A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PHASE 2 STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ROZANOLIXIZUMAB IN ADULT STUDY PARTICIPANTS WITH LEUCINE-RICH GLIOMA INACTIVATED 1 AUTOIMMUNE ENCEPHALITIS

PROTOCOL AIE001 AMENDMENT 6

PHASE 2

SHORT TITLE:

A Phase 2 study evaluating the efficacy and safety of rozanolixizumab in participants with leucine-rich glioma inactivated 1 autoimmune encephalitis

Sponsor:
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Regulatory agency identifying number(s):

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IND Number:	157206

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 6	18 Jul 2023	Substantial
Amendment 5	09 Feb 2023	Substantial
Amendment 4	19 Oct 2022	Substantial
Amendment 3	14 Jan 2022	Substantial
Amendment 2[a]	07 Sep 2021	Substantial
Amendment 1/Addendum C (CN)	21 Jun 2021	Not applicable
Amendment 1/Addendum C (IT)	24 May 2021	Not applicable
Amendment 1/Addendum B (DE)	17 May 2021	Not applicable
Amendment 1/Addendum A (UK)	26 Feb 2021	Not applicable
Amendment 1	04 Dec 2020	Substantial
Original Protocol	31 Jul 2020	Not applicable

[a] Protocol Amendment 2 was not submitted to all regulatory authorities prior to submission of Protocol Amendment 3. Details of the changes between Protocol Amendment 1 and Protocol Amendment 2 are provided in Section 10.11.

Amendment 6 (date: 18 Jul 2023)

Overall Rationale for the Amendment

The overall rationale for the amendment is to address a request from FDA to re-introduce certain safety assessments to support the safety profile of rozanolixizumab in a new population. Since Amendment 5, there has been no change in the benefit/risk profile of rozanolixizumab.

Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

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.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of activities 3 Objectives and Endpoints 8.9.1 Immunology 9.4.2.4 Immunological analyses 10.2 Appendix 2 Clinical laboratory tests	Endpoints, procedures, and text relating to the assessment of serum [redacted] concentrations re-instated as per Protocol Amendment 3.	As per FDA request.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall design 6.8 Treatment after the end of the study	Protocol sections updated with part or all of the following text: Study participants who complete the 24-week Treatment Period and require further treatment may have the option to access rozanolixizumab via another clinical study or an access program, if available, as per local laws and regulations. Study participants continuing with rozanolixizumab must complete an End of Treatment Visit and be transitioned to rozanolixizumab provided by those alternative options without undergoing SFU or EOS Visits.	To facilitate plans for optional post-trial access to rozanolixizumab, where applicable.
1.3 Schedule of activities 5.2 Exclusion criteria 7.1.2 Permanent discontinuation due to other AEs 10.2 Appendix 2 Clinical laboratory tests	The IGRA TB test was re-instated as a Screening procedure as per Protocol Amendment 4, with exclusion criterion #11 updated to exclude participants with a positive TB test at Screening unless the positive test result is related to adequately treated latent TB infection. Footnote *j* of Table 1-1 updated to include a cross-reference to Section 10.12. Protocol updated to indicate that participants with LTBI at Screening can be randomized after undergoing 4 weeks of TB prophylactic treatment. Exclusion criterion #12 re-instated to that used in Protocol Amendment 4 to exclude participants with LTBI (unless prophylaxis initiated 4 weeks prior to first dose of IMP) and participants with current or a history of NTM infection (unless fully recovered). Section 7.1.2 updated to state that participants who develop active TB, LTBI, or NTM infection must be permanently discontinued from IMP.	As per FDA request.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	Vital sign assessments re-instated at Week 17 and Week 21 (Visits 22 and 26) and removed from Week 22 (Visit 27).	Correction.
5.2 Exclusion criteria	Exclusion criterion #6 re-instated as per Protocol Amendment 4.	As per FDA request.
5.2 Exclusion criteria	Exclusion criterion #8b (previously #8a) updated to exclude participants with a serious infection 6 weeks prior to the first dose of IMP.	As per FDA request.
5.2 Exclusion criteria	Exclusion criterion #15 (excluding participants with an [redacted] deficiency) re-instated as per Protocol Amendment 4.	As per FDA request.
6.5.2 Prohibited prior and concomitant treatments (medications and therapies)	Any use of cyclophosphamide prior to the Baseline visit is prohibited (re-instatement of Protocol Amendment 4 timeframe)	As per FDA request.
7.1.2 Permanent discontinuation due to other AEs	The phrase 'and move to the Safety Follow-up Period' was removed as the procedure is better described in Section 7.1.	For clarity.
8 Study assessments and procedures	Text in penultimate paragraph updated to indicate that unscheduled assessments (as well as unscheduled visits) can be performed at the investigator's discretion.	To remind investigators that safety assessments can be performed if required.
9.3 Planned efficacy/outcome analyses	Text describing the additional adjustments to be made to the statistical modelling to accommodate prior disease-related therapies has been removed from Section 9.3.	Details of subgroup analyses based on prior treatment will be provided in the SAP.
9.3.2 Secondary efficacy analysis	Clarified that there are 4 alpha-controlled secondary endpoints	As per FDA request.
9.3.3.2 Seizure control	Added text that defines seizure count categories.	For clarity.
10.3 Appendix 3: Adverse Events – Definitions and Procedures for Recording, Evaluating , Follow-up and Reporting	Text added to remind investigators that safety reporting requirements for the TB are provided in Section 10.12	For clarity.

Section # and Name	Description of Change	Brief Rationale
10.12.2 Screening Period 10.12.3 Physical examination 10.12.4 Interferon gamma release assay (IGRA) 10.12.5 Practical steps 10.12.7 Latent TB 10.12.8 Active TB	Text revised to require participants with LTBI undergo 4 weeks (instead of 1 week) of TB prophylactic treatment prior to randomization. The removal of the possibility for participants to remain receiving IMP in the event of a new diagnosis of LTBI.	To align with changes made in the body of the protocol.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
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 2 study to evaluate the efficacy, safety, and pharmacokinetics of rozanolixizumab in adult study participants with leucine-rich glioma inactivated 1 autoimmune encephalitis

Short title: A Phase 2 study evaluating the efficacy and safety of rozanolixizumab in participants with leucine-rich glioma inactivated 1 autoimmune encephalitis

Rationale: Autoimmune encephalitis (AIE) is a group of disorders where the immune system causes inflammation of the brain, leading to debilitating neurological and psychiatric symptoms. There are currently no approved treatments for AIE. Leucine-rich glioma inactivated 1 AIE (LGI1 AIE) has a distinct clinical presentation and has been identified as a variant that may be suitable for immunotherapy, and therefore for treatment with rozanolixizumab, which blocks the activity of neonatal Fc receptor (FcRn), accelerates the catabolism of antibodies and reduces the concentration of immunoglobulin (Ig) G.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of rozanolixizumab as measured by seizure freedom	• Seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25)
Secondary	
• To assess the efficacy of rozanolixizumab as measured by a change in cognitive function	• Change from Baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scale index score at the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab on study participants' overall disability	• Proportion of participants with a favorable outcome in the Modified Rankin Scale (mRS) during the Treatment Period, where favorable outcome is defined as no worsening for participants with a Baseline mRS score of ≤1 or improvement of ≥1 point for participants with a Baseline mRS score of ≥2
• To assess the efficacy of rozanolixizumab as measured by use of rescue medication	• Use of rescue medication due to an absence or loss of clinical benefit during the Treatment Period

Objectives	Endpoints
• To assess the efficacy of rozanolixizumab as measured by the onset of seizure freedom	• Time to first occurrence of seizure freedom (TTFSF) defined by the number of days after randomization to the first day of the first 28 consecutive days without seizures during the Treatment Period
• To assess the safety and tolerability of rozanolixizumab	• Incidence of treatment-emergent adverse events (TEAEs) during the study
Exploratory	
• To assess the time of onset of efficacy of rozanolixizumab for the subgroup of study participants who achieve the primary endpoint as measured by the onset of seizure freedom	• Time to achieving seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab as measured by seizure control	• 'Good' or 'Moderate' seizure control maintained over a period of 4 consecutive weeks until the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab as measured by a change in cognitive function (domains of RBANS)	• Change from Baseline in the domain scores of RBANS (immediate memory; visuospatial/constructional; delayed memory; language; and attention) during the Treatment Period
• To assess the efficacy of rozanolixizumab using an integrated ranked analysis of combined clinical and functional outcome measures	• Ranked outcome derived from the combined integrated analysis of clinical and functional assessments (including mRS, seizure freedom, and, cognitive function) at the end of the Treatment Period (Week 25)
• To assess the safety and tolerability of rozanolixizumab	• Change from Baseline in vital signs and laboratory results during the study
• To assess the pharmacodynamic (PD) effect of rozanolixizumab as measured by the total IgG concentrations in serum	• Value and change (absolute and percentage) from Baseline in serum total IgG and IgG subclass concentrations during the study

Objectives	Endpoints
• To assess the PD effect of rozanolixizumab as measured by LGI1 autoantibody levels using the flow cytometry LGI1 quantitative assay	• Value and change from Baseline in LGI1 autoantibody serum levels during the Treatment Period • Value and change from Baseline in LGI1 autoantibody cerebrospinal fluid (CSF) levels during the Treatment Period (for consenting participants)
• To evaluate the effects of rozanolixizumab on patient-reported health-related quality of life (HRQoL)	• Value and change from Baseline in the 36-item Short Form Survey (SF-36) Physical Component Summary (PCS) score, Mental Component Summary (MCS) score, and individual domain scores during the Treatment Period • Value and change from Baseline in the EuroQol-5D-5L (EQ-5D-5L) during the Treatment Period • Value and shift from Baseline in Clinical Global Impression of Severity (CGI-S) during the Treatment Period
• To evaluate the effects of rozanolixizumab on healthcare resource utilization (HCRU)	• Disease-related hospitalizations (number, duration)
• To assess the pharmacokinetic (PK) characteristics of rozanolixizumab	• Plasma concentration of rozanolixizumab during the Treatment Period
• To evaluate the impact of concomitant antiepileptic drugs (AEDs) on rozanolixizumab plasma levels	• Plasma concentration of rozanolixizumab during the Treatment Period
• To evaluate the incidence and emergence of antidrug antibody (ADA) of rozanolixizumab and impact on PK and PD	• ADA status

Objectives	Endpoints
• To evaluate the effects of rozanolixizumab on the concentration of total protein, albumin, [redacted] and serum and plasma complement levels	• Values and change from Baseline in total protein, albumin, and serum immunoglobulin concentrations ([redacted] during the Treatment Period • Values and change from Baseline in serum complement levels ([redacted]), and plasma complement levels ([redacted]) in case of infusion or hypersensitivity reaction
• To assess exploratory biomarkers	• Deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and genetic analysis that may be measured to understand the cause and appropriate treatment of LGI1 AIE • Exploratory biomarkers such as but not limited to [redacted] • Proteins and metabolite changes may be measured to understand the cause, progression, and appropriate treatment of LGI1 AIE

Overall Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, 2-arm, repeat dose study to evaluate the efficacy, safety, and PK of rozanolixizumab for the treatment of LGI1 AIE.

Approximately 68 adult study participants with LGI1 AIE with onset of disease symptoms between 0 to 12 months prior to study entry, as assessed by the investigator, will be randomized to receive rozanolixizumab [redacted] or placebo, administered by subcutaneous (sc) infusion at [redacted] intervals for 24 weeks. A Treatment Period of 24 weeks has been selected to ensure a sufficient time period to evaluate a difference between rozanolixizumab and placebo in key symptoms of the disease. The primary objective of the study is to assess the efficacy of rozanolixizumab as measured by seizure freedom.

Down titration of steroids will begin after at least 3 days on the initial high dose corticosteroids (based on the decision of the investigator).

The study participants will be stratified at randomization by:

- Time from disease symptom onset (≤6 months or >6 months from disease symptom onset)
- Cognitive function (RBANS score of ≤85 or >85)

After the initial 5 investigational medicinal product (IMP) administrations have been performed at the clinic (if applicable), the study participant may have the opportunity to be treated at home by a visiting healthcare practitioner.

Although the use of rescue medication is allowed at any time during the study, the use of rescue medications should be delayed, if clinically feasible, for at least 4 weeks following the initiation of study treatment. Study participants who require use of rescue medication will discontinue blinded treatment and complete the assessments for the Early Discontinuation (EDisc) Visit. Following this, the selection of an appropriate rescue medication will be made at the investigators discretion, and the study participant will enter the Safety Follow-Up (SFU) Period. Unscheduled study visits are permitted for any study participant including those study participants who have initiated rescue medication.

An Independent Data Monitoring Committee (IDMC) will be established for the study to monitor the emerging safety data within the clinical study on a periodic basis.

Number of Participants

To account for an expected 10% dropout rate within each treatment arm, approximately 68 participants will be randomly assigned to study treatment arms such that approximately 60 evaluable study participants complete the study.

Treatment Groups and Duration

The maximum study duration per study participant is upto 38 weeks. There are 3 study periods:

- Screening Period: Eligibility will be assessed during the Screening Period of up to 42 days. If a study participant becomes seizure free as a result of steroid treatment, the participant may still be randomized in the study, providing the prior occurrence of seizures is well documented.

  Following screening and completion of the Baseline assessments, treatment will be initiated in study participants who are deemed appropriate for initiation or re-initiation of high dose corticosteroids (500 to 1000mg methylprednisolone [MP] equivalent /day) based on clinical symptoms and history, or who have initiated corticosteroids within 42 days prior to randomization at a dose of 500 to 1000mg MP equivalent/day. Corticosteroids can be initiated prior to the start of the Screening Period, however, the study participant must be randomized within 42 days of corticosteroids initiation. If the study participant has initiated a steroid taper, the study participant cannot receive oral steroids at a dose lower than 40mg/day when randomized. Study participants receiving a steroid dose of 60mg/day, 50mg/day or 40mg/day at the time of randomization, will have to maintain that dose for 7 days (±2 days), 14 days (±2 days) or 21 days(±2 days), respectively, before resuming [redacted] down-titration steps. Each subsequent down-titration step will last for 7 days (±2 days; see Section 1.2). For those participants that have not initiated a steroid taper, the down-titration of the oral steroid dose will begin after at least 3 days on the initial high dose corticosteroids, as per investigator' discretion.

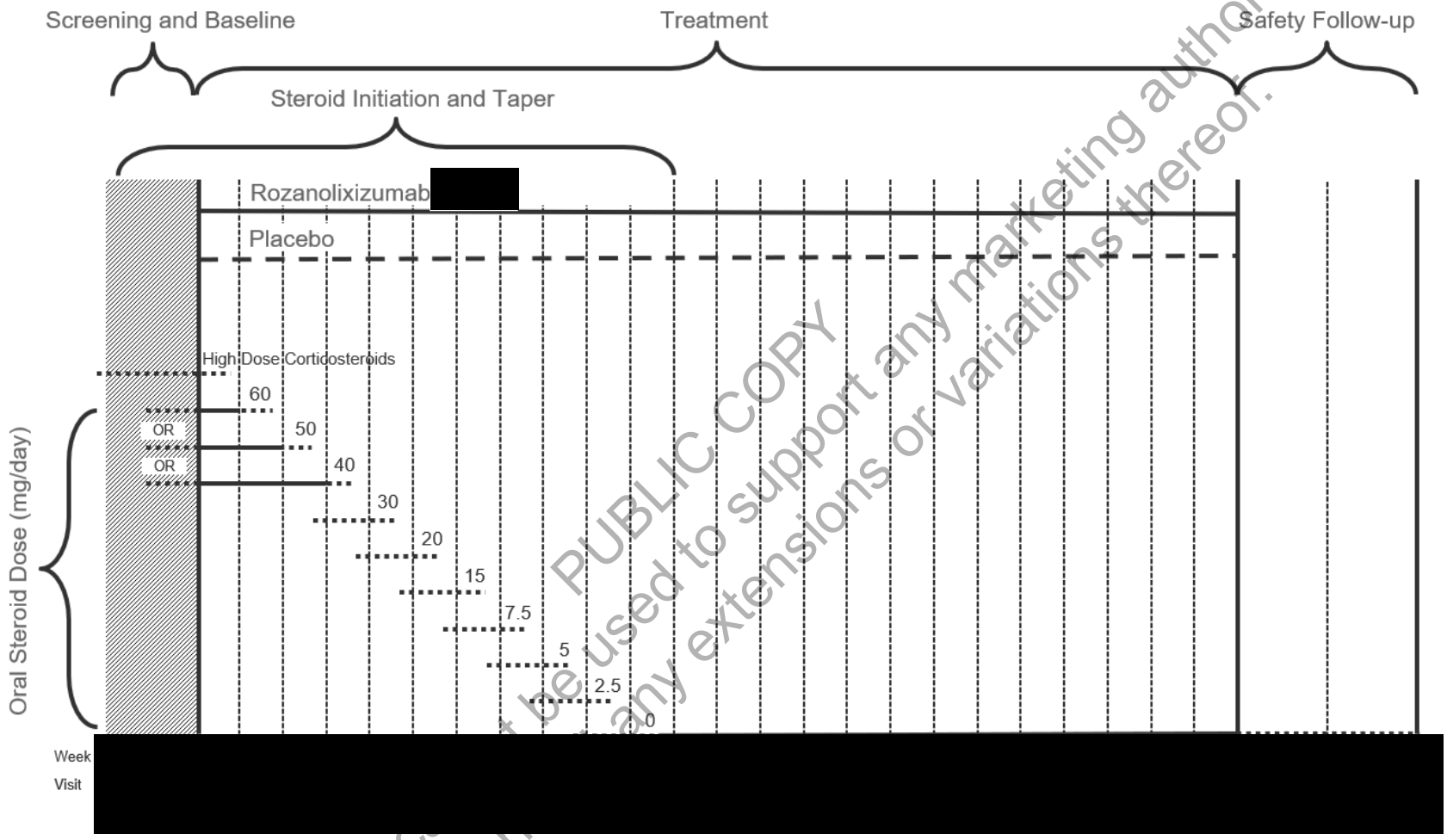
- Treatment Period: Participants who have been confirmed eligible will be randomized in a 1:1 ratio to receive rozanolixizumab [redacted] or placebo at [redacted] intervals over a 24-week Treatment Period. Initially, study participants will receive rozanolixizumab or placebo in addition to intravenous (iv) or oral steroids that will be tapered as described in Section 1.2.

- Safety Follow-Up Period: Study participants who complete the 24-week Treatment Period or prematurely discontinue IMP, as well as study participants who receive rescue medication during the 24-week Treatment Period will undergo the End of Treatment (EOT) Visit/EDisc

Visit and enter the SFU Period. At 4 weeks after the final dose, study participants will undergo a SFU phone call, and at 8 weeks after the final dose, study participants will undergo the End of Study (EOS) Visit.

Study participants who complete the 24-week Treatment Period and require further treatment may have the option to access rozanolixizumab via another clinical study or an access program, if available, as per local laws and regulations. Study participants continuing with rozanolixizumab must complete an End of Treatment Visit and be transitioned to rozanolixizumab provided by those alternative options without undergoing SFU or EOS Visits.

1.2 Schema



EDisc=early discontinuation; EOT=end of treatment; EOS=end of study; MP=methylprednisolone; SFU=safety follow-up; W=Week
Note: Rozanolixizumab or placebo will be initiated in study participants who are deemed appropriate for initiation or re-initiation of corticosteroids based on clinical symptoms and history, or have initiated corticosteroids within 42 days prior to randomization at a dose of 500 to 1000mg MP equivalent/day. Study participants will be administered rozanolixizumab or placebo in addition to iv or oral steroids that will be tapered. The dotted line indicates the period in which each down-titration step may occur.
Note: Visit 17 and Visit 18 were removed in Protocol Amendment 4 and Visit 4 was removed in Protocol Amendment 5; however, the Visits were not renumbered.

1.3 Schedule of activities

The Schedule of Activities is provided in Table 1-1. Visit 32 (Week 25) is designated as the EOT Visit however, study participants that undergo early discontinuation will undergo these assessments as part of the EDisc Visit, which may occur at any week of Treatment Period. Study participants who undergo the EDisc Visit should then follow the same temporal schedule for subsequent visits (ie, complete the SFU phone call and EOS Visit at 3 and 7 weeks after the EDisc Visit, respectively).

Some study-specific investigations may not be conducted according to the study protocol during a pandemic or other exceptional circumstances due to the need to implement safety measures and guidance from regulatory authorities (see Section 8 for further information).

Table 1-1: Schedule of Activities

Period	Scr[a]	Treatment Period (24 Weeks)																			EOT/EDisc	SFU	EOS	Unsch
[redacted]																								
Visit type	S	S	TH[b]	S	S	S	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	S	T[d]	S	S
[redacted]																								
Procedure																								
Informed consent	X																							
Verification of inclusion/ exclusion criteria	X	X[e]																						

Table 1-1: Schedule of Activities

Period	Scr[a]	Treatment Period (24 Weeks)																			EOT/EDisc	SFU	EOS	Unsch
[redacted]																								
Visit type	S	S	TH[b]	S	S	S	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	S	T[d]	S	S
[redacted]																								
Procedure																								
Demography	X																							
Randomization		X																						
Full neurological examination & full PE[f]	X																				X		X	
Brief neurological examination & brief PE[f]		X					X		X		X		X		X									X
LGI1 detection	X																							
Study withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Table 1-1: Schedule of Activities

Period	Scr[a]	Treatment Period (24 Weeks)																				EOT/EDisc	SFU	EOS	Unsch
[redacted]																									
Visit type	S	S	TH[b]	S	S	S	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	S	T[d]	S	S
[redacted]																									
Procedure																									
C-SSRS[g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
General medical/ procedure history	X																								
Contact IRT		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Pregnancy test (serum)	X																								
Pregnancy test (urine)[h]		X		X			X		X		X		X		X							X		X	O
FSH test[i]	X																								
Hematology, chemistry[o], urinalysis	X	X		X			X		X		X		X		X							X		X	X

Table 1-1: Schedule of Activities

Period	Scr[a]	Treatment Period (24 Weeks)																			EOT/EDisc	SFU	EOS	Unsch
[redacted]																								
Visit type	S	S	TH[b]	S	S	S	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	S	T[d]	S	S
[redacted]																								
Procedure																								
Serology testing (HIV, Hepatitis B and Hepatitis C)	X																							
IGRA TB test[j]	X																							
12-lead ECG	X																				X			
Vital signs[k]	X	X		X	X	X	X	X	X		X		X		X						X		X	X
Record AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record prior and concomitant (including rescue) medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1-1: Schedule of Activities

Period	Scr[a]	Treatment Period (24 Weeks)																			EOT/EDisc	SFU	EOS	Unsch
[redacted]																								
Visit type	S	S	TH[b]	S	S	S	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	S	T[d]	S	S
[redacted]																								
Procedure																								
[redacted]																								
Blood sampling for PK of RLZ[m]		X	X				X		X		X		X					X	X	X	X			O
Blood sampling for DNA and RNA analysis		X																						
Serum complement [redacted] and plasma complement [redacted][n]		X																						
Total IgG[o,p]	X	X		X	X	X	X	-/X/-	X	-/X/-	X	-/X/-	X	-/X/-	X		X				X		X	O

Table 1-1: Schedule of Activities

Period	Scr[a]	Treatment Period (24 Weeks)																			EOT/EDisc	SFU	EOS	Unsch
[redacted]																								
Visit type	S	S	TH[b]	S	S	S	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	S	T[d]	S	S
[redacted]																								
Procedure																								
IgG subclasses		X										X								X			
[redacted]		X																		X			
LGI1 IgG (total and subclasses) serum quantification		X		X			X		X		X		X							X		X	
Anti-drug antibodies[q]	X	X					X		X		X		X					X		X		X	
CSF sample collection for LGI1[r]	O																			O			

Table 1-1: Schedule of Activities

Period	Scr[a]	Treatment Period (24 Weeks)																			EOT/EDisc	SFU	EOS	Unsch
[redacted]																								
Visit type	S	S	TH[b]	S	S	S	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	S	T[d]	S	S
[redacted]																								
Procedure																								
Blood sampling for exploratory biomarker analysis[s]		X																		X			
Seizure evaluation[t]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X
Provide seizure diary	X																							
Medical resource utilization	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RBANS[v]	X						X				X				X						X			O
mRS[w]	X	X					X				X				X						X			O
CGI-S[v]	X						X				X				X						X			O

Table 1-1: Schedule of Activities

Period	Scr[a]	Treatment Period (24 Weeks)																		EOT/EDisc	SFU	EOS	Unsch
[redacted]																							
Visit type	S	S	TH[b]	S	S	S	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	S	TH[c]	TH[c]	TH[c]	TH[c]	TH[c]	S	T[d]	S	S
[redacted]																							
Procedure																							
SF-36		X								X										X			O
EQ-5D-5L		X								X										X			O
MRI scan[u]	X																			X			

ADA=antidrug antibody; AE=adverse event; BL=Baseline (predose); BP=blood pressure; [redacted] CGI-S=Global Impression of Disease Severity; CSF=cerebrospinal fluid; C-SSRS=Columbia Suicide Severity Rating Scale; CT=computed tomography; Disc.=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EDisc=Early Discontinuation Visit; EOS=end of study; EOT=end of treatment; EQ-5D-5L=EuroQol-5D-5L; FSH=follicle stimulating hormone; GI=gastrointestinal; HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; IVMP=intravenous methylprednisolone; LGI1=leucine-rich glioma inactivated 1; MRI=magnetic resonance imaging; mRS=Modified Rankin Scale; No.=number; O=optional; PD=pharmacodynamic; PE=physical examination; Per.=Period; PK=pharmacokinetic(s); Proc.=Procedure; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RLZ=rozanolixizumab; RNA=ribonucleic acid; S=site visit; Scr=Screening; SFU=Safety Follow-up; SF-36=36-item Short Form Survey; T=telephone call; TB=tuberculosis; TH=telephone call and home visit; Unsch=Unscheduled Visit

[a] Recording of seizures will be initiated and conducted on each day of Screening. These daily seizure recordings will be used to calculate the Baseline seizure frequency.

[b] The study participant will be telephoned by a qualified site personnel and be assessed for AEs, concomitant medications, withdrawal criteria, and the seizure diary. A healthcare professional will also visit the study participant at their home to collect PK samples. Alternately, the visit can be conducted at the site as deemed necessary by site personnel and/or the study participant. There should be at least 1 day between visits.

[c] Visits may be performed by a healthcare professional visiting the study participant at their home. During the home visit, a qualified site personnel will assess AEs, concomitant medications, withdrawal criteria, and the seizure diary by telephone call prior to IMP administration. Alternately, the visits can be conducted at the site as deemed necessary by site personnel and/or the study participant. Feasibility of IMP dosing in a home setting must be confirmed before the visit is conducted.

[d] During the SFU phone call, the qualified site personnel will assess AEs, concomitant medications, and evaluation of seizure diary by telephone.

[e] For eligibility criteria, the laboratory and body weight data from Screening will be used. However, the urine pregnancy test at Visit 2 also must be negative for eligibility.

[f] A brief PE can also be performed on the occurrence of an AE. A full or brief PE should include evaluation 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, W13, W21, EDisc if applicable and EOS (see Section 10.12). A full neurological examination should also be performed for any study participant who experiences severe and/or serious headache and for study participants with suspected aseptic meningitis. For details of the assessments included in these examinations see Section 8.2.1 (description of full and brief PE), and Section 8.2.2 (description of full and brief neurological examination).

[g] 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.

[h] A urine pregnancy test will be performed using a dipstick test; a positive urine pregnancy test must be confirmed using a serum pregnancy test. The serum pregnancy test must be negative before dosing.

[i] The FSH test will only be performed to confirm menopausal status in female study participants (as applicable).

[j] The IGRA test will be performed by a local laboratory. Study participant should not be dosed in case of any positive IGRA or 2 indeterminate IGRAs until the study participant has been evaluated by a TB specialist. Further details are provided in Section 10.12.

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

[l] The interval between administration of 2 consecutive rozanolixizumab doses should be 7 ±2 days. On dosing days for the first 2 weeks (Visit 2 and Visit 5), a 4-hour post-dose observation will be in place. Assuming the first 2 doses were well tolerated, on dosing days in Week 3, 4, and 5 (Visit 6, Visit 7, and Visit 8), a 1-hour post dose observation will be in place. Assuming the first 5 doses were well tolerated, on subsequent weeks, a 15-minute post-dose observation will be in place. Following a missed dose due to temporary IMP discontinuation, a 1-hour observation will be in place for the first 2 doses followed by a 15 minute observation per above. The minimum post dose observation time frame may be extended at the discretion of the investigator or study nurse at home dosing visits. These recommendation are applicable for dosing at site and at home except where specified.

[m] At Visits 2, 8, 12, 16, 22, and 29, blood samples for PK will be obtained predose. At nondosing Visits 3, 30, 31, and 32, samples will be obtained once during the visit.

[n] Serum and plasma complements are to be obtained predose at Baseline (Day 1) for all study participants.

[o] Ad hoc assessments of IgG and albumin can be performed to monitor the recovery of IgG and albumin levels, or for random sampling of study participants to maintain the blind. These results will be reviewed by the unblinded medical monitor only (Section 7.1.4).

[p] For Visits 9–11, Visits 13–15, Visits 19–21, and Visits 23–25, samples for total IgG assessments are only required to be taken at the middle visit (ie, Visits 10, 14, 20, and 24). In the table, the samples required at these visits are described as '-/X/-' representing no sample (-)/sample (X)/no sample (-).

[q] For study participants who withdraw from the study, a sample should be taken for ADA analysis upon his/her EDisc Visit. A Screening sample will be taken for the purpose of assay parameter characterization (eg, setting ADA cut points and PK selectivity assessments).

[r] This optional CSF sample will be used to test for LGI1 autoantibodies using an independent research-use only, quantitative assay (flow cytometry LGI1 assay). Further details are provided in Section 8.9.

[s] Exploratory biomarker samples will be taken predose at Baseline (Day 1) and at EOT/EDisc Visit for all study participants. In study participants who experience severe and/or serious headaches or suspected aseptic meningitis, 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.

[t] Seizure data should be recorded in the seizure diary starting from the day of consent.

[u] MRI should be collected per local guidelines during the Screening Period or at the Baseline Visit.A MRI performed within 3 months of the Screening Period may also be acceptable as per the investigators judgement. Additional MRI may be performed at any timepoint in the study as deemed necessary by the investigator/local radiologist.

[v] The assessments of RBANS and CGI-S should be performed as close as possible prior to the Baseline Visit.

[w] The assessment of mRS at Screening should be performed as close as possible to consent.

[x] Visit 17 and Visit 18 were removed in Protocol Amendment 4,; however, the Visit schedule was not renumbered.

[y] Visit 4 was removed in Protocol Amendmet 5; however, the Visit schedule was not renumbered.

1.3.1 Additional study assessments

In addition to those detailed in Table 1-1, the assessments in Table 1-2 may be required in case of adverse events of special monitoring (AESM) (severe and/or serious headache, or 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 based on the timing of the assessments.

Table 1-2: Additional study assessments

Assessment	When applicable
For study participants who experience severe, and/or serious headache or for study participants with a 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	Assessments required for all study participants are detailed in the Schedule of Activities (Table 1-1). In study participants who report severe and/or serious headache or features suggestive of 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 (Section 8.2.2) 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 (gadolinium-enhanced preferred) and/or LP for CSF collection are to be performed if indicated at the discretion of the investigator.
For study participants who experience aseptic meningitis:	
LP	In study participants who report signs and/or symptoms of meningitis which require a LP, results of the CSF analysis 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 (i.e. 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 in the eCRF 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.

Table 1-2: Additional study assessments

Assessment	When applicable

AE=adverse event; AESM=adverse event of 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

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 Table 1-1.

2 INTRODUCTION

Rozanolixizumab is a humanized IgG4 monoclonal antibody that is being developed as an inhibitor of the activity of the 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.

Rozanolixizumab binds with high affinity to FcRn at both neutral and acidic pH. Immunoglobulin G that is constitutively taken up by pinocytosis into cells fails to bind to FcRn, even at the acidic pH found in the endosome. It is therefore not recycled and is trafficked to the lysosomes for degradation.

Production of pathogenic IgG autoantibodies is the major pathophysiology leading to a number of autoimmune diseases, which include myasthenia gravis (MG), pemphigus vulgaris, immune thrombocytopenia (ITP), Goodpasture's syndrome, neuromyelitis optica, Guillain-Barré Syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and AIE.

As individual disease entities, IgG autoantibody-mediated conditions are relatively rare. Treatment of these disorders remains a difficult clinical problem, requiring in many of these conditions the long-term use of corticosteroids alone or combined with other immunomodulatory therapy. These therapeutic approaches are not effective in all patients and conditions, and have broad immunosuppressive effects causing considerable toxicity and treatment-related morbidity.

Treatments aimed at reducing the quantity of circulating IgG autoantibodies, including plasmapheresis, immunoadsorption, or high dose intravenous immunoglobulin (IVIg), are being used for primary and secondary therapy of autoimmune diseases. The therapeutic approach of these treatments is thought in part to be based on lowering levels of pathogenic autoantibodies, which represents rational and effective treatment modalities of autoimmune diseases.

Therefore, the removal of IgG antibodies by FcRn blockade may provide an effective therapeutic option for IgG autoantibody-mediated autoimmune disorders.

More 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

Autoimmune encephalitis comprises a group of related immune system-mediated conditions whereby the individual's immune cells erroneously target antigens in healthy cells in the central nervous system (CNS), including brain cells, resulting in localized swelling and inflammation (Kelley et al, 2017; Genetic and Rare Diseases Information Center, 2017).

Symptoms of AIE may be neurologic and/or psychiatric. Examples of neurologic symptoms include impaired memory; problems with balance, speech or vision; and seizures. Examples of psychiatric symptoms include psychosis, aggression, panic attacks, euphoria, fear and compulsive behaviors (Lancaster, 2016). The classical presentation of encephalitis consists of a subacute (days to a few weeks) progressive decrease in the level of consciousness, often with fluctuations and altered cognition. Memory, especially retention of new information, may be impaired early in the clinical course. Patients may progress to coma.

The primary symptoms of LGI1 AIE include cognitive impairment (recent memory loss or spatial disorders), seizures (including faciobrachial dystonic seizures [FBDS], other focal seizures, and tonic-clonic seizures), hyponatremia, and sleep disorders. Faciobrachial dystonic seizures are the pathognomonic sign of LGI1 AIE, and describe a distinctive adult onset, frequent, brief dystonic seizure semiology that predominantly affects the arm and ipsilateral face (Irani et al, 2011; van Sonderen et al, 2016). Leucine-rich glioma inactivated 1 autoantibodies are detected in serum and occasionally in CSF (van Sonderen et al, 2016). In addition, brain MRIs may indicate abnormal signals in the temporal lobe, hippocampus, or basal ganglia (Lancaster, 2016).

Leucine-rich glioma inactivated 1 AIE defines a clinical disease with a homogeneous patient population that may be responsive to immunotherapy, making it an appropriate target for treatment with rozanolixizumab. Leucine-rich glioma inactivated 1 AIE has an estimated prevalence of 0.7/100,000 person-years (Dubey et al, 2018), which translates to approximately 2320 patients in the US. Characteristic clinical presentation of patients with LGI1 AIE includes:

- Predominantly male (66%); typically adults in their later adult years (60+ years old) (Vogrig et al, 2019; Hermetter et al, 2018); rarely observed in children or adolescents.
- Faciobrachial dystonic seizures as the pathognomonic sign (Irani et al, 2011). This seizure type is unique to LGI1 AIE. Patients may also experience other types of focal seizures as well as secondarily generalized seizures.
- Cognitive symptoms including memory loss and confusion, hallucinations, rapid eye movement sleep disturbance, and psychiatric disturbance.
- Muscular symptoms which may include neuromyotonia, causing spontaneous muscular activity or twitching.
- Hyponatremia is common.
- Brain MRI showing hyperintensities in the mesial temporal lobe (Vogrig et al, 2019).

- Rarely associated with a tumor (thymoma <5%; Geis et al, 2019).
- Frequently associated with specific human leukocyte antigen haplotypes as with other IgG4-mediated diseases (Vogrig et al, 2019).
- Anti-LGI1 autoantibodies are detected in serum but often undetected in CSF (van Sonderen et al, 2016).

The array of disease features causes significant clinical burden for the patient, in particular, seizures and cognitive impairment. The majority of patients with LGI1 AIE are expected to develop seizures (~90% of patients), and all will experience at least some cognitive dysfunction over the course of their disease (van Sonderen et al, 2016). Patients with LGI1 AIE may experience various types of seizures, including FBDS, which may occur up to 100 times a day (median 40/day) with a very short duration of <15 seconds per episode (van Sonderen et al, 2016). Faciobrachial dystonic seizures are often the presenting clinical feature, with a later onset of cognitive impairment (Thompson et al, 2018). Seizures with bilateral tonic-clonic evolution usually appear in later stages of the disease at a time when cognitive impairment is also present (Vogrig et al, 2019).

Although LGI1 AIE has a clinical presentation that is distinct from other AIE, diagnosis is challenging due to initial similarity in presentation to other types of epilepsy, which can result in delayed diagnosis, a subsequent delay in appropriate treatment (de Bruijn et al, 2019) and poorer outcome.

There are currently no approved therapies for the treatment of AIE overall. Current acute and chronic treatment paradigms are variable, mainly based on expert opinions, a select number of case studies and retrospective reviews, with no approved treatment options. Controlled studies are needed to guide treatment decisions in the management of LGI1 AIE, and for more specific immunotherapies, to reduce the side effect profile of current chronic treatment options that address seizures as well as cognitive and psychiatric symptoms.

By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of antibodies and reduces the concentration of IgG, thus offering an alternative to existing treatments. This Phase 2, randomized, placebo-controlled study will evaluate the efficacy, safety, and PK of rozanolixizumab in adult study participants with LGI1 AIE.

2.2 Background

Rozanolixizumab has been administered to human study participants in several clinical studies (see the updated IB for listing of completed and ongoing studies).

Overall, data from completed studies suggest that repeated administrations of rozanolixizumab at a dose approximating 7mg/kg and 10mg/kg sc is generally well tolerated, with an acceptable safety profile. Treatment-emergent AEs were most frequently reported in the system organ class of Nervous system disorders. In study participants with generalized myasthenia gravis (gMG) receiving repeated cyclic treatment with rozanolixizumab, the most common TEAEs were headache, diarrhoea, pyrexia, nausea, and arthralgia. Dose-dependent, statistically significant reductions in levels of total IgG and dose-dependent reductions in levels of IgG subclasses (IgG 1 to 4) were observed after rozanolixizumab was administered by iv or sc routes. In study participants with gMG, clinically relevant improvements in day-to-day functioning were observed following treatment with rozanolixizumab compared with placebo.

Further details may be found in the IB.

2.3 Benefit/Risk Assessment

As individual disease entities, IgG autoantibody-mediated conditions are relatively rare. Treatment of these disorders remains a difficult clinical problem, requiring in many of these conditions the long-term use of corticosteroids alone or combined with cytotoxic agents. These therapeutic approaches are not effective in all patients and conditions, and have broad immunosuppressive effects causing considerable toxicity and treatment-related morbidity.

Treatment of patients with LGI1 AIE is comprised of immunotherapy and symptomatic therapy including antiseizure medications. Immunotherapeutic agents are classically divided into first-line (acute phase) and second-line therapies (maintenance phase). First-line therapies include high-dose IVMP, IVIg, immunoadsorption, and plasma exchange (PEX). Second-line agents such as rituximab, cyclophosphamide, mycophenolate, azathioprine, bortezomib, or tocilizumab are used in refractory cases, during relapses or as a maintenance therapy to prevent relapses. However, only 1 small prospective study has evaluated the efficacy of immunotherapy (IVIg) in LGI1 AIE (Dubey et al, 2020). Current immunotherapy recommendations are based on case series and clinical experience.

Rozanolixizumab represents an innovative, sc anti-FcRn monoclonal antibody that may provide a novel and specific therapeutic approach for the treatment of patients with LGI1 AIE. While not previously evaluated in LGI1 AIE, 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 the [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, injections site reactions, vomiting, myalgia and herpes simplex infections. Headache is the most commonly reported ADR, 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 hypersensitivity is provided in Appendix 14 (Section 10.14) and Appendix 15 (Section 10.15), respectively, and the management and expedited reporting requirements of the AESMs (severe and/or serious headache and suspected aseptic meningitis) to UCB are specified in Appendix 13 (Section 10.13).

Restrictions on the use of live vaccines have been defined in exclusion criterion 20. If vaccination with non-live vaccines (including COVID-19 vaccines) is considered necessary once

a study participant has started therapy with IMP, the degree of protection afforded with a vaccine may be compromised while the participant is being treated with IMP.

Based on its mechanism of action, rozanolixizumab will reduce total IgG levels including vaccine specific IgG. However, it is unknown if the immunogenicity of a vaccine will be compromised by FcRn inhibition. Given the study population characteristics (eg, status of the underlying disease, concomitant immunosuppressive therapies, etc), it is recommended to perform individualized benefit-risk assessment for vaccination and specifically vaccination against COVID-19 infection. If vaccination is planned, information regarding vaccine should be recorded (Section 6.5.1). Vaccination should be scheduled, if at all possible, to allow differentiation of safety profiles of IMP and vaccine (eg, a minimum window of 72 hours between COVID-19 vaccination and IMP administration). If any adverse events (AEs) were to occur, they should be handled as described in Section 6.5.1 with causality assessment provided for both IMP and vaccine. Additionally, to further characterize the effect of rozanolixizumab on vaccination response, measurement of vaccine titres are being tested in our development programs.

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

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the efficacy of rozanolixizumab as measured by seizure freedom	• Seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25)
Secondary	
• To assess the efficacy of rozanolixizumab as measured by a change in cognitive function	• Change from Baseline in RBANS total scale index score at the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab on study participants' overall disability	• Proportion of participants with a favorable outcome in the mRS during the Treatment Period, where favorable outcome is defined as no worsening for participants with a Baseline mRS score of ≤1 or improvement of ≥1 point for participants with a Baseline mRS score of ≥2
• To assess the efficacy of rozanolixizumab as measured by use of rescue medication	• Use of rescue medication due to an absence or loss of clinical benefit during the Treatment Period

Objectives	Endpoints
• To assess the efficacy of rozanolixizumab as measured by the onset of seizure freedom	• Time to first occurrence of seizure freedom defined by the number of days after randomization to the first day of the first 28 consecutive days without seizures during the Treatment Period
• To assess the safety and tolerability of rozanolixizumab	• Incidence of TEAEs during the study
Exploratory	
• To assess the time of onset of efficacy of rozanolixizumab for the subgroup of study participants who achieve the primary endpoint as measured by the onset of seizure freedom	• Time to achieving seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab as measured by seizure control	• 'Good' or 'Moderate' seizure control maintained over a period of 4 consecutive weeks until the end of the Treatment Period (Week 25)
• To assess the efficacy of rozanolixizumab as measured by a change in cognitive function (domains of RBANS)	• Change from Baseline in the domain scores of RBANS (immediate memory; visuospatial/constructional; delayed memory; language; and attention) during the Treatment Period
• To assess the efficacy of rozanolixizumab using an integrated ranked analysis of combined clinical and functional outcome measures	• Ranked outcome derived from the combined integrated analysis of clinical and functional assessments (including mRS, seizure freedom, and, cognitive function) at the end of the Treatment Period (Week 25)
• To assess the safety and tolerability of rozanolixizumab	• Change from Baseline in vital signs and laboratory results during the study
• To assess the PD effect of rozanolixizumab as measured by the total IgG concentrations in serum	• Value and change (absolute and percentage) from Baseline in serum total IgG and IgG subclass concentrations during the study

Objectives	Endpoints
• To assess the PD effect of rozanolixizumab as measured by LGI1 autoantibody levels using the flow cytometry LGI1 quantitative assay	• Value and change from Baseline in LGI1 autoantibody serum levels during the Treatment Period • Value and change from Baseline in LGI1 autoantibody CSF levels during the Treatment Period (for consenting participants)
• To evaluate the effects of rozanolixizumab on patient-reported HRQoL	• Value and change from Baseline in the SF-36-PCS score, SF-36-MCS score, and individual domain scores during the Treatment Period • Value and change from Baseline in the EQ-5D-5L during the Treatment Period • Value and shift from Baseline in CGI-S during the Treatment Period
• To evaluate the effects of rozanolixizumab on HCRU	• Disease-related hospitalizations (number, duration)
• To assess the PK characteristics of rozanolixizumab	• Plasma concentration of rozanolixizumab during the Treatment Period
• To evaluate the impact of concomitant AEDs on rozanolixizumab plasma levels	• Plasma concentration of rozanolixizumab during the Treatment Period
• To evaluate the incidence and emergence of ADA of rozanolixizumab and impact on PK and PD	• ADA status
• To evaluate the effects of rozanolixizumab on the concentration of total protein, albumin, [redacted] and serum and plasma complement levels	• Values and change from Baseline in total protein and albumin, and serum immunoglobulin concentrations [redacted] during the Treatment Period • Values and change from Baseline in serum complement levels ([redacted] and plasma complement levels ([redacted]) in case of infusion or hypersensitivity reaction

Objectives	Endpoints
• To assess exploratory biomarkers	• DNA, RNA, and genetic analysis that may be measured to understand the cause and appropriate treatment of LGI1 AIE • Exploratory biomarkers such as but not limited to B-cell activating factor and circulating immune complexes • Proteins and metabolite changes may be measured to understand the cause, progression, and appropriate treatment of LGI1 AIE

4 STUDY DESIGN

4.1 Overall design

AIE001 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, 2-arm, repeat dose study to evaluate the efficacy, safety, and PK of rozanolixizumab for the treatment of LGI1 AIE. The primary endpoint of the study is seizure freedom defined by 28 consecutive days of no seizures, maintained until the end of the Treatment Period (Week 25).

Approximately 68 study participants with LGI1 AIE with onset of disease symptoms between 0 to 12 months prior to study entry, as assessed by the investigator, will be randomized to receive rozanolixizumab [redacted] or placebo, administered by sc infusion at [redacted] intervals for 24 weeks.

The study participants will be stratified at randomization by:

- Time from disease symptom onset (≤6 months or >6 months from disease symptom onset)
- Cognitive function (RBANS score of ≤85 or >85)

After the initial 5 IMP administrations have been performed at the clinic, the study participant may have the opportunity to be treated at home by a visiting healthcare practitioner.

Although the use of rescue medication is allowable at any time during the study, the use of rescue medications should be delayed, if clinically feasible, for at least 4 weeks following the initiation of study treatment. Study participants who require rescue medication will discontinue blinded treatment, and complete the assessments for the EDisc Visit. Following this, the selection of an appropriate rescue medication will be made at the investigator's discretion, and the study participant will enter the SFU Period. Unscheduled study visits are permitted for any study participant, including those study participants who have initiated rescue medication.

An IDMC will be established for the study to monitor the emerging safety data within the clinical study on a periodic basis.

The maximum study duration per study participant is up to 38 weeks. There are 3 study periods:

- Screening Period: Eligibility will be assessed during the Screening Period of up to 42 days. If a study participant becomes seizure free as a result of steroid treatment, the participant may

still be randomized in the study, providing the prior occurrence of seizures is well documented.

Participants who have previously received a first line AIE treatment in the 6 months prior to randomization (counted from the onset of treatment to randomization date) may be considered for enrollment provided that:

– The participant is considered to have been under treated in the opinion of the investigator

AND

– Currently the participant is experiencing a seizure rebound that requires initiation or re-initiation of high dose corticosteroids (500-1000mg MP equivalent /day) in the opinion of the investigator.

Following screening and completion of the Baseline assessments, treatment will be initiated in study participants who are deemed appropriate for initiation or re-initiation of high dose corticosteroids (500 to 1000mg MP equivalent/day) based on clinical symptoms and history, or who have initiated corticosteroids within 42 days prior to randomization at a dose of 500 to 1000mg MP equivalent/day. Corticosteroids can be initiated prior to the start of the Screening Period, however, the study participant must be randomized within 42 days of corticosteroids initiation. If the study participant has initiated a steroid taper, the study participant cannot receive oral steroids at a dose lower than 40mg/day when randomized. Study participants receiving a steroid dose of 60mg/day, 50mg/day or 40mg/day at the time of randomization will have to maintain that dose for 7 days (±2 days), 14 days (±2 days) or 21 days(±2 days), respectively, before resuming [redacted] down-titration steps. Each subsequent down-titration step will last for 7 days (±2 days; see Section 1.2). For those participants that have not initiated a steroid taper, the down-titration of the oral steroid dose will begin after at least 3 days on the initial steroid dose, as per investigator.

- Treatment Period: Participants who have been confirmed eligible will be randomized in a 1:1 ratio to receive rozanolixizumab [redacted] or placebo at [redacted] intervals over a 24-week Treatment Period. Initially, study participants will receive rozanolixizumab or placebo in addition to iv or oral steroids that will be tapered as described in Section 1.2.
- Safety Follow-Up Period: Study participants who complete the 24-week Treatment Period or prematurely discontinue IMP, as well as study participants who receive rescue medication during the 24-week Treatment Period will undergo the EOT Visit/EDisc Visit and enter the SFU Period. At 4 weeks after the final dose, study participants will undergo a SFU phone call, and at 8 weeks after the final dose, study participants will undergo the EOS Visit.

Study participants who complete the 24-week Treatment Period and require further treatment may have the option to access rozanolixizumab via another clinical study or an access program, if available, as per local laws and regulations. Study participants continuing with rozanolixizumab must complete an End of Treatment Visit and be transitioned to rozanolixizumab provided by those alternative options without undergoing SFU or EOS Visits.

4.2 Scientific rationale for study design

Leucine-rich glioma inactivated 1 is a protein mainly expressed in the hippocampus and the temporal cortex, where it is secreted into the synaptic space. It is part of an inhibitory pathway

linking the presynaptic voltage-gated potassium channel complex and the postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Fukata et al, 2010; Ohkawa et al, 2013). Specifically, it is classified as an antineuronal surface antigen or antisynaptic protein-associated AIE. Kornau et al (2020) have recently demonstrated that LGI1 antibodies alone are sufficient to promote neuronal excitability, a basis of seizure generation. Seven of the overall 26 LGI1 antibodies efficiently blocked the interaction of LGI1 with its receptor ADAM22 in vitro and their mean LGI1 signal on mouse brain sections was weak as compared to the remaining, non-ADAM22-competing antibodies. Nevertheless, both types of LGI1 antibodies increased the intrinsic cellular excitability and glutamatergic synaptic transmission of hippocampal CA3 neurons in slice cultures.

The binding of autoantibodies to LGI1 disrupts pre- and postsynaptic LGI1 signaling, resulting in neuronal hyperexcitability (Petit-Pedrol et al, 2018). By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of antibodies and reduces the concentration of pathogenic IgG, thus offering an alternative to existing treatments. Treatment with rozanolixizumab is expected to result in a decrease in LGI1 autoantibodies and thus to reduce the associated pathological processes and ongoing clinical sequelae.

Current therapeutic approaches for AIE are thought in part to be based on lowering levels of pathogenic autoantibodies, which represents targeted, rational, and effective treatment modalities of autoimmune diseases. Therefore, removal of the IgG autoantibodies by FcRn blockade may provide an effective therapeutic option for IgG autoantibody-mediated autoimmune disorders, in this case for the treatment of LGI1 AIE.

AIE001 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, 2-arm, repeat-dose study that aims to enroll approximately 68 study participants with LGI1 AIE. To be eligible for inclusion in the study, participants must have disease symptoms onset within 12 months of Screening, be deemed appropriate for initiation or re-initiation of high dose corticosteroids (500 to 1000mg MP equivalent/day) based on clinical symptoms and history, or have initiated high dose corticosteroids within 42 days of randomization, and be seropositive for LGI1 antibodies. Study participants are eligible for inclusion if they are experiencing FBDS (with or without focal [partial] seizures) or focal (partial) seizures including focal to bilateral tonic-clonic seizures, or have experienced such seizure which subsided following initiation of high dose corticosteroids (500 to 1000mg MP equivalent/day).

As described in Section 2.1, the FBDS type is unique to LGI1 AIE; however, patients with LGI1 AIE may also experience focal and tonic-clonic seizures, that are not unique to LGI1 AIE. Therefore, participants eligible via these seizure types must also meet additional criteria for possible AIE, as outlined by Graus et al (2016) in a position paper designed to provide a practical clinical approach to diagnosing AIE. Coupled with this, study participants are excluded if they have previously been diagnosed with epilepsy, have a new-onset seizure that is unrelated to LGI1 AIE, or if there is any known or suspected medical cause for the onset of seizures, other than possible AIE. Therefore, although AIE001 permits the entry of study participants with focal (partial) including focal to bilateral tonic-clonic seizures in the absence of FBDS, these participants must also meet additional criteria designed to reduce the potential risk of enrolling study participants who do not have LGI1 AIE. In this way, AIE001 intends to enroll a study population that reflects the characteristics of the real-world LGI1 AIE population.

At randomization, study participants will be stratified by:

- Time from disease symptom onset (≤6 months or >6 months from disease symptom onset)
- Cognitive function (RBANS score of ≤85 or >85)

The decision to stratify based on disease symptom onset and cognitive function is based on data from Thompson et al (2018) who showed in a multivariate regression analysis, that the time to the initiation of immunotherapy, and the presence of cognitive impairment significantly affected the likelihood of FBDS cessation. Factors such as the time to antiepileptic drug administration, age, sex, or the frequency of FBDS were not statistically significant in the model. These findings were supportive of Dubey et al (2017) who showed that early initiation of therapy (<6 months from symptom onset) was an independent predictor of favorable seizure outcome. Based on these observations, study participants will be stratified at randomization according to time since disease symptom onset (≤6 months or >6 months) and the presence or absence of cognitive impairment.

The stratification by cognitive impairment will be based on the RBANS index score. The RBANS cognitive battery measures performance across a range of cognitive domains (see Section 8.1.2). The RBANS index score reflects an aggregate of performance on these domains, and is computed with reference to age-based normative data derived from a cognitively normal population. In this context, an RBANS index score of 85 reflects a value of 1 standard deviation (SD) below the mean of the age relevant normal population (Duff et al, 2008; Randolph et al, 1998), such that an RBANS index score of ≤85 is indicative of clinically important cognitive impairment, while an RBANS index score above 85 can be categorized as cognitively normal. Therefore, to address the extent to which cognitive impairment at baseline may influence the nature and magnitude of response to treatment in AIE001, study participants will be stratified by RBANS score of ≤85 or >85.

There are currently no approved treatments for any of the AIE conditions. Given this, and the need for appropriately controlled studies to investigate the impact of a new treatment on the symptoms of LGI1 AIE, AIE001 has been designed with a placebo control. In AIE001, all study participants will enter the study having initiated or having been deemed appropriate for initiation or re-initiation of the first-line treatment that will be tapered as per the schedule in Section 1.2. In this way, the study aims to ascertain if rozanolixizumab offers a benefit beyond steroid therapy. The planned treatment duration for AIE001 is 24 weeks. This duration was selected to allow for the steady down-titration of oral steroids, and a sufficient interval for rozanolixizumab to exert a pharmacodynamic effect on IgG levels and the hypothesized therapeutic effect on the symptoms of LGI1 AIE. To ensure that all study participants are receiving appropriate clinical care throughout the duration of the study, participants who do not experience a clinical improvement (ie, an absence of clinical benefit) within the first 4 weeks of the Treatment Period or experience a clinical worsening (ie, a loss of clinical benefit) at any time (Section 7.1.3) or require rescue treatment at any time (Section 6.5.3) must be withdrawn.

4.3 Justification for dose

The planned dose of rozanolixizumab for this study is [redacted] by sc infusion. As outlined below, this dose is justified by:

- Clinical data from the pivotal Phase 3 study (MG0003) showing a meaningful improvement at repeated doses of 7mg/kg and 10mg/kg by body weight tiers in gMG.

- 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 reduction for a [redacted] fixed dose and weight-tiered doses approximating 7mg/kg and 10mg/kg.

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 study participants with gMG, clinically relevant improvements in day-to-day functioning were observed following treatment with rozanolixizumab 7mg/kg compared with placebo. In study 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.

A Phase 3 study, MG0003, has been completed to evaluate the efficacy and safety of rozanolixizumab in study participants with gMG. The dose regimens being evaluated in these studies were weight-tiered doses approximating 7mg/kg and 10mg/kg Q1W.

The proposed [redacted] fixed dose of rozanolixizumab is selected to achieve a comparable range of exposures and IgG reductions as the weight-tiered doses that have been evaluated in the completed Phase 3 pivotal study in gMG.

A population PK-PD model was developed based on observed PK and IgG data from the pivotal Phase 3 study (MG0003), 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 [redacted] 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 Q1W 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 physicians and patients and to reduce the potential for dosing errors. Thus, a dose regimen of [redacted] is planned for investigation in this study.

4.3.1 Justification for IgG target

Rozanolixizumab administration resulted in a rapid clearance of serum IgG levels in both healthy volunteers (UP0018 and UP0060) and patients with gMG (MG0002 and MG0003) or ITP

(TP0001). In MG0003, serum IgG levels decreased reaching a mean maximum reduction of approximatley 71% for the rozanolixizumab ≈7mg/kg group and 78% for the ≈10mg/kg group. The reduction in IgG was mirrored by a reduction in anti-acetylcholine receptor (AChR) autoantibodies in patients with gMG and demonstrated a [redacted] clinically meaningful improvement in clinical outcome scales (MG-ADL and QMG) 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 PEX, and falls within the range associated with clinical benefit in various autoimmune indications.

For AIE, 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 those proved to be efficacious in gMG.

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 Visit performed 1 week after the final dose of IMP or upon discontinuation of the study, followed by a SFU phone call 4 weeks after and an EOS Visit 8 weeks after the final dose.

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 to ≤89 years of age, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Study participant must be seropositive for LGI1 antibody measured by LGI1 serum autoantibody cell-binding assay.

3a. Study participant must have ≥2 seizures/week during the Screening Period or have experienced such seizures that stopped following high dose corticosteroids (500 to 1000mg MP equivalent/day):

- Either FBDS with or without other focal (partial) seizures including focal to bilateral tonic clonic
- Or focal (partial) seizures including focal to bilateral tonic clonic and fulfil the following new-onset AIE criteria:
    a. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change), or psychiatric symptoms.

AND

b. At least one of the following:

i. New focal CNS finding, as per the investigator's assessment

ii. Seizures not explained by a previously known seizure disorder

iii. CSF pleocytosis (white blood cell count of >5 cells/mm^3)

iv. MRI features suggestive of encephalitis (Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes [limbic encephalitis], or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation).

AND

c. Reasonable exclusion of alternative causes

4a. Study participant has initiated or re-initiated corticosteroids at a dose of 500 to 1000mg MP equivalent/day within 42 days prior to randomization. Participants re-initiating corticosteroids are eligible only if re-initiation is due to seizure rebound and within the timeframe outlined in Section 4.1.

If the study participant has initiated a steroid taper, the study participant cannot receive an oral steroid dose lower than 40mg/day when randomized.

5. Study participant with onset of disease symptom between 0 to 12 months prior to Screening, per investigator's assessment.

Weight

6. Study participant weighs at least 35kg (for males and females) at Screening.

Sex

7a. Male or Female

- A female participant is eligible to participate if she is not pregnant (see Appendix 4 [(Section 10.4]), not breastfeeding, and at least one of the following conditions applies:
  - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)
    OR
  - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the treatment period and for at least 90 days after the final dose of study treatment.

Informed consent

8a. Study participant is capable of giving signed informed consent or has a legal representative to consent for him/her as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other

9a. Study participant has a reliable caregiver who will be available during the whole study period, as determined by the investigator.

10a. Removed in Protocol Amendment 4.

5.2 Exclusion criteria

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

Medical conditions

1. Study participant has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study.

2. Study participant has a history of alcohol use disorder or other substance use disorder (as per Diagnostic and Statistical Manual of Mental Disorders-5) within the previous 12 months.

3. 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 [redacted], since [redacted] is a constituent of the rozanolixizumab formulation.

4a. Study participant has a confirmed prior diagnosis of epilepsy or new onset seizures that are unrelated to LGI1 AIE or has any known or suspected medical cause for the onset of seizures other than possible AIE.

5. Study participant has a known active neoplastic disease or 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 definitively treated with standard of care approaches).

6. Study participant has 12-lead ECG with findings considered clinically significant by the investigator.

7a. Study participant has renal impairment, defined as glomerular filtration rate (GFR) <30mL/min/1.73m^2 at the Screening Visit.

8b. Study participant has a clinically important active infection (including unresolved or not adequately treated infection) as assessed by investigator, including participants with a serious infection within 6 weeks prior to the first dose of IMP.

9a. Study participant has a history of chronic ongoing infections (eg, Hepatitis B or C, human immune deficiency virus [HIV], active tuberculosis [TB]) or who tests positive for HIV, Hepatitis B or C at the 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.

10. 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).

11. Study participant has positive TB test at the Screening Visit unless it is determined by a TB specialist that the positive result is related to an adequately treated latent TB infection (see Section 10.12).

12. Study participants met 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 (WHO)/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 4 weeks 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
- Current nontuberculous mycobacterial (NTM) infection or history of NTM infection unless proven to be fully recovered.

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

13. Study participant has a lifetime history of suicide attempt (including an [redacted]), 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 Visit 1.

14. Removed in Protocol Amendment 4.

15. Study participant has a current or medical history of [redacted] deficiency.

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

17. Study participant has undergone a splenectomy.

18. Study participant has a current or medical history of primary immune deficiency.

Prior/concomitant therapy

19. Study participant has been treated with prohibited immunosuppressants, biologics, and other therapies within the timeframe specified in Section 6.5.2.

20a. Study participant has received a live vaccination within 4 weeks prior to the Baseline Visit; or intends to have a live vaccination during the course of the study or within 8 weeks following the final dose of IMP.

Prior/concurrent clinical study experience

21. Study participant has been previously randomized in this study (rescreening for screen-failed participants is allowed with prior consultation and permission of the medical monitor/study physician).

22. Study participant has previously received rozanolixizumab drug product.

23. Study participant has participated in another study of an IMP (and/or an investigational device) within the previous 3 months or 5 half-lives prior to Baseline (whichever is longer) or is currently participating in another study of an IMP (and/or an investigational device).

Diagnostic assessments

24b Alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) are >3x 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 judgement, 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 #24b 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).

25. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

26. Removed in Protocol Amendment 5 as already incorporated in exclusion criterion #10.

27. Removed in Protocol Amendment 2, and incorporated in exclusion criterion #24.

28. Removed in Protocol Amendment 2, and incorporated in exclusion criterion #24.

29. Removed in Protocol Amendment 2, and incorporated in exclusion criterion #24.

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

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

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

33. Removed in Protocol Amendment 4.

5.3 Lifestyle restrictions

There are no lifestyle restrictions during the study. The use of medicinal cannabidiols and medicinal marijuana (prescribed by a physician) is permitted. The study participant must be on a stable dose of cannabidiols and/or medicinal marijuana for 4 weeks prior to Screening Visit and remain stable for the duration of the study.

5.3.1 Meals and dietary restrictions

There are no meal or dietary restrictions during the study.

5.3.2 Caffeine, alcohol, and tobacco

There are no restrictions for caffeine or tobacco during the study.

Study participants are to avoid excessive alcohol consumption during the study particularly prior to the assessment of cognitive function.

5.3.3 Activity

There are no restrictions on activity during the 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 participants should be assigned a new participant number for rescreening and repeat all Visit 1 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 and the study participant may be randomized, provided all other eligibility criteria are met.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit at Screening may be repeated once for confirmation. Eligibility assessment will be based on the best of the 2 results available before initiating randomized treatment.

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

Eligible study participants will be randomized 1:1 to receive rozanolixizumab [redacted] or placebo (0.9% saline) by sc infusion [redacted] for 24 weeks. The interval between administration of 2 consecutive doses should be [redacted] days. A summary of the treatment administered is provided in Table 6-1.

Table 6-1: Study medications administered

Study treatment name	Rozanolixizumab	Placebo
Dose formulation	Solution for injection	Solution for injection
Unit dose strength(s)	A vial of rozanolixizumab at a concentration of 140mg/mL, formulated with [redacted]	0.9% sodium chloride aqueous solution (physiological saline, preservative free)
Dosage level(s)	[redacted]	Not applicable
Route of administration	Subcutaneous infusion	Subcutaneous infusion
Post-dose observation	On dosing days, for the first 2 weeks (Visit 2 and Visit 5), a 4-hour post-dose observation will be in place. Assuming the first 2 doses were well tolerated, on dosing days in Week 3, 4, and 5 (Visit 6, Visit 7, and Visit 8), a 1-hour post dose observation will be in place. Assuming the first 5 doses were well tolerated, on subsequent weeks, a 15-minute post-dose observation will be in place. Following a missed dose due to temporary IMP discontinuation, a 1-hour observation will be in place for the first 2 doses followed by a 15-minute observation per above. The minimum post-dose observation time frame may be extended at the discretion of the investigator or study nurse at home dosing visits. These recommendations are applicable for dosing at site and at home except where specified. The investigator is required to complete a check list to confirm that all conditions for home dosing have been met (as outlined in Section 8) prior to the start of home dosing.	
Use	Experimental	Placebo comparator
Sourcing	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 47abelled as required per country requirement.	Packaging will be described in the IMP Handling Manual. Packaging will be 47abelled as required per country requirement.
Current/Former name(s) or alias(es)	UCB7665	Not applicable

IMP=investigational medicinal product; w/v=weight/volume

6.2 Preparation, handling, storage, and accountability requirements

The investigator or designee must confirm 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 or healthcare professionals 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-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 and/or the healthcare professional.

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

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 randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for kits of study medication, as appropriate, according to the visit schedule.

To enroll a study participant (Visit 1), the investigator or designee will contact the IRT and provide brief details about the 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 participant number during the course of the study. The randomization number must be incorporated into the eCRF.

The randomization will be stratified by:

- Time from disease symptom onset (≤6 months or >6 months from disease symptom onset)
- Cognitive function (RBANS score of ≤85 or >85)

Early initiation of therapy (<6 months from symptom onset) and detection of a plasma membrane protein antibody were independent predictors of favorable seizure outcome ($p<0.01$; Dubey et al, 2017).

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 the IRT system.

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

- Designated bioanalytical staff analyzing PK samples
- IRT provider

The IMP for rozanolixizumab and placebo will not be identical in appearance. Therefore, study site pharmacists, other suitably qualified site personnel, or healthcare professionals who are responsible for preparation of IMP treatments will have access to treatment allocations for individual study participants via the IRT. 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 (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 (volumes, color, viscosity). The IMP preparation will be performed by unblinded personnel (unblinded qualified site staff or unblinded home healthcare practitioner at the participant's home). 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 personnel (blinded qualified site staff or blinded home healthcare practitioner at the study participant's home).

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

- Sponsor Patient Safety staff as needed for reporting SAEs to regulatory authorities.

- Members of the IDMC 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.
- The designated unblinded statistician and supporting programmer(s) responsible for the preparation of the data outputs for the IDMC 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 sponsor 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 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 clinical project manager 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 has to 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 medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

Investigator should take utmost precaution for the dosage of concomitant medications for study participants who might have impaired renal function (GFR 30ml/min/1.73m^2 to 45ml/min/1.73m^2) and should refer to the prescribing information for potential dose adjustment.

Given that study participants will be administered steroids up to Week 12 of the study, it is up to the discretion of investigator to initiate prophylaxis for pneumocystis carinii pneumonia if deemed appropriate.

The following concomitant medications are permitted during the study:

- Antiepileptic drugs: all study participants should preferably continue to take their Baseline AED regimen unchanged over the whole study period. Decreases in daily dose or discontinuation of AEDs are permitted, per investigator assessment. However, initiation of new AEDs or dose increase of a AED are not allowed.
- Corticosteroids (only as specified in the protocol)
- Topical steroids: the use of topical or local is permitted
- Antipsychotics: the dose should be stable within 1 week of the cognitive assessments
- Benzodiazepines may be used if at stable daily dosage regimen as concomitant medication. However, per needed benzodiazepine treatment that is deemed medically necessary in the opinion of the investigator should be administered, and the study participant's continuation in the study must be discussed between the medical monitor and the investigator.

Administration of COVID-19 vaccines will be recorded in the concomitant medication eCRF page. The specific name of the vaccine and the exact date of administration should be recorded, as instructed in the completion guideline. See Section 8.3.9 for details.

6.5.2 Prohibited prior and concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the Treatment Period except for use as specified or as rescue medication:

- High dose corticosteroids (500 to 1000mg MP equivalent/day) within 1 year prior to randomization, for any indication, is prohibited, except:
  - as permitted per protocol inclusion criteria (see Section 5.1)
  - if used as first line AIE treatment in the 6 months prior to randomization (counted from the onset of treatment to randomization date) (see Section 4.1)
- Prednisolone is prohibited during the Treatment Period if used outside of the protocol-specified steroid taper.

All treatments listed in Table 6-2 are prohibited during the Treatment Period, except for use as a rescue medication.

Table 6-2: Prohibited concomitant treatments and treatment-free period for exclusionary immunosuppressants, biologics, and other therapies prior to Baseline Visit

Generic name (commercial/trade names)	Timeframe for prohibition
Intravenous or sc Ig	Used within 4 weeks prior to the Baseline Visit
PEX or plasmapheresis	
Immunoadsorption	
Immunosuppressants:	
Cyclophosphamide	Any use prior to the Baseline Visit
Pimecrolimus	Used within 4 weeks prior to the Baseline Visit
Vinca alkaloids (vincristine, vinblastine)	Used within 12 weeks prior to the Baseline Visit
Azathioprine	
Mycophenolate mofetil	
Biologics (mAbs and fusion proteins):	
Eculizumab	Used within 3 months prior to the Baseline Visit
Abatacept (CTLA 4-Ig)	Used within 6 months prior to the Baseline Visit
Belimumab	
Golimumab	
Natalizumab	
Ofatumumab	
Veltuzumab	
Satralizumab	
Other biologics	
Rituximab	Used within 6 months prior to the Baseline Visit, or used ≥6 months prior to the Baseline Visit with B cells that have not returned to normal levels
Ocrelizumab	
Inebulizumab	
TACI-Ig (Atacicept)	Used within 10 months prior to the Baseline Visit

Table 6-2: Prohibited concomitant treatments and treatment-free period for exclusionary immunosuppressants, biologics, and other therapies prior to Baseline Visit

Generic name (commercial/trade names)	Timeframe for prohibition
Others	
Antineoplastic or treatments for neoplastic disease (including Anti-PD-1 mAb)	Used within 3 months prior to the Baseline Visit

Anti-PD-1=anti-program cell death-1; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; Ig=immunoglobulin; mAb=monoclonal antibody; PEX=plasma exchange; sc=subcutaneous

6.5.3 Rescue medication

Rescue medication considered most appropriate for the study participant will be selected by the investigator. The study site will supply rescue medication that will be obtained locally. The effect of rozanolixizumab on the efficacy of IgG biologics and Fc-fusion proteins is not known.

Although the use of rescue medication is allowable at any time during the study, the use of rescue medications should be delayed, if clinically feasible, for at least 4 weeks following the initiation of study treatment. Study participants who require rescue medication will discontinue blinded treatment, and complete the assessments for the Edisc Visit. Following this, the selection of an appropriate rescue medication will be made at the investigator's discretion, and the study participant will enter the SFU Period during which unscheduled visit' may be performed. Rescue medications are permitted during the SFU Period.

6.6 Dose modification

Dose modifications of IMP are not permitted in this study.

6.7 Criteria for study hold or dosing stoppage

The sponsor's decision for study hold or dosing stoppage will be based on IDMC recommendation.

6.8 Treatment after the end of the study

Study participants who complete the 24-week Treatment Period and require further treatment may have the option to access rozanolixizumab via another clinical study or an access program, if available, as per local laws and regulations. The 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

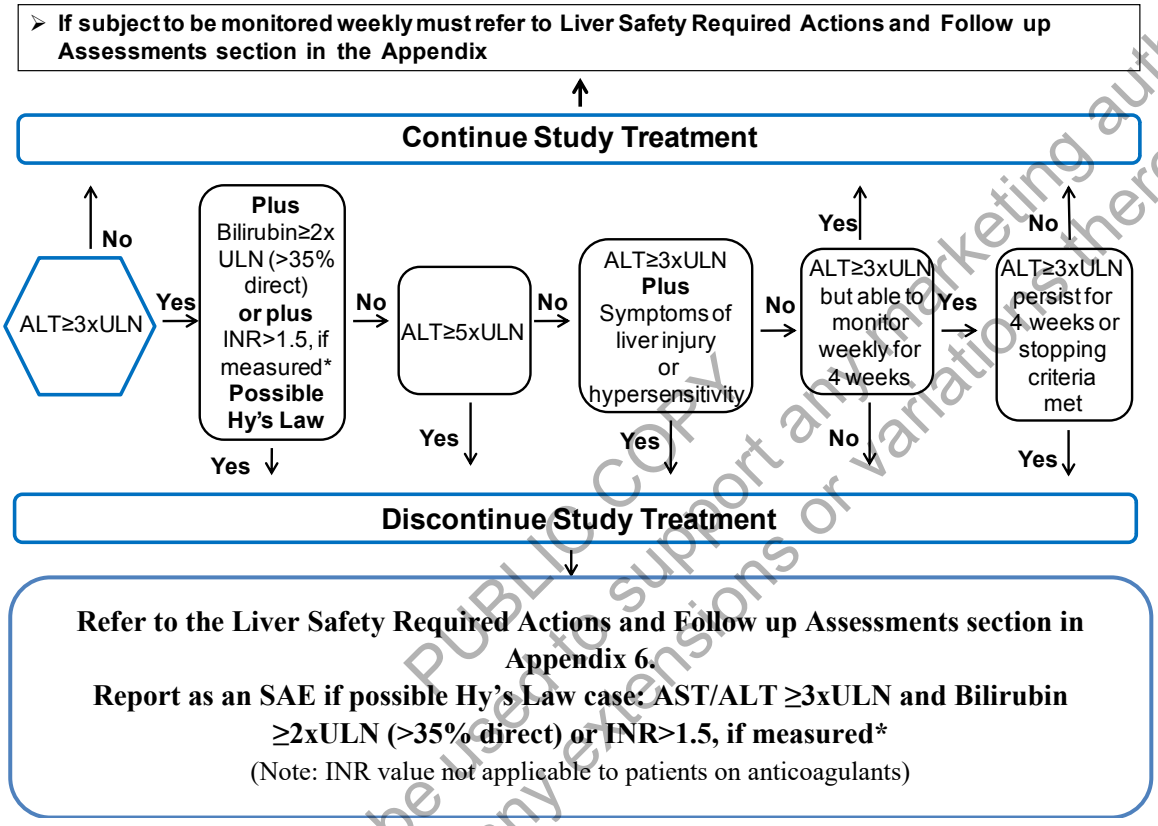
7.1 Discontinuation of study medication

Participants who are permanently discontinued from IMP will undergo an EDisc and SFU Visit. 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 participant meets one of the conditions outlined Figure 7-1 or if the investigator believes that it is in best interest of the 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 are provided in Appendix 6 (Section 10.6).

7.1.2 Permanent discontinuation due to other AEs

Study participants **must be permanently discontinued from IMP** if any of the following safety-related events occur:

1. Study participant develops an illness that would interfere with his/her 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 judgement 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 (see 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 (Section 10.13).
5. Study participant who develops active TB, LTBI, or NTM infection during the study, regardless of initiation of TB treatment.
6. 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.
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).

7.1.3 Permanent discontinuation due to absence or loss of clinical benefit

Study participants **must be permanently discontinued from IMP** if they do not experience a clinical improvement within the first 4 weeks of the Treatment Period (ie, an absence of clinical benefit) or if they experience clinical worsening (ie, a loss of clinical benefit) at any time as defined by any of the following:

1. mRS assessment
   a. Worsening of 1 point compared with Baseline; or
   b. Lack of improvement of a severe score (4 or 5) after 4 weeks
2. Worsening of cognitive function: A decrease of ≥8 points in the total RBANS score compared to Baseline, and per the assessment of the investigator that the study participant has worsened
3. A clinically meaningful recurrence of seizures of a previously experienced type or a new seizure type, either of those requiring a change in therapy (per the assessment of the investigator)
4. Lack of seizure improvement (per the assessment of the investigator)

If study participant permanently discontinues from IMP for any reason, investigators should contact the medical monitor, whenever possible, to discuss the withdrawal of a participant in advance. Study participants who permanently discontinue the IMP should complete the assessments outlined for the EOT/EDisc Visit and enter the 8-week SFU Period. If IMP is permanently discontinued, the requirement for, and selection of, rescue therapy will be made by the investigator.

7.1.4 Temporary discontinuation of IMP

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

1. Study participant develops an event of hypogammaglobulinemia with a serum total IgG of <1g/L irrespective of infection. When the IgG level reaches ≥2g/L, the study participant may be allowed to continue treatment with IMP (see Appendix 14; Section 10.14). In view of re-

initiating the IMP, additional samples will be collected to monitor participants' IgG levels during the period of temporary discontinuation. In order to preserve the blind (see Section 6.3.1.1 for details of mock infusions), additional 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 participant may be allowed to resume treatment with IMP. In view of re-initiating the IMP, additional samples will be collected to monitor participants' serum albumin levels during the period of temporary discontinuation. In order to preserve the blind (see Section 6.3.1.1 for details of mock infusions), additional participants may be selected at random and requested to provide additional samples.
3. Study participant has a suspected drug-induced aseptic meningitis. The IMP may be restarted if clinically appropriate when signs and symptoms have resolved.

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.

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

1. Study participant develops a non-serious persisting or recurrent infection with serum total IgG level between ≥1 and <2g/L. Upon resolution of infection and the IgG returning to level of ≥2g/L, the study participant may be allowed to resume treatment with the IMP (see Appendix 14; Section 10.14).
2. Study participant may be temporarily discontinued from study medication at the discretion of the investigator in cases deemed strictly necessary for the participant's medical care. Efforts should be made to keep the length of temporary discontinuation to a minimum.

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

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

A 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, persistent non-manageable noncompliance, or administrative reasons.

If the 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 participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the Schedule of Activities 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. Participant withdraws his/her consent.
2. The sponsor or a regulatory agency requests withdrawal of the participant.
3. Study participant becomes pregnant during the study, as confirmed by a positive serum pregnancy test.

Study participants **may be withdrawn from the study** at the discretion of the investigator, if the study participant is persistently noncompliant with the study procedures or medications and this noncompliance is not manageable in the opinion of the investigator.

Study participants who choose to withdraw from the study during the Treatment Period should complete the assessments outlined for the EOT/EDisc Visit.

Study participants who are withdrawn from the study during the Treatment Period should complete the assessments outlined for the EOT/EDisc Visit and be encouraged to enter the 8-week SFU Period.

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

7.3 Lost to follow up

A 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 participant fails to return to the clinic for a required study visit:

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

Should the 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.

Study participants who are withdrawn will not be replaced.

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, hurricanes) 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.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the 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 may 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.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

The study participant may have the option to have home-nursing visits as specified in Section 1.3. Home-nursing visits will be conducted by up to 2 fully trained healthcare professionals (1 unblinded for IMP preparation and 1 blinded for the other assessments) visiting the study participant at his/her home or other locations (eg, rehabilitation or day care centers, etc). Alternatively, these visits can be conducted at the site as deemed necessary by site personnel and/or study participant, or when home-nursing visits are not available. Where dosing is performed at home or at other locations, the same safety monitoring schedule will be followed as if in the clinic. Healthcare professional(s) will be present during the full duration of the visit. Home visits and visits at other locations can be conducted in case the following conditions are met:

- The study participant is willing to be dosed and monitored at home, or at an alternative location for up to 4 hours by healthcare professionals.
- The study participant has shown good acute tolerability to previous administrations of IMP (namely they must have had no moderate or severe infusion reactions, or other AEs which the investigator considers could increase the risk of home administration).

- The study participant does not require specific medical supervision based on their medical history/condition.
- The team delivering the home dose must be trained in the identification and management of infusion reactions and hypersensitivity and must have access to immediate treatments (eg, an EpiPen).
- The study participant's home or alternative location allows rapid access to emergency treatment if required (ie, the study participant must not live so remotely that a reasonable arrival time of an ambulance could not be predicted).
- The investigator is contactable to support the healthcare provider if needed.
- UCB has not requested to limit the possibility to perform home visits or visits at other locations (eg, based on IDMC recommendation).

During the home visit, a qualified site personnel will assess AEs, concomitant medications, withdrawal criteria, and the seizure diary by telephone call prior to IMP administration. During the SFU phone call, the qualified site personnel will assess AEs, concomitant medications, and evaluation of seizure diary by telephone.

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

An Unscheduled Visit or assessment can be conducted at the discretion of the investigator at any time (eg, due to an AE) or to follow study participants who experience symptom worsening during the SFU Period and opt to receive rescue therapy. Assessments to be performed during an Unscheduled Visit are provided in Section 1.3.

Blood samples for PK, IgG, hematology, biochemistry, and other laboratory testing and assessments may be performed as clinically indicated at discretion of the investigator. 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 provided in the Schedule of Activities (Section 1.3).

8.1.1 Assessment of seizures

The primary objective of the study is to assess the efficacy of rozanolixizumab as measured by seizure freedom, where seizure freedom is defined by 28 consecutive days of no seizures, maintained until the end of the Treatment Period (Week 25). Seizures will be assessed during the treatment and SFU Period and the information will be recorded using a mobile device with a pre-installed application (app) which contains a seizure diary to be completed. The presence or absence of seizures will be recorded, and if seizures were present, the number of seizures and type of seizures will be recorded. Study participants or caregivers have up to 72 hours after the end of each day to complete the seizure diary in the mobile device app. The date of data entry will be captured in the audit trail. If seizure recording is not completed within the allotted time, it will no longer be available for completion and will show as blank in the data record. An overdue

or missed entry will not impact the availability of the next day's seizure diary, as each new calendar day triggers a new diary for completion. Retrospective edits to seizure diary entries recorded in the mobile device application are not allowed after 72 hours. Daily seizure documentation is submitted electronically to the investigator. A printout of electronic records will be reviewed and discussed with the patient to ensure completeness and accuracy during the next scheduled visit. If any changes are identified during this review, they must be documented on the paper printout. Data from the printout with updates as needed are entered into the eCRF. Printed records are filed as part of the participant's source documents at site.

As a result of the discussion, the investigator will assess the seizures according to the International League Against Epilepsy codes and record the seizure types and frequency on the printout of electronic records and eCRF; he/she will also confirm the presence of AEs (if applicable). Printed records will be filed as part of the participant's source documents at site.

The recording of seizures should begin from Visit 1 (Screening). At Visit 2 (Baseline), the printout of the electronic seizure diary from Screening must be reviewed for seizure data to confirm that the study participant meets eligibility criteria before randomization.

The study participant/caregiver should be educated on how to complete the electronic seizure diary daily.

8.1.2 Assessment of Cognitive Function: Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS was developed for the dual purposes of identifying and characterizing abnormal cognitive decline in the older adult. The RBANS consists of 12 subtests that contribute to 5 age-based domain index scores (immediate memory, visuospatial, language, attention, delayed memory) that are aggregated for a total scale index score. All index scores have an age-based mean of 100, with a SD of 15. Higher scores reflect better neurocognitive performance (Phillips et al, 2015). The total scale index score is the score typically used to reflect global neurocognitive status. The entire battery takes less than 30 minutes to administer. The RBANS has been found to be useful in a retrospective assessment of cognitive improvement in patients with AIE following treatment with methylprednisolone (Kelley and Bratt, 2015). Thus, RBANS may be suitable for evaluating the effects of rozanolixizumab on cognitive function in LGI1 AIE. The RBANS is administered by the healthcare provider or qualified designee. Training on administering the RBANS is mandatory.

8.1.3 Assessment of Disability: Modified Rankin Scale

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability (Bonita and Beaglehole, 1988; van Swieten et al, 1988; Rankin, 1957). The mRS has been used previously to assess the level of functioning in the LGI1 population (de Bruijn et al, 2019). The scale included categories from 0 (perfect health) to 6 (death). The mRS is administered by the healthcare provider or qualified designee. Training and certification on administering the mRS is mandatory.

8.1.4 Patient-reported outcomes

The PRO questionnaires should be completed in a quiet place prior to any discussion regarding study-related issues, disease status, or treatment effect with the investigator/site staff, and prior to

any procedures. The patient-reported outcome questionnaires will be self-completed by the study participant electronically on a tablet during study visits.

The PROs should be completed in the following order: SF-36 and EQ-5D-5L. The PROs should only be checked for completeness. On dosing days, the PROs will be completed prior to dosing.

8.1.4.1 36-item Short Form Survey

The SF-36 Version 2.0 (acute version, 1-week recall) is a 36-item generic HRQoL instrument that uses a recall period of 1 week. Items are grouped into 8 domains as follows: physical functioning (10 items), role physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role emotional (3 items), mental health (5 items), and 1 item for perceived stability or change in health (health transition) during the last year. The concepts represented by these domains contribute to physical, mental, and social aspects of HRQoL.

In addition to domain scores, the PCS and MCS scores are calculated from the 8 domains (excluding the Health Transition item). Component scores appreciate the impact of each domain on physical and mental health status (Maruish, 2011). Each of the 8 domain scores and the component summary scores range from 0 to 100, with a higher score indicating a better health status. The 2 component summary scores and the domain scores are standardized with a mean of 50 and a SD of 10 in the general US population.

8.1.4.2 EuroQol-5D-5L

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EuroQol visual analogue scale (EQ VAS). The 5-level EQ-5D is designed to improve the instrument's sensitivity and to reduce ceiling effects.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The study participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the study participant's health state.

The EQ VAS records the study participant's self-rated health on a vertical visual analogue scale, where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine." The VAS can be used as a quantitative measure of health outcome that reflect the study participant's own judgement.

8.1.5 Clinical Global Impression of Severity

The Clinical Global Impression of Severity (CGI-S) scale is a clinician-rated measure that assesses the severity of cognitive impairment of the study participant of clinical signs and symptoms of AIE. The CGI-S scale will include 5 response options: none, mild, moderate, severe, and very severe.

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, GI, and musculoskeletal systems. Height and weight will be measured and recorded at Visit 1 (Screening). Body weight will be measured with the study participant wearing light clothing and without wearing shoes.

A full or brief physical examination should include evaluation 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, W13, W21, EDisc if applicable and EOS (see Section 10.12).

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

8.2.2 Neurological examination

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

A full neurological assessment will include: (1) General appearance, including posture, motor activity and meningeal signs and, 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 assessment will include a selected assessment of the following: cognition, general, reflexes, muscle strength, and coordination/cerebellar function.

8.2.3 Vital signs

Temperature, pulse rate, and blood pressure will be assessed at the time intervals specified in the Schedule of Activities (Section 1.3).

Blood pressure (systolic and diastolic), and pulse rate 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.

On dosing days for the first 2 visits (Visit 2 and Visit 5), vital signs will be measured prior to IMP administration, at the end of the infusion (+5 minutes), at 2 hours after the end of infusion and at 4 hours after the end of infusion (both ±15 minutes). At Visit 6, Visit 7, and Visit 8, vital signs will be measured prior to IMP administration, at the end of the infusion (+5 minutes), and 1 hour after the end of infusion (±15 minutes). From Visit 9, the vital signs will be measured 15 minutes prior to IMP administration. At nondosing visits, vital signs need only be taken once during the visit.

8.2.4 Electrocardiogram

12-Lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

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

Findings will be recorded in the eCRF.

8.2.5 Magnetic resonance imaging

Serial structural brain MRIs will be performed during the Screening Period (or at the Baseline Visit) and at an EOT or an EDisc Visit. These MRIs will be used to detect eventual emergent alterations in brain structure that may be associated with safety readout issues, as well as any structural changes that may indicate a treatment effect. A MRI performed within 3 months of the Screening Period may also be acceptable as per the investigators judgement. Brain MRIs will be performed using an MRI scanner with a field strength of at least 1.5 Tesla in accordance with local guidance and practice. At any time during the study, additional brain MRIs may be performed in any study participant if deemed as appropriate by the investigator/local radiologist. Brain MRIs shall be analyzed by a local radiologist, and clinical assessment of the findings will be based on the investigator's judgement.

8.2.6 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.

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.

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.

8.2.7 Suicidal risk monitoring

Study participants 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 should be instructed to monitor 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 (Oquendo et al, 2003). This scale will be used at Screening, Baseline, and all subsequent visits 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) and in Appendix 12 (Section 10.2) for TB events. Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the 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 participant to discontinue the study treatment or AIE001 (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 Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF 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 participant, and to also inform 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 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 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 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 by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of 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, Institutional Review Boards (IRB)/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 a 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 IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male 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 participant should be withdrawn from the study as soon as pregnancy is known (by positive serum pregnancy test), and the following should be completed:

The participant should complete the assessments outlined for the EOT/EDisc Visit and encouraged to enter the 8-week SFU Period.

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 adverse event 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. An AESI should be reported within 24h. Potential Hy's Law, defined as ≥3xULN 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 must always be reported to UCB as an AESI (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 participant.

All AESIs 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 AESM is a product-specific AE, adverse reaction or safety topic requiring special monitoring by one or more regulatory authorities or by UCB. For rozanolixizumab, AESM that require immediate reporting (within 24 h regardless of seriousness) to UCB are:

- Severe and/or serious headache
- Suspected aseptic meningitis

Procedures for the management of AESMs are provided in Appendix 13 (Section 10.13).

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 the guidance provided in Section 10.15 (Appendix 15). Suspected anaphylactic reactions should be diagnosed using Sampson's Criteria (Sampson et al, 2006).

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

8.3.8 Anticipated serious adverse events

Serious AEs anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure are shown in Table 8-1.

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 SAEs for LGI1 AIE population

MedDRA System Organ Class	MedDRA Preferred Term
Injury, poisoning, and procedural complication	Fall, fracture[a], injury[a]
Nervous system disorders	Cluster seizures, convulsion, incontinence[a], memory impairment
Psychiatric disorders	Abnormal behavior, acute psychosis, anxiety, cognitive disorder, confusional state, psychotic behavior, sleep disorder and disturbances

AIE=autoimmune encephalitis; LGI1= leucine-rich glioma inactivated 1; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SOC=system organ class
[a] Event is anticipated when occurring in the context of seizure but not classified in MedDRA primary SOC

8.3.9 COVID-19 vaccination

Use of COVID-19 vaccines will be recorded in the concomitant medication eCRF page (Section 6.5.1).

In the AE eCRF page, there is the possibility to assess causality to the IMP and to any concomitant medication. If an AE is considered related to COVID-19 vaccine, causality

assessment should be entered in the AE eCRF. Note that in this case, the national recommendation for reporting AE-related to COVID-19 vaccines should be followed. If an AE is the result of an interaction of a COVID-19 vaccine with an IMP in the study, then the causal association should be for both IMP and COVID-19 vaccine. In case of a seriousness criteria, the SUSAR process will be followed.

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 IRBs/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 a blinded manner.

In addition, an IDMC will be responsible for monitoring safety data during the study. A detailed description of the IDMC composition, processes, and responsibilities will be provided in a separate IDMC 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 participant for any AE/SAE or laboratory abnormalities for at least 5 days.
3. Obtain a plasma sample for PK analysis and a serum sample for IgG (total and subclasses) autoantibodies and within 3 days from the date of the final dose of study treatment 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 or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics and immunogenicity

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

samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of rozanolixizumab and ADA and may be used for establishing assay parameters (eg, ADA cut point setting and PK selectivity assessment). Samples collected for analyses of rozanolixizumab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising before study completion.

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

Drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.7 Genetics

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

8.8 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 concentrations
- Serum IgG subclass concentrations
- Serum LGI1 autoantibody (total and subclasses) concentrations

Cerebrospinal fluid will be collected as specified in the Schedule of Activities (Section 1.3) for measurement of LGI1 autoantibody (total) concentrations. This sampling is optional for study participants and requires informed consent. A decision not to consent does not exclude the study participant from the study. Cerebrospinal fluid samples collected between onset of disease and Visit 2 are eligible to replace Visit 2 samples.

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.

8.9 Biomarkers

The investigational LGI1 cell-binding assay is a qualitative assay to determine the presence of circulating LGI1 autoantibodies in serum, which is used as part of the inclusion criteria (Section 5.1).

Leucine-rich glioma inactivated 1 autoantibodies will also be tested with an independent, research-use only, quantitative assay (flow cytometry LGI1 assay) to assess the PD effect of rozanolixizumab as quantified by changes in LGI1 autoantibody concentrations in serum and CSF (for consenting study participants only). Samples for the LGI1 IgG autoantibody concentrations in serum will be collected predose at Baseline (Day1) and at various other visits as specified in the Schedule of Activities (Section 1.3) for all study participants. The CSF sampling (for consenting participants only) will occur at Screening and the EOT/EDisc Visit. Other blood samples specified in the Schedule of Activities (Section 1.3) may be tested for protein, metabolites, and biomarkers, such as, but not limited, to albumin, α- and β-globulins, B-cell activating factor, and circulating immune complexes. Blood sampling for other exploratory biomarkers will occur at predose at Baseline (Day 1) and at the EOT/EDisc Visit for all study participants. These samples will be used to explore the effect of rozanolixizumab on exploratory biomarkers and the cause, progression, and appropriate treatment of LGI1 AIE.

In addition, where local regulations and IRB/IEC allow, blood samples for pharmacogenomics and biomarker research are required and will be collected from all study participants as specified in the Schedule of Activities (Section 1.3). 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 LGI1 AIE. Details on genetic analysis are described in Appendix 5 (Section 10.5).

If not used immediately, the samples are planned to be stored at -80°C for up to 20 years to allow for later analyses. Any future diagnostic test development or exploratory biomarker analysis will only ever be related to the exploration of the cause, progression, and appropriate treatment of LGI1 AIE.

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

8.9.1 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:

[redacted]

Samples for serum complement ([redacted] and plasma complement ([redacted]) are collected predose at Baseline (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.

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

8.10 Medical resource utilization and health economics

Medical resource utilization will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of disease-related hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit]).

9 STATISTICAL CONSIDERATIONS

9.1 Definition of analysis sets

The following analysis sets have been defined for this study:

- The Enrolled Set: All study participants who have signed the informed consent.
- The Randomized Set (RS): All enrolled study participants who were randomized to treatment arms. This is an equivalent to the Intent-to-Treat (ITT) Population. The study participants will be analyzed according to the randomized treatment.
- The Safety Set (SS): All randomized study participants who received at least one dose of IMP. Analysis of this set will be according to the treatment the study participants actually received and will be used for the demographic and safety analyses.
- The Full Analysis Set (FAS): All study participants in the RS, who have a Baseline value and at least one post-Baseline efficacy endpoint assessment. In the case of treatment error, the study participants will be primarily analyzed according to the predominant treatment actually received.
- The Pharmacokinetic Per-Protocol Set (PK-PPS) is a subset of the SS, consisting of those study participants who have at least one quantifiable concentration of rozanolixizumab and no important protocol deviations affecting the PK variable. Post-Baseline deviations will not necessarily lead to total exclusion of a study participant from the PK-PPS but may lead to exclusion of specific data.
- The Pharmacodynamic Per-Protocol Set (PD-PPS) is a subset of the SS, consisting of those study participants who had at least one valid post-Baseline measurement of total IgG, or IgG subclasses, and no important protocol deviations affecting the PD variable. Post-Baseline deviations will not necessarily lead to total exclusion of a study participant from the PD-PPS but may lead to exclusion of specific data.

9.2 General statistical considerations

Summary statistics will be provided for all efficacy, safety, and Baseline or demographic variables.

Continuous variable outcomes will be summarized by visit (where applicable) with descriptive statistics represented by the number of study participants, arithmetic mean, standard deviation, median with 25th and 75th percentiles, minimum, and maximum. For the purpose of the statistical analysis or graphical presentations, some of the continuous variable outcomes may be log-transformed to accommodate the observed heterogeneity, mitigate influence of the outliers,

or fulfill the distributional assumptions required for statistical testing. Categorical variable outcomes will be summarized by visit (where applicable) using number of study participants, frequency counts, and percentages.

If not otherwise stated, a Baseline value will be the last available predose value and will be clearly defined in the study Statistical Analysis Plan (SAP). All relevant data will be listed by treatment group, visit (where applicable) and study participant.

Unless otherwise mentioned, all the statistical hypotheses will be tested at a two-sided 5% significance level.

All the analyses will be performed using SAS® version 9.3 or later (SAS Institute, NC, USA).

9.3 Planned efficacy/outcome analyses

All planned primary and secondary efficacy analyses will be conducted on the RS and additionally only for specified estimands for the primary and secondary endpoints on the FAS as part of the sensitivity analysis. The analyses on the FAS will only be carried out if this population differs by more than 10% of study participants to the RS/ITT.

The efficacy analysis, unless otherwise specified, will use all available efficacy data collected over the Treatment Period, and account for stratification factors.

The following sections outline the planned statistical analyses of the primary, secondary, and exploratory efficacy endpoints.

Further details regarding the statistical analysis will be described in the SAP.

9.3.1 Primary efficacy analysis

9.3.1.1 Seizure freedom

The primary objective of the study is the assessment of the efficacy of rozanolixizumab as measured by seizure freedom. The definition of the primary endpoint together with the description of its primary and supportive analyses are provided in Table 9-1. The main intercurrent event is permanent IMP discontinuation resulting in withdrawal from the randomized Treatment Period, and entering the SFU, or the complete withdrawal from the study (see Section 7). This will include by design participants who take any rescue anti-seizure medication who will be required to be withdrawn from the randomized treatment. The other intercurrent event is a temporary IMP discontinuation. For the analyses on the RS, participants who withdraw from the study prior to receiving the IMP or who do not have any post-randomization assessment will be considered as not having met the primary endpoint.

For the purpose of deriving the primary efficacy endpoint, any intermittent missing diary seizure count recording will be imputed to non-zero in both treatment arms.

Table 9-1: Estimands for the primary efficacy endpoint

Statistical category	**Estimand:** **Treatment:** Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids. **Population:** Study participants with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively. **Endpoint (Variable)**: Seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25). **Intercurrent events:** The study participant: 1. Temporarily discontinued from the IMP 2. Permanently discontinued from the IMP		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
Primary	RS	1. Treatment policy strategy: Temporary discontinuation of the IMP will not affect the assessment of the primary endpoint. 2. Composite strategy: Permanent discontinuation of the IMP will be considered as a failure in meeting the primary endpoint.	The association between randomized treatment exposure and the primary endpoint will be measured by the rozanolixizumab versus placebo common OR derived from the 2x2 contingency tables corresponding to the stratification factors (see Section 6.3). The null hypothesis, H0: (true) common OR=1, indicating no effect between the treatment exposure and the primary endpoint, will be tested using a CMH test. The CMH estimate of the common OR will be reported with its 95% CI and the CMH test p-value. The assumptions of the CMH test will be validated (Mantel-Fleiss criterion) and, if appropriate, the exact stratified test of independence alternative will be considered.
Sensitivity	FAS	As described for the primary estimand analysis.	As described above.
Sensitivity	RS	As described for the primary estimand analysis.	Logistic regression model including effect for randomized treatment, conditional on the stratification factors (see Section 6.3), will be used to test the primary efficacy hypothesis. The resulting rozanolixizumab versus placebo common OR estimate with its 95% CI and the treatment factor p-value from the model will be reported. As a part of the analysis, the model will be extended to include an additional binary covariate to

Table 9-1: Estimands for the primary efficacy endpoint

Statistical category	Estimand: **Treatment:** Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids. **Population:** Study participants with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively. **Endpoint (Variable)**: Seizure freedom (defined by 28 consecutive days of no seizures) maintained until the end of the Treatment Period (Week 25). **Intercurrent events:** The study participant: 1. Temporarily discontinued from the IMP 2. Permanently discontinued from the IMP		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
			indicate if the participant had achieved seizure freedom for at least 1 day over the Screening Period (effect of the prior IVMP treatment). In the case of model convergence issues, the appropriate alternatives to the maximum likelihood estimation will be considered.
Supplementary	RS	As described for the primary estimand analysis.	The association between randomized treatment and seizure freedom at Week 25 will be measured by the rozanolixizumab and placebo difference in the proportion of the study participants reaching the primary endpoint, controlling for the effect of the stratification factors (see Section 6.3). The proportion differences for each stratum and the CMH-weighted common effect estimate will be reported with its 95% CI.

AIE=autoimmune encephalitis; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; FAS=Full Analysis Set; H0=null hypothesis; IMP=investigational medicinal product; iv=intravenous; IVMP=intravenous methylprednisolone; LGI1=leucine-rich glioma inactivated 1; OR=odds ratio; RS=Randomized Set

9.3.2 Secondary efficacy analysis

The secondary study objectives are the assessment of the efficacy of rozanolixizumab as measured by a change from Baseline in cognitive function (assessed using the RBANS; Section 9.3.2.1), change in overall disability function (assessed using the mRS scores; Section 9.3.2.2), use of rescue medication due to an absence or loss of clinical benefit (Section 9.3.2.3), and time to first occurrence of seizure freedom (Section 9.3.2.4).

A fallback hierarchical testing procedure will be implemented to control the overall type I familywise error rate at 0.05 over the primary endpoint and the 4 alpha-controlled secondary endpoints. In the event that the null hypothesis relating to the primary endpoint is rejected at 2-

sided 5% significance, then the secondary endpoints will be tested in the following order with the corresponding allocations of alpha, implementing the fallback method of multiplicity control:

1. Change from Baseline in RBANS total scale index score at the end of the Treatment Period (Week 25; Alpha=0.046) (Section 9.3.2.1)
2. Proportion of participants with a favorable outcome in mRS at the end of the Treatment Period (Week 25; Alpha=0.002) (Section 9.3.2.2)
3. Use of rescue medication due to an absence or loss of clinical benefit during the Treatment Period (Alpha=0.001) (Section 9.3.2.3)
4. Time to first occurrence of seizure freedom (Alpha=0.001) (Section 9.3.2.4)

For each of the listed endpoints, the hypothesis test will only be considered inferential if the endpoint meets statistical significance at its individual allocated level, or in accordance with the fallback methodology where the preceding endpoints are statistically significant thus allowing the alpha allocated to these preceding endpoints to be carried forward to subsequent endpoints. This carryforward of the alpha level is automatically halted at the point that an endpoint in the defined sequence is not statistically significant at the testing level assigned by the fallback rule.

Hence, if the sequential tests are successful, the alpha will accumulate for the later endpoints in the sequence. Specifically, if the analysis of the RBANS endpoint results in a p-value ≤0.046 then the mRS endpoint will be tested at an alpha level of 0.048; if the analysis of the mRS endpoint results in a p-value ≤0.048, then the use of rescue medication may be tested at an alpha level of 0.049, and so on. However, if a test fails in the sequence, the later endpoints may only be tested using the specific 0.002 or 0.001 alpha assigned to them (fallback).

9.3.2.1 Change in cognitive function: RBANS

Table 9-2: Estimands for the secondary efficacy endpoint: RBANS

Statistical category	**Estimand:** **Treatment:** Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids. **Population:** Study participants with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively. **Endpoint (Variable)**: Change from Baseline in RBANS total scale index score at the end of the Treatment Period (Week 25). **Intercurrent events:** The study participant: 1. Temporarily discontinued from the IMP 2. Permanently discontinued from the IMP		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
Secondary	RS	1. Treatment policy strategy: Temporary discontinuation of the IMP will not affect the assessment of the endpoint.	The mean change from Baseline in RBANS total scale index score at Week 25 will be estimated using the MMRM approach utilizing information across all the available scheduled visit outcomes for

Table 9-2: Estimands for the secondary efficacy endpoint: RBANS

Statistical category	Estimand: **Treatment:** Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids. **Population:** Study participants with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively. **Endpoint (Variable)**: Change from Baseline in RBANS total scale index score at the end of the Treatment Period (Week 25). **Intercurrent events:** The study participant: 1. Temporarily discontinued from the IMP 2. Permanently discontinued from the IMP		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
		2. Hypothetical strategy: For permanent discontinuation the intervention effect will be estimated.	each study participant. The model covariate set will include the Baseline response, stratification factors (see Section 6.3), randomized treatment group indicator, visit as a categorical variable, and treatment-by-visit interaction term. From the model, the LSM for each treatment arm, and their differences will be estimated and reported with their 95% CI for each scheduled visit. The inference will be based on the Week 25 visit treatment comparison, which will be tested for statistical significance. For the analysis, the unstructured covariance structure will be used in the first instance. Other structures will be considered if necessary.
Sensitivity	FAS	As described for the secondary estimand analysis.	As described above.
Sensitivity	RS	As described for the secondary estimand analysis.	The mean change from Baseline in RBANS total index score at Week 25 will be estimated and compared between the treatment arms for statistical significance utilizing the ANCOVA model including the Baseline response, stratification factors (see Section 6.3), and randomized treatment group as covariates. Any missing score readouts at the Week 25 visit will be imputed with the multiple imputation approach assuming other than the MAR mechanism.

AIE=autoimmune encephalitis; ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; IMP=investigational medicinal product; iv=intravenous; LGI1=leucine-rich glioma inactivated 1;

Table 9-2: Estimands for the secondary efficacy endpoint: RBANS

Statistical category	**Estimand:** **Treatment:** Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids. **Population:** Study participants with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively. **Endpoint (Variable)**: Change from Baseline in RBANS total scale index score at the end of the Treatment Period (Week 25). **Intercurrent events:** The study participant: 1. Temporarily discontinued from the IMP 2. Permanently discontinued from the IMP		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**

LSM=least-squares mean; MAR=missing at random; MMRM=mixed model repeated measures; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RS=Randomized Set

9.3.2.2 Change in overall disability: mRS

The Modified Rankin Scale (mRS) is a 7 point ordinal categorical scale running from perfect health (0) to death (6).

The overall disability of the study participants will be assessed using the mRS score (see Section 8.1.3) measured at the visits specified in the Schedule of Activities (see Section 1.3). The changes from Baseline in mRS scores will be descriptively summarized at all visits.

The analysis of mRS will be carried out on the proportion of participants who experience a favorable outcome at Week 25, where a favorable outcome will be defined as:

- No worsening for participants with a Baseline mRS score of ≤1.
- An improvement of ≥1 point on the mRS scale for participants with a Baseline mRS of ≥2.

The proportion of participants will be analyzed as detailed below, where a Cochran-Mantel-Haenszel test will be used as the primary estimand, and the resultant odds ratio reported.

Additionally, the difference in the proportions of participants achieving a favorable mRS outcome will be reported.

To provide the most conservative level of potential improvement for all participants in the analysis, the Baseline mRS score used in the analysis will be the better (ie, the lower) score from either the Screening or Baseline Visit.

Table 9-3: Estimands for the mRS improvement efficacy endpoint

Statistical category	**Estimand:** **Treatment:** Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids. **Population:** Study participants with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively. **Endpoint (Variable)**: mRS Improvement (defined according to the definition above) at the end of the Treatment Period (Week 25). **Intercurrent events:** The study participant: 1. Temporarily discontinued from the IMP 2. Permanently discontinued from the IMP		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
Secondary	RS	1. Treatment policy strategy: Temporary discontinuation of the IMP will not affect the assessment of the primary endpoint. 2. Hypothetical strategy: Permanent discontinuation of the IMP; the assessment of mRS at the discontinuation assessment will be used in place of the Week 25 assessment.	The association between randomized treatment exposure and the mRS endpoint will be measured by the rozanolixizumab versus placebo common OR derived from the 2x2 contingency tables corresponding to the stratification factors (see Section 6.3). The null hypothesis, H0: (true) common OR=1, will be tested using a CMH test. The CMH estimate of the common OR will be reported with its 95% CI and the CMH test p-value. The assumptions of the CMH test will be validated (Mantel-Fleiss criterion) and, if appropriate, the exact stratified test of independence alternative will be considered.
Sensitivity	RS	As described for the primary estimand analysis.	Logistic regression model including effect for randomized treatment, conditional on the stratification factors (see Section 6.3), will be used to test the primary efficacy hypothesis. The resulting rozanolixizumab versus placebo common OR estimate with its 95% CI and the treatment factor p-value from the model will be reported. In the case of model convergence issues, the appropriate alternatives to the maximum likelihood estimation will be considered.
Supplementary	RS	As described for the primary estimand analysis.	The association between randomized treatment and mRS improvement at Week 25 will be measured by the rozanolixizumab and placebo difference

			in the proportion of the study participants achieving improvement, controlling for the effect of the stratification factors (see Section 6.3). The proportion differences for each stratum and the CMH-weighted common effect estimate will be reported with its 95% CI.

AIE=autoimmune encephalitis; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; FAS=Full Analysis Set; H0=null hypothesis; IMP=investigational medicinal product; iv=intravenous; LGI1=leucine-rich glioma inactivated 1; mRS=Modified Rankin Scale; OR=odds ratio; RS=Randomized Set

9.3.2.3 Use of rescue medication due to an absence or loss of clinical benefit

Table 9-4: Estimands for the secondary efficacy endpoint: absence or loss of clinical benefit - use of rescue medication

Statistical category	**Estimand:** **Treatment:** Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids. **Population:** Study participants with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively. **Endpoint (Variable)**: Use of rescue medication due to an absence or loss of clinical benefit during the Treatment Period. **Intercurrent events:** The study participant: 1. Temporarily discontinued from the IMP 2. Permanently discontinued from the IMP		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
Secondary	RS	1. Treatment policy strategy: Temporary discontinuation of the IMP will not affect the assessment of the endpoint. 2. Composite strategy: Permanent discontinuation of the IMP due to a reason other than an absence or loss of clinical benefit will not be considered as meeting the endpoint.	The association between the randomized treatment and the use of rescue medication during the Treatment Period will be measured by the rozanolixizumab versus placebo common OR and tested for a conditional (across the strata effects; see Section 6.3) independence using the CMH test. The outcomes will be summarized and analyzed as described in the primary estimand analysis (see Section 9.3.1.1).
Supplementary	RS	As described for the secondary estimand analysis.	The association between the randomized treatment and the use of rescue medication during the Treatment Period will be measured by the difference between

Table 9-4: Estimands for the secondary efficacy endpoint: absence or loss of clinical benefit - use of rescue medication

<table>
<tr><td rowspan="3">Statistical category</td><td colspan="3">Estimand:
Treatment: Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids.
Population: Study participants with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively.
Endpoint (Variable): Use of rescue medication due to an absence or loss of clinical benefit during the Treatment Period.
Intercurrent events: The study participant:
1. Temporarily discontinued from the IMP
2. Permanently discontinued from the IMP</td></tr>
<tr><td>Analysis set</td><td>Intercurrent event handling strategy</td><td>Population-level summary (Analysis):</td></tr>
<tr><td></td><td></td><td>rozanolixizumab and placebo arms in the proportion of study participants reaching the secondary endpoint, controlling for the effect of stratification factors (see Section 6.3). The outcomes will be summarized and analyzed as described in the relevant primary estimand supplementary analysis (see Section 9.3.1.1).</td></tr>
</table>

AIE=autoimmune encephalitis; CMH=Cochran-Mantel-Haenszel; FAS=Full Analysis Set; IMP=investigational medicinal product; iv=intravenous; LGI1=leucine-rich glioma inactivated 1; OR=odds ratio; RS=Randomized Set.

9.3.2.4 Time to first occurrence of seizure freedom

Table 9-5: Estimands for the secondary efficacy endpoint: TTFSF

Statistical category	Estimand: **Treatment:** Randomized rozanolixizumab or placebo in study participants who are concurrently treated with iv or oral steroids. **Population:** Patients with LGI1 AIE as specified in the inclusion and exclusion criteria (Section 5.1 and Section 5.2), respectively. **Endpoint (Variable):** TTFSF defined by the number of days after randomization to the first day of the first 28 consecutive days without seizures during the Treatment Period. **Intercurrent events:** The study participant: 1. Temporarily discontinued from the IMP 2. Permanently discontinued from the IMP		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
Secondary	RS	1. Treatment policy strategy: Temporary discontinuation of the IMP will not affect the assessment of the endpoint. 2. While on treatment strategy: For permanent discontinuation of the IMP the participant will be censored on the final day while on the IMP.	The null hypothesis of no difference between the TTFSF hazard functions for the randomized treatment arms adjusting for the effect of stratification factors (see Section 6.3), will be tested using a stratified log-rank test with the Breslow approach for handling ties. The rozanolixizumab versus placebo hazard ratio estimate based on the stratified log-rank test and its 95% CI will be reported together with the stratified log-rank test p-value. The assumption underlying the utilized statistical methodologies is that any censoring is non-informative, ie, independent from the event of interest. The TTFSF will be presented graphically by treatment arm using a Kaplan-Meier plot, along with median TTFSF estimates reported.

AIE=autoimmune encephalitis; CI=confidence interval; FAS=Full Analysis Set; IMP=investigational medicinal product; iv=intravenous; LGI1=leucine-rich glioma inactivated 1; RS=Randomized Set; TTFSF=time to first occurrence of seizure freedom

9.3.3 Exploratory efficacy analyses

9.3.3.1 Time to seizure freedom maintenance (TTSFM)

The time to seizure freedom maintenance (TTSFM) defined by the number of days after randomization to the first day of the 28 consecutive days without seizures, 'maintained until the end of the Treatment Period (Week 25)'.

This analysis and summaries of the time to seizure freedom maintenance endpoint will be performed on the RS utilizing the methodology as described for the TTFSF endpoint (see

Section 9.3.2.4). The participants who do not reach the described endpoint criteria will be censored at the last follow-up timepoint.

In addition, as a further exploratory endpoint, this analysis and summaries will be repeated for only the subgroup of participants who achieved the seizure freedom endpoint criteria.

9.3.3.2 Seizure control

Seizure frequencies will be recorded on a daily basis across the 24 weeks of randomized therapy and during a variable Screening Period, based on the specific categories of seizure count ("0-None," "1-5," "6-10," "11-20," and "More than 20") that are collected in the myUCB 4me participant seizure app.

For each participant, a median category of seizure counts will be calculated for each week that the participant is in the randomized treatment period, such that each participant has one average median value for that week, along with a minimum and maximum category range. For the Screening Period, a Baseline median category will be calculated for each participant, in the same way as described for each week of randomized treatment. This will be to utilize the screening data collected in the period up to 6 weeks immediately prior to randomisation. All data will then be summarized across time for all participants giving the number of participants falling into each of the median categories across the 24 weeks by randomized treatment arm.

Two success criteria will be considered based on seizure control. 'Good control' and 'Moderate control'; full details will be provided in the SAP.

Any participant who does not reach the end of Week 24 will be considered to have failed both these success criteria. In the case of 7 missing data points over an entire week, this will be imputed from the previous weeks data.

The proportion of participants who achieve 'Good control' and 'Moderate control' will be summarized and analyzed on the RS. Specifically 2 models will be created to analyze this data, one for each of the success control criterion. A logistic regression model adjusting for the effect of randomized treatment, Baseline median seizure category level, stratification factors and also the use of prior disease modifying treatments, will be used to test for any difference between the randomized treatment arms. The resulting rozanolixizumab versus placebo common OR will be reported. Additionally, the other estimands as described for the primary endpoint in Section 9.3.1.1 will be considered. Full details will be provided in the SAP.

9.3.3.3 Duration of seizure-free period

The duration of the seizure-free period will be measured from the first day the participant reports no seizures for at least 28 consecutive days until the last day without seizures during the Treatment Period. The endpoint will be descriptively summarized on the RS with respect to the randomized treatment arm and stratification factors (see Section 6.3).

9.3.3.4 Change in RBANS domain scores

The changes from Baseline in the domains of RBANS (immediate memory, visuospatial/constructional, delayed memory, language, and attention) will be descriptively summarized on the RS with respect to randomized treatment and stratification factors (see Section 6.3). The changes in RBANS memory-related domains will be analyzed on the RS as

described for the secondary estimand for the change from Baseline in cognitive function endpoint (see Section 9.3.2.1).

9.3.3.5 Ranked outcome from the integrated score

The integrated ranked outcome scale comprises three equally weighted key components of LGI1 AIE: mRS, seizure freedom, and cognitive function. The mRS has been used previously to assess the level of functioning in the LGI1 population (de Bruijn et al, 2019) and seizure freedom is considered a key factor corresponding to epileptic events (Irani et al, 2011). The assessment of seizure freedom component does not require individual seizure counting, minimizing the effect of potential inaccuracies in seizure counting. The cognitive function component will utilize the RBANS assessment (Dubey et al, 2020).

The overall summary score for each participant is the unweighted sum of the individual comparison scores across all three endpoint components (O'Brien, 1984), which provides a comprehensive output with equal contribution from each of the selected clinical domains. In the following step, each study participant is ranked from 1 to N based on the overall summary score, with the rank of 1 corresponding to the lowest summary output. The individual rank outcomes will be summarized within the treatment arms and the observed differences will be compared between arms providing a basis for the treatment efficacy assessment.

Detailed description and discussion regarding the scoring rules corresponding to each of the combined endpoint elements and associated statistical methods will be fully described in the SAP.

9.3.3.6 Values and changes in participant and clinician-reported HRQoL assessments

The study participant-reported health-related quality of life assessments, represented by SF-36, EQ-5D-5L and CGI-S scores (see Section 8.1.4), will be collected at the visits specified in the Schedule of Activities (see Section 1.3). The changes from Baseline in SF-36 scores will be descriptively summarized at each visit. All scoring of the SF-36 will be conducted and weighted according to the recommendations and guidelines of the authors of the SF-36 instrument and as detailed in the latest version of the test manual. Item scores will be re-coded according to the guidelines such that higher scores correspond to better health status. The full derivation of this scoring will be described in detail in the SAP. The analysis of the SF-36 endpoint will adhere to the guidelines.

For the semi-quantitative EQ-5D-5L index and categorical CGI-S score, outcomes will be summarized across the visits.

Decisions with respect to the outcome of this study will utilize the operating characteristics as described for the primary endpoint but will also consider the strength of evidence of treatment effect provided by the secondary endpoints as well as consideration to the safety data observed.

9.3.4 Withdrawals from the study

The proportion of the study participants who withdraw or are withdrawn from the study by the end of the Treatment Period (Week 25) will be reported for both treatment groups.

9.4 Planned safety and other analyses

9.4.1 Safety analyses

All safety analyses will be listed and summarized for the SS.

The frequency and severity of all TEAEs will be presented for each treatment group separately by System Organ Class, high level term, and preferred term (Medical Dictionary for Regulatory Activities). The data will be displayed as number of study participants experiencing the TEAE, percentage of study participants, and number of TEAEs. A TEAE is defined as any event that was not present prior to the first administration of IMP or any unresolved event already present before the first administration of IMP that worsens in intensity following exposure to treatment up to the end of the Treatment Period (Week 25) and including the 8-week SFU.

Laboratory evaluations and vital signs as well as ECG data 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 PK and immunogenicity analyses

9.4.2.1 Rozanolixizumab

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

Plasma concentration data of rozanolixizumab may be subjected to population pharmacokinetic analysis to derive population estimates of PK parameters and test the effect of various covariates such as anti-drug antibodies, age, weight, sex. Details of the analysis will be described in a separate Data Analysis Plan (DAP). This analysis may be performed by combining the data from the current study with data from other rozanolixizumab studies if deemed appropriate. The results of the population PK analysis will not be reported in the clinical study report (CSR) but in a separate modelling report.

9.4.2.2 Immunogenicity analysis

A tiered ADA approach will be used for the 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 Pharmacodynamic 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, IgG subclass concentrations, serum LGI1 levels, and LGI1 levels in CSF.

Population PD or population PK/PD analyses may be conducted for the PD variables of interest. Details of such PD or PK/PD analyses will be described in a separate DAP. The results of the analyses will not be reported in the CSR, but in a separate report.

9.4.2.4 Immunological analyses

All immunologic variables including serum concentrations of immunoglobulins [redacted]) serum ([redacted]) and plasma ([redacted]) complement levels, will be summarized by treatment group and visit using descriptive statistics.

9.5 Handling of protocol deviations

Important protocol deviations are identified as part of the data cleaning process in the Data Cleaning Plan (DCP). Ongoing data cleaning meetings will be held throughout the duration of the study. Objectives of these meetings include to review and update (if necessary) the important protocol deviations in the DCP. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting. Through this ongoing data cleaning and evaluation process, all decisions regarding important protocol deviations are made on an ongoing basis.

9.6 Handling of dropouts or missing data

All imputation of missing or partial dates for safety assessments, as well as the handling of missing efficacy data (where applicable), will be detailed in the SAP. Data handling conventions for data from study participants affected by COVID-19 will also be detailed fully in the SAP.

9.7 Planned interim analysis and data monitoring

There are no plans for an interim analysis.

9.8 Determination of sample size

The study sample size of 60 participants is considered sufficient to provide acceptable study operating characteristics for the primary efficacy endpoint (Section 9.3.1.1). To account for an assumed 10% dropouts within each treatment arm and to enable an equal study participant allocation between treatment arms, 68 study participants will be randomly assigned to study treatment arms.

Given that there are no randomized published studies in the LGI1 patient population, there is uncertainty with respect to the expected proportion of participants who may achieve seizure freedom by 24 weeks in the control arm. While the targeted desirable treatment difference is 40%, a difference of 30% would be considered both clinically relevant and important in this disease area, given the lack of approved treatments and the length of prior corticosteroid treatment that is permissible in the study, along with potential prior disease specific treatment.

The study operating characteristics, presented in Table 9-6, were derived based on the assumed seizure freedom proportions in the study treatment arms observed at the end of Treatment Period (Week 25). Based on Thompson et al (2018), after 30 and 90 days 51% and 88% of LGI1

patients, respectively, experienced cessation of FBDS once treated with immunotherapy. These rates were consistent with de Bruijn et al (2019) median time to the FBDS freedom of 28 days once treated with immunotherapy.

For the purposes of the dual criteria framework as presented in Table 9-6, the proportions at the end of the Treatment Period (Week 25) were assumed not to be lower than 70% in the rozanolixizumab treatment arm and 40% in the placebo arm. The treatment effect evaluation, based solely on statistical significance testing, was complemented with an assessment of its clinical relevance following the dual criteria framework as presented by Fisch et al (2015).

Assuming 50% seizure-free proportions in the control arm, the sample size of 60 study participants will be able to detect a resulting 40% proportion difference with approximately 85% and a resulting 30% difference with approximately 55 to 65%. For a target difference (TD) of 40% in the proportions between the treatment groups, the probability that both significance and relevance criteria are met, given a true difference of 40%, is at least 45% with only 9.5% of studies where none of the key criteria are met. If the TD achieved is 30%, the probability that both key criteria are met is at least 76%.

If the difference in proportions increases to 50%, because of a larger (90%) seizure-free proportion in the rozanolixizumab arm, the power to detect that effect is at least 95% with the sample size of 60. For this design, the probability that both the criteria are met is 79% and 44.5% for TD of 40% and 50%, respectively, with less than 1% probability that none of the criteria are fulfilled.

Decisions with respect to the outcome of this study will utilize the operating characteristics as described for the primary endpoint but will also importantly consider the strength of evidence of treatment effect provided by the secondary endpoints, according to the prescribed criteria for alpha spending, as outlined in Section 9.3.2, as well as consideration to the safety data observed.

Table 9-6: Study operating characteristics

Sample size	PBO arm SF proportion (%) at the end of Treatment Period	R arm SF proportion (%) at the end of Treatment Period	Power CMH[a] (%)	Power logistic[b] (%)	Target R-PBO SF proportion difference (%)	Probability[c] (%)		
						Scenario A	Scenario B	Scenario C
60	40	70	54.6	63.2	30	45.7	20.6	33.8
					40	17.3	49.1	33.6
					50	3.7	62.8	33.5
60	40	80	84.5	86.0	30	76.3	14.1	9.6
					40	45.2	45.3	9.5
					50	16.1	74.7	9.2
60	40	90	98.3	95.4	30	95.6	3.8	0.6
					40	79.1	20.0	0.9
					50	44.5	54.8	0.7

CMH= Cochran-Mantel-Haenszel; PBO=placebo; R=rozanolixizumab; SF=seizure freedom
[a] Power to detect a statistical difference at a 2-sided 5% significance level based on the CMH test with continuity correction (Wittes and Wallenstein, 1987).
[b] Power to detect a statistical difference at a 2-sided 5% significance level from a standard logistic regression model adjusting for treatment group (Demidenko, 2007).
[c] Derived from the Fisch et al (2015) decision framework based on dual criteria: Significance – high confidence (0.975) that the effect of the investigational drug, relative to placebo, is greater than zero; Relevance - moderate confidence (0.5) that the drug effect, relative to placebo, is larger than the target difference. Possible scenarios: A – both criteria hold as an evidence of sufficiently high effect; B – inconclusive as only one criterion holds, suggesting a marginal effect (Significance only) or too much variability to make a clear decision (Relevance only); C – neither of the criteria holds. The probability of each scenario calculated from S=10,000 simulated study outcomes for a given sample size and seizure freedom proportions combination.

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 IRB/IEC, as defined in local regulations, International Council on 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 IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, Informed

Consent form, Investigator's Brochure, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

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

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

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

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

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant (or legal representative, if applicable and where local regulations allow) in both oral and written form by the investigator (or designee). Each participant (or legal representative, if applicable and where local regulations allow) and caregiver will have the opportunity to discuss the study and its alternatives with the investigator.

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

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

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

The participant (or legal representative, if applicable and where local regulations allow) may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given 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 participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant number assigned at Screening.

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

The 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 participant.

The 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 IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees structure

An IDMC will review the safety and tolerability data in this study in order to make recommendations for the sponsor to decide on whether to proceed with the study.

An IDMC will be set up in line with the Food and Drug Administration regulatory requirements and European Medicines Agency Guideline on iDMCs (EMEA/CHMP/EWP/5872/03 Corr, adopted 27/05/2005). The IDMC will consist of external experts who are independent from UCB and the clinical operations CRO, and have no conflict of interest related to the conduct or the outcomes of the study. The voting members of the IDMC will include, at minimum, a biostatistician and 2 neurologists.

10.1.6 Data quality assurance

All participant data relating to the study will be recorded on printed or electronic eCRF 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 eCRF.

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

The investigator must permit study-related monitoring, audits, IRB/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 eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of 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 will be established for the study using parameters related to patient safety reporting and reliability of study results. 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.

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.7 Apps

Study participants will be given a smart phone with the myUCB 4me app to enter information about seizures experienced between scheduled visits to the site.

The data recorded in the myUCB 4me app are not intended to be used to influence the treatment decisions of study participants during the conduct of this study. Rather, the site investigator will get access to the electronic data (e-diary), and all records should be printed and filed with the source documentation. The site investigator will use the information recorded to discuss with the participant and/or caregiver to report seizure related information in the eCRF.

To ensure the confidence in the reliability, quality, and integrity of the data, several security measures have been put in place. The iPhone itself is protected by a Personal Identification Number that is known only to the participant in AIE001. Furthermore, the myUCB site portal

also allows for qualified and trained site personnel to personalize the configuration for each participant. The access to the personalized configuration within the myUCB site portal is password protected, and the password is only known to the site personnel.

The participant and/or caregiver responds to the questions and acts on the requested activities in the myUCB 4me app. All data collected as part of these activities will be stored locally in the myUCB 4me app and are synchronized with the myUCB site portal when the iPhone is online and connected to a viable network. All data are reviewable for the investigator in real-time, provided the device has been synchronized. The data collected are fully encrypted within the app and its transmission to UCB Systems. All data in the myUCB 4me app will be erased upon configuration for a new participant. All data collected will be available to the sites in a human readable way, via the myUCB site portal and a printable Patient Data Report.

10.1.8 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 eCRFs are not considered acceptable source documents.

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

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the 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).

10.1.9 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 IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

- Discontinuation of further study medication development

10.1.10 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.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of 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

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="4">Hematology</td><td>Platelet Count</td><td rowspan="4">RBC Indices:
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
%Reticulocytes</td><td rowspan="4">WBC Count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>RBC Count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td>Clinical Chemistry[a]</td><td>Blood urea nitrogen (BUN)</td><td>Potassium</td><td>Aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
</table>

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
	Creatinine	Sodium	Alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT)	Total protein[b] Albumin[b]
	Glucose (non-fasting)	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 (FSH) and estradiol (as needed in women of non-childbearing potential only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) • Serology testing (for Hepatitis A, Hepatitis B surface antigen, Hepatitis C virus antibody, and human immunodeficiency virus [HIV])			
Other Tests	The following tests are performed locally: – IGRA TB test – Dipstick urinalysis (including any microscopy where required) – Urine pregnancy dipstick test[c]			

IGRA=interferon-gamma release assay; TB=tuberculosis.
The results of each test must be entered into the CRF.
NOTES:
[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 ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Other protocol-required laboratory assessments

Laboratory Assessments	Parameters
Other laboratory assessments	• LGI1 detection • Blood sampling for PK of rozanolixizumab[a] • Blood sampling for DNA and RNA analysis[b] • Serum complement ([redacted]), and plasma complement ([redacted])[b] • Total IgG[a] • IgG subclasses[a] • LGI1 IgG (total and subclasses) serum quantification[a] • [redacted] • Anti-drug antibodies[a] • Optional CSF sample collection[a] • Blood sampling for exploratory biomarker analysis[b]

AED=antiepileptic drug; [redacted] COVID-19= coronavirus 2019; CSF=cerebrospinal fluid; DNA=deoxyribonucleic acid; Ig=immunoglobulin; LGI1=leucine-rich glioma inactivated 1; NF-L=neurofilament light chain; PK=pharmacokinetic(s); RNA=ribonucleic acid.

[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

Assessment and management of TB and TB risk factor as well as safety reporting requirements are provided in Section 10.12 (Appendix 12).

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 fulfil 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 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).

A 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 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 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 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 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 participant identifiers, with the exception of the 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 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 a 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 a 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 healthcare 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 participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a 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 UCB 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 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 post-menopausal 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 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 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.

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
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 participant.
NOTES: a) In case of newly started contraception pills/IUDs, PI 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 participants participating in clinical studies.

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.
- Additional pregnancy testing should be performed as specified in the Schedule of Activities (Section 1.3) during the treatment period and at the EOT visit, corresponding to protocol-defined time frame in Appendix 4 after the final dose of study medication 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. A serum and urine pregnancy test will be completed at Screening and Baseline, respectively.

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 study medication. If the study 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 1 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.

Female Participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.
- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 1 working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the 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.

10.5 Appendix 5: Genetics

Genetics analyses may evaluate genetic features and epigenetic changes associated with the cause, progression, and appropriate treatment of LGI1 AIE.

Use and Analysis of DNA

- Genetic variation may impact a 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 IRB/IEC allow, a blood sample will be collected for DNA analysis from participants in the AIE001 study.
- Genetics samples will be used for research related to cause, progression, and appropriate treatment of LGI1 AIE. They may also be used to develop tests/assays including diagnostic tests related to rozanolixizumab and LGI1 AIE. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome. Deoxyribonucleic acid samples will be analyzed for genetic and epigenetic changes that may promote understanding of the cause, progression, and appropriate treatment of LGI1 AIE.

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to the study medication to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the blood or isolated DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on study medication 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

Participants with potential drug-induced liver injury 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 potential drug-induced liver injury 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 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 study physician and the investigator for study participants who have ALT >3 ULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values). Liver chemistry stopping criteria and criteria for increased monitoring are designed to assure study participant safety and to evaluate liver event etiology. They are presented in the tables below.

Phase 2 Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[b]	ALT ≥3xULN **and** international normalized ratio (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.**	• Viral hepatitis serology[d]

Liver Chemistry Stopping Criteria	
• Complete the liver event case report form (CRF), and complete a serious adverse event (SAE) data collection tool if the event also met the criteria for an SAE. [b] • Perform liver chemistry follow-up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**). • **Do not restart/rechallenge** participant with study medication. • Permanently discontinue study medication and continue participant in the study for any protocol specified follow up assessments. • Consider the need for a toxicology screening **MONITORING:** **<u>If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:</u>** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **<u>If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis as soon as feasible after the most recent dose[e]. • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (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 adverse event (AE) report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF. • Record alcohol use on the liver event alcohol intake CRF • Exclude pregnancy **<u>If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay for assessing the potential acetaminophen contribution to liver injury • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver

[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 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 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 [redacted] antibody; HbsAg and HbcAb; hepatitis C RNA; cytomegalovirus [redacted] antibody; Epstein-Barr viral capsid antigen [redacted] antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E [redacted] antibody.

[e] PK sample may not be required for 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 final dose of study medication prior to the blood sample draw on the CRF. If the date or time of the final dose is unclear, provide the participant's best approximation. If the date/time of the final 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.

Liver Chemistry Increased Monitoring Criteria with Continued Study medication

Liver Chemistry Increased Monitoring Criterion and Follow-Up	
Criterion	**Actions**
ALT ≥3xULN 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 participant safety. • Participant can continue study medication • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize or return to baseline. • If at any time, the 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 participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

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	acetylcholine receptor
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
AESM	adverse event of special monitoring
AIE	autoimmune encephalitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
App	application
AST	aspartate aminotransferase
CASE	Clinical Assessment Scale in Autoimmune Encephalitis
CGI-S	Global Impression of Disease Severity
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CNS	central nervous system
COVID-19	coronavirus 2019
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DAP	Data Analysis Plan
DCP	Data Cleaning Plan
DIAM	drug-induced aseptic meningitis
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDisc	early discontinuation
EOS	end of study
EOT	end of treatment

EQ-5D-5L	EuroQol-5D-5L
EQ VAS	EuroQol visual analogue scale
FAS	Full Analysis Set
FBDS	faciobrachial dystonic seizure(s)
FcRn	neonatal Fc receptor
FSH	follicle stimulating hormone
GI	gastrointestinal
gMG	generalized myasthenia gravis
HCRU	healthcare resource utilization
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH-GCP	International Council for Harmonisation Good Clinical Practice
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
ITP	immune thrombocytopenia
ITT	Intent to treat
iv	intravenous
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
LGI1	leucine-rich glioma inactivated 1
LLOQ	lower limit of quantification
LTBI	latent tuberculosis infection
MCS	Mental Component Summary
MedDRA®	Medical Dictionary for Regulatory Activities®

MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MP	methylprednisolone
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
NTM	nontuberculosis mycobacteria
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PD-PPS	Pharmacodynamic Per-Protocol Set
PEX	plasma exchange
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Disease Severity
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PLEX	plasma exchange
PRO	patient-reported outcome
Q1W	once a week
QTcF	QT interval corrected using Fridericia's formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RNA	ribonucleic acid
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
SD	standard deviation
SF-36	36-item Short Form Survey
SFU	safety follow up
SS	Safety Set
SUSAR	suspected unexpected serious adverse reaction(s)
TB	tuberculosis
TD	target difference
TEAE	treatment-emergent adverse event

TTFSF	time to first occurrence of seizure freedom
TTSFM	time to seizure freedom maintenance
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 5 (date: 09 Feb 2023)

Overall Rationale for the Amendment

In the past 3 years (since the initial protocol), there is an emerging understanding about the experiences of patients with LGI1 AIE, changes in medical management of such patients, and more widespread use of the clinical outcome assessments supporting efficacy endpoints selected for this study. Therefore, changes to the protocol have been made to update the secondary endpoints and associated statistical methods and better align the protocol with the current treatment practices and understanding of the disease.

Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

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.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of activities 4.1 Overall design	Duration of Screening Period changed from upto 14 days to upto 42 days.	To allow participants who initiated treatment outside study centers to still be considered for admission into the study and to ensure there is sufficient time for all eligibility assessments to be performed before dosing.
1.1 Synopsis 4.1 Overall design	Maximum study duration per study participant updated from 34 weeks to 38 weeks. Text related to Screening Period was updated as follows: - New text was added to clarify eligibility for treatment initiation/re-initiation. - The term IVMP was replaced with high dose corticosteroids in the text. - The timeframe for the randomization of study participants following corticosteroids initiation was updated from upto 14 days to upto 42 days.	To align with the increase in the duration of the Screening Period.

Section # and Name	Description of Change	Brief Rationale
	- Text describing corticosteroids initiation and steps for down titration was added. New text describing eligibility of participants who have previously received a first line AIE treatment was added.	
4.2 Scientific rationale for study design	Text regarding eligibility for inclusion in the study was updated.	Clarification and improvement.
1.1 Synopsis 3 Objectives and endpoints 9.3.2.2 Change in overall disability function (mRS)	The endpoint relating to the change from Baseline in the mRS has been moved from exploratory to secondary endpoints. The analysis of the mRS has been amended from comparing a change from Baseline to comparing the proportion of participants meeting criteria for favorable outcome.	To offer a basis of comparison with other studies in AIE, the mRS parameter will be assessed as a secondary endpoint. The updated analysis is of greater clinical relevance. Emerging literature suggests that over time, the impacts of signs and symptoms of AIE, including cognitive impairment, lead to worsening of functional abilities. The expectation is that functional ability in the treatment groups may not decline/worsen as in the placebo arm; the endpoint is therefore being revised to identify groups with better mRS outcomes, similar to endpoints evaluated in stroke trials.
1.1 Synopsis 3 Objectives and endpoints	The endpoint relating to seizure control was updated.	The analysis for this endpoint has been modified to reflect the new data type collected in the participant daily seizure diary. This is now categorical data rather than continuous data, hence the endpoint and the subsequent data analysis has been modified to align it with the revised format of the data.
1.1 Synopsis 3 Objectives and endpoints 1.3 Schedule of activities 8.1.5 Clinical global impression of severity	The endpoints relating to PGIS and PGIC have been removed and replaced with CGI-S.	To reduce the frequency of assessments and in turn reduce protocol complexities, site and patient burden while still collecting required data for adequate assessment of the relevant endpoints.

Section # and Name	Description of Change	Brief Rationale
		Given that the participants are congnitively impaired, CGI-S is considered to be more accurate and relevant than PGIS.
1.2 Schema 1.3 Schedule of activities	Visit 4 (Day 5) has been removed. Procedures have been removed from Visits 12, 22 and EOS (RBANS, mRS, SF-36 and EQ-5d-5L).	To reduce the frequency of assessments and in turn reduce protocol complexities, site and patient burden while still collecting required data for adequate assessment of the relevant endpoints.
1.1 Synopsis 1.3 Schedule of activities 3 Objectives and endpoints 8.9.1 Immunology 9.4.2.3 AED	The following laboratory assessments were removed: PTT, INR, [redacted] and COVID-19 antibodies. The assessments of CASE was removed. Blood sampling for concomitant AED assay was removed.	These measures are deemed not mandatory for the safety monitoring of the study participants and were removed to decrease the protocol complexities.
5.1 Inclusion criteria	Inclusion criterion #4a updated with consistent terminology on corticosteroids and dose range.	To provide clarification and for consistency with Section 6.5.2.
5.2 Exclusion criteria	Exclusion criterion #6 was removed as it was covered under exclusion criterion #1. Exclusion criterion #8a (previously #8) has been modified to limit the exclusion of a participant due to a current active infection, an unresolved, or an inadequately treated infection. Exclusion criteria #11 and #15 have been removed. Exclusion criterion #20a (previously #20) has been modified to exclude study participants who have received a live vaccination within 4 weeks prior to the Baseline Visit instead of 8 weeks. Exclusion criterion #26 was removed as it was covered under exclusion criterion #10.	Update 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 points. Also, exclusion criterion #11 is covered by exclusion criterion #12 and Appendix 10.12. Exclusion criterion #15 was removed to align with the IMP mechanism of action as it does not interfere with [redacted] isoforms.
6.5 Concomitant medication(s)/treatment(s)	Prior medication and duration of those medications updated.	To align with current therapeutic practices.

Section # and Name	Description of Change	Brief Rationale
	The type of permitted prior and concomitant medications (BZD, AEDs, corticosteroids, PEX, IvIG, immunoadsorbtion) has been updated.	
7.1 Discontinuation of study medication	New text was added: "Participants who are permanently discontinued from IMP will undergo an EDisc Visit and SFU Visit."	To align across the rozanolixizumab program.
7.1.2 QTc stopping criteria 7.1.4 Temporary discontinuation of IMP 8.11 COVID-19 vaccination	The section describing the QTc stopping criteria was removed. Text related to temporary discontinuation in the event of COVID-19 was removed.	This update was based on safety knowledge gained from the rozanolixizumab program.
1.3 Schedule of activities 5.2 Exclusion criterion 12 sub-bullet 3 7.1.2 Permanent discontinuation due to other AEs 7.2.1 Study withdrawal criteria 8.2.1 Physical examination 8.2.7.Assessment and management of tuberculosis and tuberculosis risk factors 10.12 Appendix 12: Tuberculosis Questionnaire	Text describing diagnosis, assessment and management of TB was updated. Text related to the TB questionnaire was replaced by focused medical history. The TB questionnaire was removed from Section 10.12 Appendix 12. The chest x-ray procedure was removed. Text on the assessment and management of TB was moved from Section 8.2.7 to Section 10.12 Appendix 12. In addition, new text on safety reporting requirements related to TB was added.	To provide clarification and simplified text.
8.2.3 Vital signs	The frequency of vital signs measure was modified; the current schedule includes vital signs measure on the days of IMP administration for the first 8 weeks and thereafter the measures will be aligned with the days of the physical examinations.	This update was based on safety knowledge gained from the rozanolixizumab program.
9.3 Planned efficacy/outcome analyses	Text was updated to indicate that an additional adjustment will be made, where applicable, in any statistical modelling.	To provide clarification.

Section # and Name	Description of Change	Brief Rationale
9.3.2 Secondary efficacy analysis	Text was updated to reflect the changes made to the secondary endpoints.	To align with the list of secondary endpoints.
9.3.3 Exploratory efficacy analysis	Section 9.3.3.1 was updated to clarify that for the "Time to seizure freedom maintenance" endpoint, analysis and summaries will be repeated for only the subgroup of participants who achieved the seizure freedom endpoint criteria. Section 9.3.3.2 was updated from "Seizure reductions" to "Seizure control" and the text was updated to describe the analysis of the seizure control endpoint. Section 9.3.3.3 "Time to seizure reductions" was removed.	To provide details regarding the analysis of the seizure control endpoint.
9.8 Determintation of sample size	Updates were made to the text and additional information provided.	To provide clarification.
10.1.3 Informed consent process	The wording around the caregiver and informed consent was made consistent throughout the protocol.	To clarify the role of the caregiver.

Amendment 4 (date: 19 Oct 2022)

Overall Rationale for the Amendment

Changes to the protocol have been made to update safety information in line with the revised IB dated 06 September 2022. Additional changes have also been made to reduce the study burden for patients.

Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

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.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities 1.3.1 Additional study assessments 2.2 Background 2.3 Benefit/Risk Assessment 7.1.3 Permanent discontinuation due to other AEs	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.	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

Section # and Name	Description of Change	Brief Rationale
7.1.5 Temporary discontinuation of IMP 8.2.2 Neurological examination 8.3.7 Adverse events of special monitoring 8.9 Biomarkers 10.13 Appendix 13 Management of AESM 10.2 Appendix 2: Clinical Laboratory Tests	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)	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.
1.2 Schema 1.3 Schedule of activities	Removal of Visits 17 and 18 (Week 13), and the removal explained in new footnote *bb* in Table 1-1.	To reduce the study complexity, and decrease the burden on participants.
1.1 Synopsis 3 Objectives and endpoints 1.3 Schedule of activities 8.8 Pharmacodynamics 9.1 Definition of analysis sets 9.4.2.4 Pharmacodynamic analyses 10.2 Appendix 2: Clinical laboratory tests	Samples for neurofilament light chain have been removed from the study assessments.	As the potential scientific value of NF-L is limited, and the objectives and endpoints were amended to reduce study complexity.
1.1 Synopsis 3 Objectives and endpoints 1.3 Schedule of activities	Sampling of DNA and RNA analysis to be taken only at Baseline, sampling of [redacted] to be taken only at Screening, and sampling for serum and plasma complements to be taken only at Baseline and in the event of infusion or hypersensitivity reaction. Changes have been made to the objectives and endpoints, and other sections of the protocol to reflect these changes in sampling strategy.	To reduce the study complexity, and decrease the burden on participants.
1.1 Synopsis 3 Objectives and endpoints	The effect of rozanolixizumab on α- and β-globulins removed from the exploratory objectives and endpoints.	Correction.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and endpoints 8.2.5 Magnetic resonance imaging	The effect of rozanolixizumab on whole brain and hippocampal volume removed as an exploratory endpoint. Further, based on the investigator's judgement MRI performed within 3 months of the Screening Period may be acceptable for the Screening/ Baseline assessment. MRI may also be assessed at any visit, as needed.	To reduce the study complexity and to expedite the analysis of a safety endpoint by the investigator, MRI will be assessed locally as part of safety assessments.
1.1 Synopsis 4.1 Overall design	Text updated to note that LGI1 AIE disease onset is at the assessment of the investigator.	Clarification
1.3 Schedule of activities 7.1.2 QTc stopping criteria 8.2.4 Electrocardiogram	TB signs and symptoms questionnaire as well as 12-lead ECG assessments have been reduced to occur at Screening and EOT/EDisc visits, with optional assessments at any visit. The ECG assessments have been updated to be assessed locally, with no requirement for triplicate ECGs.	Update in line with accumulated safety data on rozanolixizumab
1.3 Schedule of activities	Samples to assess the PK of rozanolixizumab have been removed from Weeks 2, 3, 13 (Days 87 and 89), and Week 21. Footnote *m* has also been updated to align with these changes. Samples to assess ADA have been removed from Weeks 3, 13 (Day 87), and 21.	Updated to reduce the sampling burden on participants given the fact that the PK of rozanolixizumab is better defined as a result of data from other clinical studies.
1.3 Schedule of activities	Samples to assess IgG subclasses have been removed from Weeks 11, 15, 19, and 22.	To reduce the participant burden associated with this exploratory measure.
1.3 Schedule of activities 8.9.1 Immunology	Sampling for serum and plasma complements will be collected only at Baseline and after an injection site reaction or hypersensitivity reaction.	To reduce the participant burden associated with this exploratory measure.

Section # and Name	Description of Change	Brief Rationale
2.2 Background	Updates to text describing the results of completed studies in the rozanolixizumab clinical development program. Updated text to refer to the IB for status of ongoing studies.	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.
4.3 Justification for dose 4.3.1 Justification for IgG target REFERENCES	Text updated to reflect the latest clinical data from completed studies. Literature citations removed from these sections also removed from the Reference list	Updated including recent new data from completed Phase 3 study, MG0003, in gMG.
5.1 Inclusion criteria 10.4 Contraceptive guidance and collection of pregnancy information	Inclusion criterion #7 (now #7a) has been updated to remove the requirement for a male participant to use contraception or refrain from sperm donation.	To update male contraception requirements with current guidelines, after completion of the required reproductive toxicity studies and considering that rozanolixizumab has no genotoxic potential and potential exposure through seminal fluid is expected to be negligible.
5.1 Inclusion criteria	Inclusion criterion #9 (now #9a) updated to remove requirement for caregiver to provide consent, and Inclusion criterion #10a has been removed.	To improve clarity and remove redundancy across Inclusion criteria #8a and #9a.
5.2 Exclusion criteria	Exclusion criterion #14 relating to active GI disorders has been removed.	Update in line with accumulated safety data on rozanolixizumab
5.2 Exclusion criteria	Exclusion criterion #24a amended (now #24b) to exclude when ALT, AST or ALP are >3xULN (rather than >2xULN)	Update in line with accumulated safety data on rozanolixizumab
5.2 Exclusion criteria	Exclusion criterion #33 (related to prolonged QT interval) has been removed.	This criterion is redundant as abnormalities in QT interval would be excluded by criterion #6 (clinically significant ECG findings).

Section # and Name	Description of Change	Brief Rationale
5.4 Screen failures	Text added to the third and fourth paragraphs to clarify randomization procedures after rescreening.	Clarification
6.1 Study treatments 6.3.1.1 Maintenance of study treatment blind	The dose formulation of rozanolixizumab has been updated from 'liquid in vial' to 'solution for injection'. The description of the amount of extractable volume has been removed from the description of rozanolixizumab.	To give flexibility in the supply of saline, and flexibility to use alternative vial fill volumes of rozanolixizumab.
7.1.5 Temporary discontinuation of IMP	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 Study assessments and procedures	Removal of text "Protocol waivers or exemptions are not allowed."	Text is already included in Section 5 (Study population)
8 Study assessments and procedures	Text clarified to note that any additional blood samples may increase the total volume of blood collected.	Clarification.
8.2.3 Vital signs	Removed description of the time points for vital sign assessments.	To remove redundancy with the Schedule of Activities (Section 1.3).

Amendment 3 (date: 14 Jan 2022)

Overall Rationale for the Amendment

The overall rationale for the amendment is to address comments and queries from FDA raised during the IND review. Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

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.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of activities 3 Objectives and endpoints 8.9 Biomarkers	The collection and analysis of cytokines has been removed from the protocol.	The endpoint was removed as the analysis of cytokines is not required in this protocol as samples have been collected in other rozanolixizumab studies and no additional information is

Section # and Name	Description of Change	Brief Rationale
8.9.1 Immunology 9.4.2.5 Immunological analyses 10.2 Appendix 2 Clinical laboratory tests 10.17 Appendix 17 Management of infusion reactions or hypersensitivity reactions		expected from the AIE population, and the scientific value is limited.
1.3 Schedule of activities 7.1.5 Temporary discontinuation of IMP	Text has been added to footnote p of Table 1-1 and to #1 and #2 of Section 7.1.5 to indicate that ad hoc assessments of albumin and IgG can be performed to monitor the recovery of albumin and IgG levels, or for random sampling of study participants to maintain the blind.	To enhance the rigor of the study blind.
1.3 Schedule of activities 8.2.3 Vital signs	In footnote k of Table 1-1 and paragraph 3 of Section 8.2.3, text has been added to indicate a time window for the measuring of vital signs.	To provide a time window for which the measurement of vital signs can take place.
1.3 Schedule of activities	A new footnote z in Table 1-1 for RBANS, PGIS, SF-36, and EQ-5D-5L has been added to note that the assessment scheduled at Screening should be performed as close as possible to the Baseline Visit.	For the PGIS, SF-36, and EQ-5D-5L assessments, this is to capture the potential for improvement in these assessments resulting from IVMP administration between Screening and Baseline. For RBANS, this is to account for any change in cognitive status during the screening period.
1.3 Schedule of activities 9.3.3.6 Change in the overall clinical assessment (CASE) 9.3.3.7 Change in overall disability function (mRS)	The CASE and mRS assessments will also be performed at the Baseline Visit (as well as at Screening). The assessment at Screening should be performed as close as possible to consent. The better of the 2 scores will be defined as the Baseline and used in the secondary analyses.	To capture the potential for change in these assessments as a result of IVMP administration between Screening and Baseline.
1.3.1 Additional study assessments	Description of the circumstances when additional study	To add clarity to the description.

Section # and Name	Description of Change	Brief Rationale
	assessments are required was updated.	
4.3 Justification for dose	The dose currently under investigation in the Phase 3 ITP studies has been updated to weight-tiered doses of 10mg/kg Q1W.	Update in the dose being investigated in the rozanolixizumab studies in ITP.
5.2 Exclusion criteria	Exclusion criterion #7 (now criterion #7a) has been updated to exclude study participants with a GFR of <30ml/min/1.73m^2 (formerly <45ml/min/1.73m^2).	To make exclusions based on renal clearance consistent with FDA guidance. Given the accumulated data from the rozanolixizumab development program indicating an absence of a safety signal related to renal function, the protocol has been updated to exclude study participants with a GFR of impairment (ie, <30ml/min/1.73m^2.
6.5.1 Permitted concomitant treatments (medications and therapies)	Section updated to note that at the discretion of the investigator, study participants may initiate prophylaxis for pneumocystis carinii pneumonia (PCP).	As study participants will receive steroids for up to 12 weeks, they may be immune compromised and at a potential increased risk of PCP. Based on the investigator's discretion prophylaxis medication may be administered.
6.5.1 Permitted concomitant treatments (medications and therapies)	Section updated to note that in study participants with a GFR between 30 and 45mL/min/1.73m^2, the dose of concomitant medications should be adapted to the study participant's renal function.	To align with changes made to criterion #7a in Section 5.2 (Exclusion criteria).
6.5.1 Permitted concomitant treatments (medications and therapies)	The use of topical or local steroids has been added as a permitted concomitant medication.	Clarification.
7.1.3 Permanent discontinuation due to other AEs	Clarified that study participants permanently discontinuing from IMP must move to the Safety Follow-Up Period.	Correction.
7.1.3 Permanent discontinuation due to other AEs	Criterion #2 updated: Study participant has a ~~serious~~ **significant** infective episode ~~requiring hospitalization or iv~~	To add precision to the permanent discontinuation

Section # and Name	Description of Change	Brief Rationale
	~~antibiotic therapy (~~including but not limited to bacteremia/~~or~~ sepsis,~~ bacterial~~ **infectious** meningitis, ~~osteomyelitis or~~ septic arthritis, **osteomyelitis**, ~~bacterial~~ **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 judgement on continuing IMP based on the clinical situation** (see Appendix 16; Section 10.16).	criteria, and to avoid unnecessary withdrawals.
8.1.1 Assessment of seizures	Text updated to note that study participants or caregivers have up to 24h from the end of the day to complete the seizure diary, after that, the diary will no longer be available for completion. Retrospective edits to seizure records in the app are not permitted but changes can be identified during the review with the investigator and edits made to the printed record.	To provide clarity.
8.2.7.3 Tuberculosis assessment by interferon-gamma release assay 1.3 Schedule of activities	Text updated to note that the IGRA assessment should be performed first at the Screening Visit. Cross reference to Section 8.2.7.3 added to footnote j of Table 1-1. Text also updated to note that the IGRA TB screening test should be performed at a local (rather than central) laboratory, and the name of the preferred brand of IGRA test has been removed.	There is a risk of indeterminate results in the presence of steroid use. To reduce this risk, the IGRA should be the first assessment performed at Screening. To ensure that the IGRA TB test result is available within the screening period, the test can be performed at a local (rather than central) laboratory using the available IGRA test at the local site.
9.3.1.1 Seizure freedom	Text added to note that for deriving the primary efficacy endpoint, intermittent missing diary seizure count data will be imputed to non-zero.	To clarify how intermittent missing seizure diary days will be handled in the derivation of the primary endpoint.

Section # and Name	Description of Change	Brief Rationale
9.3.2 Secondary efficacy analysis	Text added to define a hierarchical testing procedure for the analysis of the secondary efficacy endpoints.	To control analyses of efficacy-related secondary endpoints for type I error.
9.3.3.2 Seizure reductions	Text updated to note that intermittent missing daily seizure counts in a given reporting period will be (indirectly) imputed with the daily average seizure count observed in that period.	For consistency with changes made to Section 9.3.1.1 relating to imputation of missing seizure count data.
10.6 Appendix 6: Liver Safety – Suggested Actions and Follow-up Assessments	A correction to state that a specific monitoring plan must be agreed for study participants with an ALT of >3 ULN (previously >5 ULN). Removal of redundant and contradictory text.	Correction and to improve clarity.
10.9.1 China	Section has been removed as the study will no longer be performed in China.	Correction.
10.16 Appendix 16: Management of Infections and Hypogammaglobulinemia	Text has been added to indicate that 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, the unblinded medical monitor may request additional IgG sampling and/or supportive information for any study participants at random to preserve the blind.	To enhance the rigor of the study blind.
10.16: Appendix 16: Management of Infections and Hypogammaglobulinemia	Paragraph 2 updated to be consistent with changes made to criterion #2 in Section 7.1.3.	To add precision to the permanent discontinuation criteria, and to avoid unnecessary withdrawals.

Amendment 2 (date: 07 Sep 2021)

Overall Rationale for the Amendment

Changes to the protocol have been made to amend the inclusion critera to ensure greater specificity for the target population, the addition of regular monitoring of lipid parameters, and to provide clarity on how the treatment blind will be maintained. This amendment also introduces

blood sampling for antibody response to COVID-19 vaccination, and provides clarity on the management of study participants undergoing COVID-19 vaccination. Requests from regulatory authorities or ethics committees have been incorporated, and country-specific revisions added to Section 10.9. Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

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.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	Inclusion criterion #3a (previously criterion #3) revised to specify the presentation of additional clinical criteria to allow for the inclusion of study participants with seizures other than FBDS.	To reduce the potential risk of enrolling participants in the study who do not have LGI1 AIE. The revised criterion was based on a position paper for a practical approach for diagnosing AIEs (Graus et al, 2016).
5.1 Inclusion criteria 1.1 Synopsis 1.2 Schema 1.3 Schedule of activities 4.1 Overall design	Inclusion criterion #4a (previously criterion #4) updated to permit inclusion of "participants who are deemed appropriate for initiation of IVMP based on clinical symptoms and history" and removal of "being currently considered for treatment with IVMP by the investigator."	Clarification of wording to indicate that the study participant would be appropriately treated with IVMP.
1.3 Schedule of activities 10.2 Appendix 2: Clinical Laboratory Tests	Addition of HDL, LDL, total cholesterol, and triglycerides to the hematology, chemistry, and urinalysis assessments with samples to be taken at Screening, Baseline, Visit 5, Visit 8, Visit 12, Visit 16, Visit 22, Visit 26, and at Unscheduled visits, as well as EOT/EDisc Visit, and EOS Visit.	Preliminary, unblinded data for another anti-FcRn mAb, IMVT-1401 showed evidence of increases in some lipid parameters in patients with thyroid eye disease (eyewire, 2021). Given rozanolixizumab acts via a similar mechanistic pathway, lipids will be assessed in this clinical study.
1.1 Synopsis 3 Objectives and endpoints 1.3 Schedule of activities 8.9.1 Immunology	Addition of COVID-19 antibody sampling to procedures to be undertaken as well as a new objective and endpoint.	To allow for an exploratory analysis assessing the effect of rozanolixizumab on response to COVID-19 vaccination.
1.1 Synopsis 3 Objectives and endpoints	Removal of 'T1-weighted' from the description of volumetric sequence, addition of 3D to description of T2 FLAIR scans.	Clarification of the MRI parameters to be assessed.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities 8.11 COVID-19 vaccination	New Section 8.11 and new footnote y in Table 1-1 noting that there should be a minimum of 72 hours between COVID-19 vaccination and IMP administration. The scheduled dosing of IMP can be adjusted to accommodate COVID-19 vaccination, provided that the interval between 2 consecutive doses is at least 5 days.	A delay between IMP administration and COVID-19 vaccination has been introduced to aid in determining the relationship between any potential AEs due to the vaccine or IMP. A 72-hour delay was selected as this falls approximately half way between [redacted] IMP administration schedule.
1.3 Schedule of activities 8.2.7.3 Tuberculosis assessment by interferon-gamma release assay	Updated to note the procedures that should be followed in the event of any positive IGRA or 2 indeterminate IGRA.	To clarify the process in the event of IGRA test results with an indeterminate outcome.
1.3 Schedule of activities 6.1 Treatments administered 8.2.3 Vital signs	Updates have been made to text in footnote l of Table 1-1 and a new row inserted into Table 6-1 of Section 6.1 to add the observation period following IMP administration, as well as text requiring that the investigator completes a checklist prior to the initiation of home dosing. The timings of vital sign assessments in footnote k and in Section 8.2.3 have also been updated to match the change in post-dose observation period.	This change is to be implemented across the development program as a result of safety monitoring from ongoing studies in other patient populations indicating that observation period can be reduced in study participants who have shown acceptable tolerability following IMP administration. The change in observation period will also reduce the clinic waiting time for the study participant. Clarification on the requirement of investigator approval preceding the initiation of home dosing added for completeness.
1.3 Schedule of activities 8.2.3 Vital signs	Updates have been made to text in footnote k of Table 1-1 and in Section 8.2.3 to remove the requirement for vital signs to be measured at 15 mins after the start of the infusion.	The infusion time is 15 mins. The schedule of activities also requires a vital sign measurement at the end of the infusion. This change removes duplication and provides clarity.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities 8.2.5 Magnetic resonance imaging	The assessment "MRI scan including T1,T2 coronal images" has been moved from the Baseline Visit to the Screening Visit, and footnote w updated to read: "MRI should be collected per imaging guidelines during the Screening Period or at the Baseline Visit."	To ensure that the MRI scan is performed as close as possible to the start of IVMP treatment.
1.3.1 Additional study assessments 2.1 Study rationale 8.3.7 Adverse events of special monitoring 10.14 Appendix 14: Management of Headache	A headache questionnaire will be used as an additional study assessment in case of moderate, severe and/or serious headache. It was originally planned only in case of severe and/or serious headache.	Extended assessment implemented across the development program to better characterize the events of headaches.
2.1 Study rationale	Changes to indicate that in patients with LGI1 AIE, LGI1 autoantibodies are detected in serum and occasionally CSF and updated literature reference.	For increased precision.
2.2 Background	The number of ongoing rozanolixizumab clinical studies has increased from 6 to 9.	Update based on current clinical information.
2.3 Benefit/Risk assessment	Text updated to add a benefit-risk assessment of vaccinations while receiving rozanolixizumab.	To incorporate guidance from health authority relating to the management of clinical studies during COVID-19.
4.1 Overall design 8.1.1 Assessment of seizures	Update to the description of the primary endpoint.	Correction.
4.1 Overall design 1.1 Synopsis	Added a clarification of the steroid taper.	For consistency and completeness.
4.2 Scientific rationale for study design	New paragraph justifying the use of a placebo control and 24-week Treatment Period.	To incorporate health authority feedback.

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific rationale for study design	The paragraph justifying the use of a placebo control and 24-week Treatment Period added to AIE001 Protocol Amendment 1, Addendum A (UK) has been reworded to reflect the change made to inclusion criterion #4a, and to improve clarity and precision.	To improve clarity and precision.
4.2 Scientific rationale for study design	New text describing the rationale of updated inclusion criteria #3a (formerly #3).	To provide a justification for the selected inclusion criteria.
5.1 Inclusion criteria	The text in inclusion criterion #8a (formerly criterion #8) has been updated to allow a legal representative to give informed consent on the study participants behalf.	Clarification and for consistency with Section 10.1.3.
5.1 Inclusion criteria	The text in inclusion criterion #10a (formerly criterion #10) has been updated to allow the investigator to assess the capability of a participant adhering to the protocol visit schedule and medication intake, based on the study participant alone or with the assistance of a caregiver.	In practice at the time of entering the study, the majority of study participants are likely to require a caregiver to assist with adhering to the protocol.
5.2 Exclusion criteria	Updated exclusion criterion #4a (previously criterion #4) excluding participants with new onset seizures unrelated to LGI1 AIE or known or suspected medical cause for the onset of seizures other than possible AIE.	Coupled with the changes to the inclusion criterion #3a, this addition is designed to reduce the potential risk of enrolling study participants who do not have LGI1 AIE.
5.2 Exclusion criteria	Exclusion criterion #9a (formerly criterion #9) has been modified to add that the presence of HBsAg and HCV Ab will be tested at Screening. In case of positivity to HCV Ab, Hepatitis C RNA testing will be performed.	Regulatory authority request to clarify this criterion.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	The removal of exclusion criteria #27, #28, and #29 and incorporation of these criteria as sub-bullets to updated criterion #24a (previously criterion #24).	A re-ordering of the liver function test-related exclusion criteria to provide greater clarity.
5.2 Exclusion criteria	In exclusion criterion #24a (previously criterion #28) the following changes have been made: "If study participant has >ULN for ALT, AST, or ALP that does not meet the exclusion limit at Screening, the test must be repeated prior to dosing to ensure there was no further ongoing clinically relevant increase. In case of a clinically relevant increase~~, inclusion of the study participants will have to be discussed with the medical monitor~~ **as per the investigators judgement, the study participant must be excluded.**"	To incorporate health authority request to remove the medical monitor from making a decision pertaining to the participants eligibility, and to ensure the investigator is responsible for determining eligibility.
5.2 Exclusion criteria	"Total IgG" added to inclusion criterion #30a (previously criterion #30).	For clarity.
6.3.1.1 Maintenance of study treatment blind	Text has been added to describe the measures being taken to maintain the treatment blind given that rozanolixizumab and placebo are not identical in appearance.	To correct an omission following health authority feedback.
6.3.1.1 Maintenance of study treatment blind	A new paragraph has been added that describes the procedures in place for the monitoring of clinical laboratory results, and in the event that IMP is discontinued, the initiation of mock infusions, while maintaining the blind of the investigator, site personnel, and the study team.	Clarification regarding the proper maintenance of the study blind and the administration of mock infusions in the event of temporary discontinuation of IMP.

Section # and Name	Description of Change	Brief Rationale
6.5.2 Prohibited prior and concomitant treatments (medications and therapies)	Prednisolone is prohibited during the Treatment Period if used outside of the protocol-specified steroid taper, and prohibited if used prior to enrollment ~~and~~ since the onset of LGI1 AIE.	Clarification.
6.5.3 Rescue medication	The text has been updated to remove the list of specified rescue medications, and replace with a statement indicating that the investigator will select the most appropriate rescue medication for the study participant.	The choice of rescue medication does not need to be specified per protocol. It is the responsibility of the investigator to choose the most appropriate treatment.
7.1 Discontinuation of study medication	Added the following text: "In addition to algorithmic stopping criteria, management of adverse events is ultimately at the investigator's discretion."	A program-level change based on regulatory authority feedback to clarify that the management of AEs is at the investigator's discretion and should not be determined solely by algorithmic stopping rules.
7.1.3 Permanent discontinuation due to other AEs	Added "Study participant develops an illness that would interfere with his/her continued participation" to the reasons for permanent discontinuation from IMP.	For further clarity.
7.1.4 Permanent discontinuation due to absence or loss of clinical benefit	Added the following text to criterion #1a: "compared with Baseline."	Clarification.
7.1.5 Temporary discontinuation of IMP	For '**must be temporarily discontinued'**, criterion #1 (hypogammaglobulinemia), text has been added to allow ad hoc assessments to monitor recovery in IgG levels.	For consistency with footnote p of Table 1-1 and Appendix 16.
7.1.5 Temporary discontinuation of IMP	For '**must be temporarily discontinued**', a new temporary discontinuation criterion (#2) has been added for the occurrence of hypoalbuminemia, and the remaining criteria have been renumbered.	A program-level change based on regulatory authority feedback.

Section # and Name	Description of Change	Brief Rationale
7.1.5 Temporary discontinuation of IMP	Added that the eCRF should be completed to include information if the visit was impacted by COVID-19 infection.	To ensure that data impacted by COVID-19 is identifiable.
7.1.5 Temporary discontinuation of IMP	For '**may be temporarily discontinued**', a new temporary discontinuation criterion (#2) has been added for events at the discretion of the investigator.	To allow for temporary discontinuation at the investigators discretion, without needing to withdraw the study participant.
7.2 Participant discontinuation/withdrawal from the study 7.2.1 Study withdrawal criteria	In Section 7.2.1, for '**may be withdrawn from the study**', changes have been made to criterion #1: Study participant is persistently noncompliant with the study procedures or medications and this noncompliance is not manageable in the opinion of the investigator. Updates have been made to Section 7.2 for consistency.	To provide clarification.
8.2.5 Magnetic resonance imaging	Added detail pertaining to what the MRIs will be used to detect.	To provide clarification.
8.3.9 COVID-19 vaccination 6.5.1 Permitted concomitant treatments (medications and therapies)	Section 8.3.9 added outlining the procedure to be followed in the event of a study participant receiving a COVID-19 vaccination. The requirement to record COVID-19 vaccination details in the eCRF were also added to Section 6.5.1.	To incorporate guidance from health authority relating to the management of clinical studies during COVID-19.

Section # and Name	Description of Change	Brief Rationale
8.4 Safety signal detection	New paragraph stating that 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 a blinded manner.	To provide additional details on the safety signal detection methods being employed in the study.
8.6 Pharmacokinetics and immunogenicity	A sentence in the second paragraph has been updated: Samples collected for analyses of rozanolixizumab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising ~~during or after the study~~ **before study completion**.	To provide clarification.
8.9 Biomarkers	Updates have been made to correct the sampling time points. Text has also been updated to describe that samples stored for later exploratory analyses may be used for future diagnostic test development related to the exploration of the cause, progression, and appropriate treatment of LGI1 AIE.	For correction and to clarify that samples may be used for diagnostic test development.
9.1 Definition of analysis sets	The definition of the FAS changed to include all study participants in the RS, who have a Baseline value and at least one post-Baseline efficacy endpoint assessment.	For compliance with ICH E9 guidelines.
9.3.1.1 Seizure freedom	Removal of sentence pertaining to participants that contract COVID-19 during the study.	This information is included in Section 7.1.5.
9.3.1.1 Seizure freedom	In Table 9-1, edits made to population-level summary for primary and sensitivity statistical analyses.	For improved accuracy.
9.3.3.1 Time to seizure freedom	Updates have been made to add detail to the description of the analysis.	To complement the endpoint analysis.

Section # and Name	Description of Change	Brief Rationale
9.3.3.2 Seizure reductions	A definition of how seizure frequency will be calculated has been added.	To improve precision.
9.6 Handling of dropouts or missing data	A sentence was added to explain that data handling conventions for data affected by COVID-19 will be detailed fully in the SAP.	Added to confirm that the potential effects of COVID-19 on the data analysis will be addressed.
9.8 Determination of sample size	Updates made to the text and Table 9-5 to reflect amendments to the power assessment.	To improve the precision of the assessment.
10.1.3 Informed consent process	Removal of a repeated sentence pertaining to the provision of informed consent for CSF sampling, and clarification that legal representatives can provide consent for CSF sampling only where local regulations allow. Genetic analyses and storage of samples do not require a separate consent and text has been updated. Clarification of the role of the legal representative during the informed consent process.	To avoid repetition, correct text, and improve clarity. Regulatory authority request to clarify that in some regions, legal representatives can not provide consent for CSF sampling.
10.2 Appendix 2: Clinical Laboratory Tests	The table describing protocol-required safety laboratory assessments has been re-ordered. A new table detailing other protocol-required laboratory tests has been added. A new footnote has been added to both tables indicating which parameters will not be reviewed by the investigator until the study has been unblinded.	For transparency to include all laboratory tests in one section of the protocol and for clarity to highlight which assessment results will not be disclosed to investigative sites or other blinded personnel.
10.2 Appendix 2: Clinical Laboratory Tests	Updates have been made to the table summarizing safety laboratory assessments clarifying HBsAg and HCV Ab	For consistency with changes to exclusion criterion #9a.
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	In contraception guidance for male participants, bullet #2 was removed.	To clarify that the use of a male condom alone is acceptable.

Section # and Name	Description of Change	Brief Rationale
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Removal of the requirement for 2 forms of highly effective contraception.	Given the mechanism of action of rozanolixizumab, there is no scientific rationale to suggest a drug-drug interaction between rozanolixizumab and hormones.
10.5 Appendix 5: Genetics	Text has been updated to differentiate between biomarker and genetic samples, and to add clarity. The following sentence has been removed: Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.	The use and analysis of biomarker samples is described in Section 8.9, and has been removed from Section 10.5 to improve clarity.
10.14 Appendix 14: Management of Headache	The text in the third paragraph has been updated to define resolution of the headache as 'mild or completely resolved, whichever comes first'. Previously, the definition also included nonserious.	To take into account the extension of the questionnaire to study participants who experience moderate headaches.
10.16 Appendix 16: Management of Infections and Hypogammaglobulinemia	Text has been added that describes the role of the independent unblinded medical monitor in maintaining the study blind and reviewing serum IgG levels. A cross-reference has been added to Section 6.3.1.1 for further details of maintaining study blind. The following sentence has been updated: The risks and benefits of the treatment should be carefully considered prior to reinitiating the IMP ~~and the decision should be discussed and agreed upon by the investigator and the sponsor-designated unblinded medical monitor of the CRO.~~	For consistency with additions to Section 6.3.1.1 (Maintenance of study treatment blind).
10.9.1 China	New section (Section 10.9.1) describing the elements of the protocol that differ for study participants and investigators based in China.	Changes made to comply with country-specific regulatory requirements.

Amendment 1 (04 Dec 2020)

Overall Rationale for the Amendment

Changes to the protocol have been made to change the dose of rozanolixizumab from weight-tiered doses approximating 7mg/kg to fixed dose of [redacted] Other corrections to ensure consistency across the rozanolixizumab clinical development program have also been made. Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

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.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall design 4.3 Justification of dose 4.3.1 Justification for IgG target 6.1 Treatments administered	Removal of text relating to the administration of rozanolixizumab in weight-range based doses of approximately 7mg/kg and replaced with rozanolixizumab [redacted] Update to the dose justification section. Inclusion of a new subsection (Section 4.3.1) to describe the rationale for the IgG target.	Following availability of PK data from Phase 1 study UP0060, the need for weight-tiered dosing for rozanolixizumab was reassessed. Simulations performed using a population PK-PD (IgG) model of rozanolixizumab show that the fixed dose of [redacted] produces PK variability similar to that with weight-tiered dosing and will provide rozanolixizumab exposures that are consistent with those obtained with an approximate 7mg/kg and 10mg/kg weight-tiered dose Q1W; and will 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 physicians and patients and to reduce potential for dosing errors.
1.1 Synopsis 1.3 Schedule of activities 4.1 Overall design 4.4 End of study definition 8 Study assessments and procedures	The SFU Visit has been corrected to SFU phone call.	Correction to align with the Schedule of activities (Table 1-1)

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	New footnote *l* stating that the interval between administration of 2 consecutive rozanolixizumab doses should be 7 ±2 days. Update to footnote *q* and the rows *Total IgG* and *IgG subclasses* assessments to clarify that total IgG and IgG subclasses only need to be assessed at the middle visit (Visits 10, 14, 20, and 24).	To provide further clarification.
1.3 Schedule of activities	The row *MRI scan, including T1, T2 coronal images* updated to note that unscheduled MRIs may be performed.	For consistency with Section 8.2.5 (Magnetic resonance imaging).
8.2.5 Magnetic resonance imaging	Updated to note that brain MRI may be performed within 2 weeks prior to Baseline, and if performed prior to the Screening Period, may be used as the Baseline MRI if performed according to Protocol specifications.	For clarity and consistency with 1.3 Schedule of activities.
	Updated to note that if needed, additional MRIs may include non-protocol specified sequences, and these additional MRIs will also be assessed by the central reader.	To allow flexibility in the assessment of AEs.
Throughout	Removal of 24-week and addition of (Week 25) to the following sentence: "… end of the ~~24-week~~ Treatment Period **(Week 25)**. . ."	Rewording to clarify that the end of the Treatment Period is at Week 25.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and endpoints	Details of the MRI endpoints updated to distinguish between assessments for volumetric changes and additional assessments for safety.	To improve accuracy and precision.
4.2 Scientific rationale for study design	Rationales for the selection of time from disease onset and cognitive impairment as stratification factors have been added.	To provide a background clarifying the reason these factors were selected.
5.2 Exclusion criteria	Exclusion criterion #3 updated to specifically exclude any other anti-FcRn mediations.	To improve precision.
	Exclusion criterion #14 updated to exclude only those with active GI disorders.	There is no scientific rationale for excluding participants who have recovered from a GI disorder from the study.
	New criterion #16 excluding study participants with a history of solid organ or hematopoietic stem cell transplant.	To correct an omission.
	Exclusion criterion #20 updated to exclude live vaccination within 8 weeks of the final dose.	A correction to ensure that the exclusion covers the entirety of the SFU Period.
	Exclusion criterion #32 updated to state that major elective surgery procedures are excluded throughout the study duration.	To exclude only major surgeries and to ensure this exclusion applies throughout the study duration.
6.5.2 Prohibited prior and concomitant treatments (medications and therapies)	Update to the list of prohibited immunosuppressants in Table 6-2 to include azathioprine and mycophenolate.	To improve precision and completeness.
	Update to the list of prohibited biologics in Table 6-2 to include inebulizumab and satralizumab.	Updated as a result of recent biologics license application approvals.
	For rituximab, ocrelizumab and inebulizumab, the prohibited timeframe updated to ensure B-cell levels have returned to normal before use.	These mAbs cause near complete depletion of B cells. Given the mechanism of action of rozanolixizumab, allowing the recovery of B cells is preferable regardless of the lapsed time.

Section # and Name	Description of Change	Brief Rationale
	The timeframe for the prohibition of eculizumab changed from 6 months prior to Baseline to 3 months prior to Baseline.	To align rozanolixizumab prohibited prior and concomitant treatments across the rozanolixizumab development program.
6.5.3 Rescue medication	Inebulizumab and satralizumab added to rescue medications.	Updated as a result of recent biologics license application approvals.
7.1.4 Permanent discontinuation due to absence or loss of clinical benefit	Addition of 'at any time' to the following sentence: Study participants must be permanently discontinued from IMP if . . . or if they experience clinical worsening (ie, a loss of clinical benefit) **at any time** as defined by any of the following:	To clarify that in the event of a protocol-defined clinical worsening, IMP must be permanently discontinued.
7.1.4 Permanent discontinuation due to absence or loss of clinical benefit	#2 Updated such that cognitive worsening defined by an ≥8-point worsening in RBANS, should be confirmed by investigator assessment before permanent discontinuation of IMP.	To allow for confirmation that any deterioration in score is a result of cognitive decline, assessed by RBANS, rather than an external confounding factors (eg, forgetting of glasses)
7.1.5 Temporary discontinuation of IMP	Text relating to the discontinuation of study participants with suspected COVID-19 infection moved from 'may be temporarily discontinued from IMP' to 'must be temporarily discontinued from IMP'. Text relating to restarting IMP after suspected COVID removed from 'may be temporarily discontinued'.	To align rozanolixizumab clinical study discontinuation criteria across the rozanolixizumab development program.
8 Study assessments and procedures	Addition of 'or when home-nursing visits are not available' to the following sentence: Alternatively, these visits can be conducted at the site as deemed necessary by site personnel and/or study participant, **or when home-nursing visits are not available.**	To clarify that in countries or sites where home-nursing visits are not available, the visits defined as home-nursing visits, may take place at the clinical site.

Section # and Name	Description of Change	Brief Rationale
9.2 Planned efficacy/outcome analyses	Updated to note that only specified estimands of the primary and secondary endpoints will be analyzed on the FAS for sensitivity, and that the analyses on the FAS will only be carried out if this population differs by more than 10% of study participants to the RS/ITT.	Correct an omission of decision criterion to carry out analyses based on FAS.
9.3.1.1 Seizure freedom	Update to the intercurrent event definitions.	Clarification and improvement.
	Updates to the text describing the primary statistical analysis, and the second sensitivity analysis.	Clarification and improvement of the estimand description.
	New supplementary analysis added.	Analysis addressing alternative to the primary measure of association.
9.3.2.1 Change in cognitive function (RBANS)	Updates to the text describing the secondary statistical analysis and the second sensitivity analysis.	Clarification and improvement of the estimand description.
9.3.2.2 Use of rescue medication due to an absence or loss of clinical benefit	Text describing the secondary statistical analysis updated. Added 'Composite strategy' name for the intercurrent event handling strategy 2.	Clarification and improvement of the estimand description.
	Second sensitivity analysis changed to supplementary.	Different measure of association used for a more complete assessment of the endpoint.
9.3.2.3 Time to first occurrence of seizure freedom	Text describing the secondary statistical analysis updated.	Clarification and improvement of the estimand description.
	Excluded the second sensitivity analysis.	Reduced level of granularity of the analysis.
9.3.3.4 Duration of seizure-free period	Text describing the endpoint analysis updated	To reduce the number of summary tables describing an exploratory endpoint.
9.8 Determination of sample size	Description updated to note that sample size selected enables an equal study participant allocation between treatment arms.	Clarification of sample size rationale.

Section # and Name	Description of Change	Brief Rationale
10.1.5 Committees structure	Removal of the clinical pharmacology expert and addition of biostatistician to the listed members of the IDMC.	Correction.
10.16 Appendix 16: Management of infections and hypogammaglobulinemia	Removal of the study participant from being involved in a discussion about resuming IMP.	Correction. This is a blinded study and this discussion would unblind the study participant.

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

IGRA TB testing should be performed at Screening, and it is recommended that it 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. Interferon gamma release assay 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.

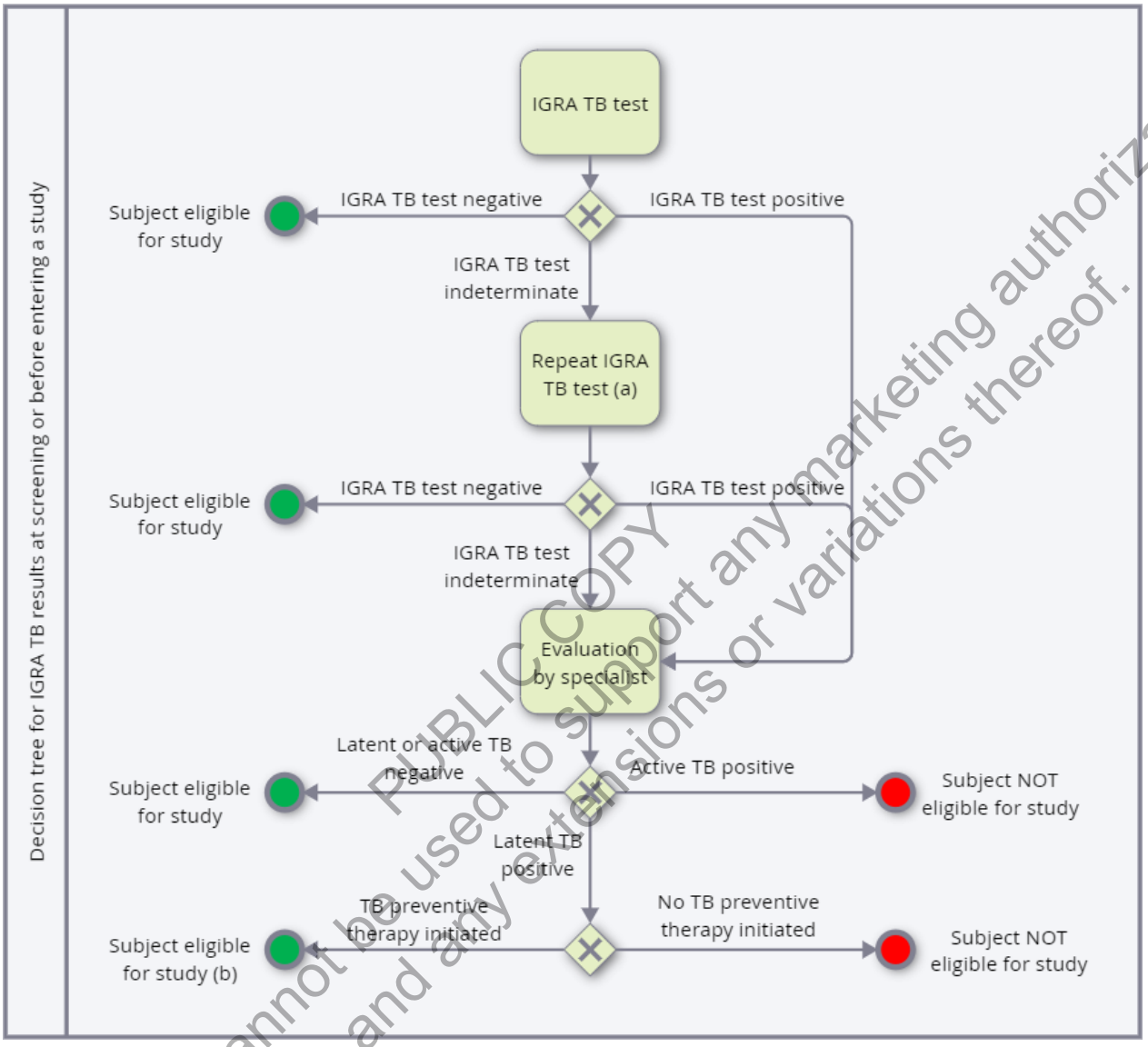
The choice of a commercially available IGRA test should be made in accordance with current clinical practice.

The result must be recorded in the eCRF.

10.12.5 Practical steps

An IGRA test 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:

Table 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 4 weeks 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 4 weeks of TB preventive therapy.

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 4 weeks duration) and discuss with the UCB study physician (or medical monitor) in an anonymized manner prior to allowing study participant to receive IMP. 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.

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

Study participants who prematurely discontinue treatment for LTBI should return for the End of Treatment/ EDisc Visit, complete all EDisc assessments, and complete an End of Study 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 4 weeks 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 immediately permanently discontinued from study medication and a EDisc 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 End of Study 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 AESM

Adverse event 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 24 hours 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 1-2 for assessments that may be required in case of 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 rozanolizamab program. Consequently, suspected aseptic meningitis is being managed as an adverse event of special monitoring (Section 8.3.7).

Participants should be monitored for signs and symptoms suggestive of CNS system involvement and evaluated immediately if meningitis is suspected. A full neurological workup should be strongly considered including, but not limited to imaging eg, computed tomography scan, or preferably gadolinium enhanced MRI, a lumbar puncture with CSF analysis inclusive of glucose, protein, differential complete blood count, cultures, gram stain, and/or viral polymerase chain reactions 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 (Table 1-1) 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 (potential 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 headache 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 self-care 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. If the 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 for other causes (eg, meningitis, intracranial bleeding) are suspected (see Section 1.3.1). 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 upon the resolution of the severe headache event. The benefit and risk of the treatment should be carefully considered prior to reinitiating the IMP. However, if a treatment-related severe headache reoccurs, the treatment must be permanently discontinued.

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 moderate or severe 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/EDisc 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 judgement 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 UCB. 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 between ≥1g/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 <1g/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 10-2. 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 10-2: 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 participant 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 ([redacted]) and plasma complement ([redacted]) should be collected as specified in the Schedule of Activities (Section 1.3). Additional tests such as [redacted] 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.

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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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