv/im, corticosteroids iv, epinephrine im, and iv fluids as appropriate. – Monitor vital signs every 2 min. – Hospitalize, if condition not improving or worsens. – Monitor patient until symptoms resolve.

CTCAE=Common Terminology Criteria for Adverse Events; im=intramuscular; IMP=investigational medicinal product; iv=intravenous(ly); NSAID=nonsteroidal anti-inflammatory drug
Note: Management criteria were adapted from the CTCAE v5.0 (National Cancer Institute, 2017).

Suspected anaphylactic reactions should be diagnosed using Sampson's Criteria (Sampson et al, 2006). The infusion must be discontinued immediately and emergency resuscitation measures implemented.

In study participants experiencing an infusion-related reaction or anaphylaxis, blood samples will be collected as soon as possible, while the event is ongoing, to investigate the nature of the reaction as per Schedule of Activities (Section 1.3).

Samples for serum complement (C3, C4) and plasma complement (C3a, C5a) should be collected as specified in the Schedule of Activities (Section 1.3). Additional tests such as IgE levels, tryptase may be performed when there is a suspicion of Type I or III hypersensitivity reaction. The results of all monitoring, including laboratory testing, should be made available to the study site and sponsor.

11 REFERENCES

Chandran A, Schaefer C, Ryan K, et al. The comparative economic burden of mild, moderate, and severe fibromyalgia: results from a retrospective chart review and cross-sectional survey of working-age U.S. adults. J Manag Care Pharm 2012;18:415–26.

Cook MK, Malkin M, Karafin MS. The use of plasma exchange in Hashimoto's encephalopathy: A case report and review of the literature. J Clin Apher. 2015:30(3):188-192.

Dyck PJ, Daube J, O'Brien P, et al. Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. N Engl. J. Med. 1986;314(8):461-5.

Goebel A, Krock E, Gentry C, et al. Passive transfer of fibromyalgia symptoms from patients to mice. J Clin Invest. 2021;131(13):e144201.

Guptill JT, Juel VC, Massey JM, et al. Effect of therapeutic plasma exchange on immunoglobulins in myasthenia gravis. Autoimmunity. 2016:49(7):472-9.

Häuser W, Ablin J, Fitzcharles MA, et al. Fibromyalgia. Nat Rev Dis Primers. 2015;1:15022. doi: 10.1038/nrdp.2015.22. PMID: 27189527.

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos. 2009;37(8):1779-84.

Jolles S, Sewell WAC, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. Drug Saf. 2000:22(3): 215-26.

Kaplan AA. Therapeutic plasma exchange: a technical and operational review. J Clin Apheres. 2013;28(1):3-10.

Krock E, Morado-Urbina CE, Menezes J, et al. Fibromyalgia patients with elevated levels of anti-satellite glia cell immunoglobulin G antibodies present with more severe symptoms. Pain. 2023 ; Online ahead of print.

Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Annals of the rheumatic diseases. 2017;76(2):318-28.

Mascarenhas RO, Souza MB, Oliveira MX, et al. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. JAMA Intern Med. 2021;181(1):104-112.

Mease PJ, Spaeth M, Clauw DJ, et al. Estimation of minimum clinically important difference for pain in fibromyalgia. Arthritis Care Res (Hoboken). 2011;63(6):821-6.

Peter HH, Ochs HD, Cunningham-Rundles C, Vinh DC, Kiessling P, Greve B, Jolles S. Targeting FcRn for immunomodulation: Benefits, risks, and practical considerations. J Allergy Clin Immunol. 2020 Sep;146(3):479-491

Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007;7(9):715-25.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and

Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

Turner MS, Sutton D, Sauder DN. The use of plasmapheresis and immunosuppression in the treatment of pemphigus vulgaris. J Am Acad Dermatol. 2000;43(6):1058-64.

Vyvgart Prescribing Information, 2021. https://www.argenx.com/product/vyvgart-prescribing-information.pdf.

White LA, Birnbaum HG, Kaltenboeck A, et al. Employees with fibromyalgia: medical comorbidity, healthcare costs, and work loss. J Occup Environ Med 2008;50(1):13–24.

Williams DA, Arnold LM. Measures applied to the assessment of fibromyalgia: Fibromyalgia impact questionnaire (FIQ), brief pain inventory (BPI), the multidimensional fatigue inventory (MFI-20), the MOS sleep scale, and the multiple ability self-report questionnaire (MASQ; cognitive dysfunction). Arthritis Care Res (Hoboken). 2011; 63(0 11): S86–S97. doi:10.1002/acr.20531.

Williams ME, Balogun RA. Principles of separation: indications and therapeutic targets for plasma exchange. Clin J Am Soc Nephrol. 2014;9(1):181-90.

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

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Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 14-Apr-2023 11:15:35 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 14-Apr-2023 11:45:11 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 14-Apr-2023 13:27:29 GMT+0000