A PHASE 3 MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ROZANOLIXIZUMAB IN ADULT STUDY PARTICIPANTS WITH PERSISTENT OR CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA (ITP)

PROTOCOL TP0003 AMENDMENT 3

PHASE 3

Short title:

A Phase 3 study evaluating the efficacy, safety, and tolerability of rozanolixizumab in adult study participants with ITP

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 3	03 Dec 2021	Substantial
Protocol Amendment 2	29 Sep 2020	Substantial
Protocol Amendment 1.3 (France)	27 Apr 2020	Substantial
Protocol Amendment 1.2 (Japan)	16 Mar 2020	Substantial
Protocol Amendment 1.1 (US and Canada)	21 Feb 2020	Substantial
Protocol Amendment 1	21 Nov 2019	Substantial
Original Protocol	27 Sep 2019	Not applicable

Amendment 3 (03 Dec 2021)

Overall Rationale for the Amendment

The primary reason for this protocol amendment is the recommendation of the external Independent Data Monitoring Committee (IDMC) to modify the dosing regimen of the study.

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
Global	IMP dosing every 2 weeks was updated to weekly dosing.	Updated based on the feedback from the IDMC recommending the option to increase the frequency in dosing, to reduce the potential risks associated with low platelet counts.
Serious adverse event reporting	For serious adverse event reporting (24h), the fax number for Japan has been removed.	A separate fax number for Japan is no longer applicable as reporting in Japan should be done under the ROW or US fax number.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The secondary efficacy endpoint for the ITP-PAQ was updated to delete “including all intermediate timepoints”.	Intermediate timepoints were removed based on FDA feedback.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The other safety endpoint "Change from Baseline in concentrations of total protein, and albumin, α globulin, and β globulin was updated to "Change from Baseline in concentrations of total protein and albumin". The other safety endpoint "Change from Baseline in cytokines during the study (for study participants experiencing infusion reactions or hypersensitivity reactions)" was deleted.	The endpoint was removed to decrease study complexity, as scientific value is limited. The endpoint was removed as the analysis of cytokines is not required in the ITP protocols as samples have been collected in other rozanolixizumab studies and no additional information is expected from the ITP population.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The following exploratory PD endpoints were updated as follows: "Minimum value in total serum IgG and maximum decrease from Baseline in total serum IgG concentration" was deleted. "Change from Baseline in serum IgG and in serum IgG subclass concentration" was updated to "Total serum IgG (absolute value) and change from Baseline (absolute value and percentage) in serum IgG and in serum IgG subclass concentration at each scheduled assessment" "Change from Baseline in serum immunoglobulin concentrations (IgA, IgE, IgM)" was updated to "Absolute value and change from Baseline (absolute value and percentage) in serum immunoglobulin concentrations (IgA, IgE, IgM) at each scheduled assessment" "Change from Baseline in ITP-specific autoantibodies in serum" was deleted	Deleted as this variable will be followed at every scheduled visit rather than only reporting the lowest value across the duration of the study Endpoint was amended to provide further details of the endpoint and to add clarity. Endpoint was amended to provide further details of the endpoint and to add clarity. The endpoint was deleted as the results of the analysis will not be part of the CSR of this study and will be described in a separate report.
1.1 Synopsis, Objectives and endpoints	The objective "To evaluate the effects of rozanolixizumab on exploratory	Objective and endpoint were removed as the exploratory biomarker

Section # and Name	Description of Change	Brief Rationale
3 Objectives and endpoints	biomarkers" and its associated endpoints were removed.	samples are taken for future analysis, with no predefined analysis objective and endpoints.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The following exploratory objective and endpoint were added: Objective: To assess the effect of rozanolixizumab on response to vaccination in study participants who received COVID-19 vaccine Endpoint: Change in biomarkers of COVID-19 vaccine response over time	New objective and endpoint are needed for the collection of information on post-vaccination biomarkers for participants who have received the COVID-19 vaccination.
1.1 Synopsis, Overall design 4.1 Overall design	The vaccination requirements for splenectomized participants were updated. The requirement for vaccination titers assessment for eligibility purposes was removed.	Updated for consistency with the changes done in Section 8.2.6.
1.1 Synopsis, Overall design 4.1 Overall design	The sentence regarding home visits was updated to state that home visits including home dosing and assessments as per Section 1.3 can be conducted once all pre-requisites for a home dosing visit are fulfilled.	Updated for consistency.
1.1 Synopsis, Overall design 4.1 Overall design	The one-time fixed unit starting dose of rozanolixizumab equivalent to [redacted] or placebo was removed.	Deleted because of the new dose regimen of [redacted] once a week. A [redacted] QW dose regimen is anticipated to achieve similar level of receptor occupancy (RO)% to a [redacted], with a range on RO% from peak to trough of 99 to 50% during the 7 days dosing interval.
1.1 Synopsis, Overall design 4.1 Overall design	Week 13 was updated to Week 12.	Updated to correct an error.
1.1 Synopsis, Overall design 4.1 Overall design	Platelet count of "$\geq 50\times10^9$/L to 200×10^9/L" was updated to "$\geq 50\times10^9$/L to $\leq 150\times10^9$/L".	For consistency to other changes in the protocol.
1.1 Synopsis, Overall design, Table 1-1 Dose	The following text was added or updated:	

Section # and Name	Description of Change	Brief Rationale
adjustments of IMP following initial dose, Figure 1-1 TP0003 dose adjustments of IMP 4.1 Overall design	Platelet count of $<10\times10^9$/L, rescue therapy is highly recommended. Platelet count of $\geq10\times10^9$/L to $<30\times10^9$/L (on at least two consecutive visits), rescue therapy is recommended. Platelet count of $<50\times10^9$/L was updated to $\geq30\times10^9$/L to $<50\times10^9$/L, Dose adjustment instructions were updated to "dose level can be increased unless the study participant is on a maintenance dose of [redacted]". Platelet count of $\geq50\times10^9$/L to $\leq200\times10^9$/L was updated to $\geq50\times10^9$/L to $\leq150\times10^9$/L. Platelet count of $>200\times10^9$/L to $<400\times10^9$/L was updated to $\geq150\times10^9$/L to $<400\times10^9$/L For platelet counts of $\geq400\times10^9$/L, instructions were updated to "Stop IMP treatment. Once the platelet count is $\leq150\times10^9$/L reinitiate treatment decreased by one dose level". The text regarding interindividual variable platelet response was moved as table footnote b.	Updated to provide further guidance on when rescue medication is highly recommended or recommended Updated to permit reduction in dose earlier in the event of a platelet increase given the change to a weekly dosing regimen Updated in order to clarify that all study participants with platelet counts $\leq150\times10^9$/L should reinitiate treatment with a dose decreased with one level. Updated to provide clarity that the text belongs to Table 1-1.
1.1 Synopsis, Overall design 4.1 Overall design	The visit window upon rollover from TP0003 or TP0006 into TP0004 has been updated from 1 week to 3 days. The requirement for a SFU visit in between the rollover, and the requirement for platelet count measurement in case of a late rollover, have both been removed. Day 211 was updated to Day 218.	Updated for consistency with the weekly dosing regimen and for consistency throughout the protocol.
1.1 Synopsis, Overall design 4.1 Overall design	The following paragraph was added: Based on feedback from the IDMC, weekly dosing was implemented in protocol amendment 3. Study participants being treated with the bi-weekly dosing regimen	To clarify the dosing for existing study participants receiving bi-weekly dosing.

Section # and Name	Description of Change	Brief Rationale
	will switch to the weekly dosing regimen once protocol amendment 3 is approved at the respective study site.	
1.1 Synopsis, Number of study participants 4.1 Overall design	The two-stage statistical design and interim analysis were deleted. The target number of study participants was updated to 90, at least 60 of which will be randomized to weekly IMP administration.	Updated for consistency with the change in dosing regimen and to reflect current statistical analysis plans.
1.1 Synopsis, Treatment groups and duration 4.1 Overall design	The total maximum study duration per study participants was updated to 35 weeks.	Updated as the final dose will be administered at Week 24 instead of Week 23 and therefore the final visit (8 weeks after the final dose) was moved to Week 32.
1.1 Synopsis, Treatment groups and duration 4.1 Overall design	The Prolonged Screening Period for splenectomized participants was updated from 14 weeks to 20 weeks.	Updated for improving study participants' experience in the study by decreasing the time pressure on the vaccination schedule.
1.1 Synopsis, Treatment groups and duration, Table 1-2 TP0003 dose levels and weight tiers of IMP	The table title was updated from "TP0003 dose levels and weight tiers of rozanolixizumab" to "TP0003 dose levels and weight tiers of IMP". The one-time fixed unit starting dose of rozanolixizumab equivalent to [redacted] or placebo was removed. Reference to "maintenance dose" was removed in the table headers. Platelet count of >200×10^9/L was updated to >150×10^9/L in the table footnote.	Table title was corrected. Deleted as the [redacted] starting dose is no longer required with the new dosing regimen of [redacted] once a week. Updated for consistency with the changes in Table 1-1.
1.2 Schema, Figure 1-2 TP0003 study schematic	IMP dosing every 2 weeks was updated to weekly dosing. The one-time fixed unit starting dose of rozanolixizumab equivalent to [redacted] or placebo was removed.	Updated upon request from the IDMC Updated as the [redacted] starting dose is no longer needed with the new dose regimen of [redacted] once a week.

Section # and Name	Description of Change	Brief Rationale
	The dose adjustment period was corrected to Week 1 to 12.	Updated for clarity
	The total maximum study duration per study participants was updated to 35 weeks.	Updated for consistency with the weekly dosing regimen
	The Safety Follow-up Period was updated to 7 weeks after Week 25 leading to the last visit moving to Week 32.	Updated for consistency with the weekly dosing and last dosing being Week 24.
	Figure footnote relating to the Prolonged Screening Period for splenectomized participants was updated from 14 weeks to 20 weeks.	Updated for consistency with the changes in Sections 1.1 and 4.1.
Table 1-3 Schedule of activities (Prolonged Screening only for splenectomized study participants)	Prolonged Screening was extended to 20 weeks.	Updated for consistency with the changes in Section 1.1 and Section 4.1.
	Vaccination titers prior to vaccination and post vaccination titers during the Prolonged Screening Period and its associated footnotes were removed.	Updated for consistency with the changes done in Section 8.2.6.
	An additional footnote was added to state that Inclusion criterion #8 is not applicable for the Prolonged Screening Period. Study participants may take ITP concomitant medication as per Table 6-2.	Updated to clarify that the splenectomized study participants needing vaccination do not need to have low platelet counts throughout the Prolonged Screening Period.
Table 1-4 Schedule of activities	IMP dosing every 2 weeks was updated to weekly dosing. Call to IRT for treatment kit number was updated accordingly. Day 5 (Week 1, Visit 4) was deleted. Subsequent visit numbering was updated accordingly. Concomitant medical procedures, vital signs and recording of AEs were added to each visit following Baseline. The EOS Visit was amended from W31, Day 211 to W32, Day 218.	Updated to harmonize the assessments and visits with the change in dosing regimen and to provide consistency with other changes made to the protocol that are outlined in this section of the protocol.

Section # and Name	Description of Change	Brief Rationale
	Column related to home visits have been grayed out. Notes were added to clarify white columns are site visits and gray column refers to optional home visits. Additional text was added to state "Home IMP administration and assessments are optional and can be conducted (if approved by regulatory agencies) at the sites as deemed necessary by site personnel and/or the study participant." Footnote "a" regarding home visits, was deleted. A new footnote "a" was added: The allowed time window for assessments is ±5 mins for assessments <30 mins and ±15 mins for assessments >30 mins. Footnote d was updated to: The visit windows are relative to the Dosing Visit 1 date. At Day 3 a visit window of +2 days is allowed. For all remaining visits a visit window of +/-2 days is allowed. However there should be a minimum interval of 5 days and a maximum interval of 9 days between two doses of IMP. Footnote g: was updated to state that the last available platelet count can be considered rather than the last two available platelet counts. A new footnote "h" was added to state that platelet counts can be taken at home visits; home visits are allowed if the previous 4 platelet counts were stable between 50 to 150×10^9/L and there was no dose change. If criteria are met, the visit may be conducted at home, administering the same dose of IMP as for the previous visit. Footnote h, now i: was updated with vital signs assessment timepoints. Footnote i, now j: was updated to remove triplicate and three ECGs. Footnote j now k: was updated to delete the vaccination titer sample at the Screening visit and W13 and a sample at Baseline was added. Footnote k was moved from Screening to the assessment name.	

Section # and Name	Description of Change	Brief Rationale
	Footnote l relating to vaccination titers against tetanus was deleted. Footnotes m, n and o relating to the IGRA test and TB chest x-ray were deleted. COVID-19 biomarkers sampling and associated footnotes (footnote "m" and "n") were added. Footnote r relating to the starting dose equivalent to [redacted] was deleted. Footnote s relating to the IMP [redacted] was deleted. Footnote q now p: was updated with more details on post-dose observation. Footnote u now r: was updated to reflect the PK and ADA sampling times. Footnote v now s and footnote y now u: were updated to include sample collection at Baseline (Day 1) and W25 for all study participants. Footnote w regarding serum and plasma complements and cytokines at W23 4 hours postdose was deleted. A new footnote "v" was added to state "If total IgG levels are <1g/L, ad hoc assessments (eg, additional IgG samples) may be performed to monitor recovery of IgG levels. See Section 10.25" Footnote 'y' (formerly footnote 'aa') was updated to state that the assessment can also be done remotely eg, via phone interview. The IGRA TB test and chest x-ray were deleted. Samples for cytokines were removed.	
2.2 Background	IMP dosing every 2 weeks was updated to weekly dosing. The one-time fixed unit starting dose of rozanolixizumab equivalent to [redacted] or placebo was removed. CIDP04, MG0004 and MG0007 were added as ongoing studies. CIDP01 was added to the list of completed studies. A summary of the safety data from	Updated for consistency with the change in dosing regimen, and with relevant completed or ongoing study information.

Section # and Name	Description of Change	Brief Rationale
	CIDP01 was added. Brief details about CIDP04 were added.	
2.3 Benefit/risk assessment	The Benefit/risk assessment was updated to include recommendations regarding COVID-19 vaccinations and to remove "important potential risks" such as effects on the kidney, and reductions in albumin and plasma proteins.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
4.1 Overall design	The text regarding post-dose observation time following the end of infusion was updated. Day 211 was updated to Day 218. The text on rozanolixizumab infusion was updated.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
4.2 Scientific rationale for study design	IMP dosing every 2 weeks until Week 23 was updated to weekly dosing until Week 24. Details of the number of study participants from CIDP01 and CIDP04 treated [redacted] with [redacted] rozanolixizumab were added.	Updated for consistency with the change in dosing regimen and to provide additional data in support of the [redacted] [redacted] dosing regimen.
4.3 Justification for dose	A more frequent dosing regimen of [redacted] once per week is introduced in TP0003,TP0006 and the OLE TP0004 study. The [redacted] starting dose is removed from the protocol.	The change follows the advice of the external IDMC on a more frequent dosing regimen, following the review of the platelet data from TP0004, where platelets are not sustained at the desired level within the [redacted].
4.4 End of study definition 6.6 Treatment after the end of the study	The visit window of 1 week for rollover into TP0004 was updated to 3 days. Visit numbers were updated according to updated schedule of activities. The SFU Visit to be conducted in between rollover was deleted. The text "In case of late rollover, platelet counts will need to be remeasured" was deleted.	Updated for consistency with the [redacted] dosing regimen and for consistency throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	Inclusion criterion 4a, now 4b, was updated to clarify ITP treatments and to add splenectomy.	Updated for clarity.
5.1 Inclusion criteria	Inclusion criterion #12, now 12a, was updated to correct "or" to "and" "as confirmed by a negative pregnancy test **and** not planning to get pregnant".	The sentence was corrected.
5.2 Exclusion criteria	Exclusion criterion 2, now 2a, updated to clarify 'current' anticoagulant treatment. Cross-reference to Table 5-1 was added. Exclusion criterion 7a, now 7b was updated to clarify a clear association with other medical conditions. Exclusion criterion 15 regarding Karnofsky Performance Status was removed. Exclusion criterion 20a, now 20b was updated to remove the requirement for *S. pneumoniae*, *N. meningitidis* and *H. influenzae* vaccine titers during the Prolonged Screening Period. Exclusion criteria 22, 23a, 27, and 29 were removed. In Table 5-1, the cross reference to Exclusion Criterion 23a was removed and the corresponding exclusionary requirements were added to Table 5-1.. Exclusion Criterion 33a, now 33b, was amended to remove the following bullet point: ALT, AST, or ALP results up to 25% above the exclusion limit may be repeated once for confirmation, including rescreening. Exclusion criterion 42 was removed.	Updated to provide additional clarity to certain exclusion criteria, remove redundancies and ensure consistency throughout the protocol. The Karnofsky score is generally used for predicting the length of survival in terminally ill patients. This score was considered as not suited for the target patient population for the study and removed. Updated to provide additional clarity to certain exclusion criteria, remove redundancies and ensure consistency throughout the protocol.
5.4 Screen failures	References to IGRA TB tests and tests that result in ALT, AST, or ALP up to 25% the exclusion limit have been removed.	Updated for consistency of the respective changes throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
5.4 Screen failures	The wording about vaccination for splenectomized participants was updated.	Updated for consistency with the changes done in Section 8.2.6.
6 Study Treatments, Table 6-1 Treatments administered	IMP dosing every 2 weeks was updated to weekly dosing. The one-time fixed unit starting dose of rozanolixizumab [redacted] was removed.	Updated for consistency with the change in dosing regimen.
6 Study Treatments, Table 6-1 Treatments administered	References to vial fill volumes was removed.	Updated to reflect the foreseeable change in vial fill volumes.
6 Study Treatments, Table 6-1 Treatments administered	Dosing instructions were updated.	To align with the latest dosing instructions.
6 Study Treatments, Table 6-1 Treatments administered	Reference to Canada was removed.	Updated as Canada is not participating in TP0003.
6.2.1.1 Maintenance of study treatment blind	Bullet point #2 was updated to delete "on request".	To align with the current procedure.
6.2.1.1 Maintenance of study treatment blind	The text was updated to state the procedure in case the serum IgG level decreases to <1g/L. A cross reference to Appendix 25 was added.	Updated to ensure consistency with the changes in Section 10.25.
6.3 Treatment compliance	The text was updated to add "study participant's home".	Updated as optional home dosing visits have been included in the schedule.
6.4.1 Permitted concomitant treatments (medications and therapies)	The text was updated to clarify that the following concomitant medications are permitted during the study and if possible, kept stable for the duration of the study.	Updated to clarify that if possible, the permitted concomitant medications should be kept at a stable dose for the duration of the study.
6.4.1 Permitted concomitant treatments (medications and therapies) Table 6-2 Permitted concomitant treatments (medications and therapies)	Permitted oral corticosteroids dose was increased to ≤20mg/day. A dose of "≤4mg/kg/day for modified" was added for cyclosporin.	Allowed dose of oral corticosteroids was increased to a maximum of 20 mg/day for more flexibility in managing the concomitant ITP treatment. Updated to clarify permitted concomitant medications.

Section # and Name	Description of Change	Brief Rationale
6.4.3 Rescue therapy	The conditions to commence IMP treatment following rescue therapy with high dose corticosteroids were updated. Permitted oral corticosteroids dose was updated to 20mg/day.	Updated for consistency with the new dosing regimen and other allowed rescue medication (platelet count is considered the more clinically relevant trigger for IMP initiation compared with a strict time interval of 4 weeks).
6.4.3 Rescue therapy	Text was updated to state that details of the rescue therapy administered must be recorded in the eCRF.	Updated for clarity.
6.5 Dose modification	Text pertaining to dose modification was modified to clarify that dose modifications of the IMP were permitted in order to maintain the platelet counts between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L. References to up and down titration of the IMP was deleted. Additional text was added to state "Dose modifications or temporary discontinuation of IMP treatment are permitted if serum IgG value is <1g/L (Section 10.26)".	Updated to reflect that platelet counts should be maintained between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L. Added to provide clarity that dose modifications based on IgG values are permitted.
6.5 Dose modification	An additional bullet point regarding moderate to severe toxicities was added.	Updated to remain consistent with the rozanolixizumab program.
7.1.2 QTc stopping criteria	"Average of triplicate" ECG was removed.	Updated to reflect the changes in Section 8.1.3.
7.1.3 Discontinuation of IMP due to other adverse events or medical condition	The text was updated to " Study participant has a significant infective episode including but not limited to: bacteremia or sepsis, infectious meningitis, osteomyelitis, septic arthritis, 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 his/her judgment on continuing IMP based on the clinical situation at hand"	Updated to reflect the current general program guidance.
7.1.3 Discontinuation of IMP due to other adverse events or medical condition	The text was updated as follows: Study participant has a serious AE of headache or GI disturbance that is considered related to the IMP in the opinion of the investigator; or recurrent severe AE of headache (see Appendix 22, Section 10.22) or GI disturbance that is considered related to the	Updated to remain consistent with Phase 3 ITP clinical program.

Section # and Name	Description of Change	Brief Rationale
	IMP in the opinion of the investigator (See Appendix 23, Section 10.23).	
7.1.3 Discontinuation of IMP due to other adverse events or medical condition	Reference to TB test was removed.	Updated for consistency with the changes in Section 8.2.5.
7.1.4 Temporary IMP discontinuation	Instructions for temporary IMP discontinuation were updated to remove individual requirements for splenectomized and non-splenectomized participants.	Updated to ensure consistency with the changes in Section 10.25.
7.1.4 Temporary IMP discontinuation	Instructions in relation to restarting IMP following COVID-19 infection/exposure were updated.	Updated for providing additional clarity on the temporary IMP discontinuation due to COVID-19 infection/ exposure.
7.1.4 Temporary IMP discontinuation	Text was added/updated as follows: Study participant **MAY temporarily discontinue IMP** if any of the following events occur: 1. A severe AE of headache that is considered related to the IMP in the opinion of the investigator (Section 10.22) 2. A splenectomised study participant develops a (persistent or re-occurring) nonserious infection, as per investigator's decision (Section 10.25) 3. Total serum IgG value is <1g/L as per investigator's decision. As IMP treatment is administered weekly, the decision to temporarily hold the treatment should be determined based on the most recently available total IgG value. As the IgG, IgG subtypes, albumin and total protein levels will be blinded to both the study site personnel and the clinical team at the sponsor and CRO, unblinded Medical Monitors will be monitoring the IgG levels and will alert the investigator in case of decreases <1g/L. Additionally,	Updated to ensure consistency with the changes in Section 10.22 and Section 10.25.

Section # and Name	Description of Change	Brief Rationale
	guidance for investigators on management of infections can be found in Appendix 25, Section 10.25.	
7.2 Participant discontinuation/withdrawal from the study	#3 was added as follows: 3. Study participant meets the mandatory IMP discontinuation criteria as per Section 7.1.1, Section 7.1.2 or Section 7.1.3 occur.	Added for consistency throughout the protocol.
8 Study assessments and procedures	Additional text was added regarding home-nursing visits.	Text added to provide additional details on the optional home-nursing visits and the conditions that need to be met prior to the conduct of home-nursing visits.
8.1.1 Platelet counts	The first endpoint was updated to clarify that the last 12 weeks refer to Weeks 13 to 25.	Updated for consistency with the Objectives section and to provide further clarity on the endpoint assessment timepoint.
8.2.2 Vital signs	Vital signs measurement time points for all visits were updated and clarified.	Updated for consistency with the change in dosing regimen and to provide consistency across the studies in the rozanolixizumab development program.
8.2.3 Electrocardiograms	Text was updated to remove references to triplicate ECGs :"Triplicate 12 lead ECG" ECG was replaced with "A 12-lead ECG".	No identification of cardio-toxicity from non-clinical data, supported by lack of signal of cardiac events in the rozanolixizumab-program. Updated in order to decrease the burden to the sites and study participants.
8.2.5 Assessment and management of TB and TB risk factors	The text was updated to clarify that assessment and management of TB and TB risk factors should follow local or national guidelines.	Patients with known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent tuberculosis infection (LTBI), or current/history of nontuberculous mycobacterial infection (NTMBI) are already excluded from

Section # and Name	Description of Change	Brief Rationale
		TP0003/TP0006, therefore the sites are expected to follow national / local guidelines for the management of TB, in case needed. In addition, the mechanism of action of rozanolixizumab is expected to have little or no impact on the immune response against intracellular organisms which is involved in controlling the infection with *Mycobacterium tuberculosis*.
8.2.5.1 Tuberculosis assessment	Sections on physical examination for TB, TB assessment by IGRA, and TB assessment by chest x-ray were removed.	Updated to ensure consistency with Section 8.2.5.
8.2.5.2 Tuberculosis management	Text on test conversion for IGRA was removed.	Updated to ensure consistency with Section 8.2.5.
8.1.5.2 Tuberculosis management	The definition for LTBI was updated. The definitions for active TB and NTMBI were added.	LTBI definition updated as per WHO and CDC guidelines. Active TB and NTMBI definitions as per WHO and CDC guidelines were added for consistency.
8.2.5.2 Tuberculosis management	Text pertaining to AE reporting for Latent TB was removed.	Updated for consistency in reporting any TB related AEs as per Section 8.2.5.1.
8.2.6 Splenectomized study participants	The vaccination requirements for splenectomized participants were updated. The requirement for vaccination titers collection during Screening was moved to Baseline. Vaccination titers at W13 were removed.	Due to the lack of evidence-based best practice in the area, updated to align with the general clinical practice standards.
8.3 Adverse events	A note was added that in order to protect the blind, the events of hypogammaglobulinemia should not be captured as an AE in the eCRF.	The blinded study teams at the Sponsor, CRO and site must remain blinded in case an event of hypogammaglobulinemia occurs. Only the unblinded Medical Monitors and the

Section # and Name	Description of Change	Brief Rationale
		investigator will have access to this information. The respective AEs will be reconciled based on the IgG values at the end of the study, after data base lock will take place and the data will be unblinded.
8.3.8 Adverse events of special monitoring	Text was added to state that the headache questionnaire should also be completed in case of moderate headache although moderate headache is not considered an AESM.	Updated to ensure consistency with the changes in Section 10.22.
8.3.10 COVID-19 vaccination	A new subsection has been included to ensure AEs considered related to COVID-19 vaccination are captured.	Implemented to ensure study participant safety in response to the COVID-19 pandemic.
8.7 Pharmacodynamics	A sentence was added to state that results of the ITP-specific autoantibodies analyses will not be outlined in the Clinical Study Report for this study.	Analysis of the ITP-specific autoantibodies is a lengthy method and therefore the results will be provided in a separate report.
8.8.2 Immunology	Serum cytokines were deleted. Week 23 was updated to Week 25.	Removed as the scientific value of the serum cytokines is limited. Updated to reflect the change in the study design due to weekly dosing.
8.9 Exploratory biomarkers	α- and β-globulins were removed.	Removed as the scientific value of these exploratory biomarkers is limited.
9.3.1 Analysis of the primary efficacy/primary endpoint	The two-stage statistical design was removed. Additional wording to clarify that platelet count from Week 14 to Week 25 will be used to assess durable clinically meaningful platelet count was included.	To reflect inclusion of weekly sc infusion treatment as the primary efficacy assessment and the requirement to randomize a fixed number of participants on weekly dosing.
Table 9-1 Estimands for the primary endpoint	The RS population was updated to those who were randomized to weekly dosing compared to placebo.	Updated to reflect that the primary objective is to assess the rozanolixizumab

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	Geographical region was removed as a stratification factor from the CMH model.	treatment effect for weekly sc infusions. Geographical region removed from the model to add convergence of the statistical model. Region will be explored through subgroup analyses detailed in the SAP.
Table 9-2 Estimands for secondary endpoints	The RS population was updated to those who were randomized to weekly dosing compared to placebo. Geographical region was removed as a stratification factor from the statistical models. Statistical tests were updated.	Geographical region removed from the analysis models to mirror the analysis of the primary endpoint. Statistical tests updated to reflect proposed analyses in the SAP.
9.3.3.1 Analysis of pharmacokinetic endpoint	The text was updated as follows: "A statistical summary of rozanolixizumab plasma concentrations will be reported by scheduled time point overall and by body weight tier, stratified by dose regimen. Further details on summaries for dose modifications will be provided in the corresponding SAP."	To reflect the change to weekly sc infusion treatment by summarising the data by bi-weekly and weekly treatment.
9.3.3.3 Analysis of pharmacodynamic endpoints	The total IgG endpoint wording was updated.	Updated to reflect that IgG will measured and analyzed at every scheduled visit rather than only reporting the lowest value across the duration of the study.
9.4.1 Safety analyses	Text was added to state that data will be further presented by randomized dosing regimen.	To reflect the change to weekly sc infusions.
9.6 Handling of dropouts or missing data	Text was added to state that if individual platelet visit data is missing it will be set to zero; participants who are lost to follow-up will be imputed as nonresponders.	To clarify how missing platelet count data will be handled in the statistical analyses.
9.7 Data monitoring	The 2-stage design and interim analysis was removed.	To reflect the requirement to randomize a fixed number of participants on weekly sc infusions and

Section # and Name	Description of Change	Brief Rationale
		removal of option to increase sample size based on an interim analysis.
9.7.1 Early stopping for efficacy 9.7.2 Early stopping for futility	Sections are no longer applicable.	To reflect the requirement to randomize a fixed number of participants on weekly sc infusions and removal of option to increase sample size based on an interim analysis.
9.8 Determination of sample size Table 9-3 Expected sample size for TP0003	The sample size calculation was updated.	To reflect the requirement to randomize a fixed number of participants on weekly sc infusions and removal of option to increase sample size based on an interim analysis.
10.2 Appendix 2 Table 10-1 Protocol-required safety laboratory assessments	Platelet reticulocytes and glycosylated hemoglobin were removed. Associated footnotes were removed.	Updated to reflect that the analysis will not be performed.
10.2 Appendix 2 Table 10-1 Protocol-required safety laboratory assessments	Footnote a was updated from "sponsor" to "study participant".	Updated to correct an error.
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Footnote c has been removed from Table 10-2.	To remain consistent with the Phase 3 rozanolixizumab clinical program.
10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments	The cross reference to the liver chemistry stopping criteria was corrected in Table 10-4.	Corrected to reference the appropriate section of the protocol.
10.8, Appendix 8: Country-specific requirements Poland	Visit 29 was updated to Visit 28.	Updated to align with the updated Visit numbering.
10.8, Appendix 8: Country-specific requirements Japan	The following text was deleted: "In reference to the overall design (Section 1 and Section 4.1), the following text has been added: In the Phase I study, UP0060 (see Section 2.2), Japanese study participants have only been administered a maximum	The [redacted] starting dose has been removed so this text no longer applies. Three Japanese study participants were observed while hospitalized under protocol amendment 2.

Section # and Name	Description of Change	Brief Rationale
	of [redacted] rozanolixizumab sc, therefore the first 4 study participants in **Japan** will be observed whilst hospitalized for the first 3 days (until Day 3) at a minimum after the starting dose."	
10.8, Appendix 8: Country-specific requirements Japan	Exclusion criteria 20b (previously 20a) was updated based on the updates to the main criterion.	Updated for consistency with changes introduced in exclusion criterion 20b.
10.8, Appendix 8: Country-specific requirements Japan	Text pertaining to IGRA TB assessment and chest x-ray for TB was removed.	Updated for consistency throughout the protocol
10.8, Appendix 8: Country-specific requirements Japan	A cross reference was added to Table 10-2 and the wording was updated.	Updated to provide clarity.
10.8, Appendix 8: Country-specific requirements Japan	Wording of the definitions of AEs and SAEs was updated.	Updated to ensure consistency in the definitions for AEs and SAEs throughout the protocol.
10.9 Appendix 9: Abbreviations and trademarks	The definitions for the following abbreviations were added: COVID-19, LTBI, OPSI, QW, Q2W and RO.	General update.
10.11 Appendix 11: Karnofsky Performance Status Scale	The Karnofsky Performance Status Scale was removed.	Updated to ensure consistency with the removal of Exclusion Criterion 15.
10.22 Appendix 22: Management of Headaches	The text was updated to clarify the management of IMP administration including dose adjustment following an AE of headache.	Updated to reflect the current general program guidance for the management of headaches
10.24 Appendix 24: Management of infusion reactions or hypersensitivity reactions	Additional text was added: "Fully trained healthcare professionals 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."	Updated for consistency.
10.24 Appendix 24: Management of infusion reactions or hypersensitivity reactions	Serum cytokines were removed.	Blood cytokine sampling was removed as analysis of cytokines is not required in the ITP protocols as

Section # and Name	Description of Change	Brief Rationale
		samples have been collected in other rozanolixizumab studies and no additional information is expected from the ITP population.
10.25 Appendix 25: Management of infections and hypogammaglobulinemia	The text was updated to clarify the management of IMP administration including dose adjustment following episodes of infections and hypogammaglobulinemia.	The total serum IgG cut-off value for informing the investigators has been aligned for all study participants based on the lack of conclusive literature supporting the previous approach. The investigators are given total flexibility in deciding if and how to continue the IMP treatment in cases of total IgG values <1g/L, based on a holistic approach of the study participant's status (platelets response, signs and symptoms of non-serious/serious infection, potential risk of acquiring a non-serious/serious infection).
10.26 Appendix 26: Protocol Amendment History	Protocol amendment 2 (global amendment) has been added.	General update.
Throughout	Minor editorial and formatting changes have been made.	Minor, therefore have not been summarized.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
All serious adverse events (SAEs) will be reported and transmitted to Patient Safety through the electronic Case Report Form (eCRF) system. The numbers below are to be used to send ancillary documentation only (eg, discharge summaries, death certificates) or in the event that the eCRF is not available.	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US:** +1 800 880 6949 or +1 866 890 3175
Email	**Global** (*for interventional clinical studies*)**:** DS_ICT@ucb.com

Serious adverse event (investigational device) and device deficiency reporting (24h)	
Fax:	**Japan:** +81 3 6864 7400
Email:	**Japan:** UCBJ-Safety@ucb.com

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title

A Phase 3 Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Rozanolixizumab in Adult Study Participants with Persistent or Chronic Primary Immune Thrombocytopenia (ITP)

Short title

A Phase 3 study evaluating the efficacy, safety, and tolerability of rozanolixizumab in adult study participants with ITP

Rationale

Immune thrombocytopenia is a clinical disorder in which thrombocytopenia manifests as a bleeding tendency, purpura, or petechiae. Autoantibodies against platelet antigens are considered to be a hallmark of ITP. Production of pathogenic immunoglobulin (Ig) G autoantibodies by plasma cells is accepted as the central underlying pathophysiological mechanism in a number of IgG-mediated autoimmune diseases, which includes ITP. In some patients, antibodies recognize antigens derived from a single glycoprotein; whereas in others, antibodies recognize multiple glycoproteins. The spleen is the key organ in the pathophysiology of ITP, not only because platelet autoantibodies are formed in the white pulp, but also because mononuclear macrophages in the red pulp destroy immunoglobulin-coated platelets.

Treatments aimed at reducing the quantity of circulating IgG autoantibodies are being used for primary and secondary therapy of autoimmune diseases including ITP, particularly where corticosteroid-based immune suppression is not or no longer effective. The therapeutic approach of these treatments is based on lowering levels of pathogenic autoantibodies, which represents rational and effective treatment modalities of autoimmune diseases. The primary goal for treatment of ITP is to achieve a platelet count that prevents major bleeding, rather than correcting the platelet count to normal levels.

Rozanolixizumab is a humanized IgG4P monoclonal antibody that is being developed as an inhibitor of the activity of neonatal Fc receptor (FcRn). The FcRn receptor recycles IgG and albumin and transports it bidirectionally across epithelial barriers. Recent studies have shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling it from the sorting endosome to the cell surface (Anderson et al, 2006). Rozanolixizumab has been specifically designed to block IgG binding to FcRn without blocking the binding and recycling of albumin. By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of IgG antibodies, including IgG autoantibodies. This Phase 3 study, TP0003, will be one of 2 studies that will provide the required data to establish the efficacy and safety of rozanolixizumab over placebo in study participants with persistent or chronic primary ITP who have failed or were intolerant to two or more prior ITP therapy and who require an increase and sustained effect in their platelet counts.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the clinical efficacy of rozanolixizumab in maintenance treatment in study participants with primary ITP	The primary efficacy endpoint is: • Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to 25) The secondary efficacy endpoints are: • Cumulative number of weeks with Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L over the 24-week treatment period • Time to first Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L: time from starting treatment to achievement of first response of $\geq 50\times10^9$/L • Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L by Day 8 • Response defined as platelet count $\geq 30\times10^9$/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit [a,b] • Time to first rescue therapy • Change from Baseline to Week 25, in ITP Patient Assessment Questionnaire (ITP-PAQ) Symptoms Score The other efficacy endpoints are: • Duration of first Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L: measured from achievement of first Response to loss of first Response (loss of Response defined as platelet count $<50\times10^9$/L) • Time to first Response: time from starting treatment to achievement of Response • Usage of rescue therapy by visit

	• Complete Response defined as platelet count $\geq 100\times10^9$/L confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit [a,b] • Cumulative number of weeks over the planned 24-week treatment period with platelet count of $\geq 100\times10^9$/L. • Cumulative number of weeks over the planned 24-week treatment period with platelet counts $\geq 30\times10^9$/L and at least doubling from Baseline. • Mean change from Baseline in platelet count by visit. • Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 4 out of 6 weeks during the last 6 weeks (Week 19 to 25). • Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 6 out of 8 weeks during the last 8 weeks (Week 17 to 25).
Secondary	
• To assess the safety and tolerability of rozanolixizumab	The safety endpoints are: • Occurrence of treatment-emergent adverse events (TEAEs) • Occurrence of TEAEs leading to withdrawal of investigational medicinal product (IMP) (ie, study discontinuation) The other safety endpoints are: • Occurrence of serious TEAEs • Occurrence of treatment related TEAEs • Occurrence of adverse events of special monitoring (AESM) • Vital signs change from Baseline (blood pressure [BP], pulse rate, body temperature) at each scheduled assessment during Treatment and Safety Follow-up (SFU) Periods

	• 12-lead electrocardiogram (ECG) change from Baseline at each scheduled ECG visit • Laboratory change from Baseline (hematology including coagulation parameters, clinical chemistry, and urinalysis) at each scheduled assessment during Treatment and SFU Periods • Change from Baseline in concentrations of total protein and albumin • Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during the study (for study participants experiencing infusion reactions or hypersensitivity reactions)
Exploratory	
• To evaluate the clinical efficacy as measured by the ITP bleeding score	• ITP-specific Bleeding Assessment Tool (ITP-BAT) bleeding events and severity by visit
• To assess the effect of rozanolixizumab on health-related quality of life (HRQoL)	• Change from Baseline in European Quality of Life (EuroQol) -5 dimension 5 Levels (EQ-5D-5L) item responses • Change from Baseline in Short form 36-item (SF-36) domain and composite scores • Change from Baseline in the ITP-PAQ domain scores
• To assess hospitalizations due to ITP	• Number and length of hospitalizations
• To assess the effect of rozanolixizumab on patient reported outcomes (PROs)	• Change from Baseline in FATIGUE-PRO Physical Fatigue Score • Change from Baseline in Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C) at all available post-baseline assessments
• To assess the pharmacokinetics of rozanolixizumab administered by subcutaneous (sc) infusion	• Plasma concentration of rozanolixizumab

• To evaluate the incidence and emergence of antidrug antibodies (ADAs) of rozanolixizumab	• ADAs at each scheduled assessment
• To assess the pharmacodynamic (PD) effects of rozanolixizumab	The exploratory PD endpoints are: • Total serum IgG (absolute value) and change from Baseline (absolute value and percentage) in serum IgG and in serum IgG subclass concentration at each scheduled assessment • Absolute values and change from Baseline (absolute value and percentage) in serum immunoglobulin concentrations (IgA, IgE, IgM) at each scheduled assessment
• To assess the influence of rozanolixizumab treatment on vaccination titers	• Percent change from Baseline in vaccination titers against *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* in splenectomized study participants • Percent change from Baseline in vaccination titers against tetanus in all study participants
• To assess the effect of rozanolixizumab on response to vaccination in study participants who received COVID-19 vaccine	• Change in biomarkers of COVID-19 vaccine response over time

[a] Absence of bleeding indicated by Grade 0 for all domains of the skin, mucosae, and organs (SMOG), or a Skin Grade of 0 or 1.
[b] Nominal visits are on-site visits where ITP bleeding scale assessment is performed.

Overall design

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study with rozanolixizumab in study participants with persistent or chronic primary ITP defined as more than 3 months, or more than 12 months of duration respectively, since diagnosis.

The study participants will be male and female adults with persistent or chronic primary ITP, history of prior ITP treatment, a platelet count measurement at Screening (Visit 1) and at Baseline with an average of the two $<30\times10^9$/L (no single count may be $>35\times10^9$/L) and a documented history of low platelet count ($<30\times10^9$/L) any time prior to Screening.

Participants should previously have received two or more ITP therapies and should have initially responded to such therapy and have a current or history of a blood smear consistent with primary ITP.

Study participants who have previously undergone a splenectomy will be included in the study provided they do not meet the protocol defined exclusion criteria (Section 5.2) in order to optimize protection against overwhelming post-splenectomy infection (OPSI). Splenectomized study participants should be vaccinated against the encapsulated organisms, such as *Streptococcus pneumoniae* (*S. pneumoniae*), *Neisseria meningitidis* (*N. meningitidis*), and *Haemophilus influenzae* (*H. influenzae*) (as per local/or national guidance, as applicable) as evidenced from immunization records or during the Prolonged Screening Period. Study participants, who are due to receive a booster, can be screened after they received the required booster.

Splenectomized study participants will be required to attend a Prolonged Screening Period prior to the Screening Visit to receive, if applicable, the required vaccinations (see Table 1-3).

The study will assess whether multiple sc infusions of rozanolixizumab will result in a durable Clinically Meaningful Platelet Count of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks of the Treatment Period (Weeks 13 to 25). Starting at Week 2, platelet counts will be measured every week at a local laboratory. Home visits including home dosing and assessments as per Section 1.3 can be conducted once all pre-requisites for a home dosing visit are fulfilled.

Once eligibility is confirmed on Day 1 (Baseline Visit), study participants will enter the Treatment Period (24 weeks) and will be randomized 2:1 to receive a fixed-unit dose of rozanolixizumab equivalent to [redacted] or placebo once a week (QW) with randomization stratified by the degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L) and history of splenectomy (yes or no). The last assessment of the Treatment Period will take place at Week 25.

During the first 12 weeks in the study (Week 1 until Week 12) IMP dose adaptations, depending on the observed levels of platelets as detailed in Table 1-1, will be allowed. The Dose Adaptation Period aims at achieving an IMP dose regimen that sustains a platelet count $\geq 50\times10^9$/L to $\leq 150\times10^9$/L until the beginning of Week 13. Following the initial dose equivalent to [redacted], subsequent QW doses can be adapted to dose equivalents to [redacted] QW or [redacted] total dose (corresponding to an average [redacted] dose in a participant weighing 70kg) QW based on the platelet count. Following this Dose Adaptation Period, study participants will enter the Maintenance Period starting at Week 13 until Week 25. The dose regimen that achieves platelet stabilization in the adaptation period will be continued throughout the Maintenance Period. During the Maintenance Period the dose regimen should remain stable and further dose adaptations should be avoided if possible. However, adjustments for safety and efficacy reasons will still be allowed as outlined in Table 1-1 and Figure 1-1, which presents the dose titration for IMP based on the platelet count.

Table 1-1: Dose adjustments of IMP following initial dose

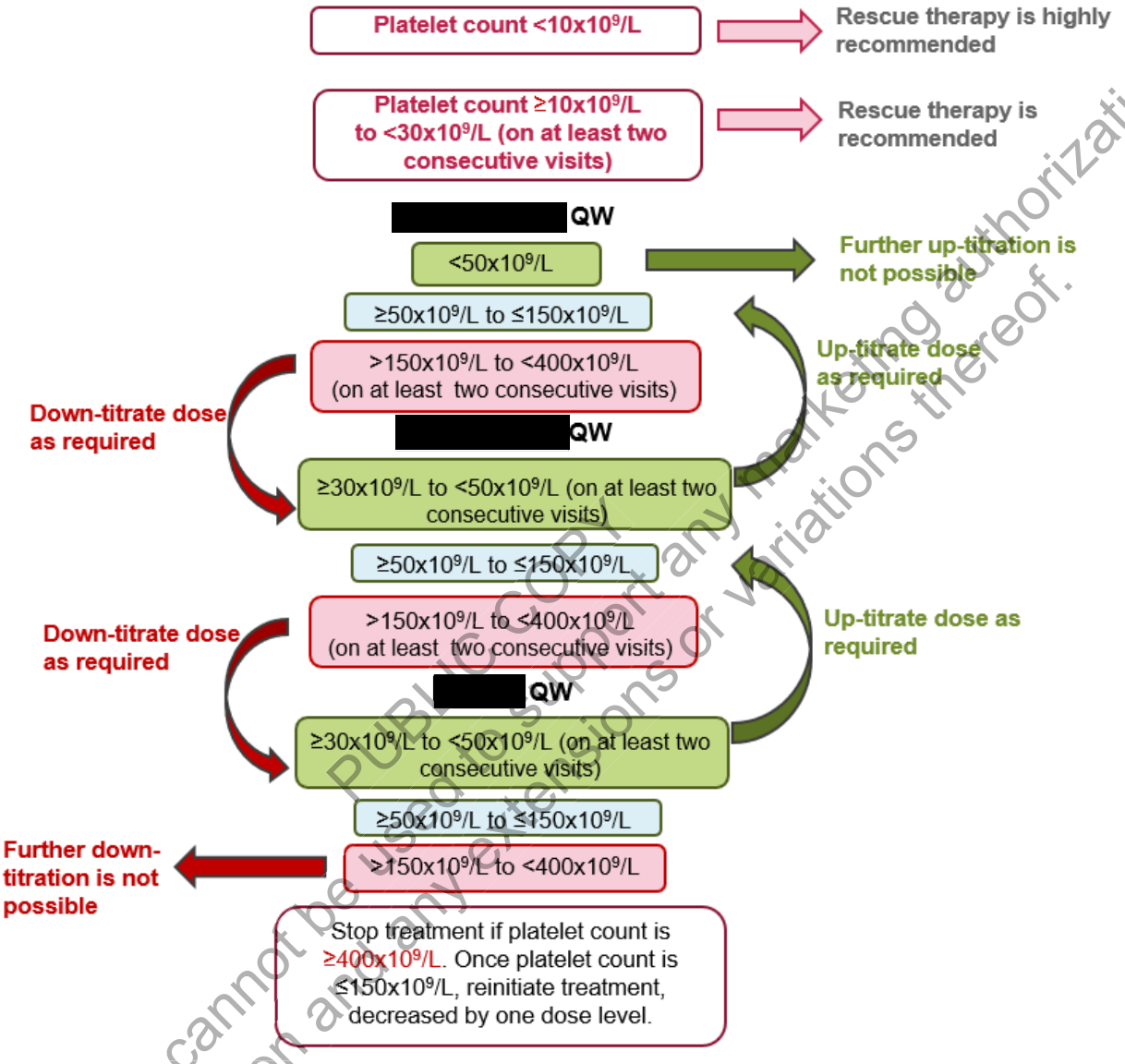
Platelet count result[a]	Dose adjustment (based on weekly platelet counts)
$<10\times10^9$/L	Rescue therapy is highly recommended as per Section 6.4.3.
$\geq10\times10^9$/L to $<30\times10^9$/L (on at least two consecutive visits)	Rescue therapy is recommended as per Section 6.4.3.
$\geq30\times10^9$/L to $<50\times10^9$/L (on at least two consecutive visits)	Increase by one dose level, unless study participant is on maintenance dose of [redacted]
$\geq50\times10^9$/L to $\leq150\times10^9$/L[b]	Continue with current dose level
$>150\times10^9$/L to $<400\times10^9$/L (on at least two consecutive visits)	Decrease by one dose level, unless study participant is on maintenance dose of [redacted]
$\geq400\times10^9$/L	Stop IMP treatment. Once the platelet count is $\leq150\times10^9$/L, reinitiate treatment decreased by one dose level

[a] All analyses of platelet counts will be based on local laboratory results

[b] Due to the interindividual variable platelet response, in some study participants platelet count may abruptly fall below 50×10^9/L after dose reduction or treatment discontinuation. In these cases, if clinically appropriate, higher cut-off levels of platelet count for dose reduction ($>150\times10^9$/L) may be considered according to medical judgment, but should not exceed 250×10^9/L.

For the dose adjustments where a decrease is required, study participants receiving [redacted] should continue at this dose level, as dose reductions below [redacted] are not applicable. If a study participant is in the lowest body weight tier (below 50kg) and is on the lowest dose level with a platelet count between $>150\times10^9$/L and $<400\times10^9$/L, the investigator might decide to temporarily stop treatment according to medical judgment based on the observation of platelet variability. If the platelet count increases to above 400×10^9/L, then IMP must be stopped.

Figure 1-1: TP0003 dose adjustments of IMP



eqv=equivalent; QW=once a week
Dose adaptations may start as early as Week 2
* eqv: fixed-unit dose with body weight tiers equivalent to the mg/kg dose in terms of IgG reductions and safety profile

If treatment as per Table 1-1 and Figure 1-1 does not lead to an increase in platelet count ≥30×10^9/L, the study participant can be treated with rescue therapy, if deemed needed by the investigator. If platelet count is ≥10×10^9/L to <30×10^9/L or active bleeding, rescue therapy is recommended (eg, commercially available medication, such as intravenous immunoglobulin [IVIg], high dose corticosteroids and pulse steroids, platelet transfusions, or any other medication listed in Section 6.4.3). If platelet count is <10×10^9/L, rescue therapy is highly recommended as per Section 6.4.3. If a study participant has been down-titrated to a fixed-unit dose equivalent to [redacted] total dose (corresponding to an [redacted] dose in

a participant weighing 70kg), and platelet count decreases to less than 50×10^9/L, then up-titration to a fixed-unit dose equivalent to [redacted] QW or [redacted] QW, respectively, would be allowed.

Study participants should be monitored for signs of arterial or venous thrombotic and thromboembolic events. If such events occur, the investigator should undertake the appropriate management per medical judgment and local guidance, and contact the Medical Monitor. Thrombotic or embolic events are considered AESM, as described in Section 8.3.8, and the reporting rules can be found in Appendix 3, Section 10.3.

All study participants completing the Treatment Period (regardless of whether they received rescue therapy or not) and fulfilling the open-label extension (OLE) study (TP0004) eligibility criteria will be allowed to enroll into the 1-year OLE treatment study TP0004. The enrollment into the TP0004 study should be conducted on the same day as Visit 27 (Week 25) of the feeder study. In case the enrollment into TP0004 is not conducted at Week 25 (Visit 27), a visit window of +3 days will be granted; therefore, rollover needs to be completed 3 days after Week 25 at the latest.

Participants that will not be enrolling into the OLE study will be followed for up for 8 weeks after the last administration of IMP. The End of Study (EOS) Visit will be performed after the SFU Period.

An external Independent Data Monitoring Committee (IDMC) will be established to review the safety data at predefined intervals and ad hoc as needed should emerging safety concerns arise during the study. The first IDMC meeting for the review of safety data is planned to occur after approximately 15 participants have received 3 doses of IMP in TP0003. The study will be put on hold if any of the following occurs

- The IDMC judges it necessary for medical or safety reasons and
- The sponsor or its designee judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations and Good Clinical Practice.
- Three study participants experience any serious adverse event (SAE) of the same type within the first 15 study participants who have received 3 doses of IMP across TP0003 and TP0006, unless the SAE is clearly unrelated to the study drug.
  - **For US and Canada only**: Three study participants experience any SAE within the first 15 study participants who have received at least one dose of IMP across TP0003 and TP0006, unless the SAE is clearly unrelated to the study drug.

It is intended to have one IDMC for both of the pivotal studies (TP0003 and TP0006), where the safety data will be initially presented unpooled, ie, data from each study will be reviewed separately. Key safety data may be pooled at the discretion of the IDMC for protection of all study participants if warranted.

Based on feedback from the IDMC, weekly dosing was implemented in protocol amendment 3. Study participants being treated with the bi-weekly dosing regimen will switch to the weekly dosing regimen once protocol amendment 3 is approved at the respective study site. Additionally, the sponsor's Safety Signal Detection Team will perform aggregated safety data reviews at predefined intervals across all rozanolixizumab programs.

For **Japan** specific regulations, see Appendix 8, Section 10.8.

Number of participants

Study participants will be randomly assigned to IMP in a 2:1 ratio to either rozanolixizumab or placebo, respectively. The total sample size will be approximately 90 study participants, at least 60 of which will be randomized to weekly IMP administration (for determination of sample size, see Section 9.8).

Treatment groups and duration

The total maximum study duration per study participant is up to 35 weeks, consisting of a Screening Period (up to 4 weeks), a Dose Adaptation Period (12 weeks), a Maintenance Period (12 weeks) and a SFU Period (8 weeks after final dose administered). The eligibility of study participants to participate in the study will be determined during the Screening Period (Day -28 to Day -1). Splenectomized participants will be required to attend a Prolonged Screening Period prior to the Screening Visit to assess and receive, if applicable, the required vaccinations, which will extend the total study duration by up to 20 weeks.

Fixed-unit doses across body weight tiers and treatment arms will be employed in this study according to the following scheme, as presented in Table 1-2.

Table 1-2: TP0003 dose levels and weight tiers of IMP

Dose* eqv / Bodyweight	[redacted] Dose level 1	[redacted] Dose level 2	[redacted] Dose level 3
>35 to <50kg	[redacted]	[redacted]	No weight adjustment [redacted]
≥50 to <70kg	[redacted]	[redacted]	
≥70 to <100kg	[redacted]	[redacted]	
≥100kg	[redacted]	[redacted]	

eqv=equivalent; IMP=investigational medicinal product

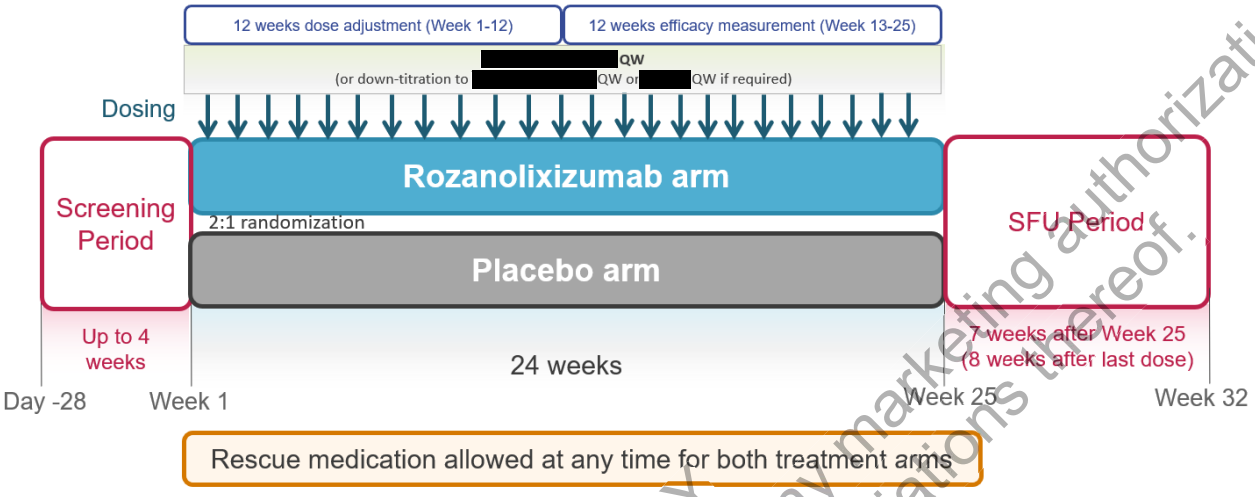
If a study participant is in the lowest body weight tier (below 50kg) and is on the lowest dose level with a platelet count between >150×10^9/L and <400×10^9/L, the investigator might decide to temporarily stop treatment according to medical judgment based on the observation of platelet variability. If the platelet count increases above 400×10^9/L then treatment must be stopped anyway.

The placebo arm will use 0.9% sodium chloride aqueous solution (physiological saline, preservative free) for sc administration, matching the volumes of the rozanolixizumab arm.

1.2 Schema

A schematic diagram of the study is presented in Figure 1-2.

Figure 1-2: TP0003 study schematic



QW=once a week; SFU=safety follow-up
Platelet counts will be measured weekly at local laboratories.
Splenectomized participants would need to attend a Prolonged Screening Period for up to 20 weeks prior to the Screening Visit.

1.3 Schedule of activities

The Schedule of Activities for TP0003 is presented in Table 1-3 (specific for splenectomized study participants) and Table 1-4 (for all study participants).

Table 1-3: Schedule of activities (Prolonged Screening only for splenectomized study participants)

		Prolonged Screening Visit Part 1[a]		Prolonged Screening Visit Part 2
	Visit	**1.1**	**Additional visits may be required depending on the vaccine and on the vaccination history**	**1.2**
	Week	**-20**	**-20 to -8**	**-4 to -1**
	Day	**-140**	**-140 to -56**	**-28 to -1**
Assessments	**Visit Window**	**±14d**	**±14d**	
Written informed consent and written pharmacogenomics substudy informed consent (for participating study participants)		X		All remaining assessments of Visit 1 as outlined in Table 1-4, including the Platelet counts (using site's local laboratory)
General medical/procedures history		X		
Vaccination[b, c]		X	X	

ITP=primary immune thrombocytopenia
[a] Inclusion criterion #8 is not applicable to the Prolonged Screening Period (Visit Part 1). Study participants may take ITP concomitant medication as per Table 6-2.
[b] Administer vaccines to splenectomized participants without previous vaccination history for *S. pneumoniae*, *H. influenzae* and *N. meningitidis*, or as applicable as per local guidance, eg in **Japan**.
[c] Administer vaccines to splenectomized participants who require a booster protection against *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* or as applicable as per local guidance, eg in **Japan**.

Table 1-4: Schedule of activities

		Screening Period	Dose	Treatment Period									SFU Period		
	Visit(s)	**1**	**BL /2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12,14, 16, 18, 20, 22, 24**	**9, 13, 17, 21, 25**	**11, 15, 19, 23**	**26**	**27** EW	**28**	**29** EOS [b, c]
	Week	**-4 to -1**	**1**	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, 14, 16, 18, 20, 22**	**7, 11, 15, 19, 23**	**9, 13, 17, 21**	**24**	**25**	**28**	**32**
	Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**29**	**36, 50, 64, 78, 92, 106, 120, 134, 148**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**162**	**169**	**190**	**218**
Assessments[a]	**Visit Window[c]**			**+2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
Written informed consent and written pharmacogenomics substudy informed consent (for participating study participants)		X											X[e]		
Verification of inclusion/exclusion criteria		X	X												
Demographic data		X													
General medical/procedures history		X													
ITP history		X													
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X

		Screening Period	Dose	Treatment Period									SFU Period		
	Visit(s)	**1**	**BL /2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12,14, 16, 18, 20, 22, 24**	**9, 13, 17, 21, 25**	**11, 15, 19, 23**	**26**	**27 EW**	**28**	**29 EOS [b, c]**
	Week	**-4 to -1**	**1**	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, 14, 16, 18, 20, 22**	**7, 11, 15, 19, 23**	**9, 13, 17, 21**	**24**	**25**	**28**	**32**
	Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**29**	**36, 50, 64, 78, 92, 106, 120, 134, 148**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**162**	**169**	**190**	**218**
Assessments[a]	**Visit Window[c]**			**+2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test		X													
Urine pregnancy test			X					X			X		X[f]		X
Platelet counts (using site's local laboratory)		X	X[g]	X	X[g]	X	X	X	X[h]	X	X	X	X	X	X
Randomization			X												
Withdrawal criteria[c]			X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[i]		X	X	X	X	X	X	X	X	X	X	X	X		X
Body weight		X													X
Height		X													
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination		X											X		X

		Screening Period	Dose	Treatment Period									SFU Period		
	Visit(s)	**1**	**BL /2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12,14, 16, 18, 20, 22, 24**	**9, 13, 17, 21, 25**	**11, 15, 19, 23**	**26**	**27 EW**	**28**	**29 EOS[b, c]**
	Week	**-4 to -1**	**1**	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, 14, 16, 18, 20, 22**	**7, 11, 15, 19, 23**	**9, 13, 17, 21**	**24**	**25**	**28**	**32**
	Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**29**	**36, 50, 64, 78, 92, 106, 120, 134, 148**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**162**	**169**	**190**	**218**
Assessments[a]	**Visit Window[c]**			**+2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
Short physical examination			X		X	X		X			X				
12-lead ECG[j]			X			X							X		
Laboratory parameters (hematology, clinical chemistry, and urinalysis)		X	X		X	X		X			X		X		X
Serology test for HIV, hepatitis B, and hepatitis C		X													
Vaccination titers (in splenectomized participants)[k]			X			X							X		X
Tetanus titer[l]			X			X							X		X
COVID-19 biomarkers sampling (in participants vaccinated prior to entry into TP0003)[m]			X										X		X

		Screening Period	Dose	Treatment Period									SFU Period		
	Visit(s)	**1**	**BL /2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12,14, 16, 18, 20, 22, 24**	**9, 13, 17, 21, 25**	**11, 15, 19, 23**	**26**	**27 EW**	**28**	**29 EOS [b, c]**
	Week	**-4 to -1**	**1**	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, 14, 16, 18, 20, 22**	**7, 11, 15, 19, 23**	**9, 13, 17, 21**	**24**	**25**	**28**	**32**
	Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**29**	**36, 50, 64, 78, 92, 106, 120, 134, 148**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**162**	**169**	**190**	**218**
Assessments[a]	**Visit Window[c]**			**+2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
COVID-19 biomarkers sampling (in participants vaccinated during TP0003)								X[n]							X
TB signs and symptoms questionnaire[o]		X	X								X W13 only		X		X
Call to IRT for treatment kit number			X		X	X	X	X	X	X	X	X			
Administration of IMP[p]			X		X	X	X	X	X	X	X	X			
Blood sampling for plasma concentration of rozanolixizumab[q]			X	X		X		X			X[r] all predose and 1 to 5 days postdose after W13 only	X[r] predose and 1 to 5 days postdose			

		Screening Period	Dose	Treatment Period									SFU Period		
	Visit(s)	**1**	**BL /2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12,14, 16, 18, 20, 22, 24**	**9, 13, 17, 21, 25**	**11, 15, 19, 23**	**26**	**27 EW**	**28**	**29 EOS [b, c]**
	Week	**-4 to -1**	**1**	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, 14, 16, 18, 20, 22**	**7, 11, 15, 19, 23**	**9, 13, 17, 21**	**24**	**25**	**28**	**32**
	Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**29**	**36, 50, 64, 78, 92, 106, 120, 134, 148**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**162**	**169**	**190**	**218**
Assessments[a]	**Visit Window[c]**			**+2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
Anti-rozanolixizumab antibodies[q]		X	X			X		X			X[r] all predose and 1 to 5 days postdose after W13 only	X			X
Serum complements (C3 and C4)[s]			X	X											
Plasma complements (C3a and C5a[s]			X	X											
Whole blood collection for DNA[t]			X										X		
Whole blood collection for RNA[t]			X										X		
Blood collection for exploratory biomarkers[u]			X	X											

		Screening Period	Dose	Treatment Period									SFU Period		
	Visit(s)	**1**	**BL /2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12,14, 16, 18, 20, 22, 24**	**9, 13, 17, 21, 25**	**11, 15, 19, 23**	**26**	**27 EW**	**28**	**29 EOS [b, c]**
	Week	**-4 to -1**	**1**	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, 14, 16, 18, 20, 22**	**7, 11, 15, 19, 23**	**9, 13, 17, 21**	**24**	**25**	**28**	**32**
	Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**29**	**36, 50, 64, 78, 92, 106, 120, 134, 148**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**162**	**169**	**190**	**218**
Assessments[a]	**Visit Window[c]**			**+2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X[v]		X[v]	X[v]		X		X
IgA, IgM, IgE			X			X					X W13 only		X		X
ITP-specific autoantibodies			X								X W13 only				X
ITP bleeding scale		X	X	X	X	X	X	X		X	X		X	X	X
SF-36[w]			X					X			X		X		
ITP-PAQ[w]			X					X			X		X		
EQ-5D-5L[w]			X					X			X		X		
PGI-C[w]								X			X		X		
PGI-S[w]			X					X			X		X		
FATIGUE-PRO Physical Fatigue Scale[w]			X					X			X		X		

		Screening Period	Dose	Treatment Period									SFU Period		
	Visit(s)	**1**	**BL /2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12,14, 16, 18, 20, 22, 24**	**9, 13, 17, 21, 25**	**11, 15, 19, 23**	**26**	**27 EW**	**28**	**29 EOS [b, c]**
	Week	**-4 to -1**	**1**	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, 14, 16, 18, 20, 22**	**7, 11, 15, 19, 23**	**9, 13, 17, 21**	**24**	**25**	**28**	**32**
	Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**29**	**36, 50, 64, 78, 92, 106, 120, 134, 148**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**162**	**169**	**190**	**218**
Assessments[a]	**Visit Window[c]**			**+2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
Headache questionnaire[x]			X	X											

ADA= antidrug antibodies; AE=adverse event; AESM=adverse event of special monitoring; BP=blood pressure; BL=Baseline; d=day(s); COVID-19=coronavirus disease 19; D=Day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EQ-5D-5L=European Quality of Life Health Status Questionnaire-5 Dimensions, 5 Levels; EW=Early Withdrawal; GI=gastrointestinal; HIV=human immunodeficiency virus; ICF=Informed Consent Form; Ig=immunoglobulin; IMP=investigational medicinal product; IRT=interactive response technology; ITP=immune thrombocytopenia; ITP-PAQ=ITP Patient Assessment Questionnaire; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetic; PRO=patient-reported outcomes; RNA=ribonucleic acid; SF-36: Short-Form 36-Item Health Survey; SFU=Safety Follow-Up; TB=tuberculosis; W=Week.

Site visit

Optional home visit (Home IMP administration and assessments are optional and can be conducted (if approved by regulatory agencies) at the sites as deemed necessary by site personnel and/or the study participant).

[a] The allowed time window for assessments is ±5 mins for assessments <30 mins and ±15 mins for assessments >30 mins.

[b] The EOS Visit is 8 weeks following the final dose.

[c] Study participants can withdraw at any time during the study, based on criteria in Section 7.

[d] The visit windows are relative to the Dosing Visit 1 date. At Day 3 a visit window of +2 days is allowed. For all remaining visits a visit window of +/-2 days is allowed. However there should be a minimum interval of 5 days and a maximum interval of 9 days between two doses of IMP.

[e] The TP0004 ICF will be given to the study participants that are willing to enroll into TP0004.

[f] Will be used to check study participant's eligibility for TP0004.

[g] If required, by site's local procedure, the platelet count assessed by the local laboratory can be done -1 day for Baseline (Visit 2) and for W2 (Visit 4). For subsequent dosing visits, the last available platelet count can be considered.

[h] Platelet counts can be taken at home visits; home visits are allowed if the previous 4 platelet counts were stable between 50 to 150×10⁹/L and there was no dose change. If criteria are met, the visit may be conducted at home, administering the same dose of IMP as at the previous visit.

[i] Vital signs will include BP, pulse rate, and body temperature. On dosing days, for the first 2 weeks (W1, W2), vital signs will be measured prior to IMP administration, at the end of the infusion, and 4 hours after the end of the infusion. For the next 3 visits (W3, W4 and W5), vital signs will be measured prior to IMP administration, at the end of the infusion, and 1 hour after the end of the infusion. From W6, vital signs will be measured prior to IMP administration, at the end of the infusion, and 15 minutes after the end of infusion. At nondosing visits, vital signs need only be taken once during the visit. In case of dose increase, vital signs will be measured prior to IMP administration, at the end of infusion, and 1 hour after the end of infusion for the next 2 infusions. In case of untoward event, additional vital signs (unscheduled assessment) should be taken at the discretion of the investigator and post-observation time can be extended. These recommendations are applicable for dosing at site and at home.

[j] The ECG should be performed prior to blood collection for assessment of laboratory parameters (central reading of ECGs). ECGs have to be recorded at W1, Day 1 (predose and 4 hours postdose), W3 (predose), and W25.

[k] Vaccination titers against *S. pneumoniae*, *N. meningitidis* and *H. influenzae* (only in splenectomized participants) collected at W1 (Baseline), W3 (predose), EW Visit and EOS Visit.

[l] Vaccination titers against tetanus to be collected in all participants at Baseline (predose), W3 (predose), EW Visit, and EOS Visit

[m] For study participants who received COVID-19 vaccine prior to entry into TP0003, biomarker samples should be taken at Baseline (predose), EW Visit, and EOS Visit.

[n] For study participants who received COVID-19 vaccine during enrollment in TP0003, the collection of COVID-19 biomarkers baseline samples should occur predose, 2 to 3 weeks after the participant has received his/her last COVID vaccination (ie, second dose of a 2-dose vaccine, or booster). A second sample should be collected 3 months after last vaccination. There should be a minimum window of 72 hours between COVID vaccination and IMP administration.

[o] TB signs and symptoms questionnaire has to be completed at Screening, W1, W13, W25, and EOS Visit.

[p] On dosing days, for the first 2 weeks, a 4-hour post-dose observation will be in place. Assuming the first 2 doses were well tolerated, on dosing days at Week 3, 4, and 5, 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. However, if the dose needs to be decreased due to a TEAE(s) or dose needs to be increased, post dose observation will be extended to 1 hour after the end of infusion for the next 2 infusions. The post-dose observation time frame may be extended at the discretion of the investigator. These recommendations are applicable for dosing at site and at home. Approval from the investigator and sponsor is required prior to the start of home dosing.

[q] PK and ADA blood samples are to be taken predose unless otherwise indicated.

[r] PK and ADA samples to be taken predose and one additional sample within 1 to 5 days postdose following administration at W13 (Days 86 to 89) for PK and ADA and one additional sample within 1 to 5 days postdose at W24 (Days 163 to 166) for PK.

[s] Serum complements (C3, C4) and plasma complements (C3a, C5a), should be taken predose at Baseline (Day 1) and W25 for all study participants. Additional samples should be collected 2 hours and 4 hours postevent or as soon as possible before the next IMP for study participants with infusion reaction or hypersensitivity reaction (see Section 8.3.8).

[t] Optional blood collection if study participant selects "yes" on the pharmacogenomics substudy ICF.

[u] Exploratory biomarker samples should be taken predose at Baseline (Day 1) and W25 for all study participants (see Section 8.9). Additional samples should be collected 4 hours postevent or as soon as possible before the next IMP for study participants with severe and/or serious headaches or severe and/or severe GI disorders (ie, abdominal pain, diarrhea, vomiting; see Section 8.3.8).

[v] If total IgG levels are <1g/L, ad hoc assessments (eg, additional IgG samples) may be performed to monitor recovery of IgG levels. Section 10.25.

[w] PROs to be completed prior to dosing and prior to any other study procedures.

[x] This assessment is applicable only to study participants experiencing moderate, severe and/or serious headaches and will be performed daily until resolution (ie, if headache becomes mild, normal collection of AEs should apply). This assessment can also be done remotely eg, via phone interview.

2 INTRODUCTION

Rozanolixizumab (UCB7665) is a humanized IgG 4P 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 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 ITP, myasthenia gravis (MG), pemphigus vulgaris, Goodpasture's syndrome, neuromyelitis optica, Guillain-Barré Syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

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 agents. 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 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, specific and sustained removal of the IgG autoantibodies 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 Investigator's Brochure (IB).

2.1 Study rationale

Immune thrombocytopenia, previously defined as immune thrombocytopenic purpura and idiopathic thrombocytopenic purpura (Rodeghiero et al, 2009), is a rare, orphan hematological autoimmune disease characterized by an isolated low platelet count (thrombocytopenia) caused by specific antibodies directed against platelets and the absence of other causes of

thrombocytopenia. In a pathological disease state these platelets are coated with autoantibodies to platelet membrane antigens, resulting in splenic sequestration and phagocytosis by mononuclear macrophages. The resulting shortened life span of platelets in the circulation, together with platelet underproduction by autoantibody-mediated megakaryocytes inhibition results in a decreased platelet count (Arnold et al, 2015; McMillan et al, 2004).

The spleen is the key organ in the pathophysiology of ITP, as it is the site of autoantibody production (white pulp) and the site of phagocytosis of autoantibody-coated platelets (red pulp). The slow passage of platelets through splenic sinusoids with a high local concentration of antibodies, and Fc-gamma receptors on splenic macrophages supports the role of the spleen as a site of platelet destruction (Sandler, 2000).

Recently, new definitions for the phases of the disease were introduced (Rodeghiero et al, 2009). Based on the time from diagnosis, the first phase (up to 3 months) is the "newly-diagnosed ITP phase;" phase 2 (>3 months up to 12 months) is the "persistent phase;" and after 12 months, the "chronic phase" starts. These phases also reflect the line of treatment.

The major goal for treatment of ITP is to achieve a platelet count that prevents major bleeding, rather than correcting the platelet count to normal levels. The management of ITP should be tailored to the individual patient and it is rarely indicated in those with platelet counts $>50\times10^9$/L in the absence of bleeding, trauma, surgery, or high-risk factors (eg, patients on anticoagulation therapy) (EMA/CHMP/153191/2013, 2014). However, there is general agreement that adults with a count of $<30\times10^9$/L with bleeding at diagnosis require treatment.

The first line of treatment for newly-diagnosed ITP is generally agreed and is based on the use of corticosteroids and IVIg. Although corticosteroids are effective, their long-term use is not recommended due to concerns over their safety (eg, osteoporosis, hypertension, immunosuppression). Patients who fail to respond or who relapse face the options of treatment with second line drug therapy or splenectomy, but there is no clear evidence to support the best approach (Rodeghiero et al, 2009; Provan et al, 2010; Neunert, 2011). Splenectomy can provide long-term efficacy in approximately 60% of cases, and recent guidelines suggest considering a splenectomy after 12 months. Splenectomy is an invasive procedure associated with acute complications (due to thrombocytopenia-like bleeding events) and long-term complications from loss of splenic functions. Asplenic individuals are at an increased risk of life-threatening infections, although minimized with vaccination prophylaxis. Splenectomy may increase morbidity from venous thromboembolism or atherosclerosis (Ghanima et al, 2012). Second-line drug therapies include high dose dexamethasone or methylprednisolone; high dose IVIg or anti-D Ig; vinca alkaloids; dapsone and danazol; the immunosuppressants cyclophosphamide, azathioprine, and cyclosporine; or mycophenolate mofetil and Helicobacter pylori eradication if applicable. The anti-CD20 monoclonal antibody rituximab, even if not licensed for the treatment of ITP, and the thrombopoietin-receptor agonists (eltrombopag, romiplostim [both approved in the US and Europe] and avatrombopag [approved in the US in 2019]) are considered as second line (Ghanima et al, 2018) as well as third line options. In 2018, in the US, fostamatinib, a SYK-inhibitor, has been approved for the treatment of chronic ITP. Each of these treatments discussed above has unique benefits, limitations, tolerability considerations, and risks. Taking the side-effect profile and long-term complications of existing treatments together, there remains a considerable unmet medical need for novel therapeutic options in the treatment of persistent and chronic ITP.

By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of antibodies and reduces the concentration of pathogenic IgG in primary ITP patients, thus potentially offering a safe, effective, and convenient alternative to existing treatments. This Phase 3 study will provide the required data to establish the safety and efficacy of rozanolixizumab in study participants with persistent or chronic primary ITP who have failed or were intolerant to two or more prior therapy and who require an increase and sustained effect in their platelet counts.

2.2 Background

To date, rozanolixizumab has been administered to human study participants in 9 clinical studies: UP0018, UP0060, CIDP01, CIDP04, MG0002, MG0003, MG0004, and its replacement study MG0007, and TP0001. UP0018 is a completed first-in-human (FIH) study. MG0002 is a completed Phase 2a study in participants with generalized MG, TP0001 is a completed Phase 2 study in study participants with primary ITP, and CIDP01 is a completed Phase 2a study in study participants with CIDP. UP0060 is a Phase 1 study in healthy volunteers, CIPD04 (OLE) is an ongoing Phase 2a study in study participants with CIDP, and MG0003 and MG0004 (OLE replaced by MG0007) are ongoing Phase 3 studies in study participants with generalized MG.

UP0018 was conducted in 49 healthy study participants. The study evaluated the safety, tolerability, pharmacokinetic (PK), and PD effect on total IgG levels of single ascending doses of intravenous (iv) and sc rozanolixizumab. Doses of rozanolixizumab [redacted] were administered by both iv and sc routes in 3 cohorts, respectively, as [redacted]

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

UP0060 is a randomized, participant-blind, investigator-blind, placebo-controlled, single dose-ascending, cohort design to compare the safety, tolerability, and PK of rozanolixizumab, and to explore the PD of rozanolixizumab administered by sc infusion in Japanese, Chinese, and Caucasian healthy study participants.

CIDP01 is a completed Phase 2a, multicenter, randomized, participant-blind, investigator-blind, placebo-controlled, parallel-group study with the primary objective of evaluating the clinical efficacy of rozanolixizumab as a treatment for study participants with CIDP. There were 2 treatment arms in this study:

[redacted]

Overall, [redacted] administration of rozanolixizumab at a dose level of [redacted] sc was generally [redacted] and well tolerated, with an acceptable safety profile. No new safety concerns were identified. The incidence of TEAEs was similar between the rozanolixizumab and placebo groups, with the exception of the TEAE of injection/infusion site reactions which was reported at a higher frequency in study participants treated with rozanolixizumab. The majority of TEAEs were of mild to moderate intensity. The only severe TEAEs reported were in the context of underlying CIDP. During the Treatment Period, 10 (58.8%) study participants in the rozanolixizumab group and 5 (29.4%) in the placebo group experienced at least 1 drug-related TEAE. During the Observation Period, 1 (5.9%) study participant each in the rozanolixizumab and placebo groups experienced at least 1 drug-related TEAE. Two (11.8%) study participants in the rozanolixizumab group experienced serious TEAEs of CIDP relapse which were in the context of their underlying CIDP. No cases of severe headache, moderate or severe abdominal pain, moderate or severe vomiting, or severe diarrhea were reported. One (5.9%) study participant each in the rozanolixizumab and placebo groups experienced moderate diarrhea. No clinically meaningful trends were observed for clinical laboratory evaluations, vital signs measurements, or physical examinations.

CIDP04 is an ongoing Phase 2a, multicenter, open-label extension study to investigate the long-term safety, tolerability, and efficacy of rozanolixizumab in participants with CIDP. The study includes [redacted].

MG0002 is a completed Phase 2a, multicenter, randomized, investigator- and participant-blind, placebo-controlled, treatment sequence study evaluating the safety, tolerability, and efficacy of rozanolixizumab in study participants with generalized MG. The study included 2 Dosing Periods with [redacted] doses of IMP at [redacted] intervals each:

[redacted]

The primary efficacy variable was the change from Baseline in Quantitative MG score (a measure of muscular strength) to Day 29.

Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] sc were generally considered [redacted] and well tolerated, with an acceptable safety profile. No new safety concerns were identified in MG0002. The TEAE profile was similar between rozanolixizumab and placebo except for headaches where increased frequency and severity was observed in the rozanolixizumab-treated patients.

MG0003 is an ongoing Phase 3 multicenter, randomized, double-blind, placebo-controlled, 3-arm, repeat-dose study evaluating the efficacy and safety of 2 doses (equivalent to [redacted] and [redacted]) of rozanolixizumab and matching placebo administered [redacted] over a period of 6 weeks [redacted] in study participants with generalized MG who experience moderate to severe symptoms and are being considered for treatment with IVIg or plasma exchange (PEX).

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

- Dose Arm 1 (15 participants): rozanolixizumab 4mg/kg sc (5 doses at 1-week intervals)
- Dose Arm 2 (15 participants): rozanolixizumab 7mg/kg sc (3 doses at 1-week intervals)
- Dose Arm 3 (12 participants): rozanolixizumab 10mg/kg sc (2 doses at 1-week intervals)
- Dose Arm 4 (12 participants): rozanolixizumab 15mg/kg sc (1 dose)
- Dose Arm 5 (12 participants): rozanolixizumab 20mg/kg sc (1 dose)

[redacted]

Data from study TP0001 indicate that rozanolixizumab was tolerated with an acceptable safety profile after multiple (4mg/kg, 7mg/kg, and 10mg/kg) and single (15mg/kg and 20mg/kg) doses. The most frequent AE was headache (mild to moderate in intensity) and no severe headache was reported. There were no TEAEs leading to IMP discontinuation. Four serious TEAEs were reported overall (none were considered to be treatment-related by the investigator and were related to the underlying disease). A dose-dependent decrease in total IgG was observed: 43.6% (range 21.9% to 68.6%) for the 4mg/kg group (~Day 29), 49.9% (range 29.5% to 65.5%) for the 7mg/kg group (~Day 22), 63.8% (range 38.4% to 75.0%) for the 10mg/kg group (~Day 15), and on Day 8, after a single dose, for the 15mg/kg and 20mg/kg groups 52.3% (range 30.1% to 68.0%) and 60.2% (range 51.8% to 65.4%), respectively. Responders were classified as having a clinically relevant platelet response ($\geq 50 \times 10^9$/L). Five (35.7%) participants in the 4mg/kg and 7mg/kg groups, 5 (45.5%) of 11 participants in the 10mg/kg group, 8 (66.7%) of 12 participants in the single administration 15mg/kg dose group, and 6 (54.5%) of 12 participants in the single administration 20mg/kg group were clinically relevant responders.

Based on the above, UCB considers that TP0001 established supportive evidence of efficacy and safety and is proceeding with the development of rozanolixizumab for the treatment of adults with persistent or chronic primary ITP. UCB is proposing a clinical development Phase 3 program in this orphan disease population comprised of two placebo-controlled, confirmatory maintenance treatment efficacy and safety studies, TP0003 and TP0006, and a one-year long-term safety, OLE study, TP0004.

The current study, TP0003, will assess the efficacy, safety, and tolerability of rozanolixizumab administered as a fixed-unit dose equivalent to [redacted] QW via sc infusion in adult study participants with persistent or chronic primary ITP.

2.3 Benefit/risk assessment

Although there were a number of treatment options approved for chronic ITP in the recent years, there is still an unmet medical need as for many of these medications the effect diminishes over time. The current available therapies like thrombopoietin-receptor agonists (TPO-RAs) have dietary exclusions, require liver function test monitoring or are increasing the risk of thrombosis or thromboembolic events. Corticosteroids are associated with significant long-term side effects.

Thus, there is an unmet medical need for new treatments that can reduce the complexity of the existing therapies.

The clinical efficacy data obtained in the Phase 2 study TP0001 indicate that rozanolixizumab has a rapid effect on lowering IgG and rapid onset of response in platelet count (increase in platelet count $>50\times10^9$/L) and an acceptable safety profile. The ability to administer via sc infusion results in low systemic fluid volumes with no impact on plasma viscosity, significant reduction in time for infusion, and reduced potential for infusion reactions.

The clinical safety data to date indicate that rozanolixizumab is well tolerated, and the common side effects are generally mild to moderate in severity, can be monitored and are manageable.

The most common adverse drug reactions observed after use of rozanolixizumab across indications are headaches and gastrointestinal (GI) disturbances (diarrhea, nausea, vomiting). Potential risks are serious infusion/hypersensitivity reactions, serious infections, and effects on vaccination response.

The risks of serious infusion/hypersensitivity and serious infections 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 GI disturbances, severe and/or serious headaches, and infusions is also provided as well as expedited reporting requirements of AESM.

Restrictions on use of live vaccines have been defined in the Exclusion Criterion #21a. 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 unlikely that the immunogenicity of 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 6.4.1). 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 AEs were to occur, they should be handled as described in (Section 8.3.10) with causality assessment provided for both IMP and vaccine. Additionally, to further characterize the effect of rozanolixizumab on vaccination response, measurement of vaccine titers 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

The objectives and corresponding endpoints for this study are presented in Table 3-1.

Table 3-1: Study objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the clinical efficacy of rozanolixizumab in maintenance treatment in study participants with primary ITP	The primary efficacy endpoint is: • Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to 25) The secondary efficacy endpoints are: • Cumulative number of weeks with Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L over the 24-week treatment period • Time to first Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L: time from starting treatment to achievement of first response of $\geq 50\times10^9$/L • Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L by Day 8 • Response defined as platelet count $\geq 30\times10^9$/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit [a,b] • Time to first rescue therapy • Change from Baseline to Week 25, in ITP Patient Assessment Questionnaire (ITP-PAQ) Symptoms Score

	The other efficacy endpoints are: • Duration of first Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L: measured from achievement of first Response to loss of first Response (loss of Response defined as platelet count $<50\times10^9$/L) • Time to first Response: time from starting treatment to achievement of Response • Usage of rescue therapy by visit • Complete Response defined as platelet count $\geq 100\times10^9$/L confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit [a,b] • Cumulative number of weeks over the planned 24-week treatment period with platelet counts of $\geq 100\times10^9$/L • Cumulative number of weeks over the planned 24-week treatment period with platelet counts $\geq 30\times10^9$/L and at least doubling from Baseline • Mean change from Baseline in platelet count by visit • Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 4 out of 6 weeks during the last 6 weeks (Week 19 to 25). • Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 6 out of 8 weeks during the last 8 weeks (Week 17 to 25).
Secondary	
• To assess the safety and tolerability of rozanolixizumab	The safety endpoints are: • Occurrence of TEAEs • Occurrence of TEAEs leading to withdrawal of IMP (ie, study discontinuation) The other safety endpoints are: • Occurrence of serious TEAEs • Occurrence of treatment related TEAEs

	• Occurrence of AESM • Vital signs change from Baseline (BP, pulse rate, body temperature) at each scheduled assessment during Treatment and SFU Periods • 12-lead ECG change from Baseline at each scheduled ECG visit • Laboratory change from Baseline (hematology including coagulation parameters, clinical chemistry, and urinalysis) at each scheduled assessment during Treatment and SFU Periods • Change from Baseline in concentrations of total protein and albumin • Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during the study (for study participants experiencing infusion reactions or hypersensitivity reactions)
Exploratory	
• To evaluate the clinical efficacy as measured by the ITP bleeding score	• ITP-BAT bleeding events and severity by visit
• To assess the effect of rozanolixizumab on health-related quality of life (HRQoL)	• Change from Baseline in European Quality of Life (EuroQol) -5 dimension 5 Levels (EQ-5D-5L) item responses • Change from Baseline in Short form 36-item (SF-36) domain and composite scores • Change from Baseline in the ITP-PAQ domain scores
• To assess hospitalizations due to ITP	• Number and length of hospitalizations

• To assess the effect of rozanolixizumab on patient reported outcomes (PROs)	• Change from Baseline in FATIGUE-PRO Physical Fatigue Score • Change from Baseline in Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C) at all available post-baseline assessments
• To assess the pharmacokinetics of rozanolixizumab administered by subcutaneous (sc) infusion	• Plasma concentration of rozanolixizumab
• To evaluate the incidence and emergence of antidrug antibodies (ADAs) of rozanolixizumab	• ADAs at each scheduled assessment
• To assess the pharmacodynamic (PD) effects of rozanolixizumab	The exploratory PD endpoints are: • Total serum IgG (absolute value) and change from Baseline (absolute values and percentage) in serum IgG and in serum IgG subclass concentration at each scheduled assessment • Absolute values and change from Baseline (absolute values and percentage) in serum immunoglobulin concentrations (IgA, IgE, IgM) at each scheduled assessment
• To assess the influence of rozanolixizumab treatment on vaccination titers	• Percent change from Baseline in vaccination titers against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* in splenectomized study participants • Percent change from Baseline in vaccination titers against tetanus in all study participants
• To assess the effect of rozanolixizumab on response to vaccination in study participants who received COVID-19 vaccine	• Change in biomarkers of COVID-19 vaccine response over time

[a] Absence of bleeding indicated by Grade 0 for all domains of the SMOG, or a Skin Grade of 0 or 1
[b] Nominal visits are on-site visits where ITP bleeding scale assessment is performed

4 STUDY DESIGN

4.1 Overall design

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study with rozanolixizumab in study participants with persistent or chronic primary ITP defined as more than 3 months, or 12 months of duration, respectively, since diagnosis.

The study participants will be male and female adults with persistent or chronic primary ITP, a platelet count measurement at Screening and at Baseline with an average of the two $<30\times10^9$/L (no single count may be $>35\times10^9$/L) and a documented history of low platelet count prior to Screening.

The primary objective of TP0003 is to evaluate the clinical efficacy of rozanolixizumab as a maintenance treatment in participants with persistent or chronic primary ITP.

The study design was selected to assess whether multiple sc infusions of rozanolixizumab will result in a durable Clinically Meaningful Platelet count increase of $\geq50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks of the Treatment Period (Week 13 to 25). On Day 1 (Baseline Visit), study participants will be randomized 2:1 to receive a fixed-unit dose of rozanolixizumab equivalent to [redacted] or placebo QW until Week 24, with randomization stratified by the degree of thrombocytopenia (platelet count < or $\geq15\times10^9$/L) and history of splenectomy (yes or no). The last assessments prior to the SFU Visit will be done at Week 25. Study participants will be observed during the 8-week SFU Period after the final administered dose. The TP0003 study schematic is presented in Figure 1-2.

The total maximum study duration per study participant is up to 35 weeks, including a Screening Period (up to 4 weeks), a Dose Adaptation Period (12 weeks), a Maintenance Period (12 weeks) and an SFU Period (8 weeks after final dose administered). Splenectomized participants will be required to attend a Prolonged Screening Period prior to the Screening Visit in order to receive, if applicable, the required vaccinations, which will extend the total study duration by up to 20 weeks.

The eligibility of study participants to participate in the study will be determined during the Screening Period. Once eligibility is confirmed, the study participants will come to the site on Day 1 (Baseline Visit) and receive a single fixed-unit dose of rozanolixizumab or placebo administered sc (based on randomization).

Rozanolixizumab or placebo will be administered as a sc infusion with an infusion pump at a [redacted]. A fixed-unit dose across different body weight tiers, as presented in Table 1-2 will be applied.

If the participant is unable to tolerate a [redacted], [redacted] may be used at the discretion of the clinical personnel administering the infusion.

The placebo arm will use 0.9% sodium chloride aqueous solution (physiological saline, preservative-free) for sc administration, matching the volumes of the rozanolixizumab arm.

Dosing will be followed by a series of postdose study assessments on Day 1 through Day 169, with a subsequent SFU Period through Day 218. On dosing days, for the first 2 weeks, 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, 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. However, if the dose needs to be decreased due to a TEAE(s) or dose needs to be increased, post dose observation will be extended to 1 hour after the end of infusion for the next 2 infusions. The post-dose observation time frame may be extended at the discretion of the investigator. These recommendations are applicable for dosing at site and at home. Approval from the investigator and sponsor is required prior to the start of home dosing.

In exceptional circumstances (eg, pandemic, hurricanes, etc) where study-specific investigations may not be conducted according to study protocol, contingency measures will be in place (see Section 8).

Approximately 150 study participants will be screened at approximately 70 sites from North America, Europe and Asia to achieve the targeted number of approximately 60 study participants randomized to weekly dosing.

All study participants completing the Treatment Period (with or without the need for rescue therapy) and fulfilling the OLE study (TP0004) eligibility criteria will be allowed to enroll into TP0004.

If study participants require rescue therapy during the Treatment Period (Week 1 to Week 25), they are allowed to receive commercially available rescue therapy (Section 6.4.3).

An external IDMC will be established to review the safety data at predefined intervals and ad hoc as needed, should emerging safety concerns arise during the study. The first IDMC meeting for the review of safety data is planned to occur after approximately 15 participants have received 3 doses of IMP in TP0003. The study will be put on hold if any of the following occurs:

- The IDMC judges it necessary for medical or safety reasons and
- The sponsor or its designee judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations and Good Clinical Practice.
- Three study participants experience any SAE of same type within the first 15 study participants who have received 3 doses of IMP across TP0003 and TP0006, unless the SAE is clearly unrelated to the study drug. After protocol amendment 3, this rule no longer applies.
  - **For US and Canada only**: Three study participants experience any SAE within the first 15 study participants who have received at least one dose of IMP across TP0003 and TP0006, unless the SAE is clearly unrelated to the study drug.

The IDMC has the possibility to unblind the data. Details of the IDMC composition, processes, and responsibilities will be documented in the IDMC charter. It is intended to have one IDMC for both of the pivotal studies (TP0003 and TP0006), where the data will be presented unpooled, ie, data from each study will be reviewed separately. Key safety data may be pooled at the discretion of the IDMC for protection of all study participants if warranted.

Based on feedback from the IDMC, weekly dosing was implemented in protocol amendment 3. Study participants being treated with the bi-weekly dosing regimen will switch to the weekly dosing regimen once protocol amendment 3 is approved at the respective study site.

Additionally, a Safety Signal Detection Team will perform rozanolixizumab program-wide aggregated safety data reviews at predefined intervals.

4.2 Scientific rationale for study design

Autoantibodies against platelet antigens are considered to be a hallmark of ITP. Production of pathogenic IgG autoantibodies by plasma cells is accepted as the central underlying pathophysiological mechanism in a number of IgG-mediated autoimmune diseases, which include ITP.

Treatments aimed at reducing the quantity of circulating IgG autoantibodies are being used for primary and secondary therapy of autoimmune diseases, particularly where corticosteroid-based immune suppression is not or no longer effective. The therapeutic approach of these treatments is based on lowering levels of pathogenic autoantibodies, which represents rational and effective treatment modalities of autoimmune diseases.

TP0003 is designed to evaluate the efficacy, safety, and tolerability of rozanolixizumab given as fixed-unit doses equivalent to [redacted], weekly until Week 24 in adult study participants with primary ITP.

Historical clinical data have demonstrated that the likelihood of bleeding is reduced with platelet counts >50×10^9/L, including both spontaneous bleeding and bleeding during minor surgical interventions such as dental manipulations. Conversely, the likelihood of bleeding events increases with platelet counts <35×10^9/L, with bleeding risk increasing as platelet count decreases. Hence, the participant population to be enrolled into this study should have a diagnosis of primary ITP (persistent or chronic) and a platelet count of <30×10^9/L. Study participants with clear evidence of a secondary cause of ITP and study participants with chronic or latent infections or active infections are excluded.

Safety and tolerability of rozanolixizumab up to [redacted] sc and iv doses have been evaluated in healthy study participants in study UP0018. In the subsequent Phase 2 study TP0001, in study participants with primary persistent and chronic ITP, different dosing regimens were tested, and a dose up to 15mg/kg as a single sc infusion was well tolerated and showed a 67% clinically meaningful responder rate, defined as platelet count increases to ≥50×10^9/L. In CIDP01, 34 study participants randomized to IMP (1:1 placebo:rozanolixizumab) followed [redacted] doses of [redacted] administrations. Of the 34 study participants, 21 study participants rolled over into the ongoing 52-week OLE study CIDP04. At least 6 participants have been treated with a [redacted] sc infusion for 1 year. Rozanolixizumab was well tolerated to date and the results of these two studies support the dosing regimen of [redacted] for 24 weeks in this study.

A 24-week Treatment Period to initiate and maintain a platelet increase and a subsequent 8-week SFU Period is considered sufficiently long to evaluate a difference between rozanolixizumab treatment and placebo.

It is generally recognized that a double-blind, randomized, parallel, placebo-controlled study is the most robust means of assessing the efficacy of a new treatment. The EMA guideline on the clinical development of medicinal products intended for the treatment of chronic ITP (effective as of Sep 2014) proposes a double-blind, placebo-controlled design. The placebo arm is justified, as rescue therapy and background treatment for ITP is allowed, provided the medication has

been taken on a stable dose for a certain period of time and below a maximum dose as specified in Table 6-2.

4.3 Justification for dose

Initially, a fixed-unit dosing regimen across body weight tiers equivalent to [redacted] (starting dose) followed by [redacted] (maintenance doses) every 2 weeks (Q2W) was proposed for use in the confirmatory TP0003 study, based upon response rate (>50×10^9/L), time to onset of the platelet count increase, and safety profile observed in the Phase 2 study, TP0001. Data from TP0001 showed that a single dose of [redacted] reached a 52% decrease in IgG from Baseline by Day 8, and a clinical response was observed for most study participants in the cohort before the IgG nadir on Day 8. The study also showed that the median (and range) duration of platelet response (platelet count >50×10^9/L) following a dose of [redacted] QW and a single dose of [redacted] was 12 (6 to 19) days and 11.96 (6 to 20) days, respectively. Hence, a starting dose of [redacted] followed by [redacted] Q2W was expected to sustain IgG levels reduced from its Baseline level by >50% and expected to be sufficient to translate into a relevant platelet response. Dose adjustments to [redacted] or approximately [redacted] were allowed if medically indicated, eg, for thrombocytosis. The proposed dose regimens were stratified by weight tiers as presented in Table 1-2.

Following the IDMC data review and the available OLE TP0004 data with the initially proposed dose regimen of [redacted], the IgG reductions appear to be in concordance with the anticipated reductions of ~50%, however the observed platelet count data are not sustained in TP0004 during the [redacted] dosing interval. Protocol Amendment 3 follows the advice from the external IDMC to increase the frequency of dosing, as in the OLE study TP0004 platelets are not sustained over a [redacted] dosing interval (observed platelet levels <50×10^9/L). Following the advice, the dose regimen for study TP0003 and OLE TP0004 will be changed to [redacted] QW. This dose regimen is anticipated to be [redacted] and more likely to sustain the platelets across the dosing interval reducing the risks associated with low platelet counts. A dose of [redacted] QW is predicted to sustain IgG levels with mean percentage change from Baseline reduction of 70% and maintain FcRn receptor occupancy (RO%) levels above 50% throughout the dosing interval as opposed to the Q2W that only sustained it above this level during the first week following each dose and not for the entire 14-day period between doses.

A [redacted] QW dose regimen is anticipated to achieve similar level of RO% to a [redacted], with a range on RO% from peak to trough of 99 to 50% during the 7 days dosing interval. A minimal difference in IgG reduction between [redacted] during the first 7 days was already observed in TP0001. Based on the minimal advantage from a RO% and IgG reduction perspective that a [redacted] starting dose will provide, the starting dose of [redacted] is therefore no longer required with the [redacted] QW dose regimen. The [redacted] QW dose is predicted to achieve mean concentrations at steady state ($C_{max,ss}$) of ~30ug/mL (2 days post dose) and C_{trough} of 0.31ug/mL.

In terms of safety, [redacted] weekly doses have been tested in TP0001 and showed a good safety and tolerability profile. In addition, this dose regimen of [redacted] QW has been studied in other indications like CIDP01, where 34 study participants (1:1 placebo:rozanolixizumab) followed [redacted] doses of [redacted] administrations. Of the 34 study participants, 21 study participants rolled over into the ongoing 52-week OLE study CIDP04. At least 6 participants have been treated with a [redacted] 1 year. The [redacted] doses were

generally [redacted] and well tolerated, with an acceptable safety profile and no new safety concerns were identified.

In addition, in order to avoid platelet count increases to ≥150×10^9/L, down-titration of the IMP dose level as described in Table 1-1 will be allowed. Weekly platelet assessments will be performed during the study, to support the dosing strategy with the aim to increase platelet counts ≥50×10^9/L and to minimize platelet counts ≥150×10^9/L in the study participants. Up titration to fixed-unit doses of [redacted] rozanolixizumab [redacted] QW will also be allowed to maintain stable platelet counts of ≥50×10^9/L over the Treatment Period if a previous down titration has occurred and subsequently platelet counts dropped again to below 50×10^9/L.

In summary, the new proposed dose regimen for Phase 3 is a [redacted] QW dose as starting and maintenance dose, allowing to down-titrate to [redacted] total dose based on the efficacy and safety profile. This regimen is supported by the observed data in the program thus far.

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, or has successfully been enrolled into TP0004 at Week 25 (Visit 27). Study participants not rolling over into TP0004 will have an EOS Visit performed 8 weeks after the final dose of IMP, or upon discontinuation of the study.

The enrollment into the TP0004 study should be conducted on the same day as Visit 27 (Week 25) of the feeder study. In case the enrollment into TP0004 is not conducted at Week 25 (Visit 27) a visit window of +3 days will be granted; therefore, rollover needs to be completed 3 days after Week 25 at the latest.

The EOS is defined as the date of the last visit of the last 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

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

Age

1a. Study participant must be ≥18 years of age at the time of the Screening Visit. For **Japan**-specific regulations, see Appendix 8, Section 10.8.

Type of participant and disease characteristics

2. Study participant is considered reliable and capable of adhering to the protocol, visit schedule, or medication intake according to the judgment of the investigator.
3. Study participant has a diagnosis of persistent (>3 months duration) or chronic (>12 months duration) primary ITP at the Screening Visit.

4b. Study participant has a documented intolerance or insufficient response to two or more appropriate standard of care ITP treatments (including but not limited to corticosteroids, immunoglobulins, TPO-RAs, azathioprine, danazol, cyclophosphamide, and/or rituximab or other immunosuppressants, splenectomy) prior to Screening. Two or more appropriate ITP treatments are defined as either at least two prior treatments if the participant is not taking concurrent ITP medications, or if the participant is on a concurrent ITP treatment at the study start (Screening), has received at least one prior ITP treatment.

5. Study participants must have prior history of a response to a previous ITP therapy.

6a. If taking allowed drugs (see Table 6-2), study participant must be on stable doses during defined time periods prior to Baseline (Day 1).

7. Study participant has a documented history of low platelet count ($<30\times10^9$/L) prior to Screening.
8. Study participant has a platelet count measurement at Screening and at Baseline (Day 1) with an average of the two $<30\times10^9$/L and no single count may be $>35\times10^9$/L (using local laboratories).
9. Study participant has a current or history of a peripheral blood smear consistent with ITP.
10. Study participant at Screening has an IgG level of:
    a. >5.5g/L for non-splenectomized participants
    b. ≥6.5g/L for splenectomized participants

Weight

11. Body weight >35kg at Screening.

Sex

12a. Study participants may be male or female:

- A male participant must agree to use contraception as detailed in Appendix 4, Section 10.4 during the Treatment Period and for at least 3 months after the final dose of study treatment and refrain from donating sperm during this period.
- A female participant is eligible to participate if she is not pregnant (see Appendix 4, Section 10.4) as confirmed by a negative serum pregnancy test and not planning to get pregnant during the participation in the study, 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 3 months after the dose of study treatment.

Informed consent

13. Study participant must be capable of giving signed informed consent 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.

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.

2a. Participant has a history of arterial or venous thromboembolism (eg, stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis or pulmonary embolism) within the 6 months prior to randomization or requires current anticoagulant treatment (Table 5-1).

3. Study participant has clinically significant bleeding that warrants immediate platelet adjustment (eg, menorrhagia with significant drop in hemoglobin).

4. Study participant has a history of alcohol use or other substance use disorder within the previous 12 months of the Screening Visit.

5a. Study participant has a known hypersensitivity to any components of the study medication or any other anti-FcRn medications.

6. Study participant has a known history of hyperprolinemia, since [redacted].

7b. Study participant has evidence of a secondary cause of immune thrombocytopenia (clear association with other medical conditions, eg, untreated *H. pylori* infection, leukemia,

lymphoma, common variable immunodeficiency, systemic lupus erythematosus, autoimmune thyroid disease or is drug induced), participant has a multiple immune cytopenia (eg, Evan's syndrome), etc. For **Japan**-specific regulations, see Appendix 8, Section 10.8.

8a. Study participant has a clinically relevant active infection (eg, sepsis, pneumonia, or abscess) in the opinion of the investigator, or had a serious infection (resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to the first dose of IMP.

9. Study participant with a known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent tuberculosis infection (LTBI), or current/history of nontuberculous mycobacterial infection (NTMBI).

10. Study participant has a history of a major organ transplant or hematopoietic stem cell/marrow transplant.

11a. Study participant has any of the following active GI disorders: inflammatory bowel disease, GI ulceration or diverticulitis.

12. Study participant has experienced a clinically symptomatic GI bleed (positive hemoccult tests without any signs and symptoms of GI bleeding will not be considered as "clinically symptomatic") in the last 6 months prior to the Screening Visit and/or has current gastritis or esophagitis and/or has a known risk for clinically relevant GI bleeding beyond ITP.

13. Study participant has experienced intracranial bleed in the last 6 months prior to the Screening Visit.

14. Study participant has a history of coagulopathy disorders other than ITP.

15. Criterion removed.

16. Splenectomized participant with past medical history of OPSI.

17a. Study participant with current or medical history of IgA deficiency, or a measurement of IgA <50mg/dL at the Screening Visit.

Prior/Concomitant therapy/procedures

18. Study participant who has received any blood or blood products within 2 weeks prior to the Baseline Visit.

19. Study participant has undergone a splenectomy in the 2 years prior to the Baseline Visit.

20b. Splenectomized participant without adequate vaccination against *S. pneumoniae, N. meningitidis,* and *H. influenzae* as evidenced by:

- a lack of documented vaccination records per local guidance, OR
- have not completed required vaccinations (*S. pneumoniae*, *H. influenzae*, and *N. meningitidis*) per Section 8.2.6 during the Prolonged Screening Period

Note: For splenectomized participants without any prior vaccination against one or all of the above-mentioned bacteria please refer to Section 8.2.6 of the protocol.

For **Japan**-specific regulations, see Appendix 8, Section 10.8.

21a. Study participant has received a live vaccination within 8 weeks prior to Day 1 (Baseline Visit); or intends to have a live vaccination during the course of the study or within 7 weeks following the final dose of IMP.

22. Criterion removed.

23a. Criterion removed.

24a. Study participant has been treated with prohibited immunosuppressants, biologics and other therapies within a timeframe shorter than detailed in Table 5-1. Medications as presented in Table 5-1 are prohibited during the study, unless required as rescue therapy (specified in Section 6.4.3) during the study.

Table 5-1: Treatment-free periods for immunosuppressants, biologics, other therapies, and antiplatelet/anticoagulant agents

Generic name (commercial/trade name)	Period relative to Baseline Visit (regardless of route of administration)
Immunosuppressants	
Cyclophosphamide	6 months
Pimecrolimus (Elidel®)	4 weeks
Vinca alkaloids (vincristine, vinblastine)	12 weeks
Biologics (monoclonal antibodies and fusion proteins)	
Abatacept (CTLA 4-Ig) (Orencia®)	6 months
Belimumab (Benlysta™)	6 months
Golimumab (Simponi™)	6 months
Natalizumab (Tysabri®)	6 months
Ofatumumab (Arzerra®)	6 months
Rituximab (Rituxan®) and ocrelizumab	6 months or if more than 6 months and B cells have not returned to normal
TACI-Ig (Atacicept®)	10 months
Veltuzumab	6 months
Other biologics	3 months or within 5 half-lives prior to the Baseline Visit (whichever is longer)
Inebulizumab	6 months and B-cell counts are within normal range
Other	
Intravenous immunoglobulin	4 weeks
Plasma exchange (PEX)	4 weeks
Anti-D	4 weeks
Romiplostim (Nplate®)	4 weeks

Generic name (commercial/trade name)	Period relative to Baseline Visit (regardless of route of administration)
Antiplatelets and Anticoagulants (eg, thrombin inhibitors, Vitamin K antagonists, factor inhibitors)[a]	
Warfarin	2 weeks
Phenprocoumon	2 weeks
Acenocoumarol	2 weeks
Heparin	1 week
Clopidogrel	1 week
Salicylates (Aspirin)	1 week (enteric coated aspirin up to 150mg daily allowed)
Dipyridamole	1 week
Prasugrel	1 week
Ticagrelor	1 week
Tirofiban	1 week
Abciximab	1 week

[a] This is not a complete list. The treatment free period relative to Baseline should be at least 5 half-lives from last dose, but a minimum of 1 week, whichever is longer.

Prior/Concurrent clinical study experience

25. Study participant has previously received rozanolixizumab in another clinical study.
26. Study participant has participated in another study of an investigational IMP (and/or an investigational device) within the previous 30 days prior to the Screening Visit or within 5 half-lives prior to Baseline (whichever is longer) or is currently participating in another study of an investigational IMP (and/or an investigational device).
27. Criterion removed.

Diagnostic assessments

28a. Study participant has absolute neutrophil count <1500 cells/mm^3 at the Screening Visit.
29. Criterion removed.
30. Study participant has a partial thromboplastin time ≥1.5x upper limit of normal (ULN) or International Normalized Ratio (INR) ≥1.5 at the Screening Visit.
31a. Study participant has 12-lead ECG with changes considered to be clinically significant upon medical review at Baseline.
32a. Study participant has renal impairment, defined as:

- Glomerular filtration rate (GFR) less than 45ml/min/1.73 m^2 at the Screening Visit.

33b. Study participant has 3.0xULN of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) at the Screening Visit.

- If participant has >ULN for ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the participant must be discussed with the Medical Monitor.
- For participants with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be recorded in the eCRF.

34a. Study participant has bilirubin >1.5xULN (unless confirmed Gilbert's syndrome). If participant has elevations only in total bilirubin, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%) at the Screening Visit.

35. 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: with exception of stable hepatobiliary conditions (including Gilbert's syndrome, asymptomatic gallstones).

36. Presence of hepatitis B surface antigen (HBsAg) at the Screening Visit.

37. 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.

38. Study participant tests positive for HIV at the Screening Visit.

39a. Study participant has a current or medical history of primary immunodeficiency.

40. Study participant has active neoplastic disease or history of neoplastic disease within 5 years of the Screening Visit (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix which has been definitively treated with standard of care approaches).

41a. Study participant has corrected QT interval for heart rate using Fridericia's formula (QTcF) >450msec (for male participants) or QTcF >470msec (for female participants) or QTcF >480msec in participants with bundle branch block at the Baseline Visit.

Other exclusions

42. Criterion removed.

43a. Study participant has planned major elective surgical procedure for the duration of their participation in the study.

44. For **Japan** specific regulations, see Appendix 8, Section 10.8.

5.3 Lifestyle restrictions

There are no lifestyle restrictions during the study unless deemed to interfere with compliance with the protocol as deemed by the investigator.

5.4 Screen failures

Screen failures are defined as study participants who consent to participate in the clinical study but are not subsequently randomly assigned 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 SAE.

Individuals who do not meet the platelet count criteria for participation in this study (screen failure) may be rescreened. Individuals who do not meet other criteria for participation in this study may be rescreened once. Additional rescreening of these individuals following upfront discussion with the Medical Monitor or Study Physician might be allowed. Rescreened study participants should be assigned a new participant number for rescreening.

If a study participant has isolated test results (specifically those mentioned in the inclusion or exclusion criteria) that are outside of the specific range but are clinically nonsignificant, the abnormal value may be rechecked at the discretion of the investigator, following discussion with the Medical Monitor or Study Physician.

Rescreening of study participants is separate from the repeating of individual tests.

Adequate vaccination for all splenectomized participants within 4 years prior to enrollment is preferred. However, non-vaccinated splenectomized study participants can receive vaccination during the Prolonged Screening Period. If a booster is due during the study, to avoid treatment interruption, the booster can be given ahead of the 5-year schedule if needed, also as part of the Prolonged Screening Period. Splenectomized participants who received vaccination during the Prolonged Screening Period, including those who received vaccination booster, can be randomized at a minimum 4 weeks after the last vaccination provided all other eligibility criteria are met.

6 STUDY TREATMENTS

Table 6-1: Treatments administered

Study Treatment Name:	Rozanolixizumab	Placebo
Dosage formulation	Solution for infusion	Aqueous solution
Unit dose strength(s)/Dosage level(s):	[redacted] QW [redacted] QW [redacted] QW	0.9% sodium chloride aqueous solution (physiological saline, preservative free) Volume matching the rozanolixizumab volume for the weight tier; QW
Route of administration	Subcutaneous infusion	
Dosing instructions:	Study treatment will be administered as a sc infusion with an infusion pump at a [redacted]. A fixed-unit dose across different body weight tiers, as presented in Table 1-2 will be applied. The study participant's body weight at the Screening Visit will be used for the dose assignation. In the case of any blockage of the infusion, a suitable flush (eg, 0.9% sodium chloride) is allowed. If the participant is unable to tolerate a [redacted] may be used at the discretion of the clinical site personnel administering the infusion.	
Packaging and labeling:	Rozanolixizumab will be provided in glass vials, will be labeled as required per country requirement.	[redacted]

hr=hour; QW=every week; sc=subcutaneous; w/v=weight/volume

Details on the rate of infusion and storage conditions are provided in the IMP Handling Manual.

6.1 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 that any discrepancies were reported and resolved before the use of the study treatment.

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

labeled storage conditions with access limited to the unblinded authorized site staff or pharmacy staff.

The investigator or designee 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.

6.1.1 Drug accountability

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

UCB is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

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

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

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

6.2 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 IMP, as appropriate, according to the visit schedule.

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

the participant based on the participant number during the course of the study. The randomization number will be incorporated from the IRT into the eCRF by automatic data transfer.

The randomization will be stratified by the following:

- Degree of thrombocytopenia (platelet count < or $\geq 15 \times 10^9$/L)
- Splenectomy: yes/no

6.2.1 Procedures for maintaining and breaking the treatment blind

6.2.1.1 Maintenance of study treatment blind

All study participant treatment details, rozanolixizumab treatment arm, planned dose, or placebo, will be allocated and maintained by the IRT system.

Study site pharmacists or other suitably qualified site personnel who are responsible for preparations of the IMP will be unblinded as they have access to treatment allocations for individual participants via the IRT. The unblinded pharmacy monitors from the contract research organization (CRO), the Clinical Supply Manager, and the unblinded Clinical Project Manager (CPM) (or designee) will also have access to the treatment allocations and to the drug accountability records, if applicable.

The following individuals may, as necessary, have access to the treatment allocations for individual participants via the IRT:

- Sponsor Patient Safety (PS) 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 participants for whom data are provided at these sessions.
- Sponsor and/or CRO staff supporting preparation of the data outputs for the IDMC review and/or any interim analyses.
- A Quantitative Clinical Pharmacologist/Modeling and Simulation Scientist may have access to the randomization code if PK data are requested for review by the IDMC.
- The bioanalytical scientific manager (or designee)

An independent Quantitative Clinical Pharmacologist/Modeling and Simulation Scientist may have access to the randomization code to review unblinded PK, platelet and serum IgG data.

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

For safety reasons, the blinded investigator (or designee) has to receive and review the platelet counts from the local laboratory, which will be documented by the blinded site personnel in the eCRF. An increase in platelet count during the Treatment Period is not considered as an unblinding. As such, an increase in platelet count is expected for approximately 60% of the study participants, and up to 10% of placebo-treated study participants may experience an increase in platelet count. Platelet counts may be shared with study participants as this is deemed necessary information for participants when engaging in activities of daily living.

Unintentional formal unblinding occurs when the unblinded study site pharmacists or other suitably qualified site personnel responsible for IMP preparation share the treatment allocations for individual participants (or equivalent information) with the blinded site personnel accidentally. The same applies to the blinded sponsor and/or CRO staff.

Unintentional informal unblinding of the blinded investigator (or designee) and the blinded site personnel is only applicable if IgG levels are shared by the central laboratory in error. Given the pharmacological property of the IMP, a change of IgG level may be suggestive of a treatment effect however, does not disclose the treatment allocation.

To maintain the study integrity, study site personnel, the UCB and CRO study teams will remain blinded to IgG levels. However, to ensure study participants' safety, serum IgG level will be monitored by unblinded Medical Monitors external to UCB. In case the serum IgG level decreases <1g/L, the unblinded Medical Monitors will inform the investigator as described in Table 10-8. Potential actions to be taken may include maintaining the dose, reducing the dose or initiation of mock infusions. Temporary treatment discontinuation due to low IgG levels may informally unblind the treatment assignment to the participant. Therefore, infusions will be continued but given as mock infusions with only placebo irrespective of IMP designation. Allocation of mock kit numbers will be handled via the IRT. Refer to Appendix 25, Section 10.25 for further information.

Further details are provided in the study manual and site blinding plan.

6.2.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the study participant has been allocated by contacting the IRT. At the start of the study, all sites will be provided with details of how to contact the system for code breaking. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

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

6.3 Treatment compliance

During the Treatment Period, IMP will be administered at the clinical site or study participant's home as a sc infusion by a qualified designee. Drug accountability must be recorded on the Drug Accountability form (see Section 6.1.1).

6.4 Concomitant medication(s)/treatment(s)

6.4.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study and if possible, kept stable for the duration of the study (Table 6-2):

Table 6-2: Permitted concomitant treatments (medications and therapies)

Permitted Medications	Dose	Comment[a]
Oral corticosteroids	≤20mg/day (prednisone equivalent dose)	Stable dose for [redacted] prior to Baseline
Mycophenolate mofetil	≤3g/day	Stable dose for [redacted] prior to Baseline
Cyclosporin	≤5mg/kg/day for unmodified ≤4mg/kg/day for modified	Stable dose for [redacted] prior to Baseline
Azathioprine	≤3mg/kg/day	Stable dose for [redacted] prior to Baseline
Danazol	≤15mg/kg/day	Stable dose for [redacted] prior to Baseline
Dapsone	100mg/day	Stable dose for [redacted] prior to Baseline
Eltrombopag, Avatrombopag	Any dose	Stable dose for [redacted] prior to Baseline
Fostamatinib	Any dose	Stable dose for [redacted] prior to Baseline

[a] Stable dose is defined as either the same dose and frequency of the respective medication taken for the period of time defined in Table 6-2, or no dose of the respective medication taken for the period of time as defined in Table 6-2.

The use of medicinal cannabidiols and medicinal marijuana (prescribed by a physician) is also permitted. When applicable, the study participant must be on a stable dose of cannabidiols and/or medicinal marijuana for [redacted] prior to Screening and remain stable for the duration of the study. For **Japan**-specific regulations, see Appendix 8, Section 10.8.

6.4.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- IVIg (unless given as a rescue therapy)
- All biologics including rituximab
- Cyclophosphamide
- Pimecrolimus
- PEX
- Immunoadsorption

- Anti-D
- Any systemically administered corticosteroids above the allowed background dose (unless required as a rescue therapy)
- Romiplostim
- Vinca alkaloids (vincristine, vinblastine)
- Anticoagulants and antiplatelets (warfarin, heparin, clopidogrel, aspirin [enteric coated up to 150mg daily allowed], salicylics, dipyridamole, prasugrel, ticagrelor, tirofiban, and abciximab).

For study participants who require a medical or surgical procedure that requires the use of general anesthesia, discussion must occur prior to the procedure with the Medical Monitor or study physician, such that a decision on the participant's continued participation in the study can be made. In an emergency situation, the discussion should occur as soon as possible after the procedure.

The use of prohibited concomitant treatment will lead to permanent discontinuation from IMP. Study participants should then complete the assessments outlined for the Early Withdrawal (EW) Visit and enter the SFU Period.

6.4.3 Rescue therapy

Rescue treatment will be given as per standard of care and at the discretion of the investigator as described below. If such rescue therapy is given, the participant is allowed to continue IMP treatment (as per guidance below), and should continue to complete all remaining scheduled visits in the Treatment Period, as per the Schedule of Activities (Section 1.3). The following rescue therapies may be used:

- Any increase in concomitant ITP therapies above Baseline dose
- Any additional ITP medication/therapies including but not limited to:
  - Platelet transfusion (only in cases of severe bleeding)
  - Commercially available IVIg
  - Any systemically administered corticosteroids (above the background doses, ie, pulse, oral and iv steroids). Any systemic corticosteroids used for the management of infusion reactions or other medical conditions are also considered rescue therapy.
  - Immunosuppressants (except for those listed in Section 6.4.2).

Although the use of rescue therapy is allowable at any time during the study, the use of rescue therapy should be delayed, if possible, for at least 2 days following the administration of study treatment.

If IVIg, high dose corticosteroids, or platelet transfusion are given as rescue therapy, IMP treatment can commence at the same dose as previously when platelet counts are $<50\times10^9$/L. Dose can be up-titrated at a later timepoint, if needed, depending on platelet level.

A high dose of corticosteroids is defined as any iv administration of corticosteroids given for any reason or doubling of an oral dose resulting in a dose more than 20mg/day prednisone equivalent dose.

In case of an increase of Baseline oral corticosteroids, not resulting in doubling of the oral dose more than 20mg/day prednisone equivalent dose, an increase in the concomitant ITP therapies above Baseline, or in case of administration of immunosuppressants as rescue therapy, IMP administration can continue as per Schedule of Activities (Section 1.3) at a dose adjusted depending on the platelet level.

The date and time of rescue therapy administration as well as the name and dosage regimen of the rescue therapy must be recorded in the eCRF.

6.5 Dose modification

Dose modifications of the IMP are permitted in order to maintain the platelet counts between $\geq 50 \times 10^9$/L and $\leq 150 \times 10^9$/L (Table 1-1 and Figure 1-1).

Dose modifications or temporary discontinuation of the IMP treatment are permitted if serum IgG value is <1g/L (Section 10.25).

In the event of treatment-related AEs, other than those that meet the IMP discontinuation criteria (as defined in Section 7.1) a dose reduction is permitted. Treatment-related AEs due to which dose modifications are recommended may include, but are not limited to:

- Moderate to severe headaches
- Severe vomiting and diarrhea
- Moderate to severe toxicities (Grade 2 and above, as defined by Common Terminology Criteria for Adverse Events version 5.0) for which rozanolixizumab cannot be excluded as a cause

6.6 Treatment after the end of the study

Study participants (regardless of whether they receive rescue therapy), upon completion of the Treatment Period and if fulfilling the eligibility criteria, will be given the opportunity to enroll into the OLE study, TP0004.

In case the enrollment into TP0004 is not conducted at Week 25 (Visit 27), a visit window of +3 days will be granted; therefore, rollover into TP0004 needs to be completed +3 days after Week 25 at the latest.

For study participants not enrolling into the OLE study, there are no plans for continued provision of rozanolixizumab after the end of the study. The participant should discuss any alternative treatment options (if needed after the study) with their healthcare provider.

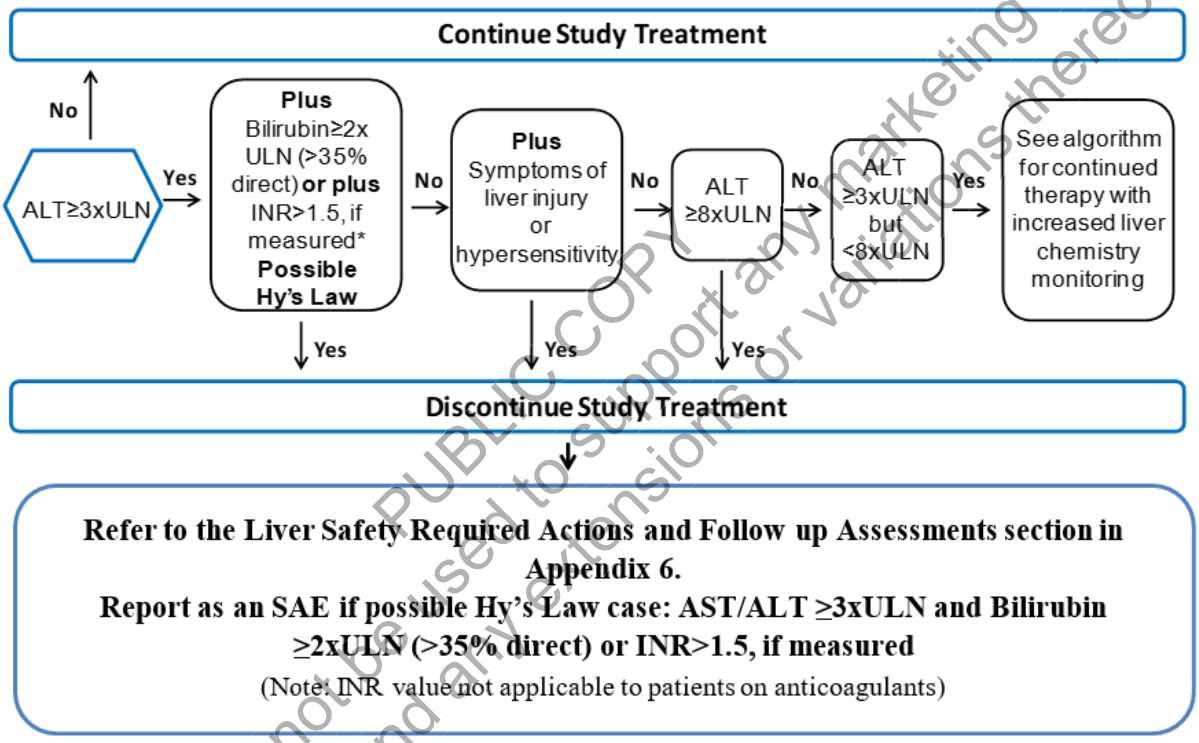
7 DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of IMP

7.1.1 Liver chemistry stopping criteria

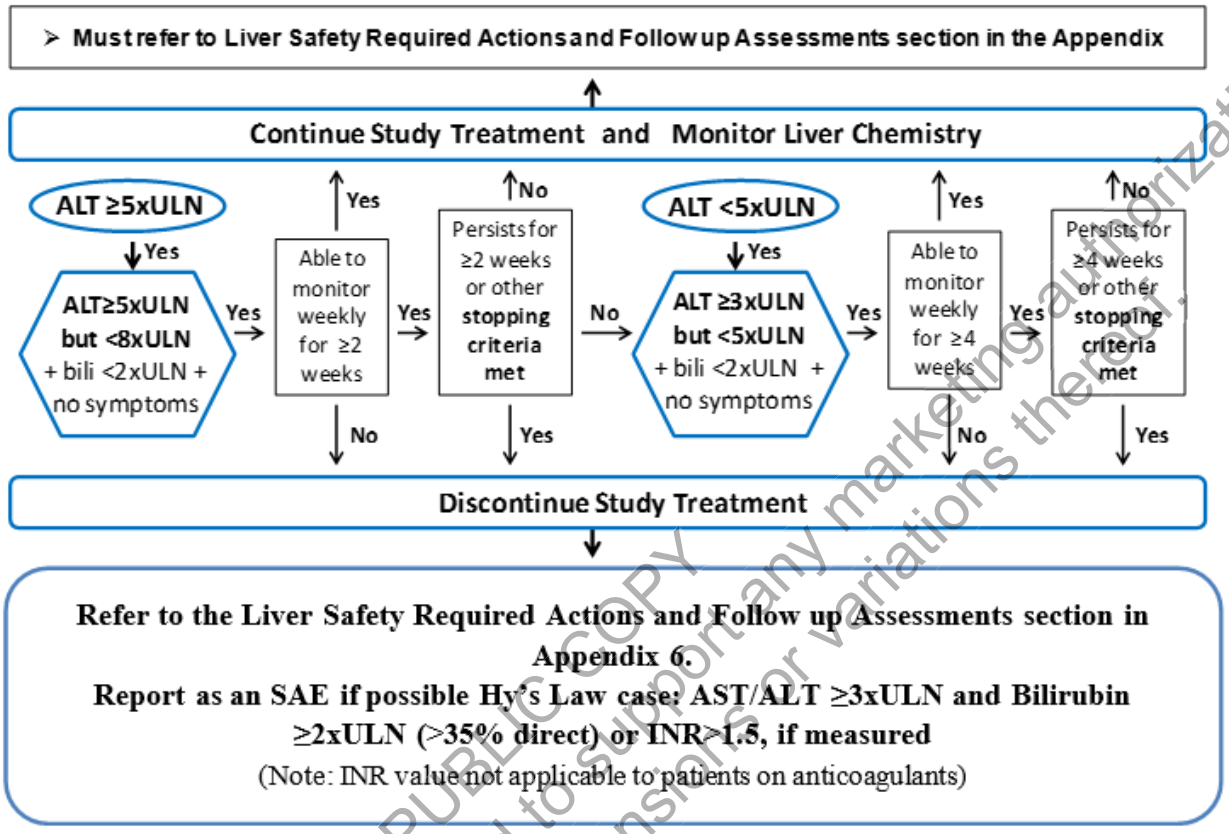
Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a study participant meets one of the conditions outlined in Figure 7-1 and Figure 7-2, or if the investigator believes that it is in the best interest of the participant.

Figure 7-1: Liver chemistry stopping criteria and increased monitoring algorithm



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

Figure 7-2: Liver chemistry increased monitoring algorithm with continued study intervention for participants with ALT ≥3xULN but <8xULN



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

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

7.1.2 QTc stopping criteria

If a clinically significant finding is identified (including but not limited to: changes from Baseline in QT interval corrected using Fridericia's formula) after enrollment, the investigator or qualified designee will determine if the study participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A study participant who meets the bulleted criteria based on the ECG readings will discontinue IMP and move into the SFU Period. The study participant should be referred to a specialist (ie, cardiologist) and managed as per local guidance.

- QTc >500 msec OR uncorrected QT >600 msec
- Change from Baseline of QTc >60 msec

For study participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc Threshold with Bundle Branch Block
<450 msec	>500 msec
450 to 480 msec	≥530 msec

7.1.3 Discontinuation of IMP due to other adverse events or medical condition

Study participants **MUST permanently discontinue IMP** and move into the SFU Period if any of the following events occur:

- Study participant has a significant infective episode including but not limited to: bacteremia or sepsis, infectious meningitis, osteomyelitis, septic arthritis, 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 his/her judgment on continuing IMP based on the clinical situation at hand (see Appendix 25, Section 10.25).
- 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).
- Study participant has an AE of severe or serious hypersensitivity, infusion related reaction (see Appendix 24, Section 10.24) or anaphylaxis requiring corticosteroid and/or epinephrine therapy (see Appendix 21, Section 10.21) (Sampson et al, 2006).
- Study participant has a serious AE of headache or GI disturbance that is considered related to the IMP in the opinion of the investigator; or recurrent severe AE of headache (see Appendix 22, Section 10.22) or GI disturbance that is considered related to the IMP in the opinion of the investigator (See Appendix 23, Section 10.23).
- Study participant has a life-threatening bleeding event.
- Study participant has an AE of arterial or venous thromboembolic event (eg stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis).
- Study participant has evidence suggestive of potential TB infection (eg, exposure), and further examinations result in a diagnosis of active TB, LTBI, or NTMBI (see Section 8.2.5).
- If a NTMBI is identified during the study, the same withdrawal procedures as those used for an active TB infection identified during the study should be followed.

Study participants who permanently discontinue IMP during the Treatment Period and hence are withdrawn from the study should complete the assessments outlined for the Early Withdrawal (EW) Visit and enter the SFU Period.

7.1.4 Temporary IMP discontinuation

Study participant **MUST temporarily discontinue IMP** if any of the following events occur:

1. Thrombocytosis (platelet count of $\geq 400 \times 10^9$/L).

2. In the event of confirmed COVID-19 infection (eg, signs/symptoms such as fever, cough, shortness of breath), or known exposure sufficient to necessitate testing or self-imposed quarantine.
   The IMP may be restarted if:
   a. COVID-19 test is negative, and signs and symptoms have resolved
   b. If test is not available, resolution of signs and symptoms and 14 days have passed since initial presentation of the clinical signs/symptoms.
   c. If asymptomatic, 14 days have elapsed since known exposure.

Study participant **MAY temporarily discontinue IMP** if any of the following events occur:

1. A severe AE of headache that is considered related to the IMP in the opinion of the investigator (Section 10.22)
2. A splenectomised study participant develops a (persistent or re-occurring) nonserious infection, as per investigator's decision (Section 10.25)
3. Total serum IgG value is <1g/L as per investigator's decision. As IMP treatment is administered weekly, the decision to temporarily hold the treatment should be determined based on the most recently available total IgG value. As the IgG, IgG subtypes, albumin and total protein levels will be blinded to both the study site personnel and the clinical team at the sponsor and CRO, unblinded Medical Monitors will be monitoring the IgG levels and will alert the investigator in case of decreases <1g/L. Additionally, guidance for investigators on management of infections can be found in Appendix 25, Section 10.25.

7.2 Participant discontinuation/withdrawal from the study

Study participants are free to withdraw from the study at any time, without prejudice to their continued care. Participants who withdraw from the study should complete the EOS Visit.

A study participant may also be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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

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

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

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

1. Study participant withdraws his/her consent.
2. Study participant takes prohibited concomitant medications as defined in this protocol.
3. Study participant meets the mandatory IMP discontinuation criteria as per Section 7.1.1, Section 7.1.2 or Section 7.1.3.

4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
5. The sponsor or a regulatory agency requests withdrawal of the study participant.

Study participants who withdraw from the study or permanently discontinue IMP during the Treatment Period should complete the assessments outlined for the EW Visit, enter the SFU Period and complete the EOS Visit.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a participant in advance. Study participants who are withdrawn will not be replaced.

7.3 Lost to follow up

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

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

- The site must attempt to contact the study participant and reschedule the missed visit as soon as possible and counsel the study participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a study participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the 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.

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor (or designee - Medical Monitor at CRO) 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 (see Section 1.3), is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) 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 (see Section 1.3).

An Unscheduled Visit can be conducted at the discretion of the investigator (eg, due to an AE).

During the Unscheduled Visit, the following assessments will be performed:

- AE reporting
- Concomitant medications
- Review of withdrawal criteria
- Physical examination
- Vital signs
- Blood samples for PK, IgG, hematology, biochemistry, other testing such as for TB or C-reactive protein (CRP) as clinically indicated in the opinion of the investigator.

Other assessments may be performed at the discretion of the investigator.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Some study-specific investigations may not be conducted according to the study protocol during a pandemic or other exceptional circumstances (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 participant 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 schedule, 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.

The participant may have the option to have home-nursing visits as specified in Section 1.3. Home-nursing visits will be conducted by 2 fully trained healthcare professionals (1 unblinded for IMP preparation and 1 blinded for the other assessments) visiting the 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 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 in the clinic. These healthcare professionals 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 participant is willing to be dosed and monitored at home, or at an alternative location by healthcare professionals.
- The 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 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 or adequate alternative).
- The participant's home or alternative location allows rapid access to emergency treatment if required (ie, the participant must not live so remotely that a reasonable arrival time of an ambulance could not be predicted).
- The investigator or site designee 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).

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

8.1 Efficacy assessments

8.1.1 Platelet counts

For assessment of platelet counts, blood samples will be collected by qualified site personnel at the same time that samples are collected for standard clinical laboratory assessments. The time and date of the blood draws will be recorded in medical source data and the eCRF. Assessment will be performed according to the Schedule of Activities (Section 1.3).

Platelet counts will be determined by a local laboratory and the following endpoints will be derived for the purpose of analysis:

- Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to 25)
- Cumulative number of weeks with Clinically Meaningful Platelet Response defined as: platelet count $\geq 50\times10^9$/L over the 24-week treatment period
- Time to first Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L defined as: time from starting treatment to achievement of first response of $\geq 50\times10^9$/L
- Clinically Meaningful Response defined as $\geq 50\times10^9$/L by Day 8
- Response defined as platelet count $\geq 30\times10^9$/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit
- Time to first Response defined as: time from starting treatment to achievement of Response
- Duration of first Clinically Meaningful Platelet Response of $<50\times10^9$/L: measured from achievement of first Response to loss of first Response (loss of Response defined as platelet count $<50\times10^9$/L)
- Complete Response defined as platelet count $\geq 100\times10^9$/L confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit
- Cumulative number of weeks over the planned 24-week treatment period with a platelet count of $\geq 100\times10^9$/L
- Cumulative number of weeks over the planned 24-week treatment period with platelet counts $\geq 30\times10^9$/L and at least doubling from Baseline
- Mean change from Baseline in platelet count by visit
- Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 4 out of 6 weeks during the last 6 weeks (Week 19 to 25)
- Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 6 out of 8 weeks during the last 8 weeks (Week 17 to 25)

The Response and Complete Response variables will be assessed only for visits for which both platelet counts and the ITP bleeding score are assessed (with the exception of the confirmatory platelet assessments which may be obtained at any visit (scheduled or unscheduled) provided that they meet the criteria below). In order to define a Response (platelet count $\geq 30\times10^9$/L), the platelet count must be confirmed on 2 separate occasions and in the absence of bleeding. The time to first Response will be taken as the time to the first platelet assessment (obtained at the same time as the corresponding ITP bleeding score assessment). If the second assessment does not fulfill the required criteria for a Clinical Response, the study participant will be considered as a nonresponder at the respective visits. Further details will be provided in the Statistical Analysis Plan (SAP).

Refer to Section 9.3 for details of statistical analysis of these variables.

8.1.2 ITP bleeding score

The International Working Group on ITP proposes a consensus-based ITP-BAT, based on a precise definition of bleeding manifestations and on the grading of their severity (Rodeghiero et al, 2013). The ITP bleeding score will be assessed using the ITP-BAT tool Version 1.0. Assessment will be performed according to the Schedule of Activities (Section 1.3).

For the ITP-BAT, bleeding manifestations were grouped into 3 major domains: S, M, and O, with the skin, mucosae, organs with grading of severity (SMOG) system. Each bleeding manifestation is assessed at the time of examination. Severity is graded from 0 to 3 or 4, with Grade 5 for any fatal bleeding. Absence of bleeding will correspond to a Grade 0 or 1 for Skin and Grade 0 for Mucosae or Organ domains. Presence of bleeding is indicated by a Mucosae or Organs Grade ≥1, or Skin Grade ≥2. Bleeding reported by the participant without medical documentation is Graded 1. Within each domain, the same grade is assigned to bleeding manifestations of similar clinical impact. The "worst" bleeding manifestation since the last visit is graded, and the highest grade within each domain is recorded. The SMOG system provides a consistent description of the bleeding phenotype in ITP.

A standardized data collection form will be used to facilitate collection of information and communication among physicians and investigators. The grading of bleeding symptoms at presentation and at each subsequent evaluation is presented in Appendix 12, Section 10.12.

8.1.3 Patient Reported Outcomes

Patient reported outcomes must be completed as per time points mentioned in the Schedule of Activities (Section 1.3). The PROs should be completed prior to any intrusive procedures in a quiet place. On dosing days, PROs will be completed prior to dosing.

The PROs should be completed in the following order: ITP-PAQ, SF-36, the FATIGUE-PRO Physical Fatigue Scale, EQ-5D-5L, PGI-S, and PGI-C.

8.1.3.1 ITP-PAQ

The ITP-PAQ is a 44-item disease-specific Health-Related Quality of Life (HRQoL) questionnaire developed for use in adults with chronic ITP. It includes 11 scales: Symptoms, Fatigue, Physical Health – Bother, Physical Health – Activity, Emotional Health – Psychological, Emotional Health – Fear, Overall QoL, Social Activity, Women's Reproductive Health – Fertility, Women's Reproductive Health - Menstrual Symptoms, and Work. Each item is rated on a Likert-type scale containing 4 to 7 responses. All item scores are transformed to a 0 to 100 continuum and are weighted equally to derive individual scale scores. Higher scores indicate better health status (Mathias et al, 2009; Mathias et al, 2007).

The ITP-PAQ Symptoms score was selected as secondary efficacy endpoint for the study to capture the benefits of rozanolixizumab in terms of patient-perceived symptoms. It covers 6 core symptoms of ITP: bruising/petechiae, wounds/scars (from blood tests, injections or IV needles), blood blisters in mouth, bleeding episodes, muscle aches, and cramps in legs.

The ITP-PAQ sample questionnaire is available in Appendix 13, Section 10.13.

8.1.3.2 SF-36

Study participants will complete the SF-36 questionnaire according to the Schedule of Activities (see Section 1.3). The SF-36 sample questionnaire is available in Appendix 14, Section 10.14.

8.1.3.3 FATIGUE-PRO Physical Fatigue Scale

The FATIGUE-PRO Physical Fatigue scale is one of the three scales of the broader FATIGUE-PRO instrument developed by UCB. It consists of 9 items rated on a 5-point frequency response scale ranging from "none of time" to "all of the time", with a 7-day recall period. The FATIGUE-PRO Physical Fatigue score ranges 0 to 100, with higher score meaning more physical fatigue.

The FATIGUE-PRO Physical Fatigue scale is available in Appendix 15, Section 10.15.

8.1.3.4 EQ-5D-5L

The EQ-5D-5L is designed to improve the instrument's sensitivity and to reduce ceiling effects.

The EQ-5D-5L consists of 2 pages: the EQ-5D descriptive system and the EuroQol visual analogue scale (EQ VAS).

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 judgment.

Study participants will complete the EQ-5D-5L questionnaire according to the Schedule of Activities (see Section 1.3). The EQ-5D-5L sample questionnaire is available in Appendix 16, Section 10.16.

8.1.3.5 PGI-S

The PGI-S is a single-state, self-report measure that rates a study participant's severity of a specific condition. The PGI-S is a 5-point scale depicting a study participant's rating of overall symptoms ("none," "mild," "moderate," "severe," or "very severe").

The PGI-S sample questionnaire is available in Appendix 17, Section 10.17.

8.1.3.6 PGI-C

The PGI-C is a single-state, self-report measure that reflects a study participant's belief about the efficacy of treatment for a specific condition. The PGI-C is a 7-point scale depicting a study participant's rating of overall improvement ("very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse").

The PGI-C sample questionnaire is available in Appendix 18, Section 10.18.

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

A full physical examination will include, at a minimum, assessments of general appearance; ear, nose, and throat; eyes, hair, and skin; assessments of the cardiovascular, respiratory, GI, neurological, musculoskeletal, and hepatic systems; and mental status.

A short physical examination will include, at a minimum, assessments of general appearance; ear, nose, and throat; skin, respiratory, GI, and neurological systems.

For full and short 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.

8.2.2 Vital signs

Oral, tympanic, or axillary temperature, pulse rate, and BP will be assessed.

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.

All vital signs should be taken before any blood sampling.

On dosing days, for the first 2 weeks, vital signs will be measured prior to IMP administration, at the end of the infusion, and 4 hours after the end of the infusion. For the next 3 visits, vital signs will be measured prior to IMP administration, at the end of infusion, and 1 hour after the end of infusion. From Week 6, vital signs will be measured prior to IMP administration, at the end of the infusion, and 15 minutes after the end of infusion. At nondosing visits, vital signs need only to be taken once during the visit. In case of dose increase, vital signs will be measured prior to IMP administration, at the end of infusion, and 1 hour after the end of infusion for the next 2 infusions. In case of an untoward event, additional vital signs (unscheduled assessment) should be taken at the discretion of the investigator and post-observation time can be extended. These recommendations are applicable for dosing at site and at home.

8.2.3 Electrocardiograms

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

Central reading of ECGs will be performed but for the assessment of the ECG during the visit, the assessment of the investigator or designee will be used to determine eligibility and continuation in the study.

All ECG recordings should be taken prior to blood collection for assessment of laboratory parameters, with the study participant resting in the supine position for at least 5 minutes before the recording.

8.2.4 Clinical safety laboratory assessments

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

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

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

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

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

If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Assessment and management of TB and TB risk factors

Precautions are being taken within this protocol to monitor the risk of TB infection in this study (see Section 5.2, Exclusion Criterion 9). Any presumptive diagnosis or the diagnosis of a TB infection is a reportable event. Assessment and management of TB and TB risk factors should follow local or national guidelines.

8.2.5.1 Tuberculosis assessment

Monitoring for TB during the study

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

Confirmed LTB, active TB, and NTMBI must be reported to UCB immediately regardless of seriousness using the SAE Report Form. Additional information received by the investigator should be provided within 24 hours of awareness.

Once withdrawn from study treatment, study participants should return for the EW and complete all EOS assessments.

TB signs and symptoms questionnaire

Study participants will be evaluated both for signs and symptoms of latent or active TB infection and for risk factors for exposure to TB using the TB questionnaire (Appendix 19, Section 10.19) as indicated in the Schedule of Activities (Section 1.3).

The TB questionnaire should be completed accurately and filed as a critical source document. The questionnaire will assist with the identification of participants who may require therapy for TB.

A "Yes" response to any of the questions in the TB questionnaire during the study may trigger further assessments to determine if the participant has either LTB infection or active TB infection. As an example, a participant who answers "Yes" at Screening to the question [redacted] should not be allowed into the study pending further assessments per local/national guidelines.

8.2.5.2 Tuberculosis management

In line with the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) guidelines, UCB has adopted the following definitions for latent TB, active TB and non-tuberculosis mycobacterium infection for the purposes of its clinical trials.

Latent TB

Latent TB infection is defined an infection by *Mycobacterium tuberculosis* with:

- a positive IGRA test or 2 indeterminate IGRA tests AND
- a chest x-ray [or other imaging]) negative for TB infection AND
- the absence of signs, symptoms (eg, evidence of organ specific involvement, or physical findings) suggestive of TB infection.

Active TB and nontuberculous mycobacterium infection

A clinically verified case of TB meets the following criteria:

- a positive Tuberculin Skin Test (TST) or positive IGRA for *Mycobacterium tuberculosis*
- other signs and symptoms compatible with TB (eg, abnormal chest radiograph, abnormal chest computerized axial tomography scan or other chest imaging study, or other clinical evidence of active disease)

Nontuberculous mycobacterium infection (NTMBI) is defined as a clinical infection caused by mycobacterial species other than those belonging to the *Mycobacterium tuberculosis* complex. Study participants who develop active TB or NTMB infection during the study must be withdrawn from the study. The participant must be permanently discontinued from IMP and the EW Visit must be scheduled as soon as possible, but no later than the next scheduled visit.

Participants should be encouraged to enter the SFU period, attend Visit 28, and keep the EOS Visit as specified by the protocol. Treatment for active TB or NTMB should be started immediately based on local guidelines.

Confirmed active TB is always considered an SAE. UCB's process requires that this must be captured on an SAE report form and provided to UCB in accordance with SAE reporting requirements. Follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves (Appendix 3, Section 10.3).

LTB infection, active TB, or other NTMB identified during study

During TP0003, study participants who develop evidence of LTB infection, active TB, or NTMB infection will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation. These study participants will not be permitted to enroll into TP0004. Study participants diagnosed with active TB or LTB infection should receive appropriate TB treatment or prophylaxis therapy. The study participant should be transferred to the care of their physician and managed according to the standard of care.

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study and compliant TB treatment shall be followed.

Follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of the start date of anti-TB treatment, including hematological and biochemical safety parameters, chest x-ray evolution data, and TB diagnostic procedures used to follow up and confirm recovery of TB.

8.2.6 Splenectomized study participants

For **Japan**-specific regulations, see Appendix 8, Section 10.8.

Study participants who have previously undergone a splenectomy will be included in the study provided they do not meet the protocol defined exclusion criteria (Section 5.2) in order to optimize protection against OPSI. Adequate vaccination for all splenectomized participants within 4 years prior to enrollment is preferred. Splenectomized study participants should be vaccinated against the encapsulated organisms such as *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* (as per local/or a national guidance, as applicable) as evidenced from personal immunization records. Study participants who are due to receive a booster, can be screened after they have received the required booster. However, if the next booster is due during the study, to avoid the treatment interruption, it can be given ahead of the 5-year schedule if needed, and prior to enrollment.

Splenectomized study participants without any prior vaccination against one or all of the above-mentioned bacteria and who are willing to participate in the study, will have to undergo a Prolonged Screening Period after signing the ICF. During this period, splenectomized study participants will receive the required vaccinations against the above-mentioned bacteria (see Table 1-3).

Splenectomized participants can be enrolled in the study if they have documentation of previous vaccination within the past 4 years *for S. Pneumoniae, H. influenzae and N. meningitidis* (as per local/national guidance) or have completed the required vaccinations during the Prolonged Screening Period.

Additionally, for the whole duration of the study, splenectomized participants will be required to carry a card indicating they have undergone splenectomy and may be at increased risk of infection particularly with encapsulated organisms. Splenectomized study participants should have a prophylactic antibiotic available or take already an antibiotic as per local guidance.

Antibody titers against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* in splenectomized study participants will be collected predose at W1 (Baseline), W3, W25 (EW Visit) and at the EOS Visit.

Antibody titers against tetanus will be collected in all participants at Baseline (Day1), W3 (predose), W25 (EW Visit), and EOS Visit.

8.3 Adverse events

The definitions of an AE or SAE can be found in Appendix 3, Section 10.3.

Adverse events will be reported by the study 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 study treatment or TP0003 (see Section 7).

In order to protect the blind, the events of hypogammaglobulinemia should not be captured as an AE in the eCRF.

8.3.1 Time period and frequency for collecting AE and SAE information

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

All SAEs will be recorded and reported to UCB or designee within 24 hours, as indicated in Appendix 3, Section 10.3. The investigator will submit any updated SAE data to UCB 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 IMP), 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 IMP 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 nonleading 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 nonserious AEs of special interest and AEs of special monitoring (AESM) (as defined in Sections 8.3.7 and Section 8.3.8, respectively), 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 provided 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 study participants and the safety of a IMP under clinical investigation are met.

UCB has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a IMP under clinical investigation. UCB will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions 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 UCB 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 3 months after dosing.

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

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

- The study participant should return for the EW visit and complete the SFU Period.

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

In case of confirmed pregnancy in TP0003, the study participant cannot enroll into TP0004.

8.3.6 Anticipated serious adverse events

The following anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure (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 serious adverse events for ITP population

Anemia	Hemorrhagic events
Fatigue	Thrombocytopenia

8.3.7 Adverse events of special interest

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

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

See Appendix 6, Section 10.6 for further information on liver safety monitoring.

8.3.8 Adverse events of special monitoring

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

- Severe headache
- Severe GI disorders (ie, diarrhea, abdominal pain, vomiting)
- Opportunistic infection
- Arterial and venous thrombotic and thromboembolic events

An AESM is not necessarily a serious adverse event unless one of the seriousness criteria defined in the Appendix 3 (Section 10.3) is met. All AESM will follow the SAE recording and reporting procedures as indicated in Appendix 3, Section 10.3.

In case of severe headache or serious headache (regardless of severity), the headache questionnaire (Appendix 20, Section 10.20) must be completed. The questionnaire should also be completed in case of moderate headache although moderate headache is not considered an AESM. Additional procedures for management of headaches are provided in Appendix 22, Section 10.22.

Procedures for the management of diarrhea are provided in Appendix 23, Section 10.23.

Although hypersensitivity reactions including infusion-related reactions and anaphylaxis are not classified as AESM, these AEs will be monitored by the investigators. If such an event is suspected it should be managed according the guidance provided in Appendix 24, Section 10.24. In case of suspected anaphylaxis, the Sampson's Criteria (Sampson et al, 2006) (Appendix 21, Section 10.21) should be completed. All hypersensitivity reactions will be recorded and reported as per the AE reporting procedure outlined in Appendix 3, Section 10.3.

8.3.9 Treatment-emergent adverse events

Treatment-emergent AEs are defined as AEs starting after the time of first IMP administration up to and including 8 weeks after the final dose.

8.3.10 COVID-19 vaccination

Coronavirus disease 2019 vaccines will be recorded on the concomitant medication eCRF page (Section 6.4.1). If an AE is considered related to COVID-19 vaccine, causality assessment should be entered on the AE eCRF (in the AE eCRF page, there is the possibility to assess causality to the IMP or to any concomitant medication). Note that in this case, the national recommendation for reporting an AE related to COVID-19 vaccines should be followed. If an AE is the result of an interaction of a COVID-19 vaccine with the IMP in the clinical study then the causal association should be for both IMP and COVID-19 vaccine. In case of a seriousness criteria, the Suspected Unexpected Serious Adverse Reaction 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 IMP so that investigators, clinical study participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

In addition, an unblinded IDMC will periodically review and monitor safety data from this study and advise UCB. Details are provided in the IDMC Charter.

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

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

8.5 Treatment of overdose

For this study, any dose increase of 10% or greater than the assigned dose for each administered dose of IMP will be considered an overdose, irrespective of the weight tier band. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess IMP 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 and laboratory abnormalities for at least 5 days.
3. Obtain a plasma sample for PK analysis 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 antidrug antibodies

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 in the laboratory manual for this study. 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 during or after the study.

Participant confidentiality will be maintained. At visits during which only plasma samples for the determination of concentration of rozanolixizumab will be taken, 1 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 UCB 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 Pharmacodynamics

Venous blood samples will be collected at time points specified in the Schedule of Activities (Section 1.3) for measurement of:

- Serum IgG and IgG subclasses concentrations
- Serum IgA, IgE, and IgM concentrations
- Serum ITP-specific autoantibodies

For all PD assessments, blood samples will be collected predose at the Baseline Visit (Day 1). Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Results of the ITP-specific autoantibodies analyses will not be outlined in the Clinical Study Report for this study.

8.8 Genetics

8.8.1 Pharmacogenomics

Blood sample for DNA and RNA biomarkers will be collected as specified in the Schedule of Activities (Section 1.3) from study participants who have consented to participate in the pharmacogenomics sub-study. This sampling is optional for study participants and requires a separate informed consent. A decision not to consent does not exclude the study participant from the study.

If not used immediately, these samples will be stored at -80°C for up to 20 years for later exploratory analyses. Any exploratory biomarker or genomic analysis will only ever be related to the exploration of the cause, progression, and appropriate treatment of ITP.

The nature and format of these tentative additional analyses will be determined at a later time. Details on the collection, storage, preparation, and shipping of samples will be presented in the laboratory manual provided separately. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Detailed information on sample analyses will be provided in a bioanalytical report. Results of the DNA and RNA biomarker analyses will not be outlined in the Clinical Study Report for this study.

8.8.2 Immunology

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

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

Serum complements (C3, C4) and plasma complements (C3a, C5a) should be taken predose at Baseline (Day 1) and at Week 25 for all study participants. In participants who experience an infusion reaction or hypersensitivity reaction at the site, samples should also be taken 2 hours postevent and 4 hours postevent or otherwise as soon as possible but prior to the next dosing, as specified in the Schedule of Activities (Section 1.3).

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

8.9 Exploratory biomarkers

Collection of samples for exploratory biomarker research is also part of this study.

Blood samples for biomarker research are required and will be collected from all study participants in this study. Exploratory biomarker samples should be taken predose at Baseline (Day 1) and Week 25 for all study participants. In study participants who experience severe and/or serious headaches or severe and/or serious GI disorders (ie, abdominal pain, diarrhea, vomiting), samples should also be taken 4 hours postevent, or otherwise as soon as possible but prior to the next dosing, as specified in the Schedule of Activities (Section 1.3).

Protein and metabolites biomarkers such as but not limited to albumin, B-cell activating factor, and Circulating Immune Complexes may be measured to assess the effect of rozanolixizumab on exploratory biomarkers, and explore the relationship between protein, and metabolite biomarkers and cause, progression, and appropriate treatment of ITP.

If not used immediately, these samples will be stored at -80°C for up to 20 years for later exploratory analyses. Any exploratory biomarker will only ever be related to the exploration of cause, progression, and appropriate treatment of ITP. They may also be used to develop tests/assays including diagnostic tests related to rozanolixizumab and/or FcRn inhibitor and ITP.

The nature and format of these tentative additional analyses will be determined at a later time. Details on the collection, storage, preparation, and shipping of samples will be presented in the

laboratory manual provided separately. Detailed information on sample analyses will be provided in a bioanalytical report.

8.10 Medical resource utilization and health economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the SAP.

9.1 Definition of analysis sets

- Enrolled Set: All study participants who have signed the informed consent.
- Randomized Set (RS): All enrolled study participants who were randomized. This is equivalent to the Intent-to-Treat Set.
- Safety Set (SS): All randomized study participants who received at least one dose of IMP (partial or full). Analysis of this set will be according to the treatment the participants actually received and will be used for the demographic and safety analyses.

  The analysis of the PD (excluding total IgG, and IgG subclasses) and immunologic variables will be performed on the SS. Selected outputs may be repeated for the PD Per-Protocol Set (PD-PPS). Further details will be provided in the SAP.
- Full Analysis Set (FAS): Consists of all study participants randomized who have received at least one complete sc infusion of IMP, have a valid Baseline, and at least 1 valid post-Baseline platelet count measurement during Weeks 13-25.
- Pharmacodynamic Per-Protocol Set (PD-PPS): A subset of the SS, consisting of those study participants who had no important protocol deviations potentially affecting the serum concentration of total IgG, as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a participant from the PD-PPS but may lead to exclusion of specific data.
- Pharmacokinetic Per-Protocol Set (PK-PPS): A subset of the SS, consisting of those study participants who received at least 1 dose, had at least 1 valid PK measurement, and no important protocol deviations affecting the PK variable, as confirmed during a pre-analysis review of the data prior to database lock.

The RS will be the primary analysis set for efficacy analyses.

The PD-PPS will be used for the analysis of the total IgG, and IgG subclasses.

9.2 General statistical considerations

All analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, USA). Continuous variables will be summarized by visit (where applicable) with the statistics including the number of participants (n), mean, standard deviation (SD), median, minimum, and maximum.

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

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

Data handling conventions for data affected by COVID-19 will be detailed fully in the SAP.

9.3 Planned efficacy/outcome analyses

9.3.1 Analysis of the primary efficacy/primary endpoint

The primary efficacy variable is the durable clinically meaningful platelet response $\geq 50 \times 10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (platelet count recorded at Week 14 to Week 25 corresponding to the response achieved following dosing at Week 13 to Week 24). Missing platelet count at any visit will be considered "worst case" and set to zero ("no platelet response") for that specific visit.

The primary and supportive analyses for the durable platelet count endpoint are detailed in Table 9-1. The main intercurrent events are rescue therapy prior to Week 25 and treatment discontinuation (withdrawal from study) due to TEAEs.

Confirmatory testing of single hypotheses is based on a closed-testing procedure.

The primary analysis of the study will use a Stratified Cochran-Mantel-Haenszel test statistic.

Table 9-1: Estimands for the primary endpoint

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES[a]**	**PLS[b] (Analysis)**
Primary Objective: To demonstrate clinical efficacy of rozanolixizumab as a maintenance treatment in participants with primary ITP					
Platelet Count	Primary/MCP	Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to Week 25)	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo.	A composite strategy will be used, in which participants who require rescue therapy, who experience any TEAEs leading to treatment discontinuation, discontinue prior to receiving IMP, or do not have a post-treatment assessment will be considered as nonresponders.	To test of the null hypothesis (H_0) in participants who have achieved a durable platelet count that the true common odds ratio between treatment arms is 1 (odds ratio = 1) vs the alternative hypothesis (H_a) that the odds ratio is less than 1, a Cochran-Mantel-Haenszel model adjusted for the stratification factors, namely baseline degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L), history of splenectomy (yes or no).
Platelet Count	Sensitivity	Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to Week 25)	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo.	A composite strategy: participants who experience any TEAEs leading to treatment discontinuation will be considered as nonresponders. All other cases included but not limited to participants who discontinue prior to receiving IMP, or do not have a post-treatment assessment or participants who require rescue therapy the response variable will be imputed using a fully conditional specification method.	To test of the null hypothesis (H_0) in participants who have achieved a durable platelet count that the true common odds ratio between treatment arms is 1 (odds ratio = 1) vs the alternative hypothesis (H_a) that the odds ratio is less than 1, a Cochran-Mantel-Haenszel model adjusted for the stratification factors, namely baseline degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L), history of splenectomy (yes or no).

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES[a]**	**PLS[b] (Analysis)**
Platelet Count	Supplemental	Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to Week 25)	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo.	A composite strategy, in which participants who require rescue therapy, who experience any TEAEs leading to treatment discontinuation, discontinue prior to receiving IMP, or do not have a post-treatment assessment will be considered as nonresponders.	Difference in proportions of participants between treatment arms who achieved a durable platelet count, analyzed using Fisher's Exact Test.
Platelet Count	Sensitivity	Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to Week 25)	FAS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo	Composite strategy as described above with the addition of excluding participants who have not received a sufficient sc infusion. Participants who are not part of the FAS population will not be included in the analysis.	To test of the null hypothesis (H_0) in participants who have achieved a durable platelet count of $\geq 50\times10^9$/L for at least 8 weeks out of the last 12 weeks (Week 13 to Week 25) that the true common odds ratio between treatment arms is 1 (odds ratio = 1) vs the alternative hypothesis (H_a) that the odds ratio is less than 1, a logistic regression model adjusted for the stratification factors, namely baseline degree of thrombocytopenia (platelet count $<$ or $\geq 15\times10^9$/L), history of splenectomy (yes or no).

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES[a]**	**PLS[b] (Analysis)**
Platelet Count	Sensitivity	Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to Week 25)	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo	Composite strategy as described for the primary analysis.	To test of the null hypothesis (H_0) in participants who have achieved a durable clinically meaningful platelet response of $\geq 50\times10^9$/L for at least 8 out of 12 weeks during the last 12 weeks (Week 13 to Week 25) that the true common odds ratio between treatment arms is 1 (odds ratio = 1) vs the alternative hypothesis (H_a) that the odds ratio is less than 1, a logistic regression model adjusted for the stratification factors, namely baseline degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L), history of splenectomy (yes or no).

H_0=null hypothesis; H_a=alternative hypothesis; IES=Intercurrent event(s) strategy; IMP=investigational medicinal product; FAS=Full Analysis Set; MCP=Multiple comparisons procedure; FWER=family-wise error-rate; PLS=Population-level summary; RS=Randomized Set; TEAE=treatment-emergent adverse event

MCP: FWER controlled for hypothesis testing of selected endpoints as specified.

[a] The potential impact of any temporary treatment discontinuations (as detailed in Section 7.1.4) on the estimand strategy will be explored and detailed in the Statistical Analysis Plan.

[b] All estimand attributes explicitly identified for primary/secondary and selected key estimands only.

9.3.2 Analysis of the secondary efficacy endpoints

The analyses for secondary endpoints are detailed in Table 9-2. The main intercurrent events are the use of rescue therapy prior to Week 25 and treatment discontinuation (or withdrawal from study) due to treatment emergent AEs.

In addition, all continuous secondary efficacy variables will be listed and summarized descriptively by treatment group and week. Descriptive statistics will be generated for the observed values and the change from Baseline. For the binary variables, frequency counts and percentages will be produced.

A sequential hierarchical test procedure will be applied to protect the overall significance level for the multiplicity of endpoints. The predefined order of formal hypotheses testing for the secondary endpoints will be performed in the following sequence:

- Cumulative number of weeks with Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L over the 24-week treatment period
- Time to first Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L: time from starting treatment to achievement of first response of $\geq 50\times10^9$/L
- Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L by Day 8
- Response defined as platelet count $\geq 30\times10^9$/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit
- Time to first rescue therapy
- Change from Baseline to Week 25 in ITP-PAQ Symptoms Score

Table 9-2: Estimands for secondary endpoints

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Population**	**IES[a]**	**PLS[b] (Analysis)**
Secondary Objective: To assess the safety and tolerability of rozanolixizumab					
Platelet Count	Secondary/ MCP	Cumulative number of weeks with Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L over the 24-week treatment period	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo.	A composite endpoint will be used where, in the case rescue therapy are taken, only the platelet data up to the start date of rescue therapy will be utilized for the statistical analysis. Participants who take rescue therapy or who are withdrawn owing to TEAEs are defined as having a loss of durable platelet response at the time of the event occurring.	Cumulative number of weeks with clinically meaningful platelet response will be analyzed using an analysis of covariance with fixed terms for treatment, splenectomy, degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L). Estimated means and 95% CI will be presented for each treatment group.
Platelet Count	Secondary/ MCP	Time to first Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L: time from starting treatment to achievement of first response of $\geq 50\times10^9$/L	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo.	A composite strategy will be used where, in the case rescue therapy are taken, only the platelet data up to the start date of rescue therapy will be utilized for the statistical analysis. Participants who take rescue therapy or who are withdrawn due to TEAEs are defined as having a loss of clinically meaningful platelet response and will be censored at the time of the event.	Time to first Clinically Meaningful Response will be analyzed using a stratified Log Rank Test with fixed terms for treatment, splenectomy, degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L). Estimated hazard ratios and 95% CIs will be presented. The time to first Clinically Meaningful Response will

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Population**	**IES[a]**	**PLS[b] (Analysis)**
					be presented graphically using a Kaplan-Meier curve.
Platelet Count	Secondary/ MCP	Clinically Meaningful Response by Day 8, defined as: platelet count $\geq 50\times10^9$/L	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo	A composite strategy will be used for rescue therapy, ie, participants who require rescue therapy will be considered a non-responder. The same strategy will be used for TEAEs leading to treatment discontinuation, and participants who discontinue prior to receiving IMP, do not have a valid Baseline assessment or do not have a post-treatment assessment.	To test of the null hypothesis (H_0) in participants who have achieved a Clinically Meaningful Response by Day 8, defined as: Platelet count $\geq 50\times10^9$/L that the true common odds ratio between treatment arms is 1 (odds ratio = 1) vs the alternative hypothesis (H_a) that the odds ratio is less than 1, a Cochran-Mantel Haenszel model adjusted for the stratification factors, namely baseline degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L), history of splenectomy (yes or no).
Platelet Count	Secondary/ MCP	Response defined as platelet count $\geq 30\times10^9$/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate	RS who were randomized to rozanolixizumab weekly dosing	A composite strategy as described for Clinically Meaningful Response by Day 8 will be used.	To test of the null hypothesis (H_0) in participants who have achieved a Response by Day 8, defined as: Platelet count $\geq 30\times10^9$/L and at least a 2-fold increase of the Baseline count, confirmed

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Population**	**IES[a]**	**PLS[b] (Analysis)**
		occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding.	compared against those who received placebo		on at least 2 separate occasions at two nominal visits at least 7 days apart, and absence of bleeding, that the true common odds ratio between treatment arms is 1 (odds ratio = 1) vs the alternative hypothesis (H_a) that the odds ratio is less than 1, a Cochran-Mantel Haenszel model adjusted for the stratification factors, namely baseline degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L), history of splenectomy (yes or no).
Platelet Count	Sensitivity	Response defined as platelet count $\geq 30\times10^9$/L and at least a 2-fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding.	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo	A composite strategy as described for Clinically Meaningful Response by Day 8 will be used.	Difference in the proportion of participants between treatment arms who have achieved a durable platelet count analyzed using logistic regression model adjusting for the covariates treatment, splenectomy, and degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L).

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Population**	**IES[a]**	**PLS[b] (Analysis)**
Rescue therapy	Secondary	Time to first rescue therapy.	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo.	A composite strategy will be used where, in the case rescue therapy are taken, only the platelet data up to the start date of rescue therapy will be utilized for the statistical analysis. Participants who take rescue therapy or who are withdrawn due to TEAEs are defined as having a loss of clinically meaningful platelet response and will be censored at the time of the event.	Time to first rescue therapy use will be analyzed using a stratified Log Rank Test model with fixed terms for treatment, splenectomy, degree of thrombocytopenia (platelet count < or ≥ 15×10^9/L). Estimated hazard ratios and 95% CIs will be presented. The time to first rescue therapy use will be presented graphically using a Kaplan-Meier curve.

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Population**	**IES[a]**	**PLS[b] (Analysis)**
PRO	Secondary/ MCP	Change from Baseline to Week 25 in ITP-PAQ Symptom score.	RS who were randomized to rozanolixizumab weekly dosing compared against those who received placebo.	A hypothetical strategy will be used for rescue therapy intake: ITP-PAQ Symptom scores after rescue medication will not be included in the estimation of the repeated measurement mixed model.	Change in ITP-PAQ from Baseline to Week 25 will be estimated from a generalized linear model including treatment and visit will be included in the model, adjusting for the covariates splenectomy, degree of thrombocytopenia (platelet count < or $\geq 15\times10^9$/L) and Baseline ITP-PAQ Symptoms score. The difference between treatment arms will be compared using model-based estimates of mean ITP-PAQ Symptom score in each arm at Week 25.

CI=confidence interval; H_0=null hypothesis; H_a=alternative hypothesis; IES=Intercurrent event(s) strategy; IMP=investigational medicinal product; ITP-PAQ=primary Immune Thrombocytopenia Patient Assessment Questionnaire; FWER=family-wise error-rate; MCP=Multiple comparisons procedure; PLS=Population-level summary; PRO=patient reported outcome; RS=Randomized Set; TEAE=treatment emergent adverse event

MCP: FWER controlled for hypothesis testing of selected endpoints as specified (to be determined).

[a] The potential impact of any temporary treatment discontinuations (as detailed in Section 7.1.4) on the estimand strategy will be explored and detailed in the Statistical Analysis Plan.

[b] All estimand attributes explicitly identified for primary/secondary and selected key estimands only.

9.3.3 Other efficacy/other outcome analyses

9.3.3.1 Analysis of pharmacokinetic endpoint

The PK-PPS dataset will be used. Rozanolixizumab plasma concentration data will be listed by study participant and actual time. A statistical summary of rozanolixizumab plasma concentrations will be reported by scheduled time point overall and by body weight tier, stratified by dose regimen. Further details on summaries for dose modifications will be provided in the corresponding SAP. Summaries by geographical region may be performed. The number of available observations, mean, median, SD, minimum, maximum, geometric mean (and associated 95% CI), and geometric coefficient of variation (assuming log normally distributed data) will be calculated. Values below the LLOQ will be reported as LLOQ/2 for calculation of descriptive statistics. Descriptive statistics of concentrations will be calculated if at least two-thirds of the individual data points are quantifiable (≥LLOQ).

Individual concentrations of rozanolixizumab may also be displayed graphically as spaghetti plots stratified by body weight tier (ie, changing color of line and type of data points when dose regimen changes, if down-titration was performed). Summaries by geographical region may be performed. Similarly individual plots will be performed where the potential change in dose will be display graphically and ADA, PK, PD and/or platelets will be evaluated and displayed.

Further details will be provided in the SAP.

If data merit, PK data may be included in a population PK analysis, further details would be provided in a separate Data Analysis Plan and reported separately.

9.3.3.2 Antidrug antibodies analyses

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 MRD). For anti-rozanolixizumab antibody positive samples (or subset of), further characterization for neutralizing ADA potential in vitro will be performed, and results will be presented in a listing. Full details will be covered in the SAP.

The impact of ADA on PK, PD, and safety will be evaluated.

Further details will be provided in the SAP.

9.3.3.3 Analysis of pharmacodynamic endpoints

For total IgG, the absolute serum IgG and change from Baseline on serum IgG with time will be summarized by dose regimen in the Adaptation Period and the Maintenance Period.

Spaghetti plots of the % change from Baseline and absolute IgG levels will be displayed, stratification by body weight tiers may be done, as well as by dose regimen during the Adaptation and Maintenance Dose Period (ie, changing color of lines in graph by dose regimen administered).

If data merits, IgG data will be included in a population pharmacokinetic/pharmacodynamic analysis and link to the platelet outcome, further details would be provided in a separate data analysis plan (DAP) and reported separately.

9.4 Planned safety and other analyses

9.4.1 Safety analyses

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). Data will be further presented by randomized dosing regimen. The data will be displayed as number of participants experiencing the TEAE, percentage of participants, and number of TEAEs.

Laboratory evaluations and vital signs as well as ECG data will be analyzed over time. All safety analyses will be based on the SS, consisting of all participants who receive at least 1 dose of IMP.

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 the review of important protocol deviations and update (if necessary) the important protocol deviation specification and discuss exclusion of participants from analysis populations. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meetings. Through this ongoing data cleaning and evaluation process, all decisions regarding important protocol deviations and exclusions from analysis populations are made on an ongoing basis.

9.6 Handling of dropouts or missing data

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

If individual platelet visit data is missing it will be set to zero; participants who are lost to follow-up will be imputed as nonresponders.

It is not anticipated that there will be missing data, due to the adoption of the responder endpoint definition, where study participants who have not met the threshold for clinically meaningful response will be imputed as nonresponders for the analysis.

9.7 Data monitoring

An external IDMC will be established to review the safety data at predefined intervals and ad hoc as needed, should emerging safety concerns arise during the study. The IDMC will have the possibility to unblind the data. Details of the IDMC composition, processes, and responsibilities will be documented in the IDMC charter. One IDMC is planned for both pivotal studies (TP0003 and TP0006), where the safety data will be initially presented unpooled, ie, data from each study

will be reviewed separately. Key safety data may be pooled at the discretion of the IDMC for protection of all study participants if warranted.

The IDMC will consist of members independent from UCB. Study enrollment will not be halted during planned IDMC review of the safety and efficacy data.

9.7.1 Early stopping for efficacy

Not applicable.

9.7.2 Early stopping for futility

Not applicable.

9.8 Determination of sample size

The observed response rates from Kuter et al (2008) in splenectomized participants were 38% (16/42) on active and 0% (0/21) on placebo. In non-splenectomized participants the rates were 61% (25/41) and 5% (1/21), respectively.

Using the true response rate of 0.45 versus 0.05, a sample size of 60 participants randomized in a 2:1 ratio (ie, n=40 on rozanolixizumab and n=20 on placebo) receiving weekly infusions will provide >90% power to detect a statistically significant difference between treatment groups using Fisher's Exact Test at an alpha level of 0.025 (1-sided). By definition participants who dropout of the study are determined as nonresponders and are incorporated in the overall response rate. If the number of dropouts is greater than anticipated by 10%, the impact on the rozanalixizumab response rate would mean that it would drop to a response rate of 0.4. In such cases, the study would still achieve >80% power if the overall response rate on placebo remains at 0.05.

If the response rate on placebo was 0.1 rather than the anticipated 0.05, the rozanolixizumab rate would need to be >0.45 to achieve 80% and >0.5 to achieve 90% power. Table 9-3 provides power estimates for a fixed study design of n=60 participants in a 2:1 randomization ratio.

Table 9-3: Expected sample size for TP0003

Scenario	Placebo Response Rate of 0.05			Placebo Response Rate of 0.10		
	Rozimab	Placebo	Power[a]	Rozimab	Placebo	Power[a]
1	0.30	0.05	56%	0.30	0.10	32%
2	0.35	0.05	73%	0.35	0.10	48%
3	0.40	0.05	85%	0.40	0.10	63%
4	0.45	0.05	93%	0.45	0.10	77%
5	0.50	0.05	97%	0.50	0.10	87%
6	0.55	0.05	98%	0.55	0.10	93%

Rozimab= rozanolixizumab

[a] Power for a Parallel Group Design with N=60 in a 2:1 randomization test computed with Fisher's exact test using NQuery Advisor 7.0.

The power of the study maybe increased by including the platelet count data from the participants who received bi-weekly placebo infusions in the assessment of the rozanolixizumab treatment effect. For instance, if 10 participants received bi-weekly infusions on the placebo arm, the overall sample size would increase to n=70 (ie, n=40 on rozanolixizumab and n=30 on placebo), and 90% power would be achieved for rozanolixizumab response rates of >0.35 and >0.45 if the true placebo response rate was 0.05 and 0.10 respectively.

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 for Harmonisation-Good Clinical Practice (ICH-GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, ICF, IB, 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

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

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

Prior to participation in the study, the ICF should be signed and personally dated by the study participant, and by the person who conducted the informed consent discussion (investigator or designee) at the site. For **Japan**-specific regulations, see Appendix 8, Section 10.8. The study participant must receive a copy of the signed and dated ICF. 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 ICF is amended during the study, the investigator (or UCB, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF 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 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 ICF. 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 external IDMC will be established to mainly review the safety data at predefined intervals and ad hoc as needed, should emerging safety concerns arise during the study. The IDMC will have the possibility to unblind the data. Details of the IDMC composition, processes, and responsibilities will be documented in the IDMC charter.

10.1.6 Data quality assurance

All participant data relating to the study will be recorded in the eCRF. The investigator is responsible for verifying that data entries are accurate and correct by 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, complete, and verifiable 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 are to be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's trial master file.

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.

10.1.6.1 Electronic Case Report Form completion

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.6.2 Apps

Not applicable.

10.1.7 Source documents

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

The following data will be recorded directly in the eCRF and will not appear in a separate source document as defined above.

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).

10.1.8 Study and site closure

The UCB 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 IMP development.

10.1.9 Publication policy

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

UCB will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, UCB 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 Table 10-1 will be performed by the central laboratory, with the exception of platelet count assessments.

- With the exception of platelet counts, local laboratory results are only required in the event that the central laboratory results are not available in time for either IMP 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, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1: Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count (local laboratory) [a]	Red blood cell (RBC) Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH)		White blood cell (WBC) Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count			
	Hemoglobin			
	Hematocrit			
Coagulation	International Normalized Ratio (INR) [d]	Activated partial thromboplastin time (aPTT) [e]		Fibrinogen [e]
Clinical Chemistry [f]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting state preferred)	Calcium	Alkaline phosphatase	C-reactive protein (CRP)
	Immunoglobulins [g]	Albumin	Low-density lipoprotein (LDL)	

Laboratory Assessments	Parameters			
			High-density lipoprotein (HDL) Total cholesterol Triglycerides	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) [h] • Serology (human immunodeficiency [HIV] antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • All study-required laboratory assessments will be performed by a central laboratory except the platelet count which is done by local laboratory. • The results of each test must be entered into the electronic Case Report Form (eCRF).			

[a] Platelet count testing will be performed by a local laboratory. Results will be unblinded to the investigator, site, and study participant (see Section 6.2.1.1).
[b] International Normalized Ratio (INR) to be done only at Screening (Visit 1) and for PDILI.
[c] Activated partial thromboplastin time (aPTT) and Fibrinogen will be done at all visits which require safety laboratory assessments.
[d] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6, Section 10.6. All events of ALT ≥3x upper limit of normal (ULN) and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as a serious adverse event (SAE) (excluding studies of hepatic impairment or cirrhosis).
[e] Includes total IgG, IgG subclasses, IgA, IgM, and IgE. Results of the IgG testing including the vaccination specific titers will be blinded to the investigator, site, and sponsor for post baseline results.
[f] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or Independent Review Board/Independent Ethics Committee.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

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

10.3.1 Definition of AE

Adverse event (AE) Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of IMP, whether or not considered related to the IMP. • 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 IMP.

Events <u>Meeting</u> 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 IMP 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 IMP or a concomitant medication. Overdose per se will not be reported as an AE/serious 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.

10.3.2 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, influenzae, 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.

10.3.3 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 eCRF.
- 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 eCRF 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 IMP 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 IMP 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 makes 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 health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, the event is otherwise explained, 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 eCRF.
- The investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

10.3.4 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 "SAE Reporting to UCB via Paper Case Report Form [CRF]" below).
- 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 "SAE Reporting to UCB via Paper CRF" below).
- 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 (>40mIU/mL) 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

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the Treatment Period and for at least 3 months after the final dose of study treatment:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the final dose of study medication.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the Treatment Period and for at least 3 months after the final dose of study treatment.

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 Table 10-2.

Table 10-2: 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 progesterone-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progesterone only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent
Implantable progesterone only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner Vasectomy is a highly effective contraception method provided that the vasectomized 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. For **Japan**-specific regulations, see Appendix 8, Section 10.8
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.

[a] In case of newly started contraception pills/IUDs, the primary investigator should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as when these newly started methods would become effective.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy testing

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

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 IMP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within one working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

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 one 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 IMP 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

Use and Analysis of DNA

- Genetic variation may impact a participant's response to IMP, susceptibility to, and severity and progression of disease. Variable response to IMP 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 deoxyribonucleic acid (DNA) analysis from consenting participants.
- DNA samples will be used for research related to cause, progression, and appropriate treatment of ITP. They may also be used to develop tests/assays including diagnostic tests related to rozanolixizumab and ITP. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to rozanolixizumab or IMPs of this class to understand ITP 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 DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on rozanolixizumab continues, but no longer than 20 years or other period as per local requirements.

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

Study treatment, including all concomitant medications and herbal supplements that are not medically necessary, should be discontinued immediately in study participants with suspected PDILI. These study participants must be assessed thoroughly and followed up closely during the Treatment Period for confirmation of PDILI. Because study participants in TP0003 will be provided the chance to enroll in the OLE study TP0004 upon completion of TP0003, if PDILI is confirmed, these study participants must not be enrolled in the OLE study TP0004.

Investigators should attempt to obtain information on study participants to complete the final evaluation.

Study participants with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study participant withdrawal (if applicable, eg, withdrawal of consent), must be recorded in the source documents. The eCRF must document the primary reason for study withdrawal in such a case.

A specific monitoring plan must be agreed between the UCB study physician and the investigator for study participants who have ALT >5 ULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values).

Phase 3-4 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology (Table 10-3).

Phase 3-4 liver chemistry increased monitoring criteria with continued IMP are designed to assure participant safety and to evaluate liver event etiology (Table 10-4).

Table 10-3: Phase 3-4 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN 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 ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN 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 IMP. • Report the event to UCB within **24 hours.** • Complete the liver event electronic Case Report Form (eCRF), 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 IMP unless allowed per protocol and UCB approval is granted. If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue IMP and continue participant in the study for any protocol specified follow up assessments. Consider the need for a toxicology screening. **MONITORING:** **<u>For bilirubin or INR criteria:</u>**	• Viral hepatitis serology [d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen), quantitative hepatitis B deoxyribonucleic acid (DNA) and hepatitis delta antibody [e] • Obtain blood sample for pharmacokinetic (PK) analysis as soon as feasible after the most recent dose [f] • 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, or hypersensitivity, on the adverse event (AE) report form

• 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. **For all other criteria** • 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.	• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF • Exclude pregnancy **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins [g] • Serum acetaminophen concentration and serum acetaminophen adduct assay (where available) 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 Imaging and/or Liver Biopsy eCRFs

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue IMP 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 immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[e] If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].

[f] Pharmacokinetic 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 IMP prior to the PK blood sample draw on the eCRF. 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 Pharmacy Manual.

[g] These tests should be obtained when IgG levels are approaching normal levels because IMP may interfere with IgG levels and interpretation.

Table 10-4: Phase 3-4 liver chemistry increased monitoring criteria with continued IMP

Liver Chemistry Increased Monitoring Criteria	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR 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 IMP • 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 ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • 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.

REFERENCES

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

10.7 Appendix 7: Medical device incidents – definition and procedures for recording, evaluating, follow up, and reporting

Not applicable.

10.8 Appendix 8: Country-specific requirements

Moldova

Specific requirements for study participants in Moldova include a description of vaccination for splenectomized study participants who have not received vaccinations according to current medical practice and are being considered for the study. Vaccinations in splenectomized patients are not routinely performed in Moldova, and the patients likely carry an undeterminable increased risk for infections. Hence, study participants who are being considered for the study will be administered vaccines accordingly to the schedule as per Table 1-3.

Poland

The Polish Health Authority's and Clinical Trial Facilitation Group have made recommendations related to contraception and pregnancy testing in a clinical study with IMP where the human data for exposure at pregnancy and nonclinical reproductive toxicology data are not available. As a mitigation measure, pregnancy testing is to be implemented monthly up to 2 months after the final dose of IMP. A urine pregnancy test is added at 4 weeks after final IMP administration, at Week 27 (Visit 28) for sites located in Poland, thus it meets the above requirement. Based on the short half-life of IMP and because genotoxicity is not a class effect of the monoclonal antibodies, it is considered safe to reduce the duration of post-IMP administration requirement on contraception for female study participants of childbearing potential from 3 months to 2 months, with implementation of monthly pregnancy testing during this period.

Romania

Previously, in TP0001, the Romanian authorities introduced the following specific requirement for Romania: change in duration for the use of permitted oral corticosteroids (prednisolone) from a stable dose of [redacted] prior to the Baseline Visit (Visit 2). It is recommended for sites located in Romania, that oral corticosteroids (prednisone) need to be stable for [redacted] as mentioned in Table 6-2 of this protocol.

Japan

Specific requirements for study participants in Japan include:

- In reference to Section 5.1, inclusion criteria 1 has been modified as shown below:

1a. Study participant must be ≥18 years of age at the time of the Screening Visit. **If a participant is <20 years of age, written informed consent will be obtained from both the participant and the legal representative.**

- In reference to Section 5.2, exclusion criteria 7 has been modified as shown below:

7a. Study participant has evidence of a secondary cause of immune thrombocytopenia (**eg**, past medical history of **untreated *H. pylori* infection**, leukemia, lymphoma, common variable immunodeficiency, systemic lupus erythematosus, autoimmune thyroid disease) or participant has a multiple immune cytopenia, eg, Evan's syndrome.

- In reference to Section 5.2, exclusion criteria 20a has been modified as shown below:

20b. Splenectomized participant without adequate vaccination against *S. pneumoniae, N. meningitidis* and *H. influenzae***, if applicable per local guidance, and** as evidenced by:

- a lack of documented vaccination records per local guidance, OR

have not completed required vaccinations (*S. pneumoniae*, *H. influenzae*, and *N. meningitidis*) per Section 8.2.6 during the Prolonged Screening Period

Note: For splenectomized participants without any prior vaccination against one or all of the above-mentioned bacteria please refer to Section 8.2.6 of the protocol.

- In reference to Section 5.2, exclusion criteria 44 has been added:

44. Study participant has undergone a partial splenic artery embolization in the 6 months prior to Baseline Visit. Any study participant with evidence of functional asplenia should be managed clinically as a splenectomized participant (eg, vaccination, antibiotics prophylaxis) as per local guidance.

- A new section (Section 6.1 Medical Devices) was added in Protocol Amendment 1.2 and has now been updated to the following:

Applicable to Japan only

UCB will supply the study-sites with the Crono S-PID pump (manufactured by Cané S.r.L, Torino, Italy) and the Cleo 90 infusion set (manufactured by Smith's Medical ASD Inc, St Paul, MN, USA) for the subcutaneous infusion.

Both the Crono syringe driver and the Cleo 90 infusion set used for the purpose of sc infusions are regarded in Japan as investigational devices, that require adherence to specific reporting obligations (Appendix 8, Section 10.8). This reporting requirement is not applicable for approved devices for the purpose of sc infusions or other purposes in the course of this study, regardless if provided by the sponsor or not.

All adverse device effects (ADEs), serious adverse device effects (SADEs), and medical device deficiency (including malfunction use error, and inadequate labeling) of these investigational devices shall be documented and reported by the Investigator throughout the study (Appendix 8, Section 10.8) and appropriately managed by the Sponsor.

- In reference to Section 6.4.1, the use of medicinal cannabidiols and medicinal marijuana are prohibited by law.

- In reference to Section 8.2.6, additional wording has been included: "if applicable" and "as per local requirements".

Vaccination for splenectomized participant will be carried out in accordance with local guidance (Kashiwagi, 2019).

- In reference to Section 10.1.3 the following has been added:

In Japan, for all study participants <20 years of age, written informed consent will be obtained from both the participant and the legal representative.

- In reference to Section 10.4, Table 10-2 the following method has been added:

"(eg, proper use of condom in combination with spermicide)"

Furthermore, specific rules for repetition of an ADE and device deficiency should be followed by all study sites in Japan; *this requirement is not applicable for locally approved devices, regardless if provided by the sponsor or not*.

For ADEs and/or device deficiencies that are not related to the natural course of the disease under study, an increase in the intensity of the original ADE, and/or device deficiency should lead to the repetition of the original ADE and/or device deficiency with the following guidelines:

- The outcome date of the original ADE and/or device deficiency must be the same as the start date of the repeated ADE and/or device deficiency.
- The outcome of the original ADE and/or device deficiency must be recorded as "worsening."
- The verbatim term for the repeated ADE and/or device deficiency must be the same as the verbatim term for the original ADE and/or device deficiency so that the repeated ADE and/or device deficiency is obviously a worsening of the original.

As per local requirements in Japan, SAEs associated to an investigational device, and device deficiencies (eg, infusion pump product provided from sponsor) should be reported in accordance with the following.

This requirement is not applicable for approved devices used in the course of the study, regardless if provided by the sponsor or not.

Medical Device – Adverse events (ADEs, SAEs, and SADEs) and device deficiencies

Medical devices are being provided for use in this study for subcutaneous infusions. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

Adverse events will be reported according to the ISO 14155:2011, while recognizing and following requirements including reporting timelines specified in other specific laws, regulations, directives, standards and/or guidelines as appropriate and as required by the countries in which the clinical investigation is conducted.

NOTE: Events fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 (Section 10.3) of the protocol.

Time period for detecting medical device deficiencies

Medical device deficiency or malfunction of the device that results in a reportable event will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any deficiency at any time after a participant has been discharged from the study, and such event(s) is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

Follow-up of medical device deficiencies

Follow-up applies to all study participants, including those who discontinue study medication and/or the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

Prompt reporting of medical device deficiencies to sponsor

Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.

The Adverse Event and Device Deficiency Report Form will be sent to the sponsor by email. If email is unavailable, then fax should be utilized.

The sponsor will be the contact for the receipt of device deficiency reports.

Regulatory reporting requirements for medical device deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution) will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

Medical Device AEs (ADEs, UADEs, SAEs, SADEs, and USADEs) and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study.

Definition of AE and ADE

AE and ADE Definition
• An AE is any untoward medical occurrence, in a patient or clinical study participant, temporarily associated with the use of IMP, whether or not considered related to the IMP. 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 IMP. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

Definition of SAE, and SADE

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

An SAE is an AE that:
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 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 fulfils 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.
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Definition of Device Deficiency

Device Deficiency definition
• A device deficiency is an inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency 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/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of 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 AE/SAE/device deficiency 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. • For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency o A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence. The investigator should inform the sponsor for all reported device deficiencies.

Follow-up of AE/SAE/device deficiency
• 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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • 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, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • 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 this protocol.

Reporting of SADEs

SADE Reporting to UCB
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency using the paper form provided by the sponsor. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found in this protocol.

Reporting of AE and/or Device Deficiencies

AE and/or Device Deficiencies Reporting to UCB
NOTE: There are additional reporting obligations for medical device deficiencies that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any AE and/or device deficiencies must be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the definition of a device deficiency using the paper form provided by the Sponsor. • The sponsor shall review all device deficiencies and determine and document in writing whether they meet device reporting requirement. • Contacts for SAE reporting can be found in this protocol.

10.9 Appendix 9: Abbreviations and trademarks

ADA	antidrug antibodies
ADE	adverse device effect
ADL	Activities of Daily Living
AE	adverse event
AESM	adverse event of special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
app	application
AST	aspartate aminotransferase
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
COVID-19	coronavirus disease 2019
CPM	Clinical Project Manager
CRF	Case Report Form
CRO	contract research organization
DCP	Data Cleaning Plan
DD	device deficiency
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
EQ-5D-5L	European Quality of Life Health Status Questionnaire-5 Dimensions, 5 Levels
eqv	equivalent
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EW	early withdrawal
FAS	Full Analysis Set
FcRn	neonatal Fc receptor
FIH	first-in-human

FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HRQoL	Health-Related Quality of Life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITP	primary immune thrombocytopenia
ITP-BAT	ITP–Bleeding Assessment Tool
ITP-PAQ	ITP-Patient Assessment Questionnaire
iv	intravenous
IVIg	intravenous immunoglobulin
K-PD	kinetic-pharmacodynamic
LLOQ	lower limit of quantification
LTB	latent tuberculosis
LTBI	latent tuberculosis infection
MG	myasthenia gravis
NTMBI	nontuberculous mycobacterial infection
OLE	open-label extension
OPSI	overwhelming post-splenectomy infection

PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per-Protocol Set
PEX	plasma exchange
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PPS	Per-Protocol Set
PRO	patient reported outcome
PS	Patient Safety
QMG	Quantitative MG
QoL	quality of life
QTc	corrected QT interval
QW	once a week
Q2W	twice a week
RNA	ribonucleic acid
RO	receptor occupancy
SADE	serious adverse device effects
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
SF-36	Short-Form 36-Item Health Survey
SFU	Safety Follow-Up
SMOG	Skin-mucosae-organs tool
SOP	standard operating procedure
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TPO-RA	thrombopoietin-receptor agonist
ULN	upper limit of normal

US	United States
VAS	visual analog scale
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.10 Appendix 10: Rapid alert procedures

Not applicable.

10.11 Appendix 11: Karnofsky Performance Status Scale

Appendix removed.

10.12 Appendix 12: ITP-BAT

Grading of bleeding symptoms at presentation and at each subsequent evaluation.[1]

Table 10-5: ITP-Bleeding Assessment Tool

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
SKIN					
Petechiae (does not include steroid–induced or senile purpura)	☐ No	☐ Less than or equal to 10 in a patient's palm-sized area[3] in the most affected body area[4] ☐ Any number if reported by the patient	☐ More than 10 in a patient's palm-sized area or more than 5 in at least 2 patient's palm-sized areas located in at least 2 different body areas[4], one above and one below the belt (in the most affected body areas) [4]	☐ More than 50, if scattered both above and below the belt	
Ecchymoses	☐ None or up to 2 in the same body area[4], but smaller than a patient's palm-sized area, if a) spontaneous or b) disproportionate to trauma/constriction[5]	☐ 3 or more in the same body area[4], but all smaller than a patient's palm-sized area, if a) spontaneous or b) disproportionate to trauma/constriction[5] ☐ At least 2 in two different body areas[4], smaller than a patient's palm-sized area, if a) spontaneous or b) disproportionate to trauma/constriction[5] ☐ Any number and size if reported by the patient	☐ From 1 to 5 larger than a patient's palm-sized area, if a) spontaneous or b) disproportionate to trauma/constriction[5] with or without smaller ones	☐ More than 5 larger than a patient's palm-sized area, if a) spontaneous or b) disproportionate to trauma/ constriction[5]	

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
Subcutaneous hematomas	☐ No	☐ 1 smaller than a patient's palm-sized area ☐ Any number and size if reported by the patient	☐ 2 smaller than a patient's palm-sized area, spontaneous ☐ 2 smaller than a patient's palm-sized area, disproportionate to trauma[5]	☐ More than 2 smaller or at least 1 larger than a patient's palm-sized area, spontaneous ☐ More than 2 smaller or at least 1 larger than a patient's palm-sized area, disproportionate to trauma[5]	
Bleeding from minor wounds[6]	☐ No	☐ Lasting <5 min ☐ Any episode if reported by the patient	☐ Lasting >5 min or interfering with daily activities	☐ Requiring protracted medical observation at the time of this visit ☐ Medical report describing patient's evaluation by a physician	
MUCOSAL					
Epistaxis[7]	☐ No	☐ Lasting <5 min ☐ Any episode if reported by the patient	☐ Lasting >5 min or interfering with daily activities	☐ Packing or cauterization or in-hospital evaluation at the time of this visit ☐ Medical report describing packing or cauterization or in-hospital evaluation	☐ RBC transfusion or Hb drop >2g/dL

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
Oral cavity – gum bleeding[7]	☐ No	☐ Lasting <5 min ☐ Any episode if reported by the patient	☐ Lasting >5 min or interfering with daily activities	☐ Requiring protracted medical observation at the time of this visit ☐ Medical report describing patient's evaluation by a physician	
Oral cavity – hemorrhagic bullae or blisters	☐ No	☐ Less than 3 ☐ Any number if reported by the patient	☐ From 3 to 10 but no difficulty with mastication	☐ More than 10 or more than 5 if difficulty with mastication	
Oral cavity - bleeding from bites to lips & tongue or after deciduous teeth loss	☐ No	☐ Lasting <5 min ☐ Any episode if reported by the patient	☐ Lasting >5 min or interfering with daily activities	☐ Interventions to ensure hemostasis or in-hospital evaluation at the time of this visit ☐ Medical report describing interventions to ensure hemostasis or in-hospital evaluation	
Subconjunctival hemorrhage (not due to conjunctival disease)	☐ No	☐ Petechiae/ hemorrhage partially involving one eye ☐ Any episode if reported by the patient	☐ Petechiae/ hemorrhage partially involving both eyes, or diffuse hemorrhage in one eye	☐ Diffuse hemorrhage in both eyes	
ORGAN (and internal mucosae)					

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
Gastrointestinal bleeding not explained by visible mucosal bleeding or lesion: Hematemesis, Melena, Hematochezia, Rectorrhagia	☐ No	☐ Any episode if reported by the patient	☐ Present at the visit ☐ Described in a medical report	☐ Requiring endoscopy[8] or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ Medical report prescribing endoscopy[8] or other therapeutic procedures or in-hospital evaluation	☐ RBC transfusion or Hb drop >2g/dL
Lung bleeding Hemoptysis Tracheobronchial bleeding	☐ No	☐ Any episode if reported by the patient	☐ Present at this visit ☐ Described in a medical report	☐ Requiring bronchoscopy[8] or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ An equivalent episode if described in a medical report	☐ RBC transfusion or Hb drop >2g/dL
Hematuria	☐ No	☐ Any episode if reported by the patient ☐ Microscopic (lab analysis)	☐ Macroscopic ☐ Described in a medical report	☐ Macroscopic, and requiring cystoscopy[8] or other therapeutic procedures or in-hospital evaluation at the time of this visit	☐ RBC transfusion or Hb drop >2g/dL

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
				☐ An equivalent episode if described in a medical report	
Menorrhagia (compared to pre-ITP or to a phase of disease with normal platelet count)[9]	☐ No	☐ Doubling number. of pads or tampons in last cycle compared to pre-ITP or to a phase of disease with normal platelet count ☐ Score >100 using PBAC in the last cycle, if normal score in pre-ITP cycles or in a phase of disease with normal platelet count	☐ Changing pads more frequently than every 2 hrs. or clot and flooding ☐ Requiring combined treatment with antifibrinolytics and hormonal therapy or gynecological investigation (either at this visit or described in a medical report)	☐ Acute menorrhagia requiring hospital admission or endometrial ablation (either at this visit or described in a medical report)	☐ RBC transfusion or Hb drop >2g/dL
Intramuscular hematomas (only if diagnosed by a physician with an objective method)	☐ No	☐ Post trauma, diagnosed at this visit, if judged disproportionate to trauma ☐ An equivalent episode if described in a medical report	☐ Spontaneous, diagnosed at this visit ☐ An equivalent episode if described in a medical report	☐ Spontaneous or post trauma (if judged disproportionate to trauma) diagnosed at this visit and requiring hospital admission or surgical intervention ☐ An equivalent episode if described in a medical report	☐ RBC transfusion or Hb drop >2g/dL
Hemarthrosis	☐ No	☐ Post trauma, diagnosed at this visit,	☐ Spontaneous, diagnosed at this visit,	☐ Spontaneous or post trauma (if	☐ Spontaneous or post trauma (if

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
(only if diagnosed by a physician with an objective method)		function conserved or minimally impaired, if judged disproportionate to trauma ☐ An equivalent episode if described in a medical report	function conserved or minimally impaired ☐ An equivalent episode if described in a medical report	judged disproportionate to trauma), diagnosed at this visit and requiring immobilization or joint aspiration ☐ An equivalent episode if described in a medical report	judged disproportionate to trauma) diagnosed at this visit and requiring surgical intervention ☐ An equivalent episode if described in a medical report
Ocular bleeding **(only if diagnosed by a physician with an objective method)**	☐ No		☐ Any post trauma vitreous or retinal hemorrhage involving one or both eyes with or without impaired/blurred vision present at this visit if judged disproportionate to trauma ☐ An equivalent episode if described in a medical report	☐ Spontaneous vitreous or retinal hemorrhage involving one or both eyes with impaired/blurred vision present at this visit ☐ An equivalent episode if described in a medical report	☐ Spontaneous vitreous or retinal hemorrhage with loss of vision in one or both eyes present at this visit ☐ An equivalent episode if described in a medical report
Intracranial bleeding10: intracerebral, intraventricular, subarachnoidal, subdural, extradural **(only if diagnosed with an objective method at the visit or described in a medical report provided by the patient)**	☐ No		☐ Any post trauma event requiring hospitalization	☐ Any spontaneous event requiring hospitalization in presence of an underlying intracranial lesion	☐ Any spontaneous event requiring hospitalization without an underlying intracranial lesion

Type of bleeding	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT[2]				
	0	**1**	**2**	**3**	**4**
Other internal bleeding: hemoperitoneum hemopericardium hemothorax retroperitoneal bleeding hepatic and splenic peliosis with organ rupture retroorbital bleeding metrorrhagia etc. **(only if diagnosed with an objective method at the visit or described in a medical report provided by the patient)**	☐ No			☐ Any event requiring hospitalization <48 hrs.	☐ Any event requiring hospitalization >48 hrs. or RBC transfusion or Hb drop >2g/dL

Hb=hemoglobin; hrs=hours; ITP=immune thrombocytopenia; PBAC=Pictorial Blood Assessment Chart; RBC=red blood cell; SMOG=Skin-Visible Mucosa-Internal Organs tool

[1] In case of study participants examined for the first time, all types of bleeding occurring at the visit and in the 15 days preceding the visit should be considered.

[2] Each type of bleeding should be graded based on the worst bleeding manifestation that occurred during each observation period or in the 15 days preceding the first visit.

[3] Study participant's own palm size is commonly considered to be proportional to body surface area. Palm=the inner surface of the hand stretching between the distal crease of the wrist and the bases of the fingers (fingers surface excluded).

[4] Body areas include: face, neck, right and left upper limbs (considered separately), right and left lower limbs (considered separately), trunk, abdomen, and recumbent areas (for the ambulatory patient means the area below the knees).

[5] Bleedings considered proportionate to trauma/constriction on a clinical ground should not be reported for skin domain.

[6] Minor wound means superficial skin cuts (eg, by shaving razor, knife, or scissors).

[7] Epistaxis and gum bleeding are also reported in some normal study participants. Thus, a critical judgment is required in grading these manifestations; they should be reported only if judged more severe when compared with pre-ITP bleeding, if any.

[8] Any endoscopic investigations should be considered for grading only if performed for therapeutic purpose and not solely for diagnostic purpose.
[9] In girls at menarche, grade 1 cannot be assigned, lacking comparison with previous cycles.
[10] Intracranial bleeding should always be reported, irrespective of its grade. For example, if a woman had S2 (subcutaneous hematoma) M2 (epistaxis) O3 (menorrhagia) and an intracranial bleeding grade 2 (post trauma, requiring hospitalization), the SMOG index is S2M2O3 (intracranial 2). If the same participant also had intracranial bleeding grade 3, the SMOG index is S2M2O3 (intracranial 3) (see text).

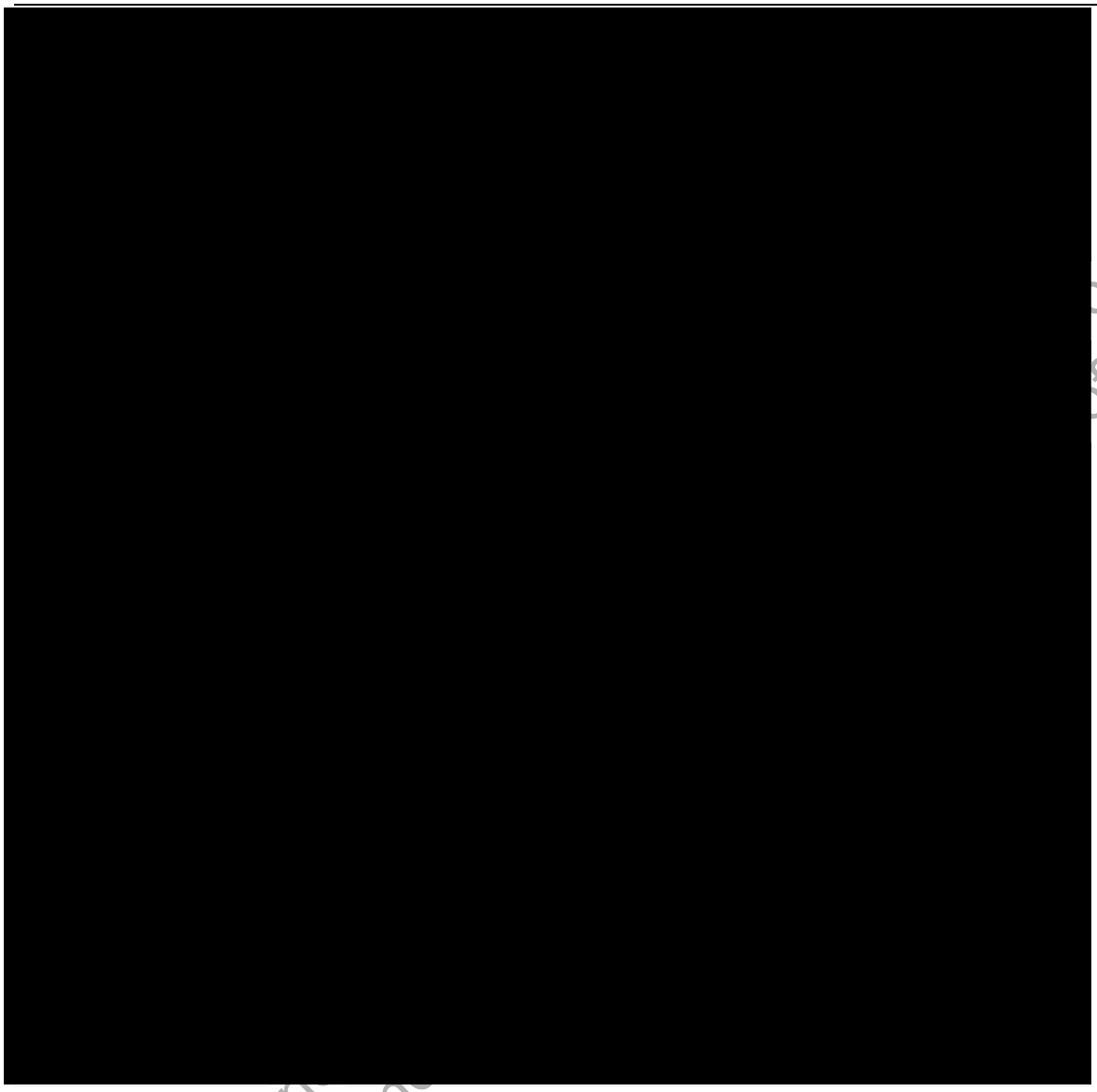
Note: Grading is based on physical examination at the time of the visit by the physician or expert nurse or on study participant's history supplemented by available medical reports. Bleeding manifestations reported by the study participant but not visible at the time of data collection are graded 1. Grade 5 is assigned to fatal bleeding.

Note: Illustrative examples are available on the website of the Hematology Project Foundation (http://itpbat.fondazioneematologia.it/).

Note: To receive a grade >1, all non-overt skin and non-overt mucosal bleeding (petechiae, ecchymoses, subcutaneous hematomas, vesicles/bullae subconjunctival bleeding) should be visible at the time of visit for grading by the physician or expert nurse taking the history.

Note: For bleeding from minor wounds and overt-mucosal bleeding (epistaxis, gum, bleeding from bites to lips & tongue or after deciduous teeth loss/extraction) and all organ bleeding, a medical record describing the symptom or indicating a specific intervention/prescription should be also taken into account for grading.

Note: Requirement for ITP-specific treatments and anti-fibrinolytics (apart from menorrhagia) was not considered for grading, due to their subjective nature and their adoption not only to control actual bleeding but also to reduce the "risk" of impendent or future bleeding.



ITP-PAQ v1.0 (05 September 2017)
US (English)

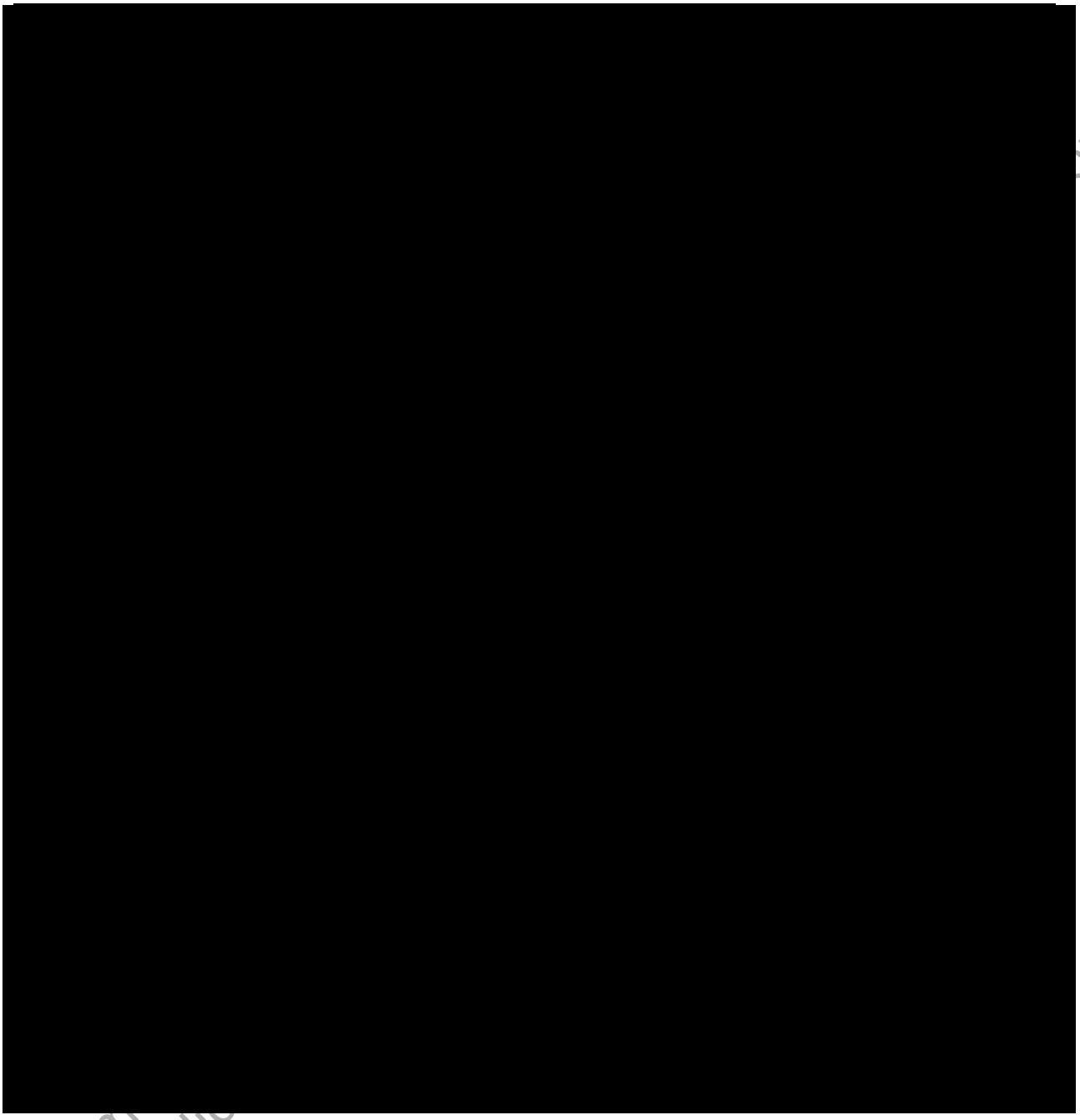
TP-PAQ v1.0 (05 September 2017)
US (English)

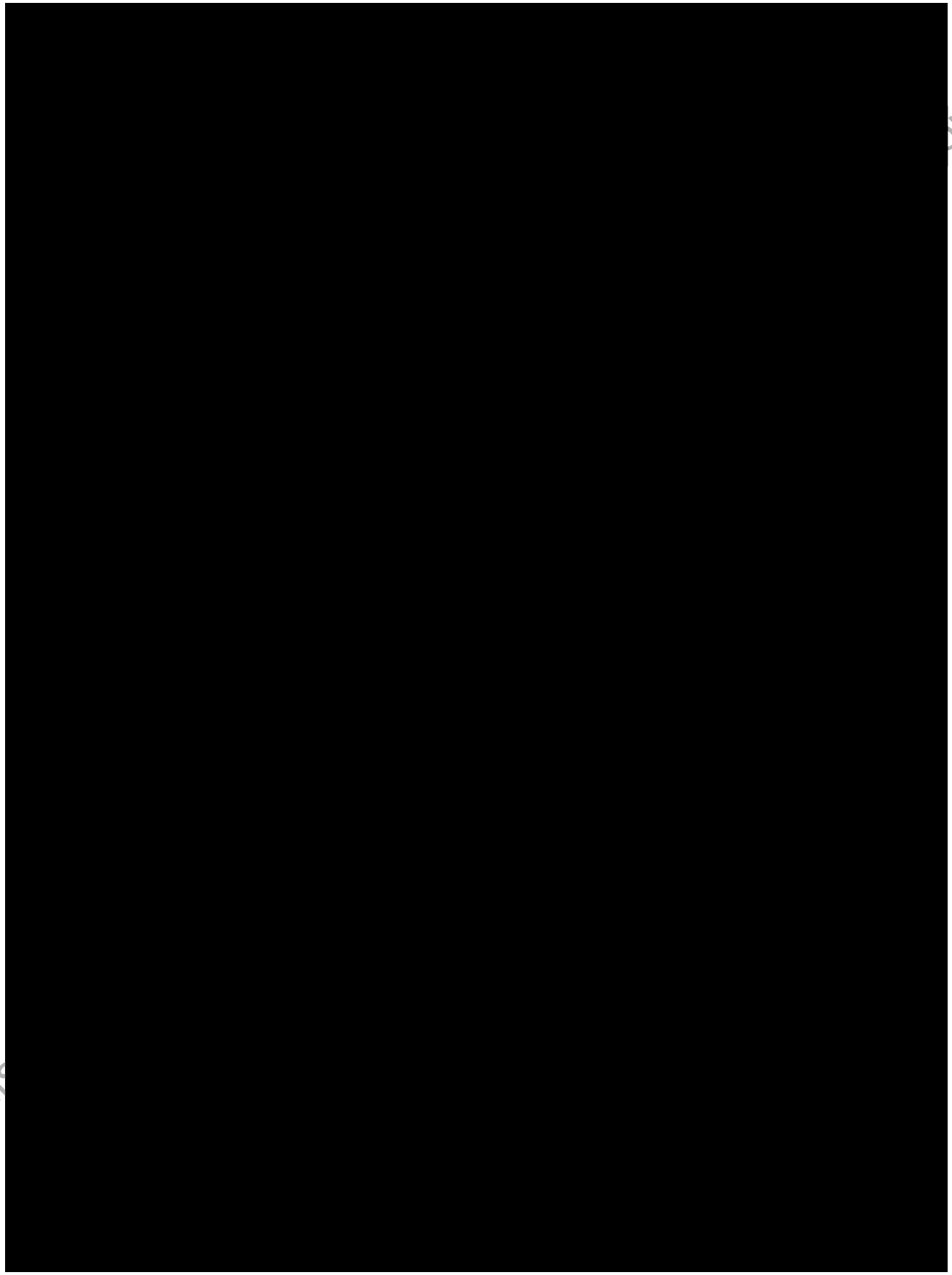
[redacted]

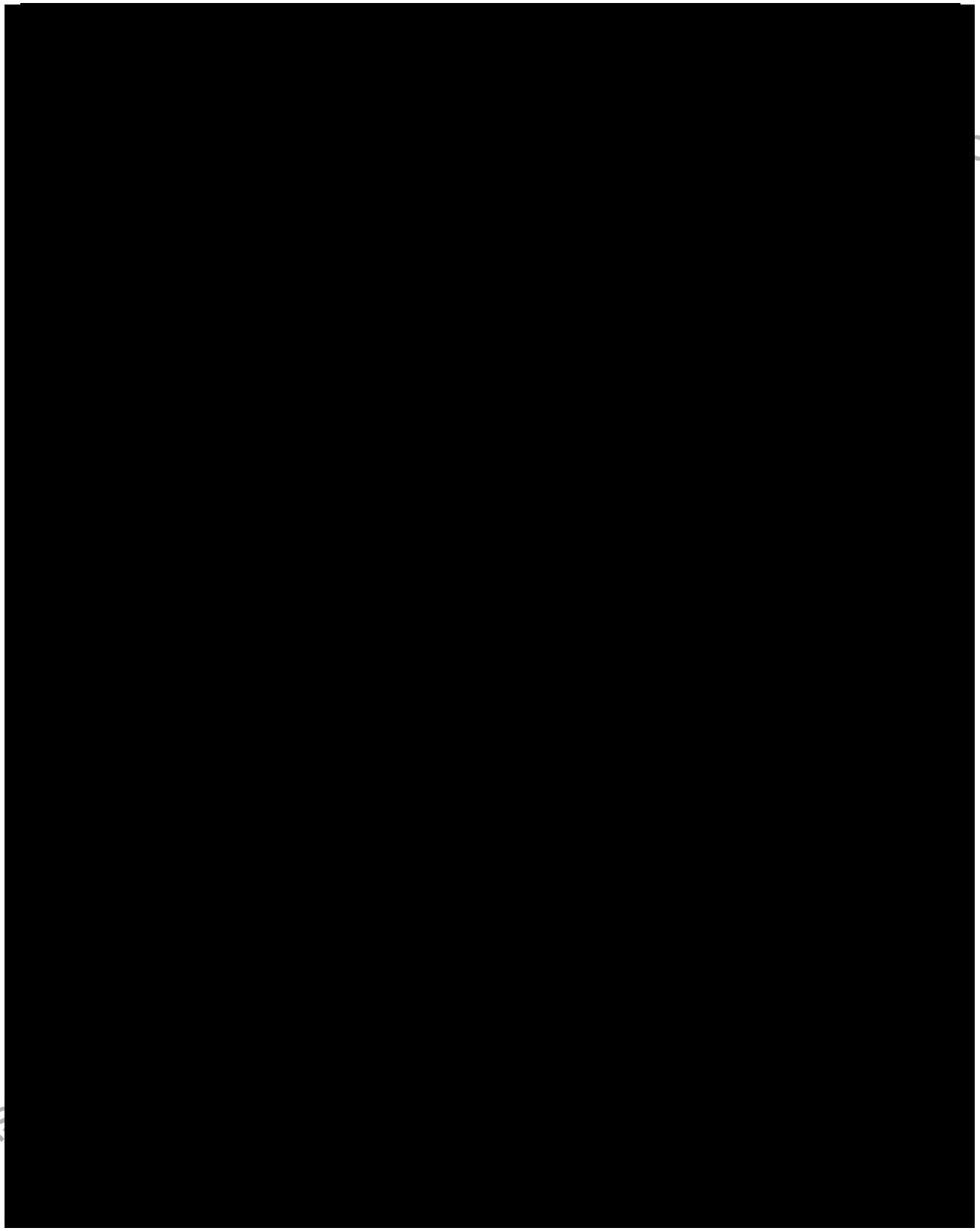
ITP-PAQ v1.0 (05 September 2017)
US (English)

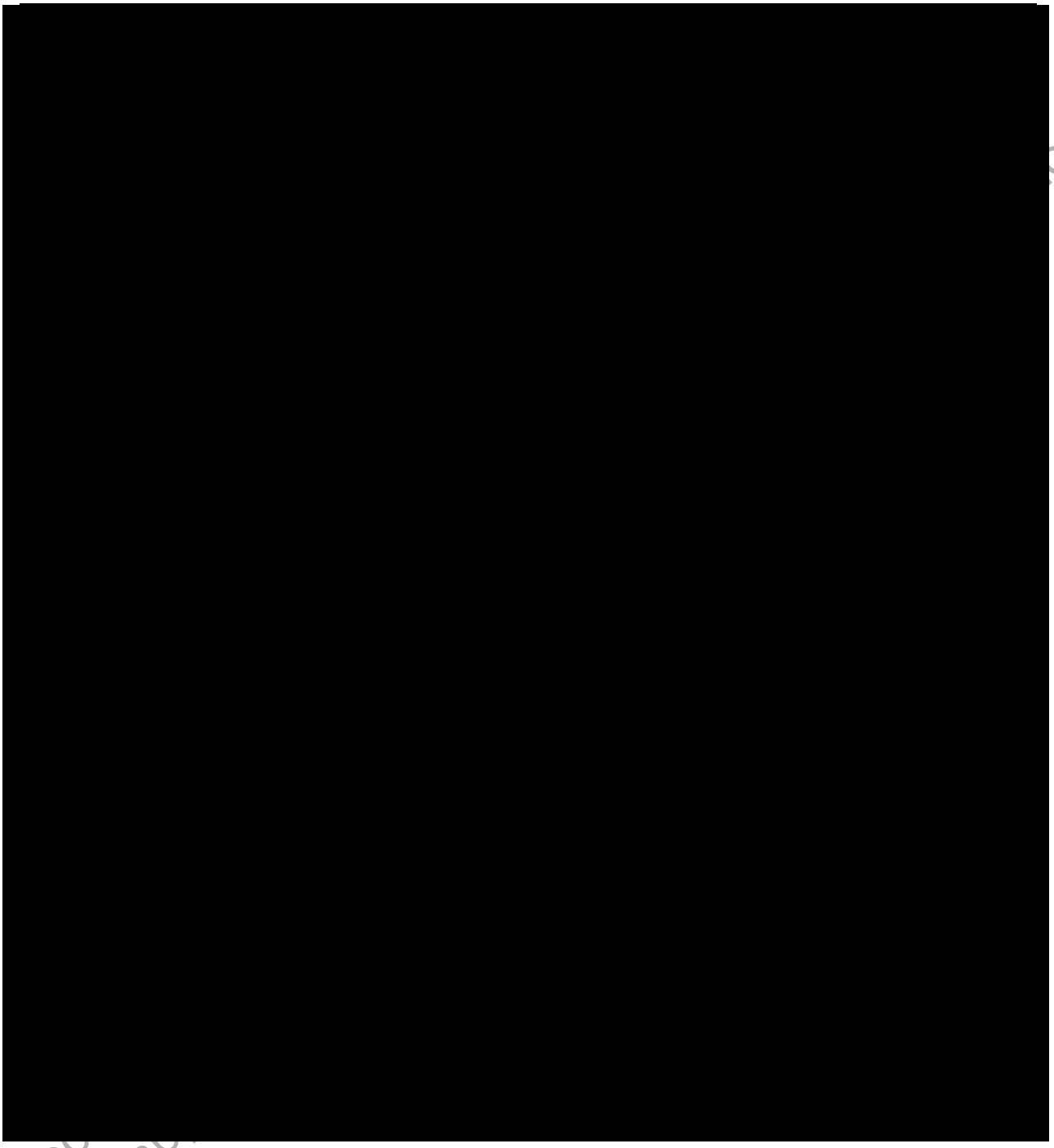
ITP-PAQ v1.0 (05 September 2017)
US (English)

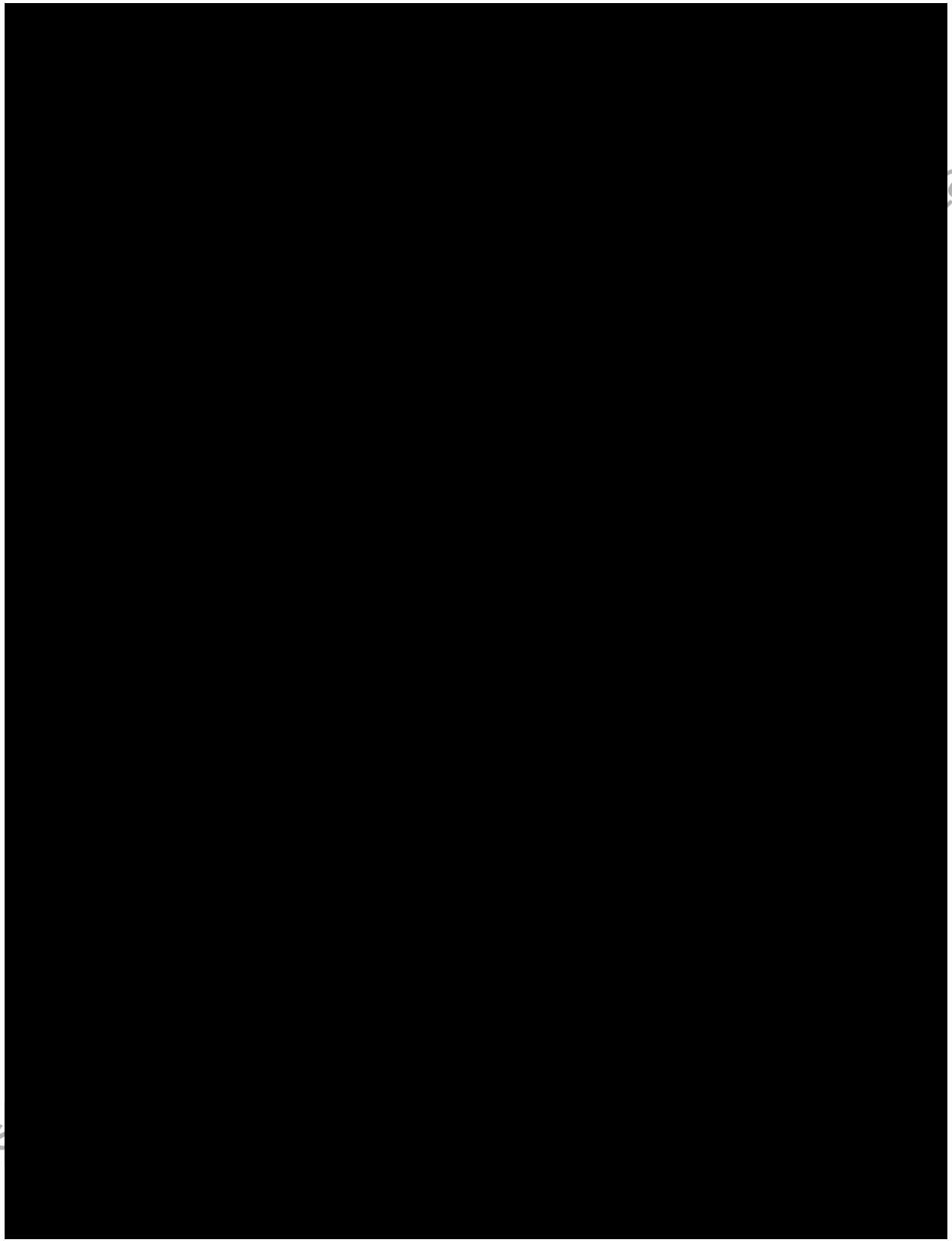
TP-PAQ v1.0 (05 September 2017)
US (English)

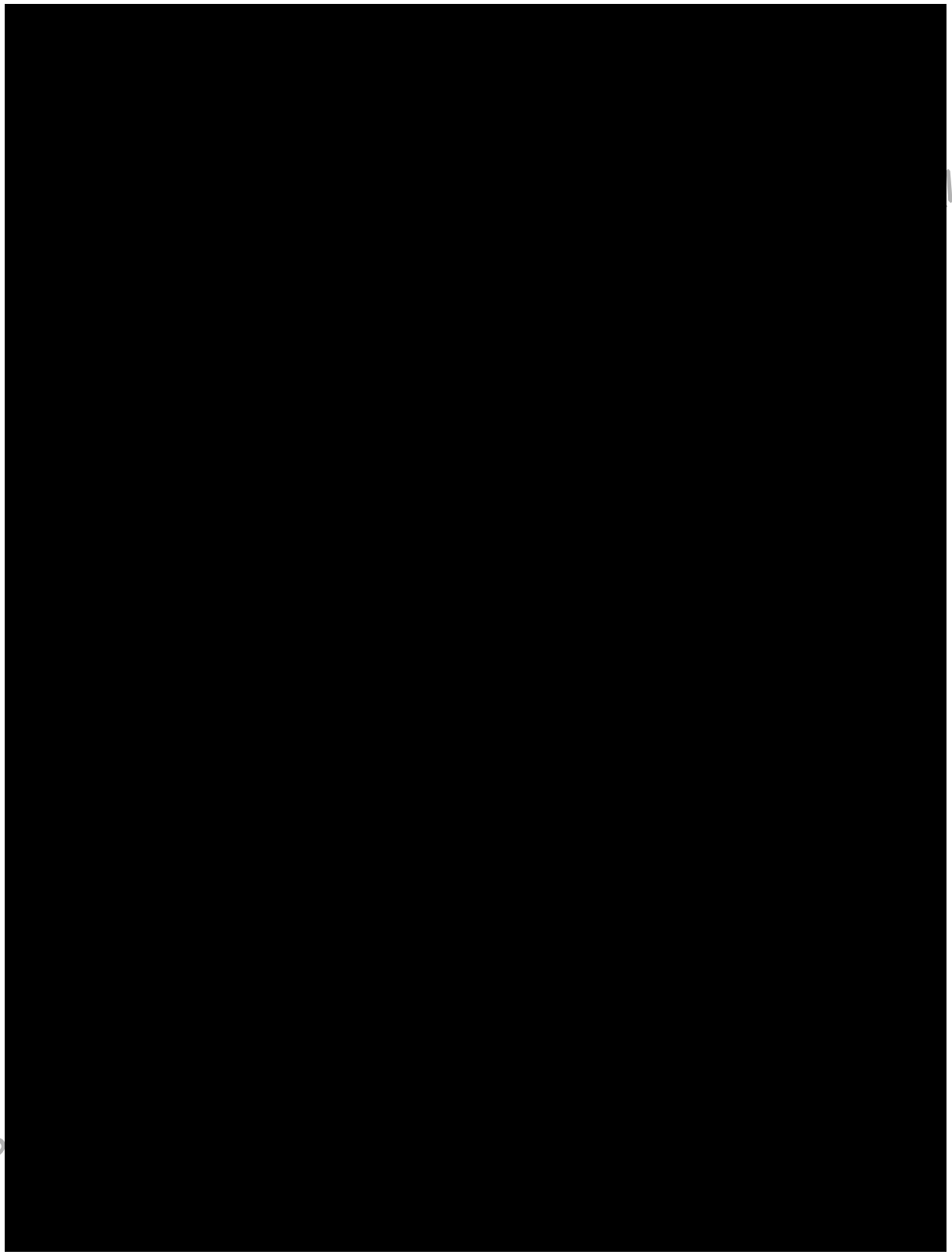












10.17 Appendix 17: PGI-S

The following question asks you about your current overall symptoms.

Please check the box that best describes your current situation.

How would you describe <u>your ITP symptoms during the past week</u>?

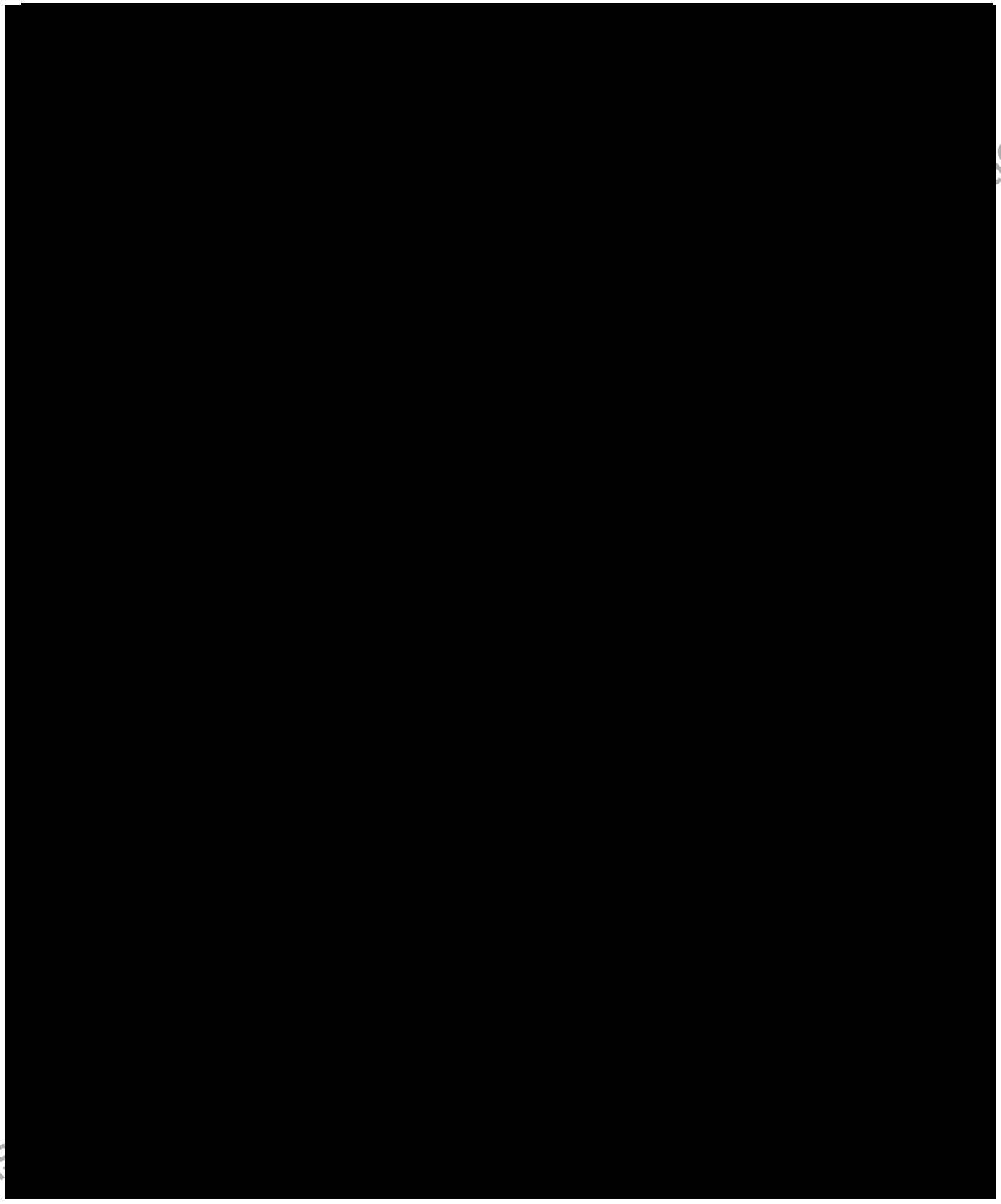
	None
	Mild
	Moderate
	Severe
	Very severe

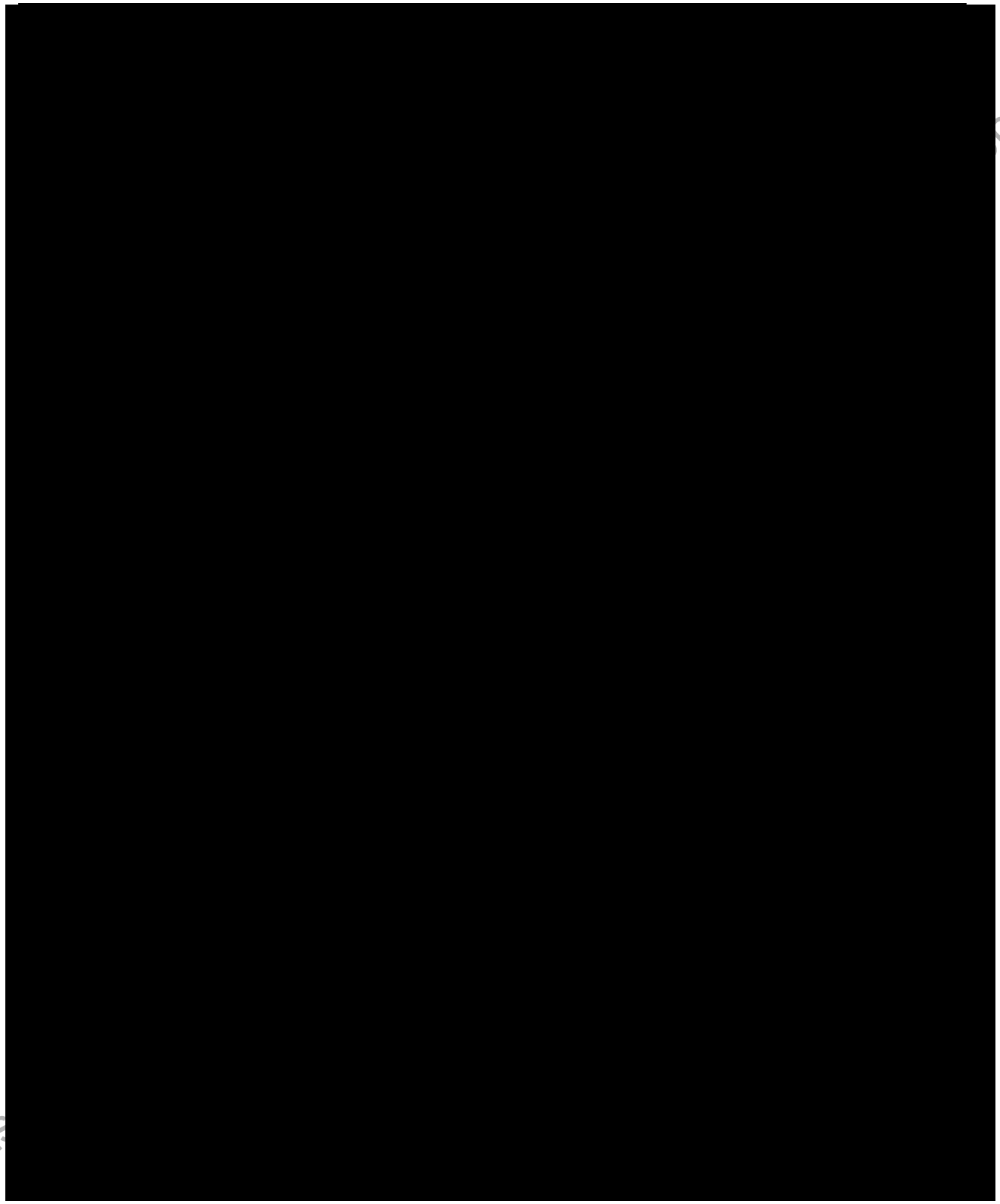
10.18 Appendix 18: PGI-C

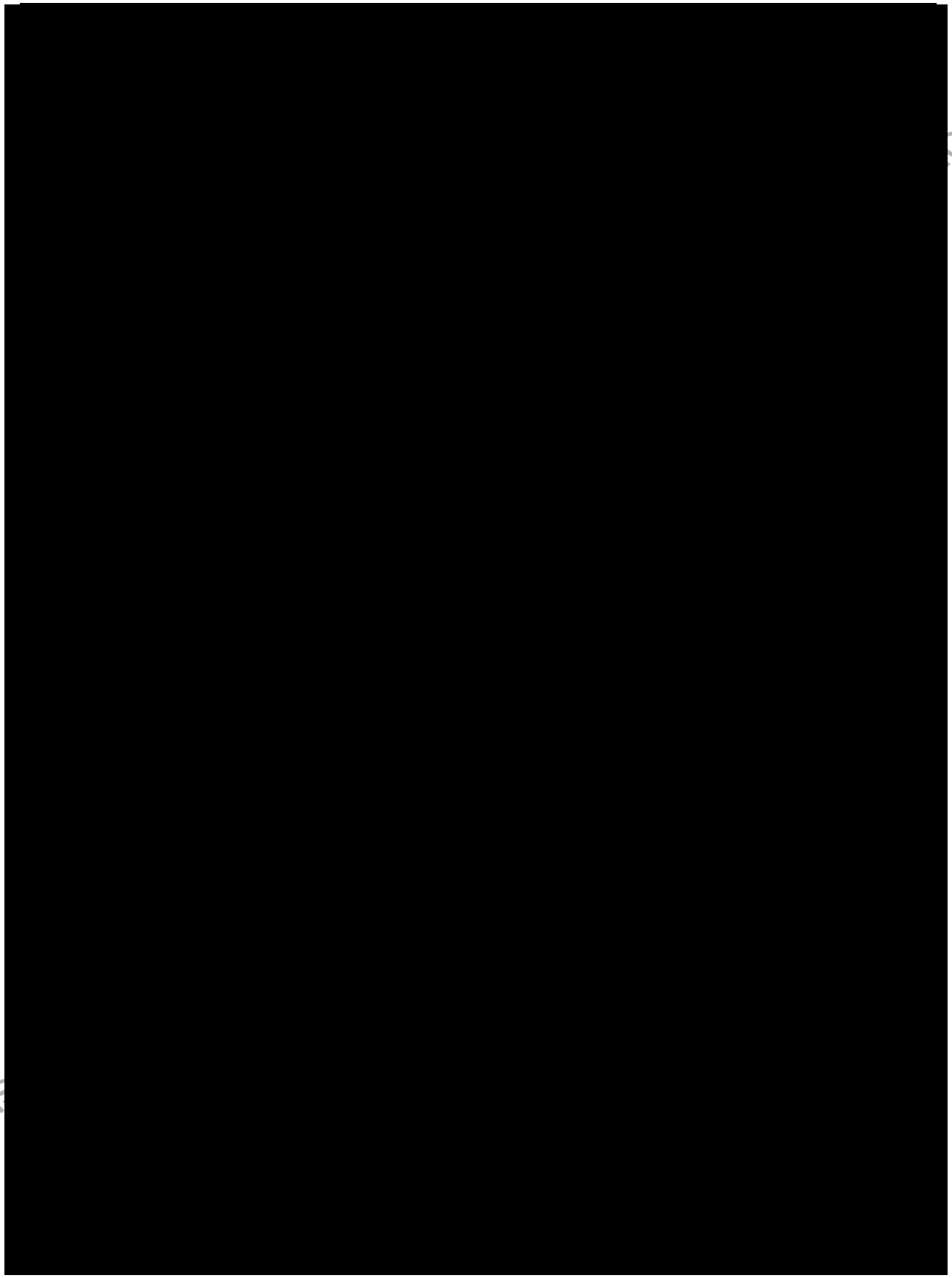
The following question asks you about your overall symptoms now compared to before starting treatment within this clinical study. Please check the box that best describes your current situation.

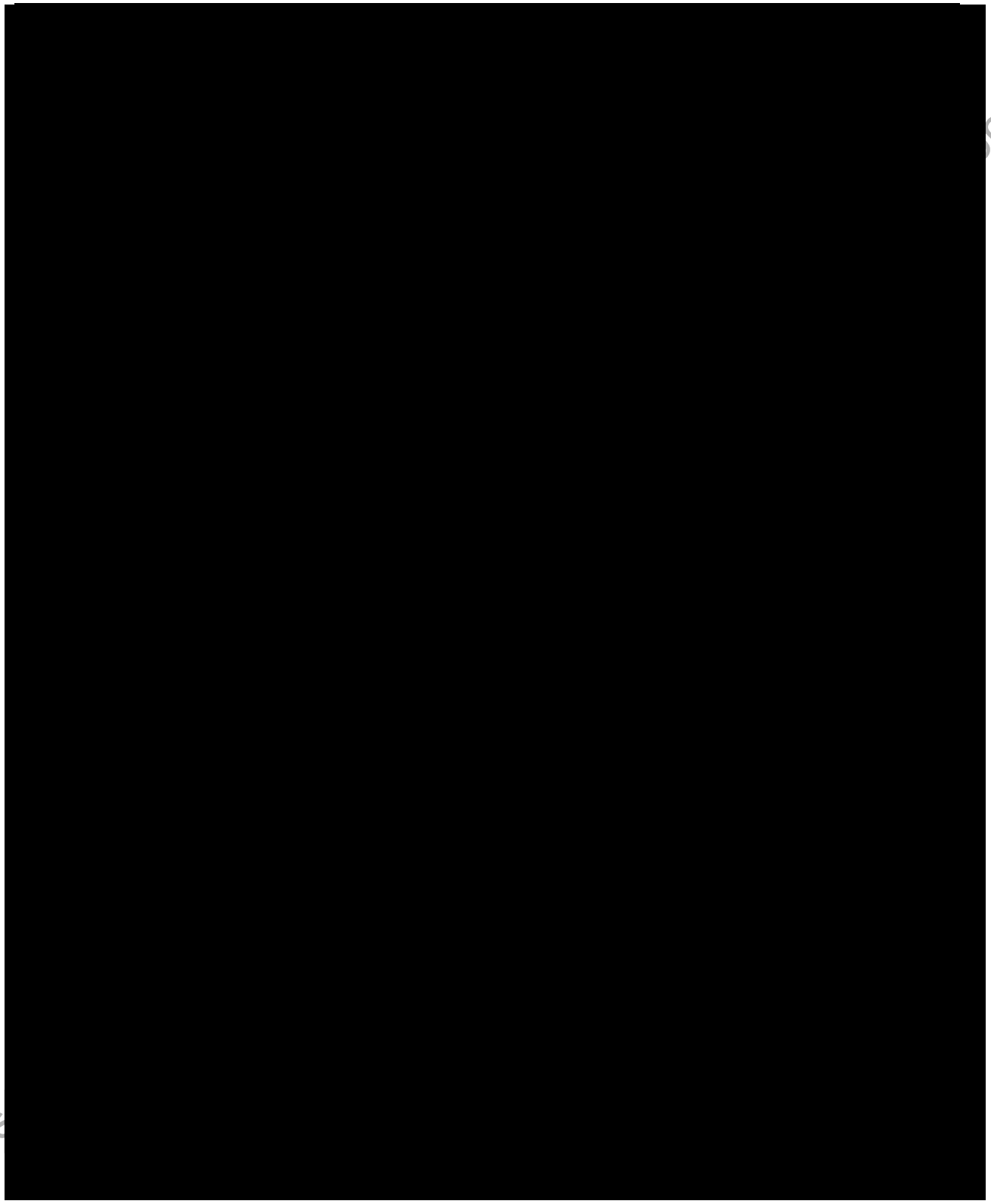
How would you describe your current ITP symptoms compared to before you started treatment in this clinical study?

☐	Very much worse
☐	Much worse
☐	A little bit worse
☐	No change
☐	A little bit improved
☐	Much improved
☐	Very much improved









10.21 Appendix 21: Sampson Criteria Questionnaire

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

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

AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

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

10.22 Appendix 22: Management of headaches

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 National Cancer Institute Terminology Criteria for Adverse Events (CTCAE) version 5.0. Severe headache is defined as severe pain limiting self-care activity of daily living (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 comorbidities (eg, asthma) into consideration.

Study participants experiencing a moderate, severe and/or serious headache will complete the Headache Questionnaire (Appendix 20, Section 10.20) daily until resolution (eg, the headache becomes nonserious, mild, or is completely resolved, whichever comes first). 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 at the study site as soon as possible for further investigations. Study participants should be monitored for signs and symptoms suggestive of central nervous system involvement and evaluated immediately if other causes (eg, meningitis, intracranial bleeding) are suspected. Further neurological workup may be performed (if indicated) at the discretion of the investigator or the treating physician and may include a computed tomography scan, magnetic resonance imaging and/or a lumbar puncture for cerebral spinal fluid collection. In addition, samples for exploratory safety biomarkers should be collected for study participants experiencing severe headache or serious headache when possible. These investigations will be performed to further understand the mechanism of headaches in the study participants.

Treatment must be permanently discontinued if a study participant has a serious headache that is considered related to the IMP in the opinion of the investigator. If a study participant experiences a severe AE of headache that is considered related to the IMP in the opinion of the investigator, the dose of IMP may be reduced or the treatment may be temporarily put on hold. 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, at the previous dose or at a lower dose. The benefit and risk of the treatment should be carefully considered prior to reinitiating the IMP. If a study participant experiences a second episode of treatment related severe headache in the opinion of the investigator, the treatment can only be continued upon agreement with the sponsor, investigator, and study participant taking benefit and risk into consideration. If the benefit-risk balance is not acceptable, then the participant must discontinue the IMP. If a participant experiences >2 severe headaches that are considered related to the IMP in the opinion of the investigator, the treatment must be permanently discontinued.

Dosing modifications are allowed if judged necessary by the investigator from [redacted] based on specific volume reduction per protocol guidance, provided the treatment is effective as evidenced by relevant efficacy measurements (eg, platelet count $\geq 30 \times 10^9$/L).

Headaches will be treated as clinically indicated according to national guidelines. It is recommended that the study participant has an analgesic available in case of headache with the

instruction for frequency and dosage provided by a health care 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 treatment with analgesics must be carefully evaluated by the investigator.

10.23 Appendix 23: Management of diarrhea

Severe (Grade 3) diarrhea is defined as an increase of ≥7 stools per day or hospitalization for management of diarrhea or limiting self-care ADL. Determination of the severity of diarrhea will be consistent with CTCAE version 5.0 (see Appendix 3, Section 10.3).

Diarrhea will be treated as clinically indicated according to the local guidelines.

Stool samples may be collected for stool analysis to rule out infection for study participants reporting severe diarrhea. Stool sampling will be done as clinically indicated in the opinion of the investigator and assessed per local guidance. In addition, collection of blood samples for assessment of exploratory safety biomarkers is required for study participants with severe GI disturbances including diarrhea.

In study participants experiencing severe treatment related diarrhea, dosing modifications are allowed, if judged necessary by the investigator, from [redacted] based on specific volume reduction per protocol guidance, provided the treatment is effective as evidenced by relevant efficacy measurements (eg, platelet count ≥30×10^9/L).

10.24 Appendix 24: Management of infusion reactions or hypersensitivity reactions

Study participants must be closely monitored for reactions during and after the IMP administration period. Standard precautions must be taken for the study participants with regard to potential infusion related reactions. Suggested management guidelines for infusion-related reactions and anaphylaxis at the study site are provided in Table 10-7. Definitions of the severity of the relevant events will be consistent with CTCAE version 5.0 (see Appendix 3, Section 10.3). Fully trained healthcare professionals 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 10-7: Suggested management guidelines at the study site for infusion reactions

Type of reaction	Suggested action
Acute – Mild Grade 1	Monitor vital signs every 10 min. If the reaction worsens to Grade 2, follow the instructions 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 or im. Consider administering paracetamol 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 study 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).

In case of suspected anaphylaxis, the Sampson's Criteria (Sampson et al, 2006) should be accessed and Appendix 21 (Section 10.21, Sampson Criteria Questionnaire) should be

completed. The infusion must be discontinued immediately, and emergency resuscitation measures implemented.

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

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

10.25 Appendix 25: Management of infections and hypogammaglobulinemia

Study participants who have the 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.

If a 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, they MUST discontinue IMP, perform the EW Visit, enter the SFU Period and complete the EOS Visit. This list is not intended to be all inclusive and the investigator is expected to apply his/her judgment on continuing IMP based on the clinical situation at hand.

To maintain the study integrity, study site personnel, the UCB and CRO study teams will remain blinded to IgG levels. However, to ensure study participants' safety, serum IgG level will be monitored by unblinded Medical Monitors external to UCB. In case the serum IgG level decreases <1g/L, as described below and in Table 10-8, the unblinded Medical Monitors will inform the investigator.

The most recently available IgG value is the trigger for discussions between the unblinded Medical Monitors and the investigator and for any decisions on changing the dose of IMP/ triggering a mock infusion. All discussions and decisions related to the benefit-risk of dose changes/mock infusions are to be based on a holistic approach of the study participant's status, including platelet response (eg, study participant's ITP history, stability of the current response, past and current platelet values), current signs and symptoms of non-serious/serious infection, potential risk of acquiring a non-serious/serious infection in the foreseeable future and are at the sole discretion of the investigator.

The investigator must document the respective benefit-risk assessments and decisions in the study participant's source documents.

Table 10-8: Management of infections and hypogammaglobulinemia

IgG value	Actions	Outcome
IgG <1g/L[a]	Unblinded medical monitor informs the investigator	Investigator decides to either[b]: • maintain the dose • reduce the dose • request for a mock infusion to be triggered based on the study participant's status regarding platelets response, signs and symptoms of non-serious/serious infection, potential risk of acquiring a non-serious/serious infection

AE=adverse event; eCRF=electronic case report form; IXRS= Interactive Voice/Web Response System
[a] Events of hypogammaglobulinemia must not be captured as an AE in the eCRF, to protect the blind.
[b] In the IXRS, the investigator can only reduce the dose, while the unblinded Medical Monitors can only trigger the mock infusion.

Dose adjustments/mock infusions

The dose of IMP can be reduced from [redacted] as needed.

The IgG would be expected to return to values ≥1g/L in up to 3 to 4 weeks (after a dose decrease/mock infusion is triggered). The level of IgG recovery will depend on the IgG observed value that triggered the intervention and the intra-study participants variability, so that the IgG level may not immediately increase, and a delayed effect could be expected.

The study participant will need to be reassessed on an ongoing basis regarding platelet response and risk of infection until the serum IgG returns to values ≥1g/L. The dose may be further decreased, or a mock infusion triggered, if needed.

In case a mock infusion is triggered, IMP administration may be restarted at a lower dose compared to the previous dose in order to decrease the likelihood of any further repeated reduction in the IgG level <1g/L.

Ad hoc assessments (eg, additional weekly IgG samples) may be performed to monitor recovery of IgG levels.

Splenectomized study participants

Splenectomized study participants are at a higher risk of infections, especially of OPSI. Irrespective of the IgG level, in case a splenectomized study participant develops a (persistent or recurring) nonserious infection, the dose of IMP can be reduced, or the IMP treatment may be temporarily stopped, when appropriate, at the investigator's discretion. The IMP treatment may

be resumed at the previous dose after the resolution of the event. The investigator may also reach out to the unblinded Medical Monitors, as needed.

Local guidelines regarding antibiotic prophylaxis in splenectomized study participants should be followed. Splenectomized study participants should have a prophylactic antibiotic available, unless they are already taking an antibiotic as per local guidance.

10.26 Appendix 26: Protocol Amendment History

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

Amendment 2 (29 Sep 2020)

Overall Rationale for the Amendment

The primary reason for this protocol amendment was to incorporate changes in the endpoints, the statistical analysis section and to incorporate agency required local protocol amendments into one global protocol.

Additional updates were incorporated to provide further clarity on the protocol or to correct errors.

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
Global	Minor administrative, consistency, formatting and typographical changes have been made.	Updated to provide clarity and be consistent with remainder of protocol.
Global	Where applicable, rozanolixizumab has been replaced with investigational medicinal product (IMP).	Updated to ensure placebo is included in the context of the applicable section.
Global	The list of the secondary efficacy endpoints has been reordered.	Updated to match the sequence of analysis.
Global	Where applicable, the wording "4-week" was removed from "the 4-week Screening Period".	Wording updated for consistency reasons.
Global	"Prednisolone" changed to "prednisone".	Updated to UCB standards.
Global	All reference to the Fisher's Exact test has been removed from the primary analysis and included as a separate supplemental estimand. For the primary analysis more details regarding the Cochran-Mantel-Haenszel test have been added.	To provide a more accurate description of the analysis and to address FDA statistical comments on confirmatory analyses.
Global	Japan specific regulations have been highlighted throughout the protocol and added to Appendix 8, Section 10.8.	In accordance with local regulations and actual condition of medical treatment in Japan.
Serious adverse event reporting	**For participants in Japan only:** Additional reporting instructions for SAE reporting (investigational	In accordance with local regulations in Japan. The infusion syringe driver and infusion set

Section # and Name	Description of Change	Brief Rationale
	device) and device deficiency reporting specific for Japan have been included.	supplied by the sponsor are not approved in Japan.[a]
1.1 Synopsis, Rationale 1.1 Synopsis, Overall design 2.1 Study rationale	The study criteria have been modified to include study participants who have failed or were intolerant to two or more prior ITP therapies.	Global implementation of an ANSM request and implement feedback received from the FDA.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The primary efficacy endpoint has been updated to delete "as defined by proportion of study participants who have platelet responses".	Updated to be consistent with UCB writing conventions.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The secondary efficacy endpoint has been updated from "Cumulative number of visits" to "Cumulative number of **weeks"** and **"over the 24-week treatment period"** was added.	Updated to provide clarity.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The secondary efficacy endpoint "Time to **first** Clinically Meaningful Platelet Response of $\geq 50x10^9/L$: time from starting treatment to achievement of first response of $\geq 50x10^9/L$" was updated to include "first".	Updated for consistency within the description of this endpoint.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The secondary efficacy endpoint "Complete Response defined as platelet count $\geq 100x10^9/L$ confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding by visit" has been moved to "other efficacy endpoints".	Endpoint did not measure different manifestation of the disease and did provide redundant information with another key secondary endpoint.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The secondary efficacy endpoint related to the ITP Patient Assessment Questionnaire (ITP-PAQ) Symptoms Score has been modified.	Corrected to clarify the variable.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The other efficacy endpoint relating to "Duration of Clinically Meaningful Platelet Response" has been updated.	Updated to clarify it is the first response.
1.1 Synopsis, Objectives and endpoints	The other efficacy endpoint "Time to first Complete Response: time	Endpoint did not measure different manifestation of the disease and

Section # and Name	Description of Change	Brief Rationale
3 Objectives and endpoints	from starting treatment to achievement of Complete Response" has been deleted.	did provide redundant information with another key secondary endpoint.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The other efficacy endpoint "Duration of first Complete Response: measured from achievement of Complete Response to loss of Complete Response (loss of Complete Response defined as platelet count <100x10^9/L or bleeding. Platelet counts confirmed on at least 2 separate occasions)" has been deleted.	The secondary efficacy endpoint on "Complete Response" was deleted as it did not measure a different manifestation of the disease. For consistency, the "Duration of Complete Response" was deleted too.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The following text has been added to the other efficacy endpoint "Usage of rescue therapy **by visit**".	To clarify the timepoint of measuring the endpoint.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	Additional "other" efficacy endpoints have been added: • Cumulative number of weeks over the planned 24-week treatment period with platelet count of ≥100x10^9/L. • Cumulative number of weeks over the planned 24-week treatment period with platelet counts ≥30×10^9/L and at least doubling from Baseline. • Mean change from Baseline in platelet count by visit. • Clinically Meaningful Platelet Response of ≥50x10^9/L, for at least 4 out of 6 weeks during the last 6 weeks (Week 19 to 25). • Clinically Meaningful Platelet Response of ≥50x10^9/L, for at least 6 out of 8 weeks during the last 8 weeks (Week 17 to 25).	Updated to include missing details.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The following text has been added to the safety endpoint: Occurrence of TEAEs leading to withdrawal of investigational medicinal product (IMP) **(ie, study discontinuation)**	Updated to provide clarity.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The exploratory endpoint related to ITP bleeding score has been changed to "ITP BAT bleeding events and severity by visit".	Updated to specify the bleeding assessment tool to be used and clarification of the timepoint.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The exploratory endpoints related to the effect of rozanolixizumab on health-related quality of life (HRQoL) have been modified.	Updated to provide clarity and to include missing details from previous version of the protocol.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The exploratory endpoints related to the effect of rozanolixizumab on patient reported outcomes (PROs) have been modified.	Updated to provide clarity and to include missing details from previous version of the protocol.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The exploratory objective has been amended from "To assess the plasma concentrations of rozanolixizumab" to "To assess the **pharmacokinetics** of rozanolixizumab".	Updated to correct an error.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	Pharmacodynamic (PD) endpoints were updated to include "total serum IgG" and "serum IgG".	To include missing details from previous version of the protocol.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints 1.3 Schedule of Activities, Table 1-4	The "Physical Fatigue Instrument" has been changed to the "FATIGUE-PRO Physical Fatigue scale".	Updated to indicate the correct name of the PRO.
1.1 Synopsis, Overall design	"Visit 1" has been added to clarify when Screening occurs.	Updated to provide clarity.
1.1 Synopsis, Overall design	Details have been added to explain that a [redacted] total dose corresponds to an average [redacted] dose in a participant weighing 70kg.	Updated to provide clarity.
1.1 Synopsis, Overall design 1.1 Synopsis, Treatment groups and duration, Table 1-2, footer	Additional wording has been provided for clarification on the action taken for study participants on the lowest dose level with a platelet count between >200×10^9/L and <400×10^9/L.	This update has been included to consider that no dose reduction to less than [redacted] (fixed dose) is set.[e]
1.1 Synopsis, Treatment groups and duration	Additional wording has been provided to explain that placebo	Updated to provide clarity.

Section # and Name	Description of Change	Brief Rationale
	will be administered at volumes matching the rozanolixizumab arm.	
1.1 Synopsis, Overall design 4.1 Overall design	The study hold criteria was amended to remove the following wording: “as soon as” and add “clearly”.	Updated to provide clarity for the stopping rule.
1.1 Synopsis, Overall design 4.1 Overall design	**For US and Canada only**: The stopping rule was updated from when 3 study participants experience SAEs of the same type within the first 15 participants who have received 3 doses of IMP across TP0003 and TP0006 to when 3 study participants experience any SAE within the first 15 study participants who have received at least one dose of IMP across TP0003 and TP0006. Clarification that the stopping rule is applicable unless the SAE is clearly unrelated to study drug.	Inclusion of the local US/CAN protocol amendment. Updated text per FDA request to change the study stopping rule.
1.1 Synopsis, Number of Participants	The number of additional participants that may be recruited into the study was changed from 75 to 60. In addition, the maximum total sample size has been changed from 105 to 90.	Number of study participants had been changed based on revised sample size calculation method and assumptions.
1.3 Schedule of Activities, Table 1-3	**For participants in Japan only:** Footnotes c and d were amended to include “if applicable as per local guidance in Japan”	Updated to provide further clarity.[a]
1.3 Schedule of Activities, Table 1-3	Assessment of 12-lead ECG: Footnote i has been added to Visit 6 and EOS Visit.	Updated to correct an error.
1.3 Schedule of Activities, Table 1-4	Assessment of PGI-C has been removed from Visit 2 (Baseline).	Entered in error as “change” cannot be assessed at baseline.
1.3 Schedule of Activities, Table 1-4	**For participants in Japan only:** Chest X-ray assessment added to EW visit and EOS visit.	To confirm safety at study termination.[a]
1.3 Schedule of Activities, Table 1-4	Blood sampling for plasma concentration of rozanolixizumab has been removed from the EOS visit.	Expected to be below the limit of quantification.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 1-4	Footnote g was added to clarify that the platelet count assessed by the local laboratory can be done -1 day for the Baseline (Visit 2) and for Week 3 (Visit 6). For subsequent dosing visits, the last two available platelet counts can be considered. Subsequent footnotes were reordered.	Updated to clarify the platelet count assessment.[b]
1.3 Schedule of Activities, Table 1-4	**For participants in Japan only:** Footnote m: Wording pertaining to T-SPOT.TB test may be performed as an alternative.	To add the T-SPOT test as a recommended IGRA test in addition to the QuantiFERON test.[a]
1.3 Schedule of Activities, Table 1-4	**For participants in Japan only:** Footnote n: Wording pertaining to chest X-ray be performed only at sites in countries at high risk for TB has been removed. New wording underlining "Chest x-ray to be performed also EW and EOS" has been added.	To confirm safety at study termination. [a]
1.3 Schedule of Activities, Table 1-4	**For participants in Japan only:** Footnote o: New footnote underlining that a chest X-ray is to be performed only in the event of an EW and EOS Visit, has been added.	To confirm safety at study termination. [a]
1.3 Schedule of Activities, Table 1-4	Footnote p has been updated to include EOS Visit.	Updated to correct an error.
1.3 Schedule of Activities, Table 1-4	Footnote z (previously footnote y): Footnote changed from "prior to the first dose" to "prior to dosing".	Updated to provide further clarity.
2.2 Background	"Ongoing" has been removed from Study UP0060.	Clinically complete with study reporting ongoing
4.1 Overall Design	The following sentence "Previously, in TP0001, a 15mg/kg dose was evaluated. In TP0003, a single fixed-unit dose equivalent to [redacted] will be administered at the Baseline Visit. Following the initial dose, study participants will then receive a fixed-unit dose of equivalent to [redacted] rozanolixizumab or placebo, every	To avoid repetition.

Section # and Name	Description of Change	Brief Rationale
	two weeks until Week 23." has been deleted	
4.1 Overall Design	A new sentence has been added to explain that contingency measures during a pandemic and other exceptional circumstances have been included.	Contingency measures have been implemented to ensure study participant safety in response to the COVID-19 pandemic causing the inability for sites to adhere to protocol visits and assessments.
4.1 Overall Design	The number of sites has been changed from 50 to 70. In addition, the maximum number of evaluable study participants has been changed from 105 to 90.	Increased to reflect the number of potential sites. Number of study participants had been changed based on revised sample size calculation method and assumptions.
4.4 End of study definition	Clarified that only study participants not rolling over into TP0004 will have an EOS Visit performed 8 weeks after the final dose of IMP, or upon discontinuation of the study.	Updated for consistency within the protocol.
5.1 Inclusion Criteria	**For participants in Japan only:** Criterion #1, now 1a: New wording has been included to provide details on the consent requirements for participants aged <20 years of age.	In accordance with local regulations in Japan. [a]
5.1 Inclusion criteria	Criterion #4 now 4a, has been amended to include documented intolerance or insufficient response to a minimum of two standard of care ITP medications.	Global implementation of an ANSM request and implement feedback received from the FDA.
5.1 Inclusion criteria	Criterion #6 now 6a, has been amended to remove "immunosuppressive".	Updated to be consistent with Table 6-2.
5.2 Exclusion criteria	Criterion #5 now 5a, has been updated to remove reference to IMP or comparative drugs (and/or an investigational device).	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
5.2 Exclusion criteria	Criterion #7 now 7a, has been amended to remove "bacterial or viral infection" and "untreated *H. pylori* infection" has been added.	Updated for exclusion criteria clarification. [a]

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	Criterion #8 now 8a, was updated to ensure the criterion was applicable to prior to the "first" dose.	Updated for exclusion criteria clarification.
5.2 Exclusion criteria	Criterion #11 now 11a, was amended to "Study participant has any of the following active GI disorders: inflammatory bowel disease, GI ulceration or diverticulitis."	No scientific reason to exclude patients with history of said disorders.
5.2 Exclusion criteria	**For participants in Japan only:** Criterion #20a has been amended to include "if applicable as per local guidance" and remove "per local guidance" for a lack of documented vaccination records.	Updated for exclusion criteria clarification.[a]
5.2 Exclusion criteria	Criterion #21 now 21a, was updated to ensure the criterion was applicable to the "final" dose.	Updated for exclusion criteria clarification.
5.2 Exclusion criteria	Criterion #23 now 23a, has been updated to clarify that study participants with treatment with rituximab more than 6 months prior to Visit 2 (Baseline Visit) are excluded if B cells have not returned to normal, irrespective of time.	Allowing recovery of B cell function is preferable regardless of the lapsed time.[e]
5.2 Exclusion criteria	Criterion #24 now 24a, has been amended to include a cross-reference to rescue therapy	Updated for exclusion criteria clarification.
5.2 Exclusion criteria	Criterion #28 now 28a, has been amended to include "at the Screening Visit".	Updated for exclusion criteria clarification.[e]
5.2 Exclusion criteria	Criterion #31 now 31a, has been amended to include a specific timepoint, ie, Baseline.	Updated for exclusion criteria clarification.
5.2 Exclusion criteria	Criterion #33 now 33a, has been amended to include a specific timepoint, ie, Screening and the order of text has been reordered. In addition, "understood and" has been deleted.	Updated for exclusion criteria clarification.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	Criterion #34 now 34a, has been amended to include "at the Screening Visit."	Updated for exclusion criteria clarification.
5.2 Exclusion criteria	Criteria #39 now 39a, was updated to replace family history with “current or medical history”.	Updated for exclusion criteria clarification.
5.2 Exclusion criteria	Criteria #41 now 41a, was updated to specify heart rate using Fridericia’s formula (QTcF), and to correct the visit to “Baseline Visit”.	QTc was not specific enough.
5.2 Exclusion criteria	Criteria #43 now 43a, has been updated to only exclude major surgeries, and only whilst participants are in the study.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
5.2 Exclusion criteria	**For participants in Japan only:** A new criterion, #44, has been added: Study participant has undergone a partial splenic artery embolization in the 6 months prior to Baseline Visit. Study participants with evidence of functional asplenia should be managed clinically as a splenectomized participant (eg, vaccination, antibiotics prophylaxis) as per local guidance.	Added as this procedure might be used for treatment of ITP in Japan and certain exclusions need to be applied. [a]
5.2 Exclusion criteria, Table 5-1	The period relative to the Baseline Visit has been updated for rituximab in line with Exclusion Criterion 23a.	Updated for required treatment-free periods. [e]
5.2 Exclusion criteria, Table 5-1	Inebulizumab was added to the table requiring a 6-month treatment-free period prior to Baseline, and B-cell counts within the normal range.	Updated for clarification of prohibited medications and required treatment-free periods.
5.2 Exclusion criteria, Table 5-1	TPO-RAs examples of Eltrombopag and Avatrombopag were removed.	Updated for clarification of prohibited medications and required treatment-free periods. [d]
5.4 Screen failures	New wording has been included pertaining to additional rescreening.	Updated to provide clarity and be consistent with study design and remainder of protocol.

Section # and Name	Description of Change	Brief Rationale
6 Study Treatments, Table 6-1	Canada has been added to Packaging and label specification.	Updated to remain consistent across the ITP Phase 3 clinical program.
6.2 Measures to minimize bias: randomization and blinding	The following text has been added to: The randomization number **will** be incorporated **from the IRT** into the eCRF **by automatic data transfer**.	Updated to provide further clarity.
6.2.1.1: Maintenance of study treatment blind	Amended to allow disclosure of platelet count results to study participants.	It is deemed necessary information for participants when engaging in activities of daily living.
6.2.1.1: Maintenance of study treatment blind	The following sentence was added "An independent Quantitative Clinical Pharmacologist/Modeling and Simulation Scientist may have access to the randomization code to review unblinded PK, platelet and serum IgG data."	Added to allow modelling activities regarding potential pharmacokinetic/pharmacodynamic analysis as specified in the statistical section to be started by and independent scientist.
6.2.1.1: Maintenance of study treatment blind 7.1.4: Temporary IMP discontinuation	Clarification that treatment will be temporarily discontinued for any participant with IgG levels below 1g/L on any occasion. Clarification of formal and informal unblinding and the role of the unblinded Medical Monitor.	Updated to clarify when treatment discontinuation is required, unblinding, and the role of the unblinded Medical Monitor.[b]
6.4.1 Permitted concomitant treatments (medications and therapies), Table 6-2	Clarification of oral corticosteroid dose.	Updated to clarify permitted concomitant medications. [b]
6.4.1 Permitted concomitant treatments (medications and therapies), Table 6-2	Addition of Eltrombopag, Avatrombopag and Fostamatinib at any dose as permitted concomitant treatments.	Updated to clarify permitted concomitant medications.[d]
6.4.1 Permitted concomitant treatments (medications and therapies), Table 6-2	The following footnote was added "a Stable dose is defined as either the same dose and frequency of the respective medication taken for the period of time defined in Table 6-2, or no dose of the respective medication taken for the period of time as defined in Table 6-2."	Added to provide additional clarity on the protocol requirements related to the stable dose of the allowed concomitant treatments.

Section # and Name	Description of Change	Brief Rationale
6.4.1 Permitted concomitant treatments (medications and therapies)	**Applicable to Japan only**: The following wording has been removed: "The use of medicinal cannabidiols and medicinal marijuana (prescribed by a physician) is also permitted. When applicable, the study participant must be on a stable dose of cannabidiols and/or medicinal marijuana for [redacted] prior to Screening and remain stable for the duration of the study."	These drugs are prohibited by law in Japan. [a]
6.4.2 Prohibited concomitant treatments (medications and therapies)	Clarification of corticosteroids.	Updated to clarify prohibited concomitant medications. [b]
6.4.2 Prohibited concomitant treatments (medications and therapies)	Addition of Romiplostim as prohibited treatment.	Updated to clarify prohibited concomitant medications. [a]
6.4.2 Prohibited concomitant treatments (medications and therapies)	Removal of TPO-RA as prohibited treatment.	Updated to clarify prohibited concomitant medications. [a]
6.4.2 Prohibited concomitant treatments (medications and therapies)	New wording has been included explaining the use of prohibited concomitant treatment will lead to permanent discontinuation from IMP. Subsequently, participants should complete the assessments outlined for the EW Visit and enter the SFU Period.	Updated for clarification of prohibited medications.
6.4.3 Rescue Therapy	Additional details related to platelet transfusion, systemically administered corticosteroids, and a definition of a high dose of corticosteroids have been included.	Updated to clarify rescue therapy.[c]
7.1.3 Discontinuation of IMP due to other adverse events or medical condition	New wording has been included on the withdrawal of study participant during the treatment period and the requirement to complete assessments outlined in the Early Withdrawal Visit.	Updated to provide further clarity on study visits following withdrawal.

Section # and Name	Description of Change	Brief Rationale
7.1.4 Temporary IMP discontinuation	Criterion #2, #3, #4, and #5 were amended. In addition, details have been added for participants that have suspected or confirmed COVID-19.	Updated to provide clarity and remain consistent.
7.2 Participant discontinuation/withdrawal from the study	This section was updated to reorder withdrawal criteria and remove repetitive information.	Updated to provide clarity and be consistent with study design and remainder of protocol.
7.3 Lost to follow up	This section was updated to remove repetitive information.	To avoid repetition.
8 Study Assessments and Procedures	A new paragraph describing contingency measures during a pandemic and other exceptional circumstances has been included.	Contingency measures have been implemented to ensure study participant safety in response to the COVID-19 pandemic causing the inability for sites to adhere to protocol visits and assessments.
8.1.1 Platelet counts	Study endpoints related to platelet counts were updated to match the updates made in Sections 1.1 and 3.	To be consistent with the rest of the protocol.
8.1.1 Platelet counts	The following sentence was modified to clarify that the analysis was not for all clinical response variables: "The **Response and Complete Response** variables will be assessed only for visits for which both platelet counts and the ITP bleeding score are assessed (with the exception of the confirmatory platelet assessments which may be obtained at any visit (scheduled or unscheduled) provided that they meet the criteria below)."	Updated to provide clarity.
8.1.2 ITP bleeding score	The following was added 'with grading of severity' to clarify the definition SMOG.	Updated to include missing information.
8.1.3 Patient Reported Outcomes	The list of PROs has been updated to replace the "Physical Fatigue Instrument" by the "FATIGUE-PRO Physical Fatigue scale".	To indicate the correct name of the PRO.
8.1.3.1 ITP-PAQ	Details have been added to explain the addition of the ITP-PAQ	Corrected to clarify the variable.

Section # and Name	Description of Change	Brief Rationale
	Symptoms score as a secondary efficacy endpoint.	
8.1.3.3 FATIGUE-PRO Physical Fatigue Scale	The "Physical Fatigue Instrument" has been replaced by the "FATIGUE-PRO Physical Fatigue scale".	To indicate the correct name of the PRO.
8.2.5 Assessment and management of TB and TB risk factors	A cross reference to the exclusion criteria was corrected: Exclusion Criterion 0 was updated to exclusion criterion 9.	Updated to correct an error.[e]
8.2.5.1 Tuberculosis assessment	Wording for Monitoring for TB during the study has been updated to clarify that study participants who have withdrawn from the study return for the EW visit and complete all EOS assessments.	Updated to correct an error.
8.2.5.1 Tuberculosis assessment	TB signs and symptoms questionnaire: "and must receive prophylactic LTB infection therapy" has been deleted.	To provide further clarity.
8.2.5.1 Tuberculosis assessment	**Applicable to Japan only**: New wording for TB assessment by IGRA has been added: the preferred screening test is IGRA performed at a Central Laboratory by QuantiFERON tube test, "or using a T-SPOT.TB test at each site"	To add the T-SPOT test as a recommended IGRA test in addition to QuantiFERON test.[a]
8.2.5.1 Tuberculosis assessment	**Applicable to Japan only**: New wording for TB assessment by chest x-ray has been included: "Although the incidence of TB is low in Japan, chest X-rays should be performed for all study participants." The following text has been amended: "A chest X-ray or other imaging test at unscheduled timepoints (see Section 1.3) should be performed only if indicated (eg, presence of signs and symptoms suggestive of TB, close exposure to persons with TB), and interpreted by a qualified specialist (ie, radiologist or pulmonologist)"	To confirm safety regarding various chest diseases. [a]

Section # and Name	Description of Change	Brief Rationale
8.2.5.2 Tuberculosis management	Active TB or nontuberculous mycobacterium infection: New wording has been included stating study participants should be encouraged to "enter the SFU period" and "attend Visit 29".	Updated to clarify procedures on active TB or nontuberculous mycobacterium infection.
8.2.6 Splenectomized study participants	**Applicable to Japan only**: Additional wording has been included: "if applicable" and "as per local requirements"	Updated to provide further clarity.[a]
8.2.6 Splenectomized study participants	Wording specific to splenectomized participants receiving adequate vaccination within 4 years of enrollment or prior to enrollment to avoid the treatment interruption has been included.	Updated to provide further clarity.
8.3.8 Adverse events of special monitoring	A sentence has been added to clarify that an AESM is not necessarily a serious adverse event unless one of the seriousness criteria defined in the Appendix 3.	Updated to provide further clarity.
8.8.2 Immunology	Text updated to specify that serum complements (C3, C4), plasma complements (C3a, C5a), and serum cytokines are collected 4 hours postdose at Baseline and at Week 23.	Updated to provide further clarity and be consistent with the rest of the protocol.
8.9 Exploratory biomarkers	Duplicate details pertaining to sample collection, processing, storage, labeling, and shipping have been deleted.	To remove repetition.
9.1 Definition of analysis sets	Text around the analysis of the PD, efficacy and immunologic variables has been updated and moved to be under the definition of the Safety Set (SS).	To clarify that all efficacy will be analyzed on the Randomized Set (RS) and the PD and immunology will be analyzed on the SS analysis set, unless otherwise specified.
9.1 Definition of analysis sets	The definition of the Full Analysis Set (FAS) has been updated.	Updated to be consistent with the SAP.
9.1 Definition of analysis sets	Updated the analysis set for the "Pharmacodynamic data" and the "Pharmacodynamic Per Protocol Set" analysis to the SS.	Updated to clarify that the pharmacodynamics will be analyzed in the safety set (all randomized study participants who received at least one dose of IMP).

Section # and Name	Description of Change	Brief Rationale
9.2 General statistical considerations	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.
9.3.1 Analysis of the primary efficacy/primary endpoint	The primary efficacy endpoint was updated to match the updates made in Sections 1.1 and 3.	To be consistent with the rest of the protocol.
9.3.1 Analysis of the primary efficacy/primary endpoint	The description of the primary analysis was updated. In addition, the test statistic for the combination test(s) was updated from t-test to Cochran-Mantel-Haenszel chi-square.	Updated to correct an error in the previous version.[b]
9.3.1 Analysis of the primary efficacy/primary endpoint	Table 9-1: The primary efficacy endpoint was updated to match the updates made in Sections 1.1 and 3. In addition, the intercurrent event strategy for the sensitivity analysis was amended.	To be consistent with the rest of the protocol.
9.3.1 Analysis of the primary efficacy/primary endpoint	Table 9-1: Updated the analysis of the primary endpoint.	To provide further clarity.
9.3.1 Analysis of the primary efficacy/primary endpoint	Table 9-1: Added a sensitivity analysis for the same endpoint, using the same analysis set (RS), but different methods for imputing missing values.	To confirm the robustness of the primary result.
9.3.1 Analysis of the primary efficacy/primary endpoint	Table 9-1: Included a 'supplemental analysis' for the difference in the proportion of responders using Fisher's Exact test.	To confirm the result should the placebo rate be low.
9.3.2 Analysis of the secondary efficacy endpoints	The secondary efficacy endpoints were updated to match the updates made in Sections 1.1 and 3.	To be consistent with the rest of the protocol.
9.3.2 Analysis of the secondary efficacy endpoints	Table 9-2: Estimands for secondary endpoints: Details for the "patient reported outcomes" have been updated.	To provide further clarity.
9.3.2 Analysis of the secondary efficacy endpoints	Table 9-2: Updated the analysis of the secondary endpoint "Cumulative number of weeks with Clinically Meaningful Platelet Response of $\geq 50x10^9$/L over the	To provide further clarity.

Section # and Name	Description of Change	Brief Rationale
	24-week treatment period" to include the geographical region.	
9.3.2 Analysis of the secondary efficacy endpoints	Table 9-2: Updated the analysis of the secondary endpoint "Time to first Clinically Meaningful Platelet Response of $\geq 50x10^9/L$: time from starting treatment to achievement of first response of $\geq 50x10^9/L$" to include the geographical region.	To provide further clarity.
9.3.2 Analysis of the secondary efficacy endpoints	Table 9-2: Updated the analysis of the secondary endpoint "Clinically Meaningful Platelet Response of $\geq 50x10^9/L$ by Day 8"	To provide further clarity.
9.3.2 Analysis of the secondary efficacy endpoints	Table 9-2: Updated the analysis of the secondary endpoint "Response defined as platelet count $\geq 30x10^9/L$ and at least a 2 fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding"	To provide further clarity.
9.3.2 Analysis of the secondary efficacy endpoints	Table 9-2: Updated the sensitivity analysis of the secondary endpoint "Response defined as platelet count $\geq 30x10^9/L$ and at least a 2 fold increase of the Baseline count confirmed on at least 2 separate occasions at two adjacent nominal visits at least 7 days apart, and absence of bleeding" to include the geographical region.	To provide further clarity.
9.3.2 Analysis of the secondary efficacy endpoints	Table 9-2: The following secondary endpoints were deleted: "Complete Response defined as: platelet count $\geq 100x10^9/L$ confirmed at two adjacent nominal visits at least 7 days apart, and absence of bleeding.", "Clinically meaningful Response defined as: platelet count $\geq 50x10^9/L$." and "Duration of Clinically Meaningful Response: measured from achievement of first Response to loss of Response (loss of Response	To be consistent with the rest of the protocol as these are no longer secondary endpoints.

Section # and Name	Description of Change	Brief Rationale
	defined as platelet count $<50x10^9/L$)."	
9.3.2 Analysis of the secondary efficacy endpoints	The study endpoint related to ITP-PAQ Symptoms Score has been updated.	To provide further clarity.
9.3.2 Analysis of the secondary efficacy endpoints	Updated the analysis of the secondary endpoint "Change from Baseline to Week 25, including all intermediate timepoints, in ITP PAQ Symptom score" to include the geographical region.	To provide further clarity.
9.3.3.1 Analysis of pharmacokinetic endpoint	Language was updated to be in agreement with the SAP, and state that individual plasma concentration data will be summarized up to Week 4 where most participants will have not followed down titration yet, if any.	Updated for clarification. Further details will be described in the SAP.
9.3.3.1 Analysis of pharmacokinetic endpoint	The following sentence was added. "Summaries by geographical region may be performed."	To provide further clarity.
9.7 Planned interim analysis and data monitoring	Details were added to explain that the interim analysis will be conducted on combined data from TP0003 and TP0006. The text for the sample size re-estimation procedure was modified to allow for the option of maintaining the minimum sample size or increasing it. An additional sentence was added to state that no decrease in sample size will be permitted. The futility stopping rule was amended to "The study may stop for futility if the difference in response rates of the combined data from TP0003 and TP0006 is <5%, ie, the rate in the experimental arm is no less than 5% greater than the placebo arm."	To provide information for the proposal to potentially combine information from TP0003 and TP0006 for the estimand of the observed treatment effect in the assessment of futility and sample size re-estimation for Stage 2. Also, to update the decision criteria for futility to the stricter 5% level.
9.7.2 Early stopping for futility	The futility stopping rule was amended to "The futility stopping rule (non-binding) utilized for the study requires that at stage 1 the response in the rozanolixizumab	Updated due to an amendment to the futility decision rule.

Section # and Name	Description of Change	Brief Rationale
	arm is less than 5% greater than the placebo arm."	
9.8 Determination of sample size	Response rates were added from a publication (Kuter et al, 2008)	To provide further clarity.
9.8 Determination of sample size	The alpha level has been changed from 0.05 (2-sided) to 0.025 (1-sided).	The 1-sided test is more correct owing to the nature of the adaptive design.
9.8 Determination of sample size	Details about the interim analysis were modified to describe the combination of studies TP0003 and TP0006. In addition, it was clarified that the Stage 1 and Stage 2 p-values for the combination test will be obtained solely on an analysis of the primary endpoint for TP0003.	To increase the precision of the estimate of the observed treatment effect for assessment of futility and sizing of Stage 2, data from TP0003 and TP0006 will be combined at the interim analysis provided the studies recruit to a similar timeline.
9.8 Determination of sample size	Table 9-3: The expected sample size for TP0003 has been updated.	Number of study participants had been changed based on revised sample size calculation method and assumptions.
9.8 Determination of sample size	Details of the simulation results were updated.	Updated following the reduction in the sample size cap of 90 participants and the change in the futility stopping rule of more than 5% better than placebo.
10.1.3 Informed consent process	**For participants in Japan only**: New wording has been included to provide details on the consent requirements for participants aged <20 years of age.	In accordance with local regulations in Japan. [a]
10.2, Appendix 2: Clinical laboratory tests	Table 10-1: Footnotes b, c, d, e, and g added to clarify collection timepoints and requirements for protocol-required safety laboratory assessments.	Updated for clarification.[b]
10.2, Appendix 2: Clinical laboratory tests	Table 10-1: Footnote h updated to include post baseline results for vaccination specific titers	To ensure blinding is consistent throughout all studies in the rozanolixizumab clinical program.
10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments	Table 10-3: The following wording has been removed: These criteria are not directly applicable to TP0003 because it is a single dose study; however, these criteria are indirectly applicable because upon completion of study TP0003, the	To remove wording that was left from a previous version and to clarify the language for suggested actions.[b]

Section # and Name	Description of Change	Brief Rationale
	study participants are to be provided a chance to enroll in the OLE study TP0004. Clarification of language related to acetaminophen contribution to liver injury and removal of wording pertaining to requirements in China.	
10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments, References	The following reference was removed: James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009; 37:1779-84	Updated to maintain consistency within the protocol. [a]
10.8, Appendix 8: Country-specific requirements	New wording on specific requirements for Japan have been added.	In accordance with local regulations and actual condition of medical care. [a]
10.9 Appendix 9: Abbreviations and trademarks	Additional abbreviations and definitions were added: ADE, DD, and SADE.	Updated to reflect the parameters measured in the study.
10.13, Appendix 13: ITP-PAQ	Removed an additional version of the ITP-PAQ questionnaire.	Updated to remove an additional version of the questionnaire that was accidentally included. [b]
10.15, Appendix 15: FATIGUE-PRO Physical Fatigue scale	The "Physical Fatigue Instrument" has been replaced by the "FATIGUE-PRO Physical Fatigue scale".	Updated questionnaire.
10.15, Appendix 15: Physical Fatigue Instrument	The Physical Fatigue PRO was updated to a new version.	Updated questionnaire. [b]
10.15, Appendix 15: Physical Fatigue Instrument	Mental fatigue and fatigability were removed.	Updated questionnaire. [e]
10.22, Appendix 22: Management of headaches	Text added to clarify that treatment may be temporarily put on hold if a study participant experiences an AE of a severe headache that is considered related to the IMP in the opinion of the investigator, and	To add clarity.

Section # and Name	Description of Change	Brief Rationale
	is not resolved prior to the next scheduled IMP.	
10.23, Appendix 23: Management of diarrhea	Definition of severe (grade 3) diarrhea has been updated.	To add clarity.
10.23, Appendix 23: Management of diarrhea	Modification of language regarding stool sample collection for participants reporting severe diarrhea.	To clarify when stool samples may be collected. [b]
10.24 Appendix 24: Management of infusion reactions or hypersensitivity reactions	Modification of language regarding potential infusion related reactions.	Updated to provide further clarity.
10.25 Appendix 25: Management of Infections and Hypogammaglobulinemia	The following sentence was modified to state that study participants who discontinue must perform the EW Visit, enter the SFU Period and complete the EOS Visit. Study participants MUST discontinue IMP, **perform the EW Visit, enter the SFU Period and complete the EOS Visit** if any of the following events occur:	To add clarity.
10.25 Appendix 25: Management of Infections and Hypogammaglobulinemia	Modification of language regarding the Medical Monitor to clarify they are unblinded. The following sentence was modified to include "must": Treatment must be temporarily discontinued for a study participant who develops an event of hypogammaglobulinemia with a serum total IgG of <1g/L irrespective of infection. The following sentence was added "Mock infusions will be administered to maintain the blind in case of low IgG levels (see Section 7.1.4)."	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.26 Appendix 26 Protocol Amendment History	Protocol amendment 1 (global amendment) has been added.	General update.
11 References	An additional reference has been added, as cited in Section 9.8.	General update.

Section # and Name	Description of Change	Brief Rationale
11 References	An additional reference has been added, as cited in Section 10.8.	General update.[a]

[a] This update was previously incorporated to local protocol amendment 1.2.
[b] This update was previously incorporated to local protocol amendments 1.1, 1.2 and 1.3.
[c] This update was previously incorporated to local protocol amendment 1.3.
[d] This update was previously incorporated to local protocol amendments 1.1. and 1.2.
[e] This update was previously incorporated to local protocol amendments 1.2. and 1.3.

Amendment 1 (21 Nov 2019)

Overall Rationale for the Amendment

The primary reason for this protocol amendment is to incorporate the feedback from the [redacted].

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
Global	Minor administrative, formatting and typographical changes have been made.	Updated to provide clarity and be consistent with remainder of protocol.
Global	The term "Observation Period" has been removed or replaced by "Treatment Period" where applicable.	Updated to provide clarity and be consistent with remainder of protocol.
Title page	The Sponsor address was changed from UCB Biopharma SPRL to UCB Biopharma "**SRL**"	Administrative update.
1.1 Synopsis 3 Objectives and Endpoints 4.1 Overall Design 8.1.1 Platelet counts 9.3.1 Analysis of the primary efficacy/primary endpoint	The wording for primary endpoint has been amended: the word "from" was replaced with "**for**".	Updated to provide clarity.
1.1 Synopsis	The following wording in reference to 8 out of 12 weeks has been amended to replace "in" with "for at": Clinically Meaningful Platelet Count of $\geq 50x10^9$/L **for at** least 8 out of 12 weeks during the last 12	Updated to provide clarity.

Section # and Name	Description of Change	Brief Rationale
	weeks of the Treatment Period (Weeks 13 to 25).	
1.1 Synopsis 4.1 Overall Design	Additional wording for study stopping rules have been included.	Per FDA request to include details on study stopping rules.
1.1 Synopsis	Under the subsection, Number of participants, the following text, "after stage 1" has been replaced by "**at this stage**". In addition, new wording "during the interim analysis, recruitment will be ongoing" has been included.	Updated to provide clarity.
1.1 Synopsis	Under the subsection, Total groups and duration, the description of a prescreening period has been changed to Prolonged Screening Period.	Updated to provide clarity and consistency.
1.3 Schedule of Activities	Table 1-3: Table title, the schedule and corresponding footnotes have been updated.	Updated to provide clarity and be consistent with study design.
1.3 Schedule of Activities	Table 1-4: Table heading has been amended to replace Observation Period with "**Treatment Period**" and include the Safety Follow-Up Period.	Updated to provide clarity and be consistent with remainder of protocol.
1.3 Schedule of Activities	Table 1-4: Urine pregnancy test was added to Week 25 (Visit 28) was added and footnote f was applied to this visit and removed from EOS visit.	As per study design, enrollment into the OLE study, TP0004, should be conducted on the same day as Visit 28 (Week 25), and urine pregnancy test will be used to check participant's eligibility.
1.3 Schedule of Activities	Table 1-4: Vital signs will be measured and collected at Visits 10, 14, 18, 22 and 26.	These visits are dosing visits and was missed from the original protocol.
1.3 Schedule of Activities	Table 1-4: A window period of "1 to 5 days postdose" for anti-rozanolixizumab antibodies samples has been added to Week 13 and Week 23.	ADA postdose samples added to facilitate the clinical validation of drug tolerance in the ADA assay.
1.3 Schedule of Activities	Table 1-4: New footnote "j" was added and applied to vaccination titers.	Added for further clarification on sample collection for the

Section # and Name	Description of Change	Brief Rationale
		measurement of post-vaccination titers.
1.3 Schedule of Activities	Footnotes corresponding to plasma complements (C3a and C5a) and blood sample for cytokines was changed from "s" to "**t**"	Error in original protocol.
1.3 Schedule of Activities	Table 1-4: IgA, IgM, IgE will be measured at Screening instead of Baseline.	This is required due to the update of Section 5.2 Exclusion criteria; Criterion #17.
1.3 Schedule of Activities	Table 1-4: IgG will be also be measured at Weeks 7, 11, 15, and 19.	These visits (weeks) were missed from the original protocol. IgG will be monitored at these visits at the time of evaluating the primary clinical endpoint.
1.3 Schedule of Activities	Table 1-4: Footnote "w" was added to physical fatigue instrument.	Added as was missed from the original protocol.
1.3 Schedule of Activities	Table 1-4: Abbreviation list was amended to include SFU (Safety Follow-Up).	Administrative update.
1.3 Schedule of Activities	Table 1-4: Additional footnote (now footnote q) was added to indicate PK and ADA blood sampling are to be taken predose, unless otherwise stated.	Added as was missed from the original protocol.
5.2 Exclusion criteria	Criterion #17 has been amended to include "or a measurement of IgA <50mg/dL at the Screening Visit"	To exclude patients with undiagnosed IgA deficiency.
5.2 Exclusion criteria	Criterion #20 was amended: to remove "N. meningitidis" and include reference to see Section 5.4, screen failures.	For further clarification of screening related activities.
5.2 Exclusion criteria	Criterion #32 was amended: Glomerular filtration rate (GFR) was changed from 60 ml/min/1.73 m^2 to **45**ml/min/1.73 m^2.	Revised following FDA advice to relax the inclusion criteria and enroll patients with moderate renal impairment.
5.4 Screen failures	The following wording has been added: Study participants who had protective titers after vaccination, but failed screening for other	For further clarification of screening related activities and to avoid

Section # and Name	Description of Change	Brief Rationale
	reasons can be rescreened without reassessing titers within one year of initial screening.	unnecessary investigations.
6 Study Treatments	Table 6-1: minor changes to the dosing instructions and storage conditions have been made.	Updated to provide clarity.
6.2.1.1 Maintenance of study treatment blind	Minor typographical changes have been made.	Updated to provide clarity.
6.4.3 Rescue therapy	Wording on steroids was amended to replace "High dose steroid, and pulse steroids" with "**Any systemically administered corticosteroids (above the background doses) for management of infusion reactions**"	Per FDA request to include any systemic increase in corticosteroids dose above the Baseline dose can be regarded as rescue therapy.
7.1.3 Discontinuation of IMP due to other adverse events or medical condition	Formatting was amended to remove assigned numbering.	Updated to provide consistency for the listed criteria.
7.1.4 Temporary IMP discontinuation	This section was amended to include the possibility of mock infusions, and the reference to Appendix 25 was moved to the end of the section. An additional criterion has been added: Thrombocytosis (platelet count of $\geq 400 \times 10^9$/L)	Updated to provide clarity. Added as was missed from the original protocol and to ensure consistency throughout the protocol.
8.2.1 Physical examination	Height and weight have been removed from the full physical examination.	Height and weight assessments will be performed separately and not part of the full physical examination.
8.2.6 Splenectomized study participants	New wording has been included: Splenectomized participants will be assessed again for vaccination titers at Screening (see Table 1-4).	For further clarification of screening related activities.
9.3.1 Analysis of the primary efficacy/primary endpoint	The measurement of a durable clinically meaningful platelet response was corrected from greater (">") to greater than or equal to ("≥") 50×10^9/L. New wording was added: "Missing platelet count at any visit will be	Updated to correct a typographical error. Per FDA request to include details on

Section # and Name	Description of Change	Brief Rationale
	considered "worst case" and set to zero ("no platelet response") for that specific visit."	handling missing platelet count.
9.3.1 Analysis of the primary efficacy/primary endpoint	Table 9-1: The measurement of a platelet count was corrected from greater (">") to greater than or equal to ("≥") $50x10^9$/L.	Updated to correct a typographical error.
9.3.2 Analysis of the secondary efficacy endpoints	New wording has been included specific to the predefined order of formal hypotheses testing and the sequence they will be performed.	[redacted]
9.3.2 Analysis of the secondary efficacy endpoints	Table 9-2: an additional estimand for a secondary endpoint was added and minor typographical changes were made.	[redacted]
10.2 Appendix 2: Clinical laboratory tests	Table 10-1: Additional laboratory measurement and parameters were added.	These laboratory measurements and parameters were missed from the original protocol.
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Wording specific to contraception guidance for male participants (first paragraph, first 3 bullet points, second paragraph, second bullet point) was removed.	This information was not applicable to the study.
10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments	Additional footnote (g) was added to follow-up assessments for bilirubin or INR: "These tests should be obtained when IgG levels are approaching normal levels because IMP may interfere with IgG levels and interpretation."	Important to provide a timing for obtaining IgG samples due to interference of other tests.
10.8 Appendix 8: Country-specific requirements	The following changes have been made: Moldova: Wording on the recommendation of the German Vaccination Recommendation Body has been removed, and reference to Table 1-3 has been added. Poland: A urine pregnancy test has been added at Week 27 (Visit 29) for sites located in Poland. The additional urine pregnancy test on Day 29 has been removed.	The information specific to Moldova was no longer applicable to the study. The updates to Poland were made to align with Polish Health Authority's and Clinical Trial Facilitation Group recommendations.

Section # and Name	Description of Change	Brief Rationale
Appendix 15: Physical Fatigue Instrument	Minor typographical changes have been made.	Updated to be consistent with template form and provide clarity.
Appendix 17: PGI-S	Minor typographical changes have been made.	Updated to be consistent with template form and provide clarity.
Appendix 18: PGI-C	Minor typographical changes have been made.	Updated to be consistent with template form and provide clarity.
10.25 Appendix 25:	New wording was added: Local guidelines regarding antibiotic prophylaxis in asplenic participant should be followed. Readily available antibiotics are encouraged for study participants.	To remind investigators about importance of antibiotic therapy in management of infections in Splenectomized patients.

11 REFERENCES

Arnold DM, Nazi I, Toltl LJ, Ross C, Ivetic N, Smith JW, et al. Antibody binding to megakaryocytes in vivo in patients with immune thrombocytopenia. Eur J Haematol. 2015;95(6):532-7.

Anderson CL, Chaudhury C, Kim J, Bronson CL, Wani MA, Mohanty S. Perspective - FcRn transports albumin: relevance to immunology and medicine. Trends Immunol. 2006;27(7):343-8.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

EMA/CHMP/153191/2013 Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia, Mar 2014.

EMA/CHMP/BPWP/94033/2007 rev.3 Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), Jun 2018.

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. Haematologica. 2018;104(6):1112-23.

Ghanima W, Godeau B, Cines DB, Bussel JB. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment. Blood. 2012;120(5):960-9.

Kashiwagi H. Reference guide for management of adult idiopathic thrombocytopenic purpura (ITP): 2019 version. Rinsho Ketsueki. 2019;60(8):877-896.

Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet. 2008;371(9610):395-403.

Lehmacher W and Wassmer G. Adaptive Sample Size Calculations in Group Sequential Trials. Biometrics. 1999;55:1286-90.

McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. Blood. 2004;103:1364–1369.

Mathias SD, Bussel JB, George JN, McMillan R, Okano GJ, Nichol JL. A disease-specific measure of health-related quality of life for use in adults with immune thrombocytopenic purpura: its development and validation. Health Qual Life Outcomes. 2007 Feb 22;5:11.

Mathias SD, Gao SK, Rutstein M, Snyder CF, Wu AW, Cella D. Evaluating clinically meaningful change on the ITP-PAQ: preliminary estimates of minimal important differences. Curr Med Res Opin. 2009 Feb;25(2):375-83.

Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190-207.

Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109.

Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-86.

Rodeghiero F, Michel M, Gernsheimer T, Ruggeri M, Blanchette V, Bussel JB, et al. Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group. Blood. 2013;121(14):2596-606.

Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113(11):2386-93.

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

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

Sandler SG. The spleen and splenectomy in immune (idiopathic) thrombocytopenic purpura. Semin Hematol. 2000;37(1):10-2.

World Health Organization. Global Tuberculosis Report. Sep 2018;ANNEX 4.

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.