AN OPEN-LABEL EXTENSION STUDY TO INVESTIGATE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF ROZANOLIXIZUMAB IN STUDY PARTICIPANTS WITH PERSISTENT OR CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA (ITP)

PROTOCOL TP0004 AMENDMENT 4

Short title:

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

Sponsor:
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Regulatory agency identifying number:

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 4	04 Apr 2022	Non-substantial
Protocol Amendment 3	09 Dec 2021	Non-substantial
Protocol Amendment 2[b]	03 Dec 2021	Substantial
Protocol Amendment 1.1 (China)	01 Jul 2021	Substantial
Protocol Amendment 1[a]	11 May 2021	Substantial
Protocol Amendment 0.3 (China)	04 Feb 2021	Substantial
Protocol Amendment 0.2 (France)	04 Feb 2021	Substantial
Protocol Addendum A (UK)	26 Oct 2020	Not applicable
Protocol Amendment 0.1 (Japan)	03 Jun 2020	Substantial
Original Protocol	21 Nov 2019	Not applicable

[a] Protocol Amendment 1 was not submitted to all regulatory authorities prior to submission of Protocol Amendment 2. Details of the changes between the original protocol and protocol amendment 1 are provided in Section 10.25.
[b] Protocol Amendment 2 was not submitted to any regulatory authorities prior to issuance of Protocol Amendment 3.

Amendment 4 (04 Apr 2022)

Overall Rationale for the Amendment

The primary reason for this protocol amendment is to correct errors and inconsistencies from Protocol Amendment 3.

This amendment is considered to be non-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	Reference to [redacted] when describing the safety of the study drug has been amended to "well	To acknowledge the common industry codes, the description of the study drug has been updated from [redacted] and well tolerated" to

Section # and Name	Description of Change	Brief Rationale
	tolerated, with an acceptable safety profile" instead.	"well tolerated with an acceptable safety profile."
1.1 Synopsis, Overall Design	Paragraph #4 was updated to clarify that all study participants will receive rozanolixizumab at the assigned dose level from the parent study, if the platelet count was between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L.	Updated for clarity.
1.3 Schedule of activities	"W13 and W25 only" was removed from the Visit column for laboratory parameters. A new footnote m was added to clarify that samples for total cholesterol, LDL, HDL, and triglycerides will be collected at Weeks 13 and 25 only. Subsequent footnotes were reorganized. Footnote j was updated to state EOS Visit (Week 60). Footnote r was added to all dosing visits.	Blood samples are taken every 4 weeks for safety assessments. Analysis of total cholesterol, LDL, HDL, and triglycerides will be done at Weeks 13 and 25 only. Updated for consistency and to correct an error. Updated for clarity.
2.1 Study rationale	[redacted] was replaced with "well-tolerated" in paragraph #5.	To acknowledge the common industry codes, the description of the study drug has been updated from [redacted] to "well tolerated."
3 Objectives and endpoints	One of the other safety endpoints, "Changes from Baseline[a] in concentrations of total protein, albumin, α-globulin, and β-globulin", was updated to remove α-globulin and β-globulin. One of the other efficacy endpoints, "Stable Response defined as platelet count $\geq 30\times10^9$/L and absence of bleeding[b] without rescue therapy at ≥70% of the visits over the planned 52-week Treatment Period at Week 4" was updated to "starting at Week 4." One of the other secondary efficacy endpoints, "Change from Baseline[a] to Week 54 including all	Updated for consistency to Section 1.1.

Section # and Name	Description of Change	Brief Rationale
	intermediate timepoints for ITP-PAQ Symptoms domain score" was updated to "Change from Baseline[a] to Week 53 including all intermediate timepoints for ITP-PAQ Symptoms domain score."	
4.1 Overall design	Paragraph #3 was updated to clarify that all study partcipants will receive rozanolixizumab at the assigned dose level from the parent study, if the platelet count was between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L.	Updated for clarity.
4.1 Overall design	Table 4-2 and Figure 4-1 were updated to clarify the dose adjustments for platelet count results of $\geq 10\times10^9$/L to $<30\times10^9$/L (on at least two consecutive visits) and $<10\times10^9$/L.	Updated for clarity.
4.1 Overall design	A sentence was added to the dose adjustments paragraph to state: If a study participant has been down-titrated to a fixed-unit dose equivalent to [redacted] or the [redacted] total dose (corresponding to an average [redacted] dose in a participant weighing 70kg), and platelet count decreases to $<50\times10^9$/L, then up-titration to a fixed-unit dose equivalent to [redacted] or [redacted] respectively, would be allowed.	Updated for clarity.
6.4.3.1 Rescue therapy not leading to discontinuation	Bullet point #2 was updated to remove reference to "intravenous" and "steroids" was updated to "corticosteroids."	Updated for consistency.
6.4.3.2 Rescue therapy leading to discontinuation	Bullet point #4: "steroids" was updated to "corticosteroids."	Updated for consistency.
6.7 Home visits	The requirement for stable platelet count "during the last two dosing visits" was updated to "during the last four dosing visits." Platelet count result between 50 to 150×10^9/L was corrected to between ≥ 50 to $\leq 150\times10^9$/L.	Updated for consistency and to correct errors.

Section # and Name	Description of Change	Brief Rationale
8.1.5.1 Tuberculosis assessment	Reference to the TB questionnaire, Appendix 18 was corrected.	Updated for consistency and to correct an error.
10.1.3 Informed consent process Appendix 10.7, Japan	Japan-specific requirement for study participants <20 was removed.	Since 01 Apr 2022, the revision to the Japan civil code has lowered the age of adulthood to 18 from 20.
Appendix 10.7, France	Anticipated timelines for completing enrollment of all participants in the parent studies were updated.	To provide the updated projected dates.
10.9 Appendix 9: Abbreviations and trademarks	Additional abbreviations and definitions were added for: UADE and USADE	General update.

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:

An open-label extension study to investigate the long-term safety, tolerability, and efficacy of rozanolixizumab in study participants with persistent or chronic primary immune thrombocytopenia (ITP).

Short Title:

A Phase 3 study evaluating the long-term safety, tolerability, and efficacy of rozanolixizumab in study participants with primary 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 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.

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. TP0003 and TP0006, the parent studies of the current open-label extension (OLE) study, TP0004, are designed to evaluate the efficacy, safety, and tolerability of rozanolixizumab given as doses equivalent to [redacted] or reduced doses equivalent to [redacted] or approximately [redacted] in adult study participants with ITP. This study, TP0004, is designed to assess whether repeat treatment over a period of 52 weeks with rozanolixizumab sc infusion is well tolerated with an acceptable safety profile and will result in platelet increases as a measure of efficacy. Data from this study will support the data from the parent studies (TP0003 and TP0006).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the long-term safety and tolerability of treatment with rozanolixizumab	The primary safety endpoints are: • Occurrence of treatment-emergent adverse events (TEAEs) • Occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab (ie, study discontinuation) The other safety endpoints are: • Occurrence of treatment-emergent adverse events of special monitoring (AESM) • Occurrence of serious TEAEs • Occurrence of treatment-related TEAEs • Vital sign change from Baseline[a] (blood pressure [BP], body temperature, and pulse rate) at each scheduled assessment during Treatment and Safety Follow-Up (SFU) Periods • 12-lead electrocardiogram (ECG) change from Baseline[a] at each scheduled ECG assessment visit • Laboratory change from Baseline[a] (hematology, including coagulation parameters, clinical chemistry, and urinalysis) at each scheduled assessment during Treatment and SFU Periods • Changes from Baseline[a] in concentrations of total protein and albumin • Changes from Baseline[a] in serum (C3 and C4) and plasma (C3a and C5a) complement levels at each scheduled assessment during study (for study participants experiencing infusion or hypersensitivity reactions)

Objectives	Endpoints
Secondary	
• To assess the long-term clinical efficacy of treatment with rozanolixizumab	The secondary efficacy endpoint is: • Stable Clinically Meaningful Response, defined as Clinically Meaningful Response (ie, platelet count $\geq 50\times10^9$/L) without rescue therapy at ≥70% of the visits over the planned 52 week Treatment Period starting at Week 4 The other efficacy endpoints are: • Stable Response defined as platelet count $\geq 30\times10^9$/L and absence of bleeding[b] without rescue therapy at ≥70% of the visits over the planned 52-week Treatment Period starting at Week 4 • Cumulative number of weeks with Clinically Meaningful Response over the 52-week Treatment Period • Cumulative number of weeks with platelet counts $\geq 30\times10^9$/L over the planned 52-week Treatment Period • Duration of first Clinically Meaningful Response starting at Week 4 • Mean Change from Baseline[a] in platelet count at each visit • Use of rescue medication by visit • ITP specific Bleeding Assessment Tool (ITP-BAT) bleeding events and severity by visit
• To assess the effect of rozanolixizumab on study participant perceived symptoms	• Change from Baseline[a] to Week 53 including all intermediate timepoints for ITP-PAQ Symptoms domain score
• To assess the reduction in use of steroids and other concomitant ITP medications	• AUC of the oral steroid dose over time • Change in dose and/or frequency of concomitant ITP medications (excluding corticosteroids) over time
Exploratory	
• To assess the effect of rozanolixizumab on patient-reported outcomes (PROs)	• Change from Baseline[a] in FATIGUE-PRO Physical Fatigue Score • Change from Baseline[a] in Patient Global Impression of Severity (PGI-S)

Objectives	Endpoints
	• Patient Global Impression of Change (PGI-C) at all available post-Baseline[a] assessments • Change from Baseline[a] in ITP-Patient Assessment Questionnaire (ITP-PAQ) domain scores
• To assess the clinical efficacy of rozanolixizumab in study participants with first exposure to rozanolixizumab	• In study participants with first exposure to rozanolixizumab: Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 4 of 6 [redacted] visits between Weeks 13 to 25 of the study • In study participants with first exposure to rozanolixizumab: 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
• To assess effect of rozanolixizumab on health-related quality of life (HRQoL) and broader disease impact	• Change from Baseline[a] in European Quality of Life (EuroQol)-5 dimension 5 Levels Assessment (EQ-5D-5L) item responses • Change from Baseline[a] in Short-Form 36-Item (SF-36) domain and composite scores
• To assess resource utilization	• Number and length of hospitalizations • Number of infusion center admissions
• To assess the experience with the subcutaneous (sc) self-administration	• PRE-Self Injection Assessment Questionnaire (SIAQ) (Infusion version) domains scores before the first sc self-administration in participants that self-administer • POST-SIAQ (Infusion version) domains scores at each available visit in participants that self-administer
• To assess the PD effect of rozanolixizumab	• Total serum IgG (absolute value) and change from Baseline[a] (absolute value and percentage) in serum IgG and in serum IgG subclass concentration at each scheduled assessment • Absolute value and change from Baseline[a] (absolute value and percentage) in serum Ig concentrations (IgA, IgE, IgM) at each scheduled assessment

Objectives	Endpoints
• To evaluate the incidence and emergence of antidrug antibody (ADA) of rozanolixizumab	• ADA at each scheduled assessment
• To assess the pharmacokinetics (PK) of rozanolixizumab administered by sc infusion	• Plasma concentrations of rozanolixizumab at each scheduled assessment
• To evaluate clinical response following end of dosing	• Platelet count by visit after end of dosing • Time from end of rozanolixizumab dosing to loss of clinically relevant response
• To assess the influence of rozanolixizumab treatment on vaccination titers	• Percent change from Baseline[a] in vaccination titers against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* in splenectomized study participants
• To assess the effect of rozanolixizumab on post-vaccination biomarker(s) in study participants who received the COVID-19 vaccine	• Change in post-vaccination biomarker(s) over time in study participants who received the COVID-19 vaccine

[a] Baseline definitions will be detailed in the SAP.
[b] Absence of bleeding indicated by Grade 0 for all domains of the Skin-Visible Mucosa-Internal Organs (SMOG) tool, or a Skin Grade of 0 or 1.

Overall Design

This is a Phase 3, multicenter, 59-week OLE study of rozanolixizumab in study participants with persistent or chronic primary ITP. Study participants from TP0003 and TP0006 who have completed the 24-week Treatment Period (irrespective of rescue therapy) and continue to meet the eligibility criteria will be offered enrollment into TP0004.

This study will assess whether continued dosing [redacted] with rozanolixizumab is well tolerated with an acceptable safety profile. This study will also assess whether continued rozanolixizumab sc infusions [redacted] over a period of 52 weeks will maintain a durable Clinically Meaningful Platelet count of $\geq 50 \times 10^9$/L.

The rollover from TP0003 or TP0006 to TP0004 needs to be completed within 3 days after Week 25 (Visit 27) of the parent studies at the latest. In case of a late rollover, platelet counts will need to be remeasured.

On Day 1 (Baseline Visit), which corresponds to Week 25 of the parent studies, TP0003 or TP0006, all study participants will enter TP0004. All study participants will receive rozanolixizumab treatment [redacted] at the assigned dose level at the end of TP0003 or TP0006, if the platelet count was between $\geq 50 \times 10^9$/L and $\leq 150 \times 10^9$/L. If outside of this range, a higher or lower dose level than the final sc infusion in TP0003 or TP0006 is permitted according to Table 4-2 and Figure 4-1. Rozanolixizumab will be administered [redacted] as a sc infusion to maintain platelet count $\geq 50 \times 10^9$/L. Dose levels equivalent to [redacted] and

[redacted] total dose (corresponding to an average [redacted] dose in a participant weighing 70kg) [redacted] can be utilized for maintenance treatment.

If treatment with rozanolixizumab does not lead to an increase in platelet counts $\geq 30\times10^9$/L, study participants can be treated with rescue therapy if deemed needed by the investigator. If platelet counts are $\geq 10\times10^9$/L to $<30\times10^9$/L or active bleeding, rescue therapy is recommended (eg, commercially available medication, such as intravenous (iv) immunoglobulin (IVIg), high dose corticosteroids and pulse steroids, platelet transfusions, or any other medication listed in Section 6.4.3). If platelet counts are $<10\times10^9$/L, rescue therapy is highly recommended as per Section 6.4.3.

An external Independent Data Monitoring Committee (IDMC) will be utilized to review the safety data at predefined intervals and ad hoc as needed, should any emerging safety concern arise during the study. 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, [redacted] dosing was implemented in protocol amendment 2. Study participants being treated with the [redacted] dosing regimen will switch to the [redacted] dosing regimen once protocol amendment 2 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 the rozanolixizumab program.

Number of Participants

Based on the number of study participants planned for the parent studies, up to a maximum of 180 study participants who complete TP0003 or TP0006 may be eligible to enroll in this OLE study.

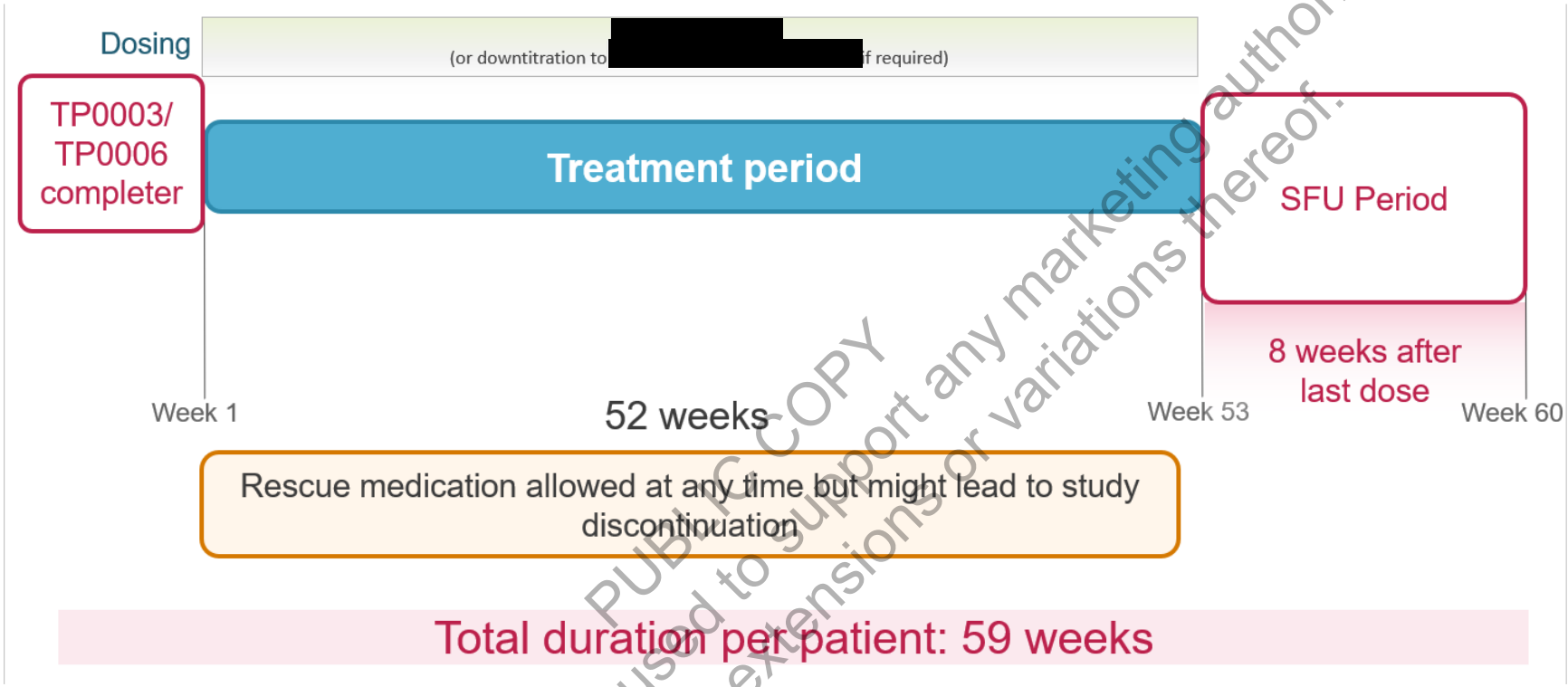
Treatment Groups and Duration

Study participants will be treated for a maximum of 52 weeks. After the final dose, study participants will be followed in an 8-week SFU Period. The maximum total duration of the study for each study participant will be 59 weeks (For **France**-specific requirements, see Appendix 7, Section 10.7).

1.2 Schema

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

Figure 1-1: TP0004 study schematic



[redacted] SFU=Safety Follow-Up

1.3 Schedule of Activities

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	1/ BL	2	3	4	5	6	7, 9, 11, 13,	8, 12, 16	10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50	15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53	20, 24, 28, 52	32, 36, 40, 44, 48	54	55	56 EOS[c]/ EW
	Week	[redacted]														
	Day															
Assessments[a]	Visit window	up to +3 days from W25 of parent study	+2 d	±2 d[d]	±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														
Verification of inclusion/exclusion criteria		X														
Demographic data		X[e]														

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	**1/ BL**	**2**	**3**	**4**	**5**	**6**	**7, 9, 11, 13,**	**8, 12, 16**	**10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50**	**15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53**	**20, 24, 28, 52**	**32, 36, 40, 44, 48**	**54**	**55**	**56 EOS[c]/ EW**
	Week	[redacted]														
	Day															
Assessments[a]	**Visit window**	**up to +3 days from W25 of parent study**	**+2 d**	**±2 d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
General medical/procedures history		X[e]														
ITP history update		X														
Prior and concomitant medication		X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[f]		X					X			X				X		X

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	1/ BL	2	3	4	5	6	7, 9, 11, 13,	8, 12, 16	10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50	15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53	20, 24, 28, 52	32, 36, 40, 44, 48	54	55	56 EOS[c]/ EW
	Week	[redacted]														
	Day															
Assessments[a]	Visit window	up to +3 days from W25 of parent study	+2 d	±2 d[d]	±2d [d]	±2d [d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]
Platelet count (local laboratory)[g]		X[h]	X	X	X	X	X	X[i]	X	X		X	X[i]	X	X	X
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[j]		X[k] pre- and postdose			X pre-dose					X pre-dose (W25 only)						X
Vital signs[l]		X[e]	X	X	X	X	X	X	X	X	X	X	X	X		X
Body weight		X								X (W25 only)				X		X

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	**1/ BL**	**2**	**3**	**4**	**5**	**6**	**7, 9, 11, 13,**	**8, 12, 16**	**10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50**	**15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53**	**20, 24, 28, 52**	**32, 36, 40, 44, 48**	**54**	**55**	**56 EOS[c]/ EW**
	Week	[redacted]														
	Day															
Assessments[a]	**Visit window**	**up to +3 days from W25 of parent study**	**+2 d**	**±2 d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**	**±2d[d]**
Height		X[e]														
Full physical examination		X[e]												X		
Short physical examination				X			X			X						X
Recording of AEs (including hospitalizations)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	1/ BL	2	3	4	5	6	7, 9, 11, 13,	8, 12, 16	10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50	15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53	20, 24, 28, 52	32, 36, 40, 44, 48	54	55	56 EOS[c]/ EW
	Week	[redacted]														
	Day															
	Visit window	up to +3 days from W25 of parent study	+2 d	±2 d[d]	±2d [d]	±2d [d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]
Assessments[a]																
Laboratory parameters (coagulation, hematology, chemistry, and urinalysis using central laboratory)		X[e]		X	X		X			X[m]				X		X
Vaccination titer (in splenectomized participants)		X[e]								X (W25 only)						X
COVID sample (for study participants vaccinated prior to entry into TP0004)[n]		X								X (W25 only)						X

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	**1/ BL**	**2**	**3**	**4**	**5**	**6**	**7, 9, 11, 13,**	**8, 12, 16**	**10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50**	**15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53**	**20, 24, 28, 52**	**32, 36, 40, 44, 48**	**54**	**55**	**56 EOS[c]/ EW**
	Week	[redacted]														
	Day															
Assessments[a]	**Visit window**	**up to +3 days from W25 of parent study**	**+2 d**	**±2 d[d]**	**±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 sample (for study participants vaccinated during enrollment in TP0004)									X[o]							X
TB signs and symptoms questionnaire[p]		X[e]								X (W13, W25, W37, W49 only)						X
Contact IRT		X		X	X	X	X	X	X	X	X	X	X			
Administration of IMP[q]		[redacted]														

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	1/ BL	2	3	4	5	6	7, 9, 11, 13,	8, 12, 16	10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50	15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53	20, 24, 28, 52	32, 36, 40, 44, 48	54	55	56 EOS[c]/ EW
	Week	[redacted]														
	Day															
Assessments[a]	Visit window	up to +3 days from W25 of parent study	+2 d	±2 d[d]	±2d [d]	±2d [d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]
Blood sampling for plasma concentration of rozanolixizumab[s]		X	X		X		X			X (W17, W29, W41 only)						X
Anti-rozanolixizumab antibodies[s]		X			X		X			X (W17, W29, W41 only)						X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)[t]		X	X	X	X	X	X	X	X	X (W33 only)	X	X	X	X		

Table 1-1: Schedule of activities

Assessments[a]	Visit[b]	1/ BL	2	3	4	5	6	7, 9, 11, 13,	8, 12, 16	10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50	15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53	20, 24, 28, 52	32, 36, 40, 44, 48	54	55	56 EOS[c]/ EW
		Treatment Period													SFU Period	
	Week	[redacted]														
	Day															
	Visit window	up to +3 days from W25 of parent study	+2 d	±2 d[d]	±2d [d]	±2d [d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]
Blood collection for DNA and RNA[u]		X[e]					X									
Blood collection for exploratory biomarker analysis[v]		X[e]	X	X	X	X	X	X	X	X (W33 only)	X	X	X	X		
Immunoglobulins (total IgG, IgG subclasses)[w]		X[e]		X	X	X	X		X	X		X (W19, W23 only)			X	X
IgA, IgM, IgE		X[e]		X			X			X (W17, W29, W41 only)				X		

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	1/ BL	2	3	4	5	6	7, 9, 11, 13,	8, 12, 16	10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50	15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53	20, 24, 28, 52	32, 36, 40, 44, 48	54	55	56 EOS[c]/ EW
	Week	[redacted]														
	Day															
Assessments[a]	Visit window	up to +3 days from W25 of parent study	+2 d	±2 d[d]	±2d [d]	±2d [d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]
ITP-specific autoantibodies		X[e]			X					X (W33 only)						X
ITP bleeding scale		X[e]	X	X	X	X	X		X (W7 and 11 only)	X		X		X	X	X
ITP-PAQ[x]		X[e]					X			X				X		
SF-36[x]		X[e]					X			X (W17, W29, W41 only)				X		

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	1/ BL	2	3	4	5	6	7, 9, 11, 13,	8, 12, 16	10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50	15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53	20, 24, 28, 52	32, 36, 40, 44, 48	54	55	56 EOS[c]/ EW
	Week	[redacted]														
	Day															
Assessments[a]	Visit window	up to +3 days from W25 of parent study	+2 d	±2 d[d]	±2d [d]	±2d [d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±2d[d]
EQ-5D-5L[x]		X[e]					X			X (W17, W29, W41 only)				X		
PGI-C[x]		X[e]					X			X				X		
PGI-S[x]		X[e]					X			X				X		
FATIGUE-PRO Physical Fatigue Scale[x]		X[e]					X			X				X		
Pre-SIAQ (self-infusion)[y]									X	X	X	X	X			
Post-SIAQ (self-infusion)[z]									X	X	X	X	X			

Table 1-1: Schedule of activities

			Treatment Period												SFU Period	
	Visit[b]	1/ BL	2	3	4	5	6	7, 9, 11, 13,	8, 12, 16	10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50	15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53	20, 24, 28, 52	32, 36, 40, 44, 48	54	55	56 EOS[c]/ EW
	Week	[redacted]														
	Day															
Assessments[a]	Visit window	up to +3 days from W25 of parent study	+2 d	±2 d[d]	±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[aa]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Site visit

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

ADA=antidrug antibody; AE=adverse event; BL=Baseline; BP=blood pressure; d=day(s); DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EQ-5D-5L=European Quality of Life-5 Dimension 5 Levels; EW=Early Withdrawal; GI=gastrointestinal; HCP=healthcare professional; HDL=high-density lipoprotein; ICF=Informed Consent form; Ig=immunoglobulin; IMP=investigational medicinal product; IRT=interactive response technology; ITP=immune thrombocytopenia; ITP-PAQ=ITP-Patient Assessment Questionnaire; LDL=low-density lipoprotein; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetic; RNA=ribonucleic acid; SF-36=Short-Form 36-Item Health Survey; SFU=Safety Follow-up; TB=tuberculosis

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

[b] Home visits, if possible, are applicable for the individual site at the Weeks displayed in the grey columns. Home visits will be performed by a healthcare professional (HCP) visiting the study participant at his/her home. Alternately, the visits can be conducted at the site as deemed necessary by site and/or study participant. Feasibility of IMP dosing in a home setting will have to be confirmed before the visit is conducted (see Section 6.7).

[c] The EOS Visit is 8 weeks following the final dose of rozanolixizumab.

[d] A visit window of ±2 days is allowed for all visits starting at Visit 3. The visit window of ±2 days is relative to the first dosing visit date.

[e] Data will be transferred from the Screening or Baseline Visit, or Week 25 (Visit 27) of TP0003 or TP0006, as applicable.

[f] If urine pregnancy test is positive, a confirmatory serum pregnancy test is required. The study participant should not be dosed if pregnancy is confirmed.

[g] If required by site's local procedure, the platelet count assessed by the local laboratory can be done -1 day for all visits. In exceptional cases for site dosing visits without a current platelet count, the last two platelet counts can be considered, provided the platelet counts were stable during the last two dosing visits (between 50 to 150×10^9/L and no dose change) and that the dose administered during the last two dosing visits was not changed and is not planned to be changed at the current dosing visit. Study participants should not have experienced any ITP signs and symptoms or AEs since the last dosing visit.

[h] If study participants rolled over from TP0003 or TP0006 using the +3 day window, then a new platelet count is needed prior to IMP dosing.

[i] Platelet counts can be taken at the indicated home visits; home visit 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.

[j] The ECG should be performed prior to blood collection for assessment of laboratory parameters. The ECGs have to be performed pre-dose and 4 hours post-dose at Day 1, and only pre-dose at Day 15, and Week 25. ECGs should also be performed at the EOS Visit (Week 60).

[k] Local reading for inclusion of study participants by qualified personnel is sufficient.

[l] Vital signs will include BP, pulse rate, and body temperature. On the 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, W5) vital signs will be measured prior to IMP administration, at the end of infusion, and 1 hour after the end of 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 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 also applicable for dosing at site and at home.

[m] Samples for total cholesterol, LDL, HDL, and triglycerides will be collected at Weeks 13 and 25 only.

[n] For study participants who received COVID vaccine prior to entry into TP0004.

[o] For study participants who received COVID vaccine during enrollment into TP0004. The collection of COVID-19 Baseline samples should occur 2 to 3 weeks after the participant has received his/her last vaccination (ie, second dose of a 2-dose vaccine, or a booster vaccination). A second sample should be collected 3 months after last vaccination and a third sample should be collected 6 months after last vaccination.

[p] The TB signs and symptoms questionnaire have to be performed every 12 weeks (90 days) starting with Week 13 and in Weeks 25, 37, 49, and at the EOS Visit (Week 60).

[q] Prior to dosing, management of infections and hypogammaglobulinemia must be considered as per Appendix 22, Section 10.22.

[r] 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.

[s] Unless specified, samples are collected predose when the IMP is administered at the same visit.

[t] Serum complements (C3, C4) and plasma complements (C3a, C5a) should be taken predose at Baseline (Day 1) and at Week 33 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 8.2.8).

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

[v] Exploratory biomarker samples should be taken predose at Baseline (Day 1) and predose at Week 33. 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 serious GI disorders (ie, abdominal pain, diarrhea, vomiting; see Section 8.2.8).

[w] If total IgG levels are <1 g/L, ad hoc assessments (eg, additional IgG samples) may be performed to monitor recovery of IgG levels. See Section 10.22.

[x] PROs to be completed prior to IMP dose and prior to any other study procedures.

[y] For study participants who self-infuse, to be completed once, prior to first self-infusion.

[z] To be completed within 1 hour after the first and second consecutive self-infusion.

[aa] This assessment is applicable only to participants experiencing moderate, severe and/or serious headache (see Section 10.20), 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 IgG4P monoclonal antibody that is being developed as an inhibitor of the activity of the FcRn for IgG.

By blocking the IgG binding site 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.

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 intravenous 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).

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 et al, 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-Rh_o (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 spleen tyrosine kinase-inhibitor, was 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 or 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 well-tolerated, effective, and convenient alternative to existing treatments. This Phase 3 OLE study will evaluate the longer-term safety and tolerability of rozanolixizumab with repeat dosing

in study participants with primary ITP who have completed the parent studies TP0003 or TP0006.

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 CIPD01 is a completed Phase 2a study in study participants with CIDP. UP0060 is a Phase 1 study in healthy volunteers, CIDP04 (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.

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:

- Treatment Arm 1: rozanolixizumab 10mg/kg sc (12 doses administered at 12 weekly visits)
- Treatment Arm 2: placebo sc (12 doses administered at 12 weekly visits)

Overall, weekly administration of rozanolixizumab at a dose level of 10mg/kg SC was generally 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 subjects with CIDP. The study includes 2 Treatment periods with 10mg/kg doses of rozanolixizumab by sc infusion at weekly intervals in two parts of the study (Treatment Period Part 1: 24 weeks, Treatment Period Part 2: 52 weeks).

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 TP0001 indicate that rozanolixizumab was tolerated with an acceptable safety profile after multiple doses (4mg/kg, 7mg/kg, and 10mg/kg) and single doses (15mg/kg and 20mg/kg). The most frequent adverse event (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 considered that TP0001 established supportive evidence of efficacy and safety, and proceeded with the development of rozanolixizumab for the treatment of adults with persistent or chronic primary ITP in two pivotal phase 3 studies prior to the start of this study, TP0004.

TP0003 and TP0006 are Phase 3, multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy, safety, and tolerability of rozanolixizumab initially administered as a single fixed dose equivalent to [redacted] sc infusion followed by repeated bi-weekly fixed doses of approximately [redacted] sc infusion in adult study participants with primary ITP. In protocol amendment 3, the starting fixed dose equivalent to [redacted] sc was removed due to the change to [redacted] weekly dosing.

The current OLE study, TP0004, is a study that will assess the long-term safety, tolerability, and efficacy of rozanolixizumab in all study participants completing the 24-week Treatment Period in TP0003 or TP0006 (irrespective of rescue medication) and fulfilling the eligibility criteria for TP0004.

2.3 Benefit/risk assessment

Although there were a number of treatment options approved for chronic ITP in 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 increase 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 burden of existing therapies to patients, both for chronic and intermittent treatment.

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 platelet response (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 headache, and GI disturbances (diarrhea, nausea, vomiting). Potential risks include serious infusion/hypersensitivity reactions, serious infections, and effects on vaccination response. These 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 headaches, and infection is also provided as well as expedited reporting requirements of AESM.

As with any other monoclonal antibody therapy, the treatment with rozanolixizumab could be associated with the development of ADA against rozanolixizumab.

Participants will be closely monitored for acute infusion reactions or hypersensitivity reactions in TP0004. In the event of a recorded infusion reaction or hypersensitivity reaction, further complements analyses will be performed alongside the planned ADA assessment to assist in immune complex disease determination. The 52-week treatment duration of TP0004 is regarded as adequate to assess the risk of immunogenicity after [redacted] treatment administration.

Restrictions on use of live vaccines have been defined in the exclusion criterion #14. 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 the 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 COVID-19 vaccination is planned, information regarding vaccine should be recorded (Section 6.4.1). COVID-19 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 8.2.9) with causality assessment provided for both IMP and vaccine. Additionally, to further characterize the effect of rozanolixizumab on COVID-19 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 TP0004 may be found in the current version of the IB.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the long-term safety and tolerability of treatment with rozanolixizumab	The primary safety endpoints are: • Occurrence of treatment-emergent adverse events (TEAEs) • Occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab (ie, study discontinuation) The other safety endpoints are: • Occurrence of treatment-emergent adverse events of special monitoring (AESM) • Occurrence of serious TEAEs • Occurrence of treatment-related TEAEs • Vital sign change from Baseline[a] (blood pressure [BP], body temperature, and pulse rate) at each scheduled assessment during Treatment and Safety Follow-Up (SFU) Periods • 12-lead electrocardiogram (ECG) change from Baseline[a] at each scheduled ECG assessment visit • Laboratory change from Baseline[a] (hematology, including coagulation parameters, clinical chemistry, and urinalysis) at each scheduled assessment during Treatment and SFU Periods • Changes from Baseline[a] in concentrations of total protein and albumin • Changes from Baseline[a] in serum (C3 and C4) and plasma (C3a and C5a) complement levels at each scheduled assessment during study (for study participants experiencing infusion or hypersensitivity reactions)

Objectives	Endpoints
Secondary	
• To assess the long-term clinical efficacy of treatment with rozanolixizumab	The secondary efficacy endpoint is: • Stable Clinically Meaningful Response, defined as Clinically Meaningful Response (ie, platelet count $\geq 50\times10^9$/L) without rescue therapy at ≥70% of the visits over the planned 52 week Treatment Period starting at Week 4 The other efficacy endpoints are: • Stable Response defined as platelet count $\geq 30\times10^9$/L and absence of bleeding[b] without rescue therapy at ≥70% of the visits over the planned 52-week Treatment Period starting at Week 4 • Cumulative number of weeks with Clinically Meaningful Response over the 52-week Treatment Period • Cumulative number of weeks with platelet counts $\geq 30\times10^9$/L over the planned 52-week Treatment Period • Duration of first Clinically Meaningful Response starting at Week 4 • Mean Change from Baseline[a] in platelet count at each visit • Use of rescue medication by visit • ITP specific Bleeding Assessment Tool (ITP-BAT) bleeding events and severity by visit
• To assess the effect of rozanolixizumab on study participant perceived symptoms	• Change from Baseline[a] to Week 53 including all intermediate timepoints for ITP-PAQ Symptoms domain score
• To assess the reduction in use of steroids and other concomitant ITP medications	• AUC of the oral steroid dose over time • Change in dose and/or frequency of concomitant ITP medications (excluding corticosteroids) over time

Objectives	Endpoints
Exploratory	
• To assess the effect of rozanolixizumab on patient-reported outcomes (PROs)	• Change from Baseline[a] in FATIGUE-PRO Physical Fatigue Score • Change from Baseline[a] in Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C) at all available post-Baseline[a] assessments • Change from Baseline[a] in ITP-Patient Assessment Questionnaire (ITP-PAQ) domain scores
• To assess the clinical efficacy of rozanolixizumab in study participants with first exposure to rozanolixizumab	• In study participants with first exposure to rozanolixizumab: Durable Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L, for at least 4 of 6 [redacted] visits between Weeks 13 to 25 of the study • In study participants with first exposure to rozanolixizumab: Time to first Clinically Meaningful Platelet Response of $\geq 50 \times 10^9$/L: time from starting treatment to achievement of first response of $\geq 50 \times 10^9$/L
• To assess effect of rozanolixizumab on health-related quality of life (HRQoL) and broader disease impact	• Change from Baseline[a] in European Quality of Life (EuroQol)-5 dimension 5 Levels Assessment (EQ-5D-5L) item responses • Change from Baseline[a] in Short-Form 36-Item (SF-36) domain and composite scores

Objectives	Endpoints
• To assess resource utilization	• Number and length of hospitalizations • Number of infusion center admissions
• To assess the experience with the subcutaneous (sc) self-administration	• PRE-Self Injection Assessment Questionnaire (SIAQ) (Infusion version) domains scores before the first sc self-administration in participants that self-administer • POST-SIAQ (Infusion version) domains scores at each available visit in participants that self-administer
• To assess the PD effect of rozanolixizumab	• Total serum IgG (absolute value) and change from Baseline[a] (absolute value and percentage) in serum IgG and in serum IgG subclass concentration at each scheduled assessment • Absolute value and change from Baseline[a] (absolute value and percentage) in serum Ig concentrations (IgA, IgE, IgM) at each scheduled assessment
• To evaluate the incidence and emergence of antidrug antibody (ADA) of rozanolixizumab	• ADA at each scheduled assessment
• To assess the pharmacokinetics (PK) of rozanolixizumab administered by sc infusion	• Plasma concentrations of rozanolixizumab at each scheduled assessment
• To evaluate clinical response following end of dosing	• Platelet count by visit after end of dosing • Time from end of rozanolixizumab dosing to loss of clinically relevant response
• To assess the influence of rozanolixizumab treatment on vaccination titers	• Percent change from Baseline[a] in vaccination titers against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* in splenectomized study participants
• To assess the effect of rozanolixizumab on post-vaccination biomarker(s) in study participants who received the COVID-19 vaccine	• Change in post-vaccination biomarker(s) over time in study participants who received the COVID-19 vaccine

[a] Baseline definitions- will be detailed in the SAP.
[b] Absence of bleeding indicated by Grade 0 for all domains of the Skin-Visible Mucosa-Internal Organs (SMOG) tool, or a Skin Grade of 0 or 1.

4 STUDY DESIGN

4.1 Overall design

This is a Phase 3, multicenter, 1-year OLE study of TP0003 and TP0006 parent studies with rozanolixizumab in study participants with persistent or chronic primary ITP.

Study participants from TP0003 or TP0006 who have completed the 24-week Treatment Period (irrespective of rescue therapy) and meet eligibility criteria for TP0004 will be offered enrollment. Splenectomized participants rolling over from parent studies will have a vaccination titer for *Streptococcus pneumoniae* (*S. pneumoniae*), *Neisseria meningitidis* (*N. meningitidis*), and *Haemophilus influenzae* (*H. influenzae*) collected per Schedule of Activities (Section 1.3). In addition, splenectomized participants should continue to carry a splenectomy card and a recommended antibiotic (if applicable per local guidance).

All study participants rolling over into TP0004 will receive rozanolixizumab at the assigned dose level from Week 25 in the parent studies if the platelet count was between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L. If outside of this range, a higher or lower dose level than the final sc infusion in TP0003 or TP0006 is permitted according to Table 4-2 and Figure 4-1.

During the first two dosing visits, all study participants will stay for 4 hours after the end of infusion for observation at the site. Assuming the first 2 doses were well tolerated, the observation time will be 1 hour after the end of infusion for another 3 infusions. Assuming the first 5 doses were well tolerated, on subsequent weeks, a 15-minute post-dose observation will be in place for the remaining visits until Week 52. If needed, observation time can be extended for each study participant. However, if the dose needs to be decreased due to a treatment-emergent adverse event(s) (TEAE[s]) or dose needs to be increased, the post-infusion observation period will be changed to 1 hour for the next 2 infusions. The post-dose observation time frame may be extended at the discretion of the investigator.

This study will assess whether continued [redacted] dosing with rozanolixizumab is well tolerated with an acceptable safety profile. This study will also assess whether continued rozanolixizumab sc infusions [redacted] over a period of 52 weeks will maintain a durable Clinically Meaningful Platelet count of $\geq 50\times10^9$/L. Starting at Week 2 and until Week 13, platelet counts will be measured every week at a local laboratory and every 2 weeks starting at Week 15. Site visits will occur every week starting at Week 2. If applicable, home visits and home dosing are permitted per the Schedule of Activities (Section 1.3).

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). If enrollment into TP0004 is not possible at the time of Week 25 (+3 days) in TP0003/TP0006, the SFU assessments should be conducted. Once the circumstances during or after the pandemic allow, these study participants may be allowed to continue in the OLE study in consultation with the UCB study physician.

The total maximum study duration per study participant is up to 59 weeks, including a Treatment Period (52 weeks) and a SFU Period (8 weeks after final dose). The eligibility to participate in the study will be determined at the Baseline Visit (Day 1). Participants will receive a dose of rozanolixizumab [redacted] through Week 52. After the final dose in TP0004, participants will be

followed in an 8-week SFU Period. The End of Study (EOS) visit will be performed after the SFU Period.

Fixed dose equivalents across body weight tiers will be employed in this study according to Table 4-1.

Table 4-1: TP0004 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
In the case of a study participant of the lowest body weight tier (below 50kg) and in 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. Otherwise the treatment must be stopped if platelets increase to above 400×10^9/L.

An external IDMC will be utilized to review the safety data at predefined intervals and ad hoc as needed should any emerging safety concern arise during the study. The IDMC will review implications of individual and cumulative cases to continuance of the study in an ongoing fashion. 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, [redacted] dosing was implemented in protocol amendment 2. Study participants being treated with the [redacted] dosing regimen will switch to the [redacted] dosing regimen once protocol amendment 2 is approved at the respective study site.

At Baseline (Day 1), which corresponds to Week 25 (Visit 27) of the parent studies, TP0003 or TP0006, all study participants (whether randomized to placebo or rozanolixizumab in the parent studies) will enter TP0004 and receive rozanolixizumab treatment [redacted] at the assigned dose level at the end of TP0003 or TP0006, if the platelet count was between ≥50×10^9/L and ≤150×10^9/L. Study participants previously randomized to placebo will also enter the study at the assigned dose level at the end of the parent studies. Doses can be adjusted if platelets are outside the specified range, as per dose adjustment in Table 4-2. After Baseline, the next administration of rozanolixizumab will be on Week 2 (Visit 3) and [redacted] thereafter, as an sc infusion to maintain platelet count ≥50×10^9/L.

Rozanolixizumab dose levels based on body weight tiers being explored in TP0004 are as follows:

- Equivalent to [redacted]
- Equivalent to [redacted]
- Equivalent to approximately [redacted] ([redacted] total dose) [redacted]

If platelet counts are >150×10^9/L or <50×10^9/L on 2 consecutive visits, the dose should be adjusted for safety reasons (ie, high platelet count or AE) or efficacy reasons as specified in Table 4-2 and Table 4-1. The same dose regimen should be maintained if possible throughout the study.

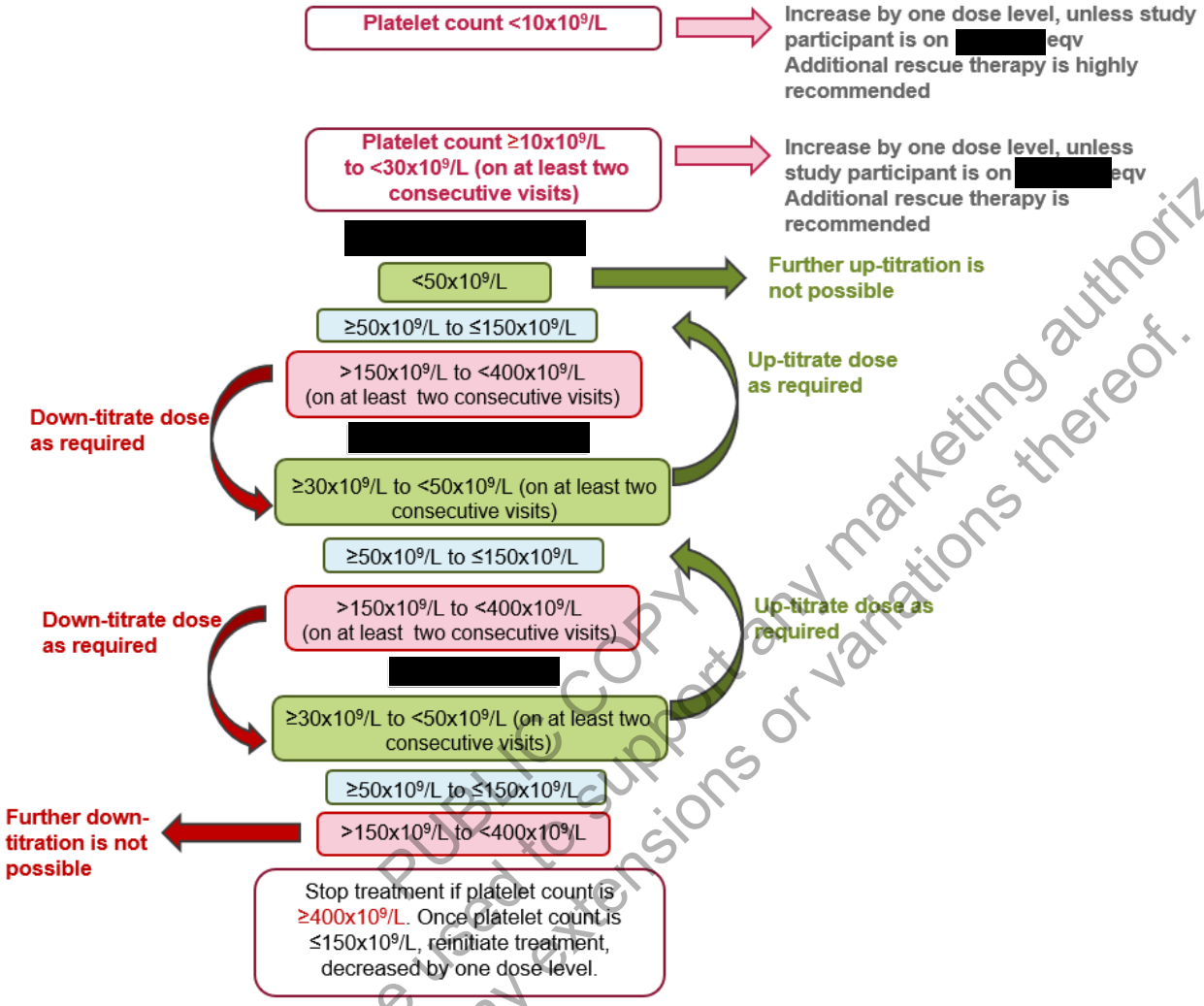
Table 4-2: Dose adjustments of rozanolixizumab

Platelet count result[a]	Dose adjustment (based on weekly platelet counts)
<10×10^9/L	Increase by one dose level, unless study participant is on maintenance dose of [redacted] Additional rescue therapy is highly recommended as per Section 6.4.3
≥10×10^9/L to <30×10^9/L (on at least two consecutive visits)	Increase by one dose level, unless study participant is on maintenance dose of [redacted] Additional rescue therapy is recommended as per Section 6.4.3
≥30×10^9/L to <50×10^9/L (on at least two consecutive visits)	Increase by one dose level, unless study participant is on maintenance dose of [redacted]
≥50×10^9/L to ≤150×10^9/L[b]	Continue with current dose level
>150×10^9/L to <400 x10^9/L (on at least two consecutive visits)	Decrease by one dose level, unless study participant is on maintenance dose of [redacted]
≥400×10^9/L	Stop IMP treatment. Once the platelet count is ≤150×10^9/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 (>150×10^9/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. In the case of a study participant of the lowest body weight tier (below 50kg) and in 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 platelet count increases to above 400×10^9/L then IMP must be stopped.

Figure 4-1: Dose adjustments of rozanolixizumab



eqv=equivalent; [redacted]
* eqv: fix 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 4-2 and Figure 4-1 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 counts are ≥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 counts are <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] or the [redacted] total dose (corresponding to an average [redacted] dose in a participant weighing 70kg), and platelet count decreases to <50×10^9/L, then up-titration to a fixed-unit dose equivalent to [redacted] or [redacted] respectively, would be allowed.

Study participants will be treated for a maximum of approximately 52 weeks. After the final dose in TP0004, participants will be followed for safety follow-up purposes in an 8-week SFU Period.

4.2 Scientific rationale for study design

The target population for rozanolixizumab is patients with IgG autoantibody-mediated autoimmune disorders. TP0003 and TP0006, the parent studies of the current OLE study TP0004, are designed to assess whether multiple sc infusions of rozanolixizumab will result in a durable clinically meaningful platelet increase to count of ≥50×10^9/L in adult study participants with ITP. TP0004 plans to assess participants from TP0003 and TP0006 for up to a year and primarily evaluate the safety and tolerability of rozanolixizumab over a longer duration of treatment.

The possibility of chronic, regular, treatment with rozanolixizumab will be assessed in TP0004. Study participants who roll over from TP0003 or TP0006 will receive rozanolixizumab at the assigned dose level at the end of the parent studies as an sc infusion on Baseline (Day 1) which will be repeated on Week 2 (Visit 3), and then [redacted] thereafter. Study participants assigned to placebo through to Week 25 (in TP0003 or TP0006) will also receive rozanolixizumab at the assigned dose level at the end of the parent studies. As the study participants previously assigned to placebo in TP0003 and TP0006 are likely to have received rescue therapy in order to keep their platelet count >30×10^9/L, it is appropriate to start dosing with the previously assigned dose (equivalent to [redacted] or below). The platelet counts in all study participants are anticipated to be already above a critical level (>30×10^9/L) through previous therapy with rozanolixizumab itself or with rescue therapies. Thus, in order to maintain the blind of the pivotal studies, it is considered adequate to start with the final dose administered in TP0003 or TP0006. However. based on platelet counts, a higher or lower dose level is permitted. Dose levels being explored are equivalent to [redacted] and approximately [redacted] ([redacted] total dose) [redacted]

In case the enrollment into TP0004 is delayed, the rollover from TP0003 or TP0006 needs to be completed 3 days after the last visit, at the latest. In case of a late rollover, platelet counts will need to be remeasured.

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) [redacted] was proposed for use in the confirmatory TP0003 and TP0006 studies, 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. Data from TP0001 showed that a [redacted] 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) of duration of platelet response (platelet count >50×10^9/L) following a dose of [redacted] and a [redacted] dose of [redacted] was 12 (6 to 19) days and 11.96 (6 to 20) days, respectively. Hence, a starting dose of [redacted] equivalent followed by [redacted] equivalent [redacted] 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 4-1.

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 do not seem to be sustained in TP0004 during the [redacted] dosing interval. Protocol Amendment 2 followed the advice from the external IDMC to increase the frequency of dosing, as in the OLE study (TP0004), platelet counts are not sustained over a [redacted] dosing interval (observed platelet counts $<50\times10^9$/L). Following the advice, the dose regimen for studies TP0003, TP0006 and OLE TP0004 will be changed to [redacted] equivalent [redacted] This dose regimen is anticipated to be well tolerated, with an acceptable safety profile and more likely to sustain the platelet counts across the dosing interval reducing the risks associated with low platelet counts. A dose of [redacted] equivalent [redacted] 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 [redacted] that only sustained it above this level during the first week following each dose and not for the entire [redacted] period between doses.

A [redacted] equivalent [redacted] dose regimen is anticipated to achieve RO% from peak to trough in a range of 99 to 50% during the [redacted] dosing interval and predicted to achieve mean concentrations at steady state ($C_{max,ss}$) of ~30µg/mL (2 days post dose) and C_{trough} of 0.31µg/mL.

In terms of safety, 2x10mg/kg weekly doses have been tested in TP0001 and showed a good safety and tolerability profile. In addition, this dose regimen of 10mg/kg of rozanolixizumab QW has been studied in other indications like CIDP01, where 34 study participants (1:1 placebo:rozanolixizumab) followed 12 weekly doses of 10mg/kg administrations, from which at least 6 study participants enrolled in the follow up study CIDP04 with a total of 52 weeks 10mg/kg QW doses. This dose regimen was generally well tolerated, with an acceptable safety profile, while no new safety concerns were identified. In addition, in order to avoid platelet count increases to $\geq150\times10^9$/L, down-titration of the IMP dose level as described in Table 4-1 will be allowed. Weekly platelet assessments will be performed during the study, to support the dosing strategy and stabilize the dose regimen leading to platelet counts $\geq50\times10^9$/L and minimize platelet counts $\geq150\times10^9$/L in the participants. Up titration to fixed-unit doses of [redacted] rozanolixizumab equivalent [redacted] will also be allowed to maintain stable platelet counts of $>50\times10^9$/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 the Phase 3 studies is a [redacted] equivalent dose on a [redacted] basis, allowing to downtitrate to [redacted] and [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. Study participants will have an EOS Visit performed 8 weeks after the final dose of IMP or the Early Withdrawal (EW) Visit.

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:

1b. Study participant completed TP0003 or TP0006 until Visit 27 (Week 25) and, in the opinion of the investigator, has been compliant with the TP0003 or TP0006 study assessments.

2. The study participant is considered reliable and capable of adhering to the protocol, visit schedule, or medication intake according to the judgment of the investigator.

Type of participant and disease characteristics:

3. Criterion removed.

4. Criterion removed.

Sex

5a. Study participants may be male or female:

- A male participant must agree to use contraception as detailed in Appendix 4, Section 10.4 of this protocol 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 urine 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 final dose of study treatment.

Informed consent

6. Study participant is 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 specific to TP0004 apply:

Medical conditions

1. Study participant has any ongoing IMP-related SAE or ongoing severe IMP-related TEAE experienced during TP0003 or TP0006.

2. Criterion removed.

3. Any withdrawal or permanent IMP discontinuation criteria from TP0003 or TP0006 met, a change in medical condition from TP0003 or TP0006, or significant bleeding requiring immediate treatment which, in the judgment of the investigator, precludes the participant from inclusion in TP0004 (eg, clinically significant bleeding, ongoing active or chronic infection, acute myocardial infarction, thromboembolic event, liver disease, high risk of GI bleeding, severe psychiatric condition).
4. Late detection of an inclusion criterion not met for TP0003 or TP0006 if it affects the health status/safety of the study participant.
5. Late detection of an exclusion criterion met for TP0003 or TP0006 that is related to ITP diagnosis or to the health status/safety of the study participant.

Diagnostic assessments

6b. Study participant has, at last available assessment of TP0003 or TP0006, 3.0x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP).

- If study participant has >ULN for ALT, AST, or ALP that does not meet the exclusion limit at enrollment (last available assessment of TP0003 or TP0006), repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase.
- For study 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 electronic Case Report form (eCRF).

7a. Study participant has bilirubin >1.5xULN (unless confirmed Gilbert's syndrome) at the last available assessment in TP0003/TP0006. If participant has elevations only in total bilirubin, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

8. Female study participant who is pregnant or lactating.

9a. Study participant has planned major elective surgical procedure for the duration of the study period.

10a. Study participant has at the last available assessment in TP0003/TP0006, any laboratory abnormality that, in the opinion of the investigator, is clinically significant, has not resolved at Visit 1 (Day 1), and could jeopardize or compromise the study participant's ability to participate in this study.

11a. Study participant has 12-lead ECG at Baseline with changes considered to be clinically significant upon medical review. The clinical significance of the findings needs to be assessed by the investigator to determine eligibility.

12. Criterion removed.

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

14. 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.

For **France**-specific exclusion criteria (criterions #15, #16 and #17), see Appendix 7 (Section 10.7).

5.3 Lifestyle restrictions

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

6 STUDY TREATMENTS

Table 6-1: Treatments administered

Study treatment name:	Rozanolixizumab
Dosage formulation:	Solution for infusion
Unit dose strength(s)/Dosage level(s):	[redacted] Fixed dose equivalent to [redacted] and approximately [redacted] based on body weight tiers.
Route of administration:	sc infusion
Dosing instructions:	Rozanolixizumab will be administered as a sc infusion with an [redacted] The study participant's body weight at Baseline (TP0004 [re-measured] Baseline and Week 25) (refer to Section 9.2 for the definition of Baseline) will be used for the dose calculation. In the case of any blockage of the infusion, a suitable flush (eg, [redacted]) is allowed. If the participant is unable to tolerate a [redacted] a slower rate may be used at the discretion of the clinical personnel administering the infusion.
Packaging and labeling:	Rozanolixizumab will be provided in glass vials and will be labeled as required per country requirement.

hr=hour; [redacted] sc=subcutaneous; w/v=weight/volume

Details on the rate of infusion 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 IMP received and that any discrepancies were reported and resolved before the use of the IMP.

Only participants enrolled in the study may receive IMP and only authorized site staff may supply or administer IMP. All IMPs must be stored in a secure, environmentally controlled, and

monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP 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 IMP 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, regulations, and UCB standard operating procedures (SOPs). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.2 Measures to minimize bias: randomization

An interactive response technology (IRT) will be used for assigning eligible participants to IMP 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.

The participant number assigned to study participants enrolled in TP0003 and TP0006 will be the same identifier used in TP0004. The participant number will be required in all communication between the investigator or designee and the IRT regarding a particular participant. Participant numbers and kit numbers will be tracked via the IRT.

6.3 Treatment compliance

Drug accountability must be recorded on the Drug Accountability form (Section 6.1.1).

Details regarding treatment compliance are outlined in the Important Protocol Deviation Specification document.

6.4 Concomitant medications/treatments

6.4.1 Permitted concomitant treatments (medications and therapies)

The concomitant medications and the highest dose permitted during the study are listed in Table 6-2. Dose tapering, especially for oral corticosteroids, is allowed. Any increase in concomitant ITP medication above Baseline (Visit 1, TP0004) dose is regarded as rescue therapy.

For study participants who started rescue medication during TP0003/TP0006 and are still receiving rescue medication when rolling over to TP0004, Table 6-2 is applicable as soon as the respective rescue medication is stopped or the dose is decreased to less than or equal to the limit specified in Table 6-2. In such a situation, the rescue medication will not be considered as Baseline concomitant ITP medication and the rules for restarting IMP administration will apply, as per Section 6.4.3.

If a study participant receives a COVID-19 vaccine, the product name and date of administration(s) should be captured in the eCRF as a concomitant medication.

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

Permitted Medications	Dose
Oral Corticosteroids	≤20mg/day (prednisone equivalent dose)
Mycophenolate mofetil	≤3g/day
Cyclosporin	≤5mg/kg/day for unmodified ≤4mg/kg/day for modified
Azathioprine	≤3mg/kg/day
Danazol	≤15mg/kg/day
Dapsone	100mg/day
Eltrombopag, Avatrombopag	Any dose
Fostamatinib	Any dose

The use of medicinal cannabidiols and medicinal marijuana (prescribed by a physician) is also permitted. For **Japan**-specific requirements, see Appendix 7, Section 10.7.

6.4.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- IVIg (unless it is given as rescue therapy)
- All biologics including rituximab
- Cyclophosphamide
- Pimecrolimus

- Plasma exchange
- 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 anti-platelets (eg, warfarin, heparin, clopidogrel, aspirin [enteric coated up to 150mg daily allowed], salicylics, dipyridamole, prasugrel, ticagrelor, tirofiban, 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, 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 EW Visit and enter the SFU Period.

6.4.3 Rescue therapy

Rescue therapy will be given per standard of care and at the discretion of the investigator. Any increase in concomitant ITP medication above Baseline (Visit 1, TP0004) dose is regarded as rescue therapy. Any systemically administered corticosteroids above the background doses (ie, pulse, oral and iv steroids) and any systemic corticosteroids used for the management of infusion reactions or other medical condition are also considered rescue therapy. Depending on the dose and/or type of rescue medication that is required a study participant may have to be discontinued as described in Section 6.4.3.1 and Section 6.4.3.2.

6.4.3.1 Rescue therapy not leading to discontinuation

The following are defined as rescue therapies and can be administered without requiring study participants to be discontinued from the study (per investigator's judgment):

- Commercially available IVIg (once platelet count is $<50\times10^9$/L, rozanolixizumab treatment can commence at the same dose as previously administered)
- High dose corticosteroids (once platelet count is $<50\times10^9$/L, rozanolixizumab treatment can commence at the same dose as previously administered)

  Note: 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 prednisolone equivalent dose.
- An increase less than 25% from Baseline (Day 1 in TP0004), in permitted concomitant ITP therapies

- An increase less than 25% from Baseline (Day 1 in TP0004), in permitted concomitant immunosuppressants

If such rescue therapy is given, the participant should continue in the study and complete all scheduled visits, as per the Schedule of Activities (Section 1.3).

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

Although the intervention 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 IMP to allow for the study treatment to have an effect.

6.4.3.2 Rescue therapy leading to discontinuation

The following rescue therapies, if administered, will lead to permanent discontinuation of the study participant from the study:

- Any increase in dose above 25% in a Baseline-permitted concomitant ITP therapy and immunosuppressants (Baseline, Day 1 in TP0004)
- Initiation of oral steroids above 20mg/day
- Platelet transfusion
- Initiation of any additional ITP therapy (apart from IVIg and high dose corticosteroids)

6.5 Dose modification

Dose modifications of the IMP are permitted in order to maintain the platelet counts between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L (Table 4-2 and Figure 4-1).

Dose modifications or temporary discontinuation of the IMP treatment are permitted if serum total IgG value is <1g/L (Section 10.22).

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

- Moderate to severe headaches (Appendix 20, Section 10.20)
- Severe vomiting and diarrhea (Appendix 21, Section 10.21)
- 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

The date and reason for dose change of rozanolixizumab is to be recorded on each study participant's eCRF.

6.6 Self-administration

Self-administration will be offered to the study participant, if desired by the participant and approved by the investigator. Self-administration can occur at home or onsite, provided the participant is willing to do so and has received appropriate training. Training consists of different sessions performed by the study nurses, in which the patient would be made familiar with the

process. Only after the healthcare professional (HCP) confirms that the patient is considered adequately prepared to perform self-administration, a checklist will be completed and filed in the medical chart. Once all of the above is completed, the patient can perform the self-administration. Self-administration will ONLY occur under the supervision of a fully trained HCP (to confirm that study participant is proceeding correctly).

Note: self-administration will be offered as an option to countries listed in Section 10.7.1.

6.7 Home visits

During the 52-week Treatment Period, certain study visits such as dosing visits (by HCP or self-administration), may be conducted at a participant's home or other locations (eg, rehabilitation or day care centers, etc), if desired by the participant and approved by the investigator.

Healthcare professional home visits will be conducted by a fully trained HCP and will follow the schedule of assessments and safety monitoring schedule as an onsite visit. Eligibility for home visits includes the following: the study participant is deemed a suitable candidate by the investigator; the study participant is willing to be seen, dosed and monitored at home by a home nurse, and the study participant has shown good tolerability to previous 6 administrations of rozanolixizumab at the site (including, but not limited to, no moderate or severe infusion reactions, nor any AEs that the investigator considers unsuitable for home administration). A further prerequisite for dosing during a home visit is that the platelet counts were stable during the last four dosing visits (between ≥50 to ≤150×10^9/L) and that the dose administered during the last four dosing visits was not changed and is not planned to be changed at the home dosing visit. Study participants should not have experienced any ITP signs and symptoms or AEs since the last dosing visit.

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.

6.8 Treatment after the end of the study

Study participants who complete participation in TP0004 may have the possibility to continue receiving rozanolixizumab through a Managed Access Program (MAP) if available, as indicated by the Sponsor and applicable per local regulations.

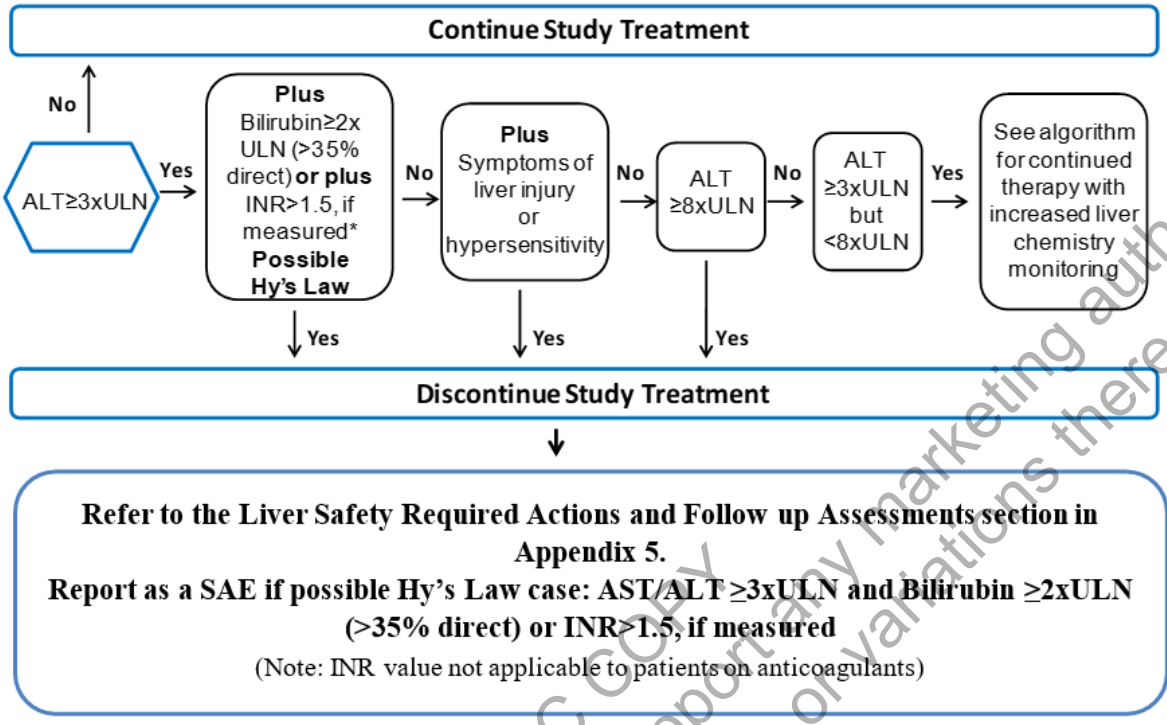
7 DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of IMP

7.1.1 Liver chemistry stopping criteria

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

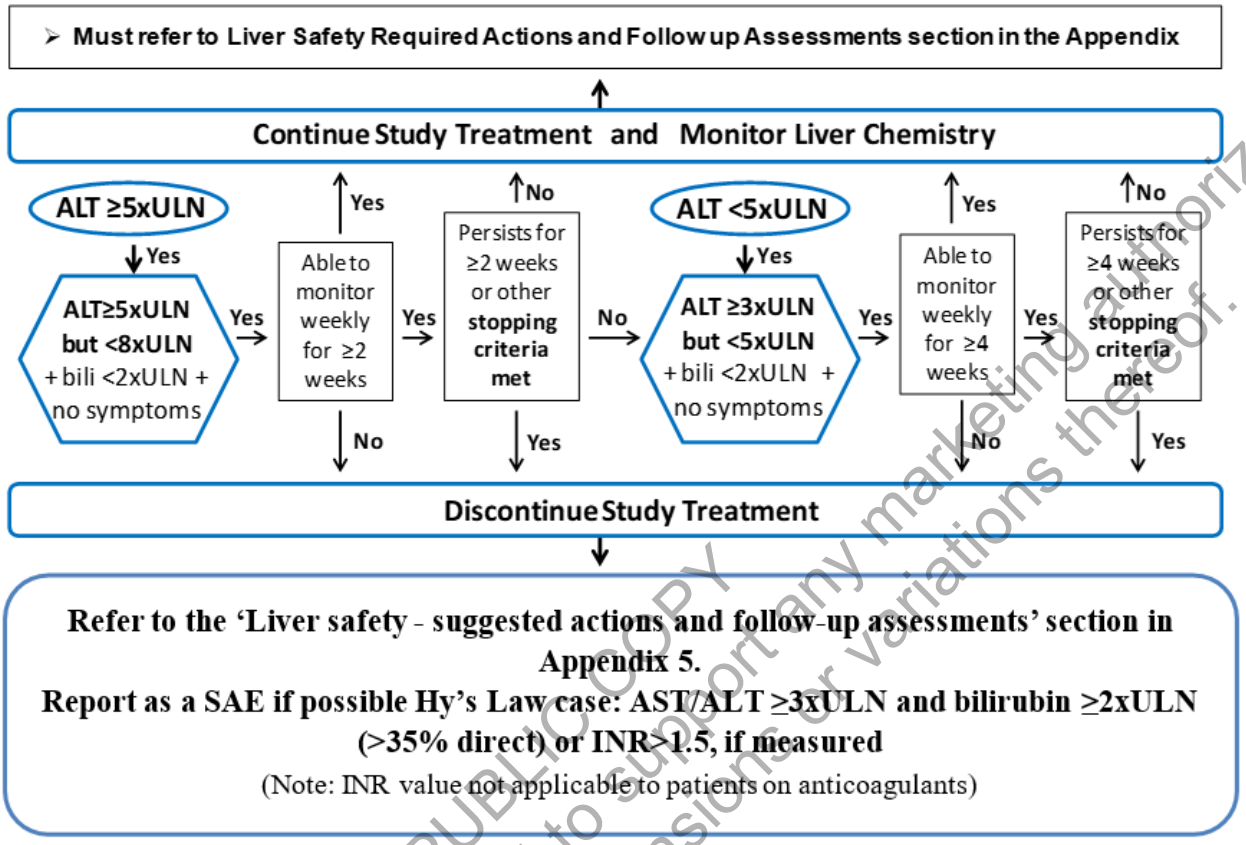
Figure 7-1: Phase 3-4 liver chemistry stopping criteria and increased monitoring algorithm



ALT=alanine aminotransferase; INR=International Normalized Ratio; ULN=upper limit of normal

Treatment with IMP may be continued with increased monitoring if a study participant meets one of the criteria outlined in Figure 7-2.

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



ALT=alanine aminotransferase; bili=bilirubin; ULN=upper limit of normal

Specific assessments and follow-up actions for potential drug-induced liver injury (PDILI) are provided in Appendix 5, Section 10.5.

7.1.2 QTc stopping criteria

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

- Corrected QT interval (QTc) >500ms OR uncorrected QT >600ms
- Change from Baseline of QTc >60ms

For 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
<450ms	>500ms
450 to 480ms	≥530ms

QTc=corrected QT interval

If a clinically significant finding is identified (including, but not limited to changes from Baseline in QT interval corrected for heart rate according to Fridericia's formula) after enrollment, the investigator or qualified designee will determine if the 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.

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

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

Study participants **MUST permanently discontinue IMP** if they develop an illness that would interfere with his/her continued exposure to IMP including, but not limited 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 (see Appendix 22, Section 10.22).
- 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 23, Section 10.23) or anaphylaxis requiring corticosteroid and/or epinephrine therapy (see Appendix 19, Section 10.19) (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 recurrence of severe AE of GI disturbance (see Appendix 21, Section 10.21) or headache (see Appendix 20, Section 10.20) that is considered related to the IMP in the opinion of the investigator.
- 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 a tuberculosis (TB) test that is confirmed positive or any further evidence suggestive of potential TB infection (eg, close exposure) and further examinations result in a diagnosis of active TB or latent TB (LTB), or nontuberculous mycobacterial infection (NTMBI) (see Section 8.1.5).
- 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 participant requires rescue therapy (for exceptions, refer to Section 6.4.3).

Study participants who permanently discontinue IMP during the Treatment Period and hence are withdrawn from the study should complete the assessments outlined for the 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 coronavirus disease (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 10.20).
2. A splenectomised study participant develops a (persistent or re-occurring) nonserious infection, as per investigator's decision (Section 10.22).
3. Total serum IgG values goes <1g/L as per investigator's decision (Section 10.22). As IMP treatment is administered [redacted] the decision is based on the most recently available total IgG value. In order to maintain the blind from the parent studies, IgG, IgG subclasses, total protein, and albumin values will be unblinded starting with the blood samples taken at Week 4 (Visit 5). Additionally, guidance for investigators on management of infections can be found in Appendix 22, Section 10.22.

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

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

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

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 contract research organization [CRO]) immediately upon occurrence or awareness to determine if the participant should continue or discontinue IMP.

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

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 Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (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.

8.1 Safety assessments

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

8.1.1 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.

8.1.2 Vital signs

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

Blood pressure and pulse 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.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will include 1 pulse, 1 BP and body temperature measurement.

8.1.3 Electrocardiograms

12-lead ECGs will be obtained as outlined in the Schedule of Activities (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

Central reading of ECGs will be performed, but for the assessment of the ECGs 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.

8.1.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and 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 that 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 or 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 (Section 1.3).

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, AE, or dose modification), then the results must be recorded in the eCRF.

8.1.5 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. Any presumptive diagnosis or diagnosis of a TB infection is a reportable event. Assessment and management of TB and TB risk factors should follow local/national guidelines.

8.1.5.1 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 18, Section 10.18) as indicated in the Schedule of Activities (Section 1.3).

The TB questionnaire at study entry of TP0004 will not be collected. The TP0003 or TP0006 Week 25 (Visit 27) questionnaire will be used as the study entry questionnaire for TP0004.

The TB questionnaire 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 may trigger further assessments to determine if the participant has either latent TB infection (LTBI) or active TB infection and, if confirmed, must be withdrawn from the study. As an example, a participant who answered "Yes" to the question "[redacted] should not be allowed into the study pending further assessments per local/national guidelines.

8.1.5.2 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 non-tuberculosis 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 NTMBI during the study must be withdrawn from the study. The participant must be permanently discontinued from study medication 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, and keep the EOS Visit as specified by the protocol. Treatment for active TB or NTMBI 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.

LTBI, active TB, or other NTMBI identified during study

During the study, study participants who develop evidence of LTBI, active TB or NTMBI must immediately stop further administration of IMP and will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Participants diagnosed with active TB treatment or LTBI should receive appropriate TB treatment or prophylaxis therapy. The participant should be transferred to the care of their physician and managed according to the standard of care.

If an NTMBI 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, x-ray evolution data, and TB diagnostic procedures used to follow-up and confirm recovery of TB.

8.1.6 Splenectomized study participants

Asplenic study participants will be required to carry a splenectomy card for the whole duration of the study indicating they have undergone splenectomy and may be at increased risk of infection particularly with encapsulated organisms. Prophylactic antibiotic may be given to these participants, if required per local guidance. Antibody titers against *S. pneumoniae*, *N.*

meningitidis, and *H. influenzae* in splenectomized study participants will be measured at the defined time points as specified in the Schedule of Activities.

Splenectomized study participants should have documented evidence of vaccinations from the parent studies against the following encapsulated organisms: *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* (as per local/or a national guidance, as applicable) or as evidenced from personal immunization records.

8.2 Adverse events

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

Adverse events can be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that caused the participant to discontinue rozanolixizumab or TP0004 (see Section 7).

8.2.1 Time period and frequency for collecting AE and SAE information

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

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

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the 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.

8.2.2 Method of detecting AEs and SAEs

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

8.2.3 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 (as defined in Section 8.2.7) will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3, Section 10.3.

8.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the 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 the IMP under clinical investigation. UCB will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

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

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

8.2.5 Pregnancy

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

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

- The participant should immediately stop the intake of the IMP.
- 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, ectopic pregnancy) are considered SAEs.

8.2.6 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 8.2.1 and Appendix 3, Section 10.3.

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

Anemia	Hemorrhagic events
Fatigue	Thrombocytopenia

8.2.7 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 5, Section 10.5 for further information on liver safety monitoring.

8.2.8 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 moderate or severe headache or serious headache (regardless of severity), the headache questionnaire (Appendix 17, Section 10.17) must be completed, though moderate headache is not considered an AESM. Additional procedures for management of headaches are provided in Appendix 20, Section 10.20.

Procedures for the management of diarrhea is provided in Appendix 21, Section 10.21.

Although hypersensitivity reactions including infused-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 23, Section 10.23. In case of suspected anaphylaxis, the Sampson Criteria (Sampson et al, 2006) (Appendix 19, Section 10.19) should be completed. All hypersensitivity reactions will be recorded and reported as per the AE reporting procedure outlined in Appendix 3, Section 10.3.

8.2.9 COVID-19 vaccination

COVID-19 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 adverse event 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 SUSAR process will be followed.

8.3 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 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 Patient Safety 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.

8.4 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/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 IMP 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.

8.5 Efficacy assessments

8.5.1 Platelet counts

As in the parent studies, TP0003 and TP0006, 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 at local laboratories and the following endpoints will be derived for the purpose of analysis.

Platelet count-related endpoints are:

- Stable Clinically Meaningful Response, defined as Clinically Meaningful Response (ie, platelet count $\geq 50\times10^9$/L) without rescue therapy at ≥70% of the visits over the planned 52-week Treatment Period starting at Week 4
- Stable Response, defined as platelet count $\geq 30\times10^9$/L and absence of bleeding without rescue therapy at ≥70% of the visits over the planned 52-week Treatment Period starting at Week 4
- Cumulative number of weeks with Clinically Meaningful Response over the planned 52-week Treatment Period
- Cumulative number of weeks with platelet counts $\geq 30\times10^9$/L over the planned 52-week Treatment Period
- Mean Change from Baseline in platelet count at each visit
- Use of rescue medication by visit
- ITP-BAT bleeding events and severity by visit

Platelet endpoints in study participants with first exposure to rozanolixizumab:

- In study participants with first exposure to rozanolixizumab: Durable Clinically Meaningful Platelet Response of $\geq 50\times10^9$/L, for at least 4 of 6 [redacted] visits between Weeks 13 to 25 of the study.
- In study participants with first exposure to rozanolixizumab: 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.

The clinical 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 consecutive 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).

8.5.2 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. This 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: skin (S), visible mucosae (M), and organs (O), with gradation of severity (SMOG). 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. Bleeding reported by the participant without medical documentation is Grade 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 10, Section 10.10.

8.5.3 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.

8.5.3.1 ITP-PAQ

The ITP-PAQ is a 44-item disease-specific quality of life (QoL) 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 11, Section 10.11.

8.5.3.2 SF-36

Study participants will complete the SF-36 questionnaire according to the Schedule of Activities (Section 1.3). The SF-36 sample questionnaire is available in Appendix 12, Section 10.12.

8.5.3.3 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 the time" to "all of the time", with a 7-day recall period. The FATIGUE-PRO Physical Fatigue score ranges 0 to 100, with a higher score meaning more physical fatigue.

The Physical Fatigue is available in Appendix 13, Section 10.13.

8.5.3.4 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 analog 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 analog scale (VAS), where the endpoints are labeled '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 (Section 1.3). The EQ-5D-5L sample questionnaire is available in Appendix 14, Section 10.14.

8.5.3.5 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 15, Section 10.15.

8.5.3.6 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 16, Section 10.16.

8.5.3.7 SIAQ (Infusion version)

To assess the experience of study participants with the sc self-administration using an infusion device, an adaptation of the SIAQ will be used in the participants that self-administer.

The SIAQ was developed by UCB to assess the perceived advantages and the potential limitations of self-administration of an sc medication (Keininger and Coteur, 2011). There are 2 modules for the SIAQ (SIAQ PRE-Self-Injection and SIAQ POST-Self-Injection). The SIAQ PRE-Self-Injection is composed of 7 items grouped into 3 domains (feelings about injection, self-confidence, and satisfaction with the current mode of administration). The SIAQ POST-Self-Injection is composed of 21 items grouped into 6 domains (feelings about injection, self-image, self-confidence, injection site reactions, ease of use, and satisfaction with self-injection).

Each domain score of the SIAQ PRE-Self-Injection and SIAQ POST-Self-Injection ranges from 0 to 10, 0 being the worst experience and 10 being the best experience.

The adaptation of the SIAQ consists in replacing the terminology "injection" with the terminology "infusion" in both modules, and removing the "ease of use" domain which is not accurate for the self-administration method used in the study from the SIAQ POST-Self-Injection module. This adapted version is named SIAQ (Infusion version). The domain scores of the SIAQ (Infusion version) are calculated the same way as the SIAQ domain scores; hence domain scores ranges from 0 to 10, 0 being the worst experience and 10 being the best experience.

The PRE-SIAQ (Infusion version) will be completed once before the first self-administration, and the POST-SIAQ (Infusion version) will be completed within 1 hour after self-administration at consecutive visits. Paper versions will be used. The sample questionnaires are available in Appendix 24, Section 10.24.

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 whole blood samples for the determination of rozanolixizumab PK and ADA will be taken, one sample of sufficient volume can be used.

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

8.7 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. 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 may not be outlined in the Clinical Study Report for this study, but in a separate report.

8.8 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 as specified in the Schedule of Activities (Section 1.3). Exploratory samples will be collected predose. Additional exploratory biomarker samples may be collected 4 hours postdose in case of severe and/or serious headache or GI-related AESM 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. Results of the DNA and RNA biomarker analyses will not be outlined in the Clinical Study Report for this study.

8.9 Immunology biomarkers

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

- Serum complements (C3, C4)
- Plasma complements (C3a, C5a)
- Biomarkers of COVID-19 vaccine response (only for study participants who received COVID-19 vaccine)

Samples for serum complements (C3, C4) and plasma complements (C3a, C5a) will be collected predose at Baseline (Day 1) for all participants. Additional samples may be collected 2 hours and 4 hours postdose for study participants with an infusion reaction or hypersensitivity reaction 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.

8.10 Medical resource utilization and health economics

Medical resource utilization will be collected by capturing number and length of hospitalizations and by capturing number of infusion center admissions.

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.
- Safety Set (SS): All study participants who received at least 1 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 for the efficacy, demographic, PK and safety analyses.
- Pharmacokinetic Per-Protocol Set (PK-PPS): A subset of the Safety Set, consisting of those study participants who received at least 1 dose, and had at least 1 valid PK measurement.

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 with statistics including the number of participants (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized with frequency counts and percentages.

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 Estimands

The aim of TP0004 is to investigate the safety (primarily) of long term treatment of rozanolixizumab.

The primary safety analysis is based on a "treatment policy" estimand to allow for the inclusion of study participants that receive rescue medication. This estimand will be based on the SS who started TP0004 on [redacted] dosing.

There is no analysis strategy to protect the type I error as there is no significance testing amongst the primary and secondary endpoints.

The primary safety estimand will be defined as follows:

- Population: participants with primary ITP that meet the protocol-specified inclusion/exclusion criteria and who started TP0004 on [redacted] dosing.
- Participant-level outcome: occurrence of TEAEs.
- Population-level summary measure: descriptive summaries.
- Intercurrent event handling: The main intercurrent events are the use of rescue medication during the course of the study and withdrawal due to TEAEs.

A further secondary safety estimand, also based on "treatment policy", will use the SS who started TP0004 on [redacted] dosing. It is defined as follows:

- Population: participants with primary ITP that meet the protocol-specified inclusion/exclusion criteria and who started TP0004 on [redacted] dosing.
- Participant-level outcome: occurrence of TEAEs.
- Population-level summary measure: descriptive summaries.
- Intercurrent event handling: The main intercurrent events are the use of rescue medication during the course of the study and withdrawal due to TEAEs.

Missing safety values will not be imputed.

Further details will be provided in the SAP.

9.4 Planned safety analyses

The frequency and severity of all TEAEs will be presented by system organ class, high level term, and preferred term (Medical Dictionary for Regulatory Activities [MedDRA]®). The data will be displayed as number of participants experiencing the TEAE, percentage of participants, and number of TEAEs. A TEAE is defined as any event that was not present prior to the first administration of IMP or any unresolved event already present before the first administration of IMP that worsens in intensity following exposure to treatment, up to and including 8 weeks after the final dose of IMP.

Laboratory evaluations, ECGs, and vital signs will be analyzed over time.

All safety analyses will be based on the SS and be presented by both the treatment the participants received during the parent studies (TP0003/TP0006), and whether they started TP0004 on [redacted] dosing.

9.5 Planned efficacy/outcome analyses

Data will be listed, and for continuous variables, descriptive statistics will be generated for the observed values and changes from Baseline. For categorical variables, frequency counts and percentages will be presented.

All summary outputs will be presented by the treatment the participants received during the parent studies (TP0003/TP0006) and whether they started TP0004 on [redacted] dosing.

The key secondary endpoint in TP0004 for efficacy is stable clinically meaningful response defined as Clinically Meaningful Response ($\geq 50\times10^9$/L platelet count) without rescue therapy at ≥70% of the visits starting at Week 4, as it is anticipated that the effect of any rescue medication that might have been administered to the study participants in the placebo arm close to the end of the parent study would have dissipated at the time of assessing the stable clinically meaningful response in TP0004.

The other platelet count-related efficacy endpoints are Stable Response (defined as platelet count $\geq 30\times10^9$/L and absence of bleeding without rescue therapy) at ≥70% of the visits starting at Week 4; cumulative number of weeks with Clinically Meaningful Response; cumulative number of weeks with platelet counts $\geq 30\times10^9$/L and mean Change from Baseline in platelet count. These efficacy endpoints will be measured over time (52 weeks of treatment) in the same manner

as the key secondary endpoint. The Baseline platelet count is defined as platelet count at Visit 1 (TP0004).

Cumulative number of weeks with Clinically Meaningful Response and cumulative number of weeks with platelet counts $\geq 30\times10^9$/L will be also be presented for the first 24 weeks of the study.

Platelet count data will be presented both as collected, and with imputation as follows: Missing platelet count at any visit will be considered "worst case" and set to zero ("no platelet response"). The same will apply to missing platelet count at any visit after the initiation of rescue therapy. Baseline platelet count for each endpoint will be defined in the SAP. Rescue therapy given to participants who received placebo in the parent studies to ensure platelet count $>30\times10^9$/L will be summarized.

Subgroup analyses split by rescue medication use in TP0003 and TP0006 may be conducted.

Further details will be provided in the SAP.

9.6 Planned other analyses

9.6.1 Analysis of pharmacodynamics endpoints

The analyses (potentially including, but not limited to albumin, and total IgG, IgG subclasses, IgA, IgE, IgM, serum complement, plasma complement, and ITP specific autoantibodies) will be presented as continuous variables. All PD and biomarker analyses will be based on the SS and by dosing regimen.

9.6.2 Analysis of pharmacokinetics endpoints

All PK analyses will be based on the PK dataset.

Individual concentrations of rozanolixizumab will be listed and may be summarized at each scheduled time point and may be stratified by ADA status and dose regimen when applicable. Descriptive statistics of concentrations will be calculated only if at least two-thirds of the individual data points are quantifiable at a certain time point (≥ lower limit of quantification [LLOQ]). For summary statistics, below the LLOQ will be represented as LLOQ/2. Individual concentrations may be depicted graphically as individual plots and/or spaghetti plots. The impact of ADA on rozanolixizumab concentrations will be evaluated.

Further details will be provided in the SAP.

9.6.3 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 provided in the SAP.

9.7 Handling of protocol deviations

Important protocol deviations are identified as part of the data cleaning process in the Data Cleaning Plan. 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 the update (if necessary) of the important protocol deviation specification. 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 are made on an ongoing basis.

9.8 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.

9.9 Planned interim analysis, data monitoring, and data snapshots

9.9.1 Interim analysis

No formal interim analysis is planned for this study.

In addition, based on data cutoffs, safety and efficacy data for submission purposes will be summarized.

9.9.2 Data monitoring

An external IDMC will be established to review the safety data at predefined intervals and ad hoc as needed, should any emerging safety concern arise during the study. Details of the IDMC composition, processes, and responsibilities will be documented in the IDMC charter. 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. The objectives and procedures for the IDMC will be detailed in the IDMC Charter.

9.9.3 Data snapshots

There will be periodic data snapshots for submission and market approval.

9.10 Determination of sample size

No formal sample size calculation can be performed. All participants from the parent studies (TP0003 and TP0006) eligible for the OLE will be included. It is expected that up to a maximum of 180 participants will be included.

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

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, 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. 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 of the parent study (TP0003 or TP0006).

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.

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) [b]	Activated partial thromboplastin time (aPTT) [c]		Fibrinogen [c]
Clinical Chemistry[d]	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

Laboratory Assessments	Parameters			
	Glucose (fasting state preferred)	Calcium	Alkaline phosphatase	C-reactive protein (CRP)
	Immunoglobulins[e]	Albumin	Low-density lipoprotein (LDL) High-density lipoprotein (HDL) Total cholesterol Triglycerides	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other 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) [f] • Serology (human immunodeficiency antibody [HIV], 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.
[b] International Normalized Ratio (INR) to be done only at Baseline (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 Section 10.5, Appendix 5. All events of ALT ≥3x upper limit of normal (ULN) and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as 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 will be unblinded starting with the blood samples taken at Week 4 (Visit 5) in TP0004 in order maintain blind of the parent studies.
[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.

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 study participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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, 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.

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 study participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with 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 make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other 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 study participant dies during participation in the study or during a recognized Follow-up Period, the investigator will provide UCB with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed 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 next section). • Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of Childbearing Potential (WOCBP)

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

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

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone 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 requirements, see Appendix 7, Section 10.7.
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, 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 study medication.
- 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 discontinue study medication or 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 study medication by the investigator will be reported to the sponsor as described in Section 8.2.5. 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: Liver safety – suggested actions and follow-up assessments

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

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

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

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

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

Table 10-3: Phase 3 or 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 case report form (CRF), and complete a serious adverse event	Viral hepatitis serology.[d] Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend.

(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:** **For bilirubin or INR criteria** Repeat liver chemistry tests (include ALT, 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.	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. Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF. Record alcohol use on the liver event alcohol intake CRF. Exclude pregnancy. **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. 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 CRFs.

[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 et al, 2005).

[f] 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 Laboratory Manual.

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.

10.6 Appendix 6: Medical device incidents – definition and procedures for recording, evaluating, follow-up, and reporting

Not applicable.

10.7 Appendix 7: Country-specific requirements

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, 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.

France

Specific requirements for study participants in the France include:

- In reference to Section 1.1 (Synopsis - Treatment Groups and Duration), the expected duration of the enrollment phase for an individual participant is defined as a visit window of up to +3 days from Week 25 of the parent study (TP0003 or TP0006). As study participants will enter this OLE study after completing participation in one of the parent studies, the overall timeline for this study is dependent on the enrollment trajectory of the parent studies. Anticipated timelines for completing enrollment of all participants in the parent studies is as follows: the last patient first visit of parent study is expected Jan 2024 with the last patient last dosing visit of parent study expected in Jul 2024. Based on these projections, the last patient first visit of TP0004 study is anticipated in Aug 2024, with the last patient last visit expected in Sep 2025.
- In reference to Section 5.2 (Exclusion Criteria), 3 additional exclusion criteria:

15. Study participant is deprived of their liberty by a judicial or administrative decision, or is receiving psychiatric care, and is admitted to a health or social institution, as defined in the French Public Health Code.
16. Study participant is subject to legal protection or is unable to express consent, as defined in the French Public Health Code.
17. Study participant is <18 years of age at the time of the Baseline Visit.

Japan

Specific requirements for study participants in Japan include:

Locally approved devices are to be used during the study. If a pump and infusion set are used that are regarded in Japan as investigational devices, then additional adherence to specific reporting obligations will be required. 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 and appropriately managed by the sponsor.

This reporting requirement is not applicable for locally 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.

- In reference to Section 6.4.1, the use of medicinal cannabidiols and medicinal marijuana are prohibited by law.
- 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 8.2.3 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, 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. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. 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 hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical events

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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
    - 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.

10.7.1 Countries where self-administration will be offered as an option

Self-administration will be offered as an option to the following countries:

- Austria
- Belgium
- Canada
- France
- Germany
- Italy
- Japan
- Poland
- Russian Federation
- Spain
- Ukraine
- United Kingdom
- United States

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Abbreviations and trademarks

ADA	antidrug antibody
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
AESM	adverse event of special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-d	anti-Rh_o
AST	aspartate aminotransferase
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CRF	Case Report form
CRO	contract research organization
CRP	c-reactive protein
ECG	electrocardiogram
eCRF	electronic Case Report form
eqv	equivalent
EOS	End of Study
EQ VAS	EuroQoL visual analog scale
EQ-5D-5L	European Quality of Life-5 Dimension 5 Levels
EW	Early Withdrawal
FcRn	neonatal Fc receptor
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HCP	healthcare professional
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
IRB	Institutional Review Board
IRT	interactive response technology
ITP	immune thrombocytopenia
ITP-BAT	ITP-specific 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
MAP	managed access program
MG	myasthenia gravis
NTMBI	nontuberculous mycobacterial infection
OLE	open-label extension
PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PEX	plasma exchange
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic
PRO	patient-reported outcome
Q2W	every 2 weeks
QoL	quality of life
QTc	corrected QT interval
QW	every week
RO	Receptor Occupancy

SADE	serious adverse device effects
SAE	serious adverse event
SIAQ	self-injection assessment questionnaire
SAP	Statistical Analysis Plan
sc	subcutaneous
SF-36	Short-Form 36-Item Health Survey
SFU	Safety Follow-Up
SMOG	Skin-Visible Mucosa-Internal Organs tool
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TPO-RA	thrombopoietin-receptor agonists
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
ULN	upper limit of normal
VAS	visual analog scale
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.10 Appendix 10: 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]	☐ 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]	

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**
		☐ Any number and size if reported by the patient			
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	

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**
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
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	

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**
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)					
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

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**
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 ☐ An equivalent episode if described in a medical report	☐ RBC transfusion or Hb drop >2g/dL

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**
Menorrhagia (compared to pre-ITP or to a phase of disease with normal platelet count)[9]	☐ No	☐ Doubling nr. 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 (only if diagnosed by a physician with an objective method)	☐ No	☐ Post trauma, diagnosed at this visit, function conserved or minimally impaired, if judged	☐ Spontaneous, diagnosed at this visit, function conserved or minimally impaired	☐ Spontaneous or post trauma (if judged disproportionate to trauma), diagnosed at this visit and requiring	☐ Spontaneous or post trauma (if judged disproportionate to trauma) diagnosed at this

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**
		disproportionate to trauma ☐ An equivalent episode if described in a medical report	☐ An equivalent episode if described in a medical report	immobilization or joint aspiration ☐ An equivalent episode if described in a medical report	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

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**
Intracranial bleeding[10]: 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
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**	☐ No			☐ Any event requiring hospitalization <48 hrs.	☐ Any event requiring hospitalization >48 hrs. or RBC transfusion or Hb drop >2g/dL

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
provided by the patient)					

Hb=hemoglobin; hrs=hours; ITP=immune thrombocytopenia; nr=number; PBAC= Pictorial Blood Loss 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).

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.

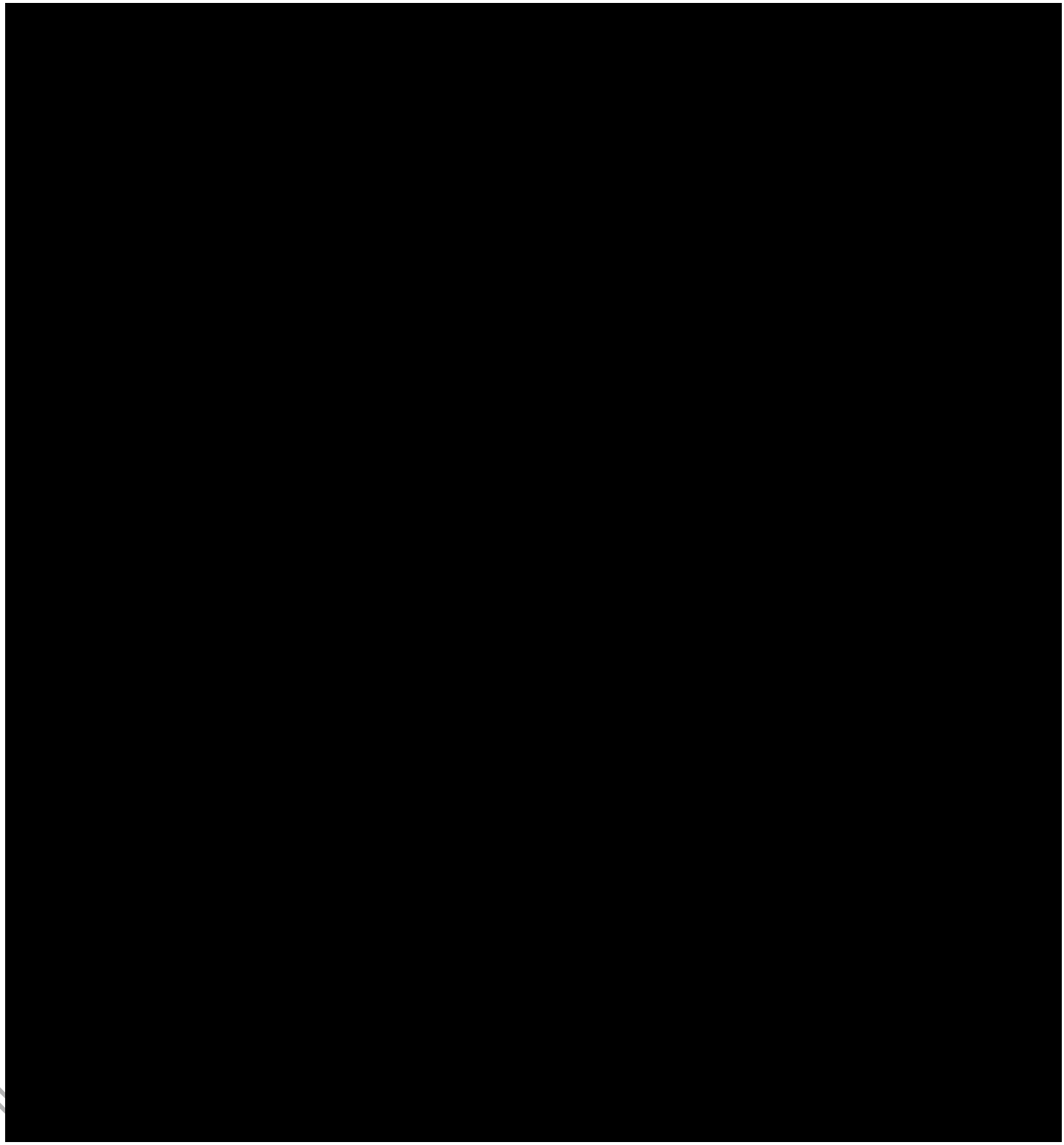
Note: Illustrative examples are available on the website of the Hematology Project Foundation (http://itpbat.fondazioneematologia.it/).

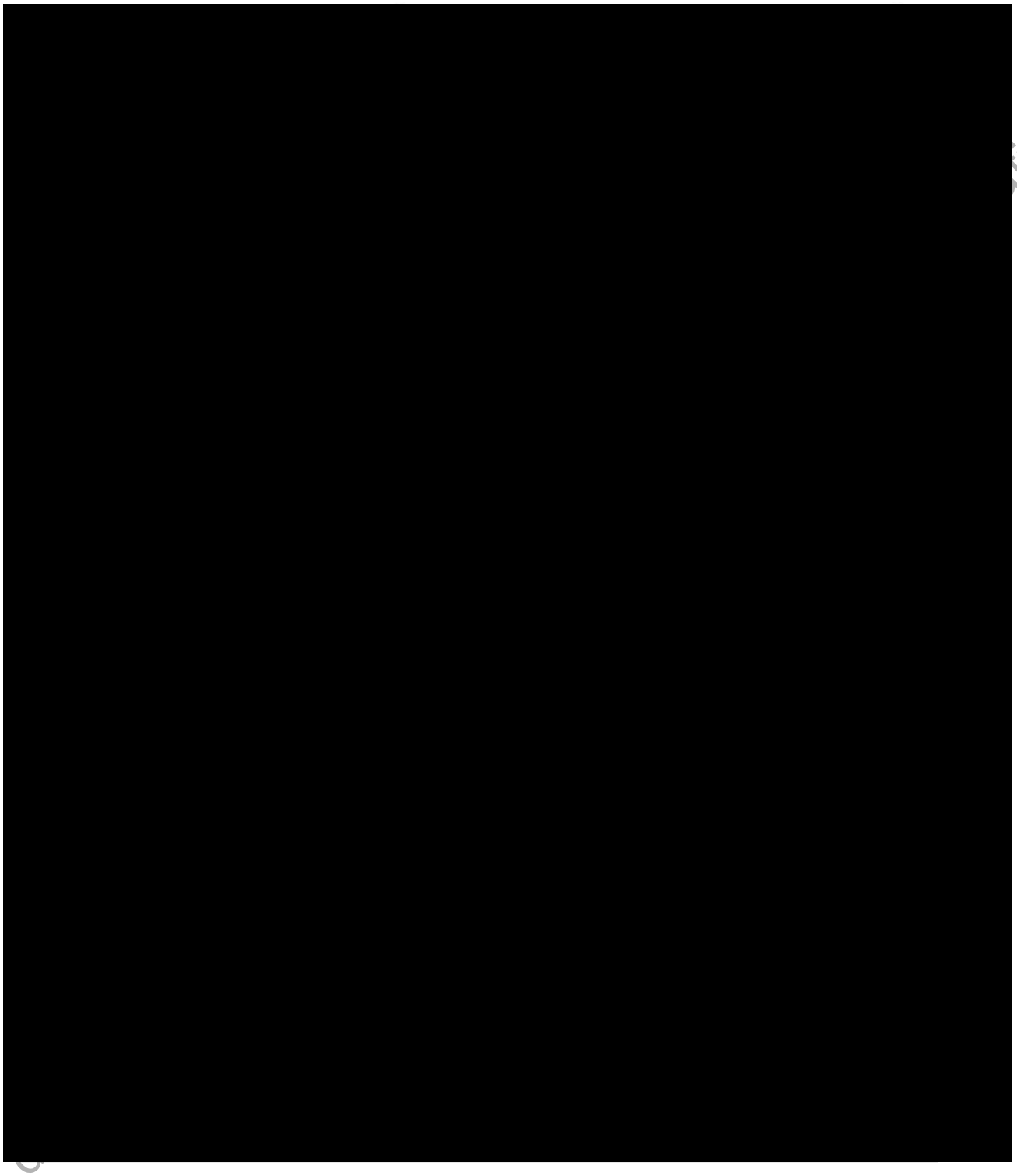
Note: To receive a grade >1, all nonovert skin and non-overt mucosal bleeding (petechiae, ecchymoses, subcutaneous hematomas, vescicles/bullae subconjunctival bleeding) should be visible at the time of visit for grading by the physician or expert nurse taking the history.

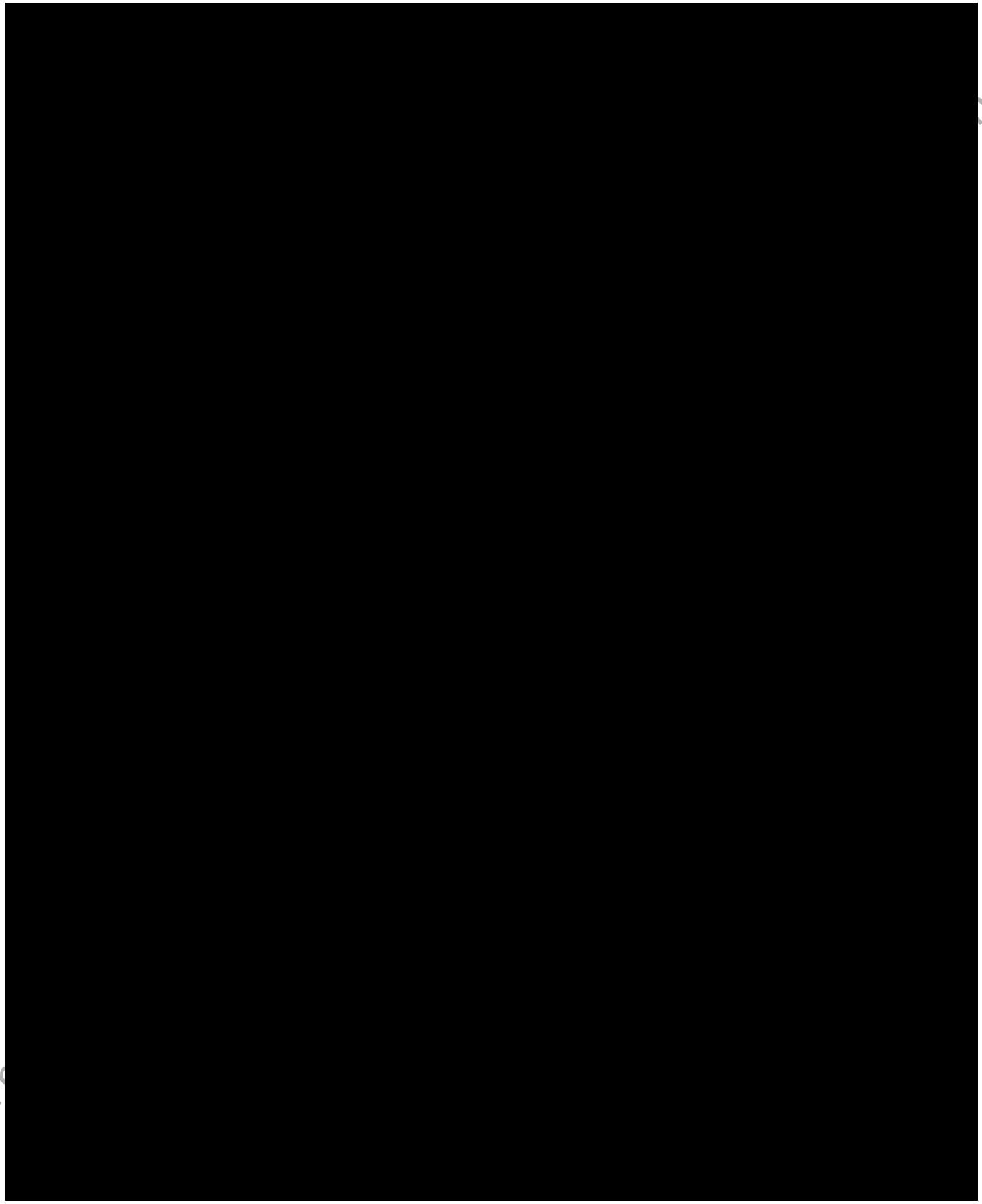
Note: For bleeding from minor wounds and overt-mucosal bleeding (epistaxis, gum, bleeding from bites to lips & tongue or after deciduous teeth loss/extraction) and all organ bleeding, a medical record describing the symptom or indicating a specific intervention/prescription should be also taken into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

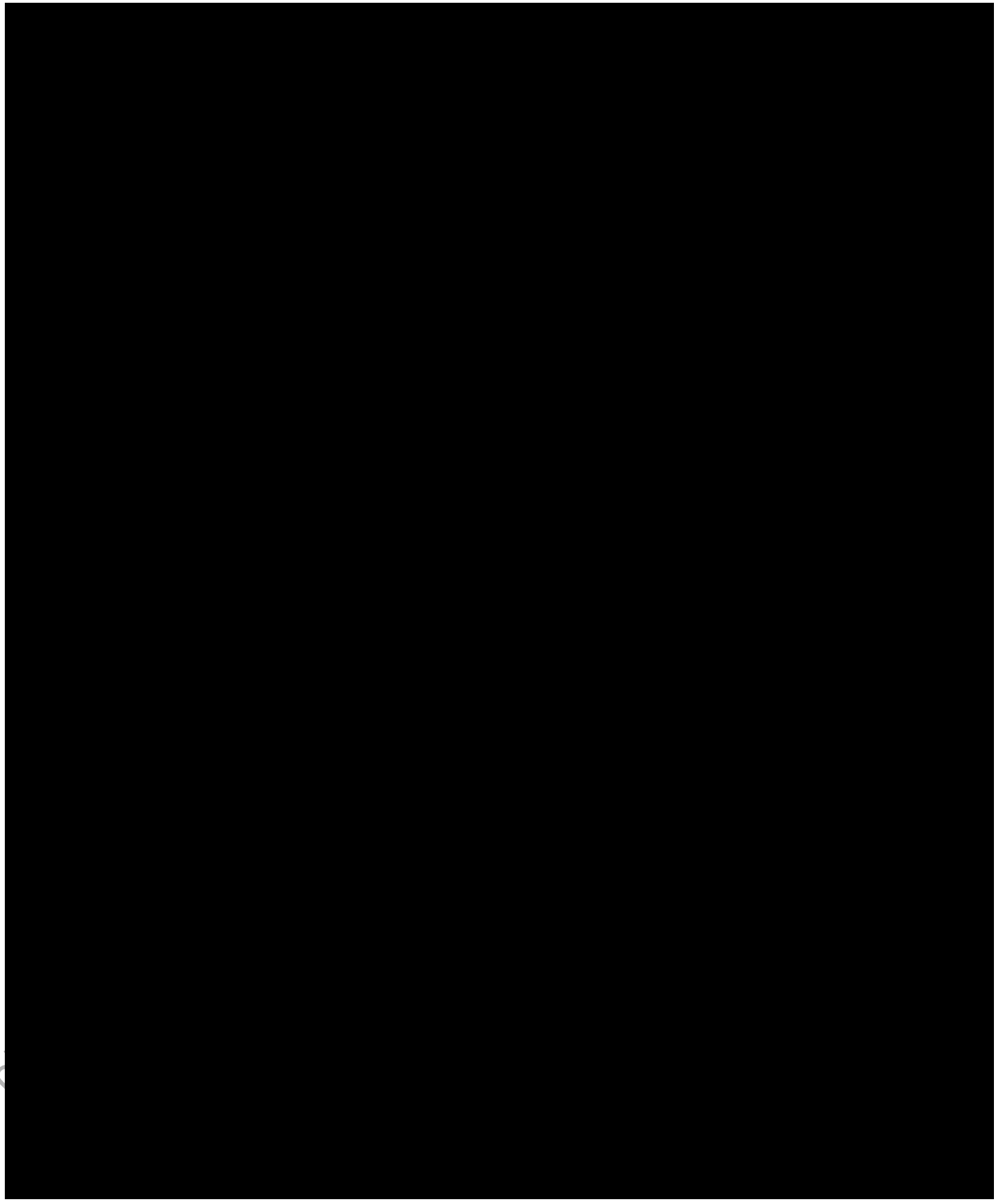
Note: Requirement for ITP-specific treatments and anti-fibrinolytics (apart from menorrhagia) was not considered for grading, due to their subjective nature and their adoption not only to control actual bleeding but also to reduce the "risk" of impendent or future bleeding.

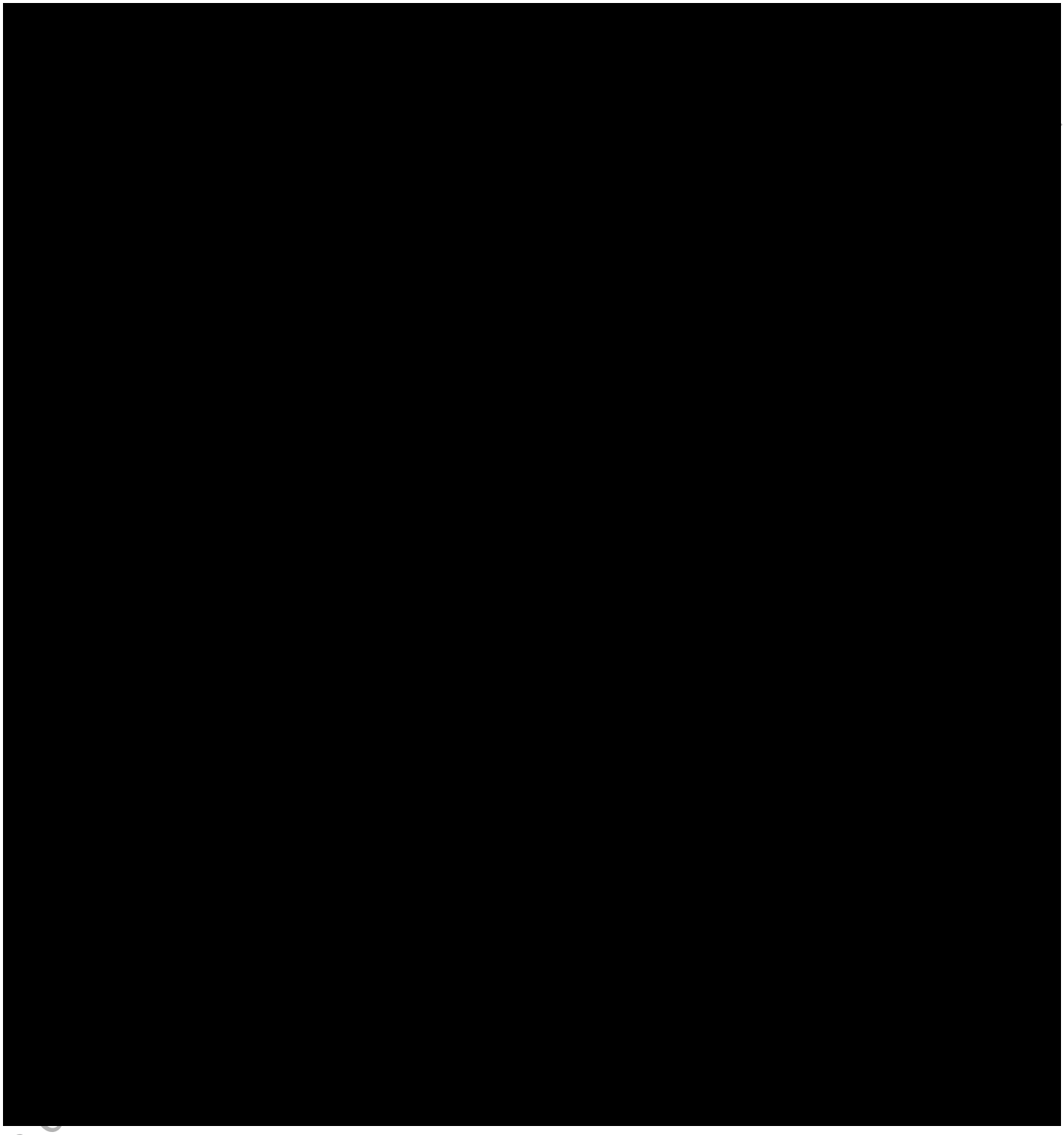
10.11 Appendix 11: ITP-PAQ

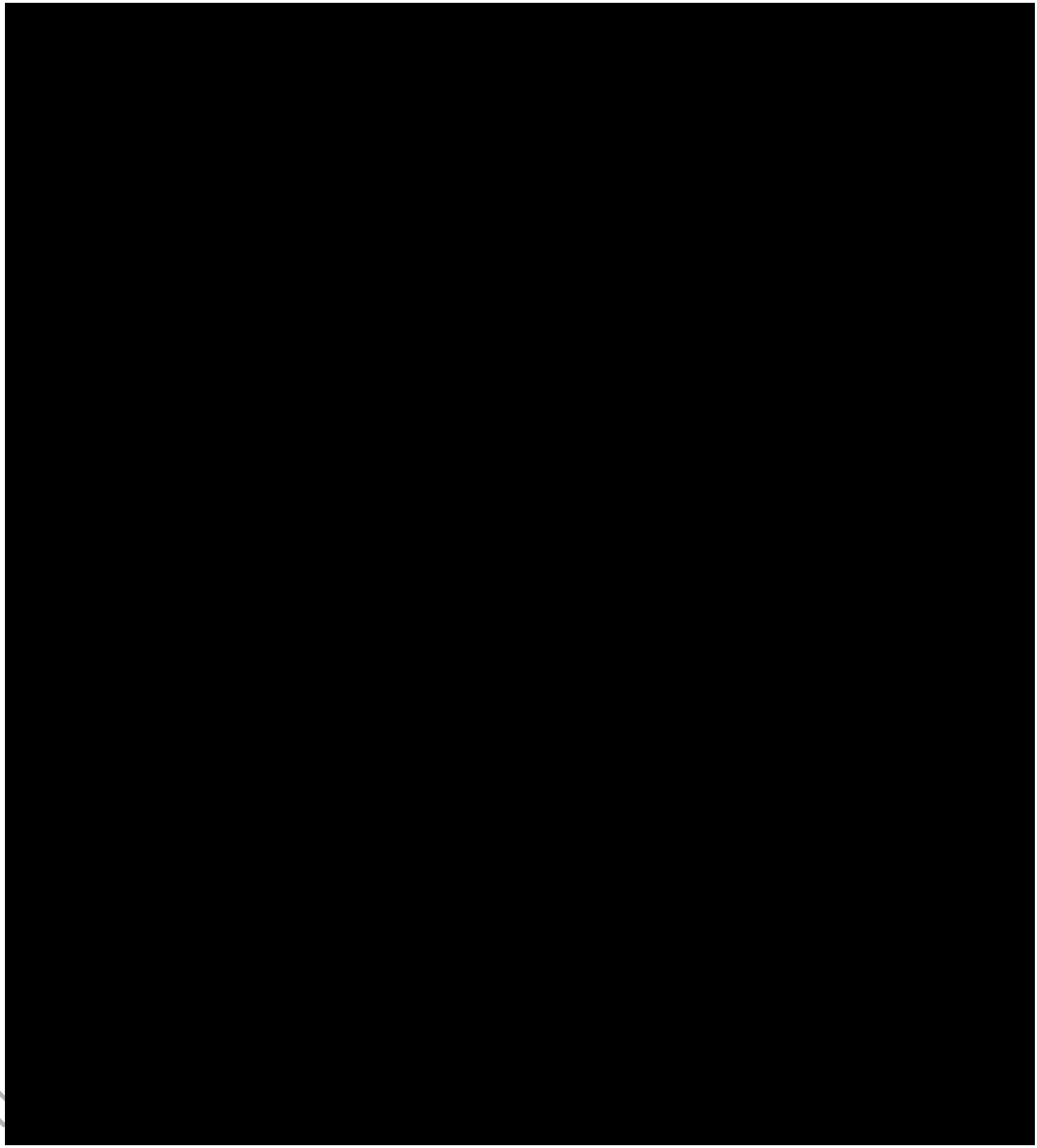


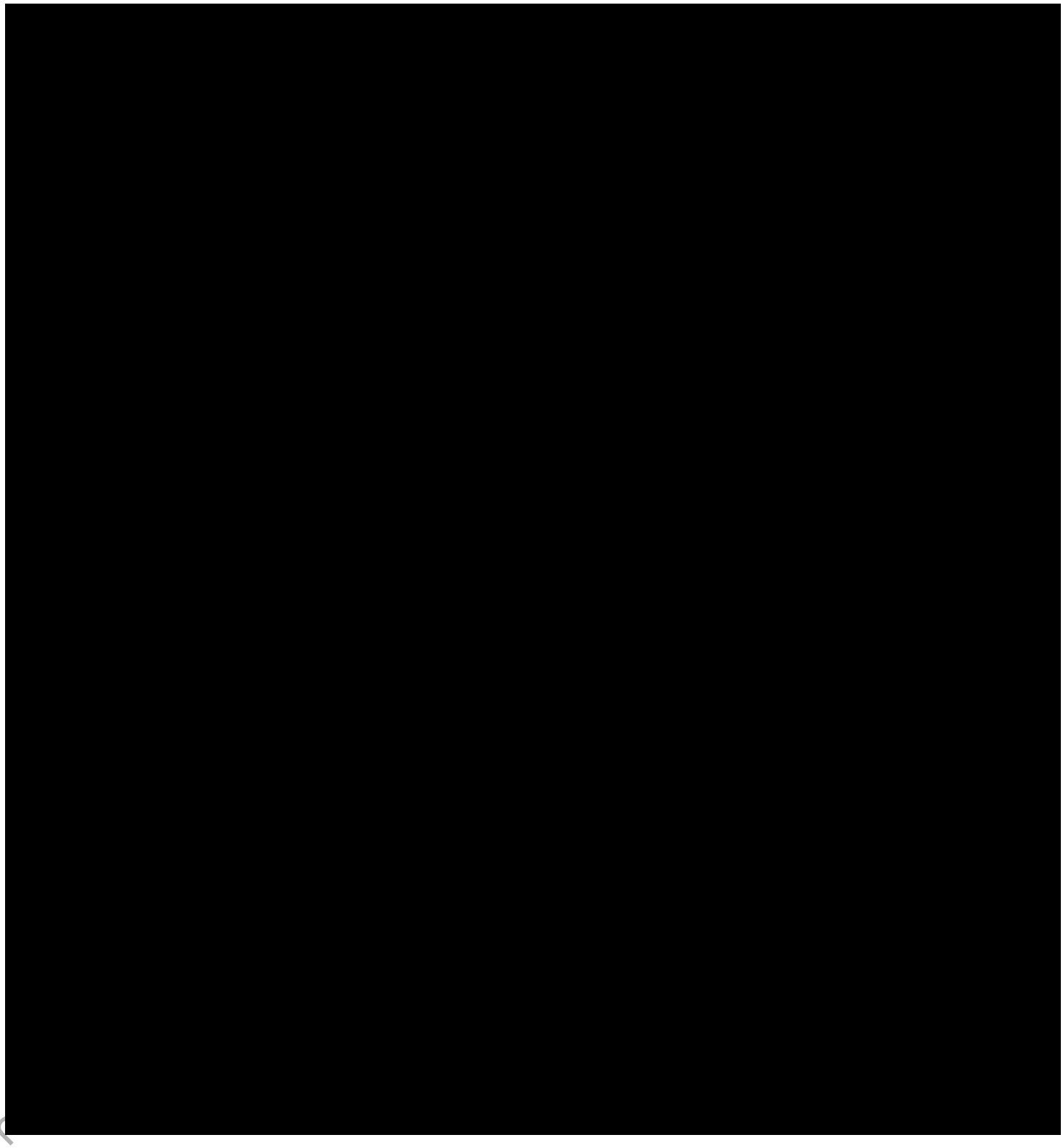


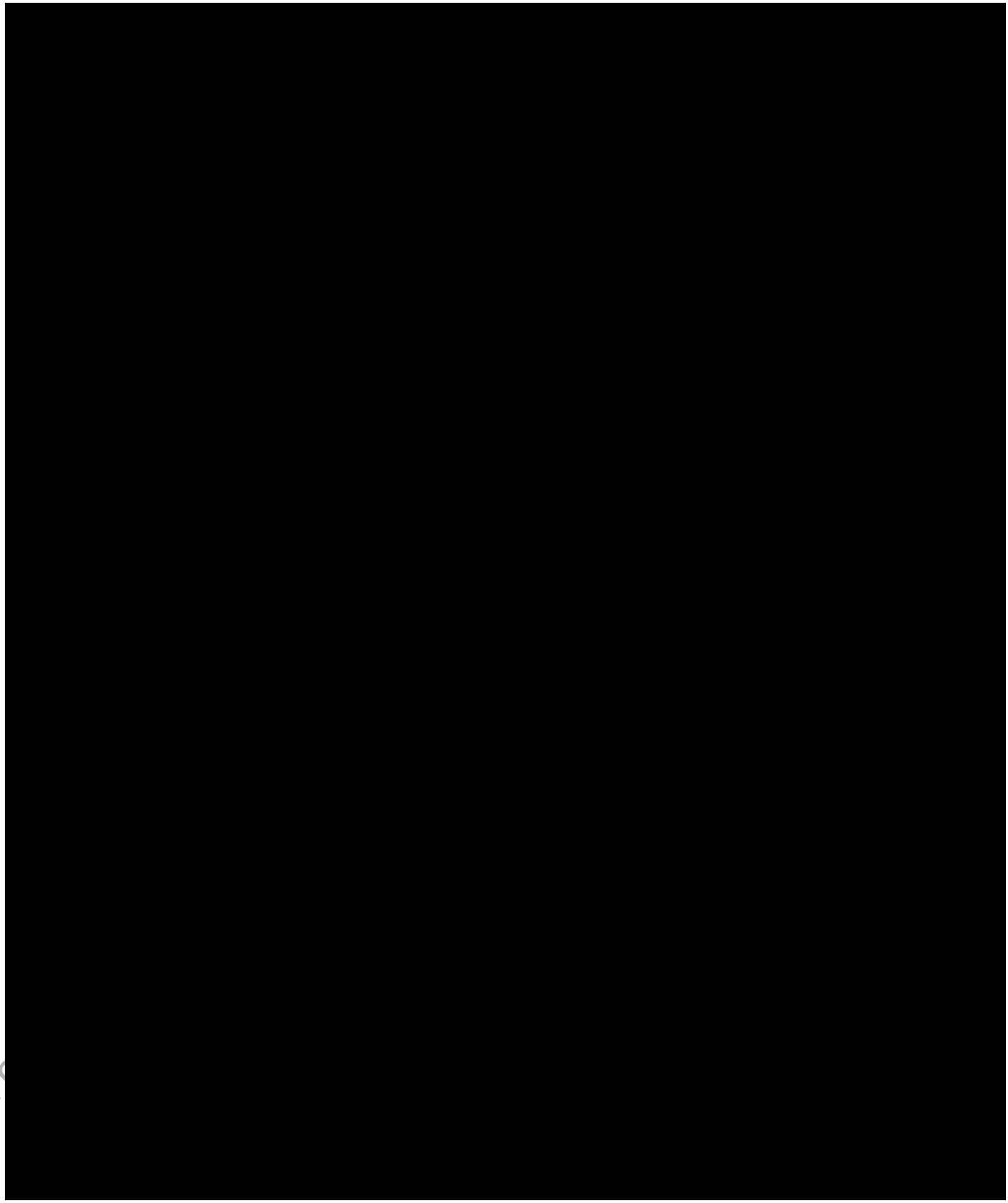


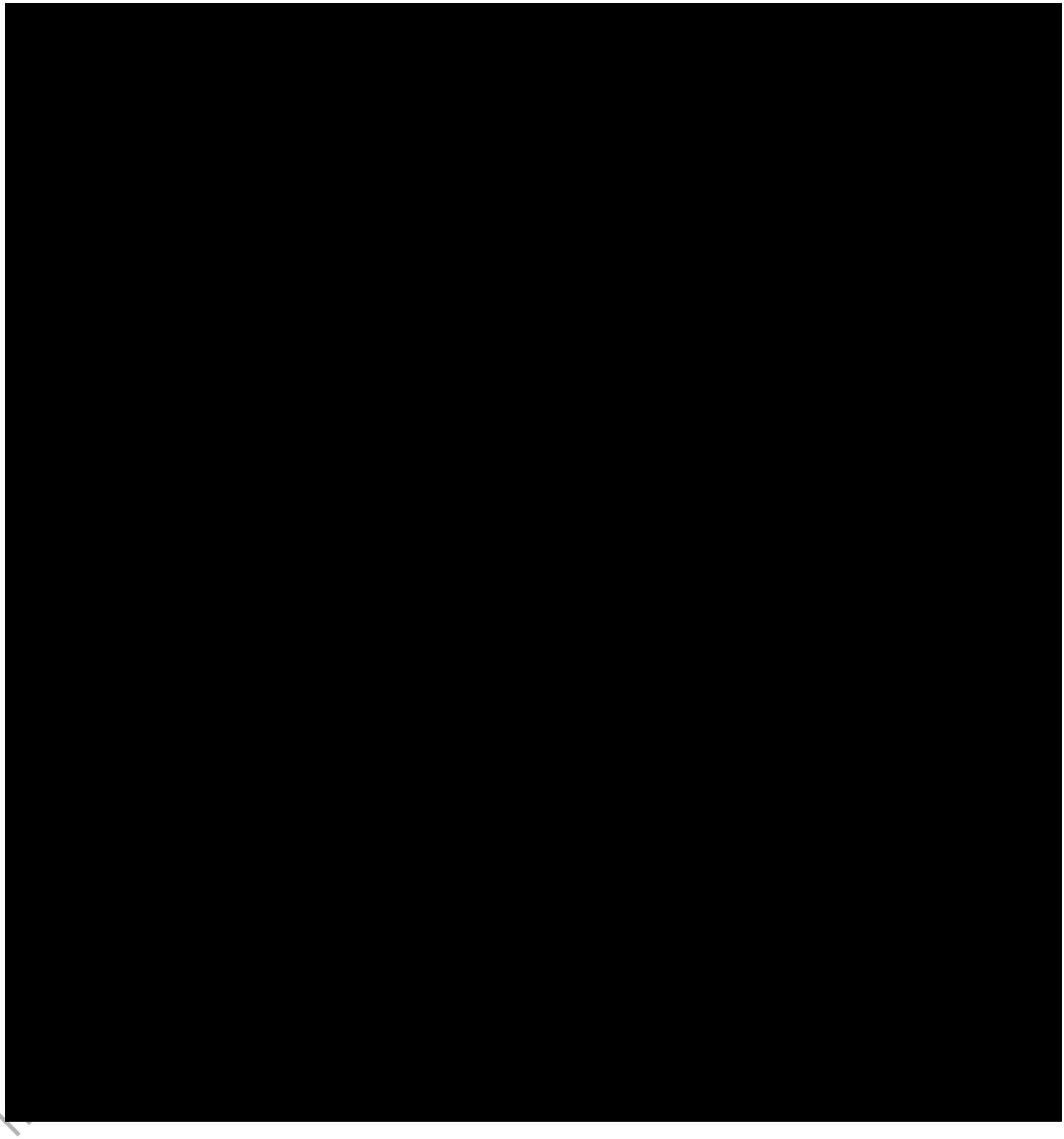


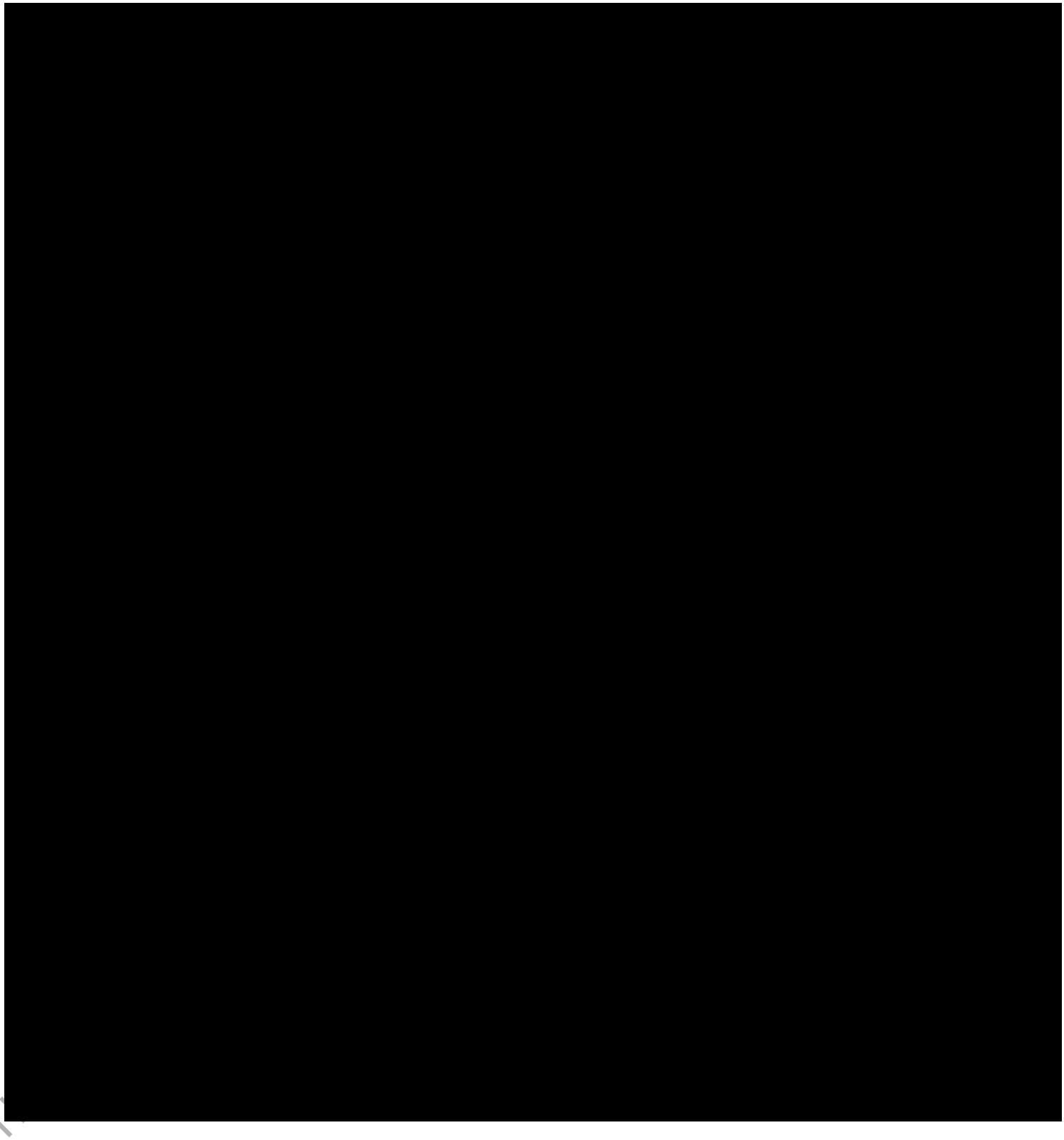


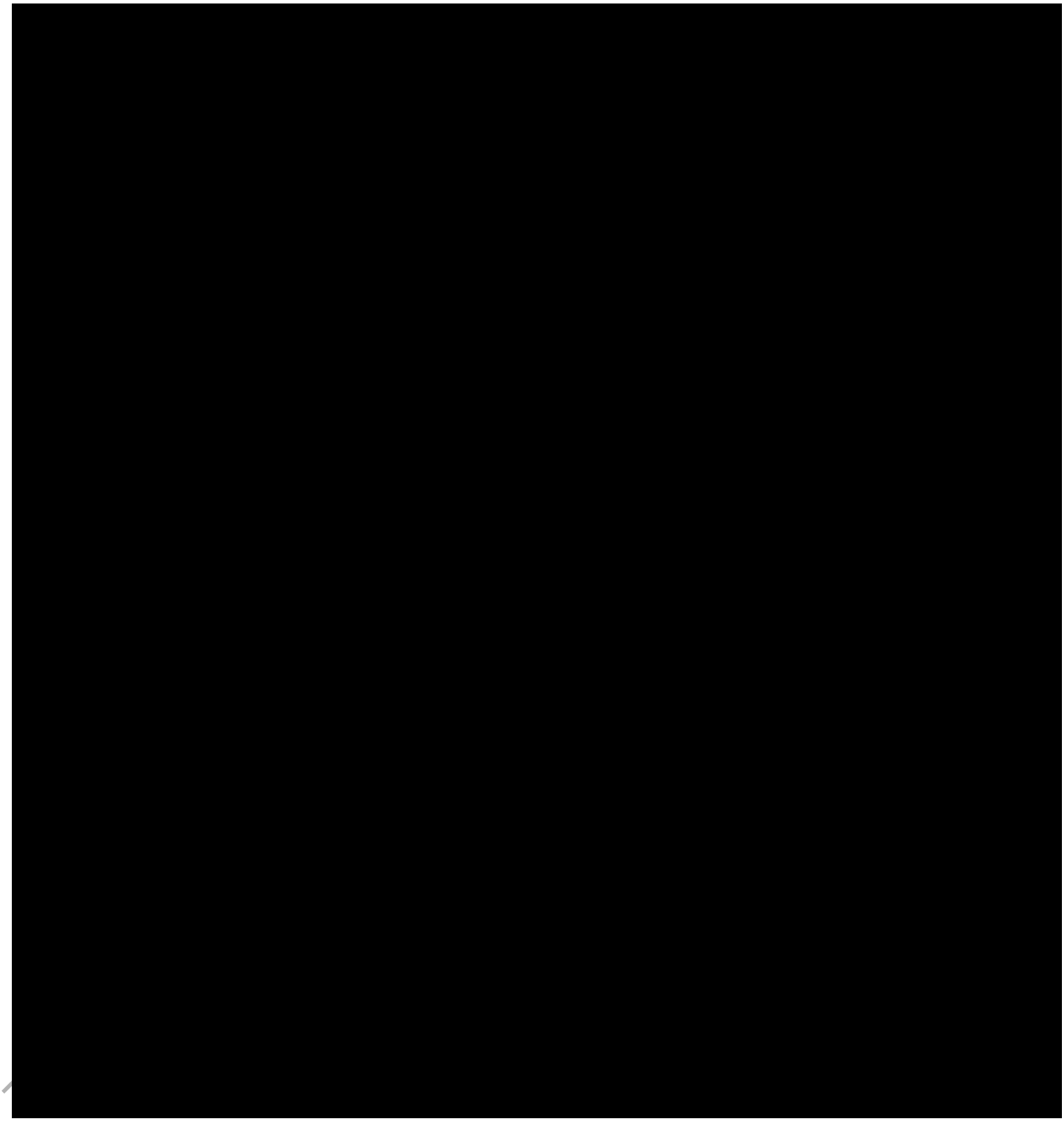






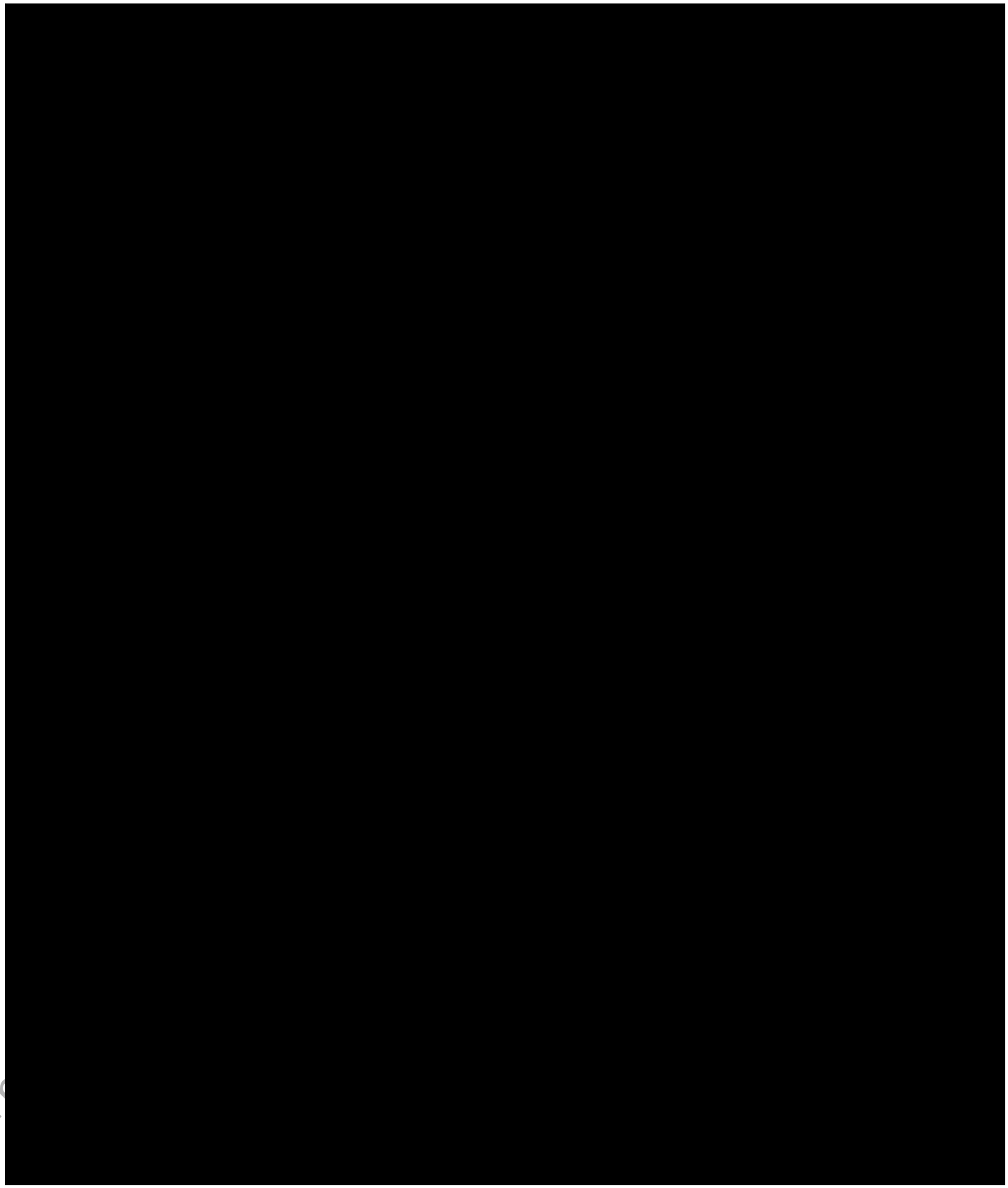


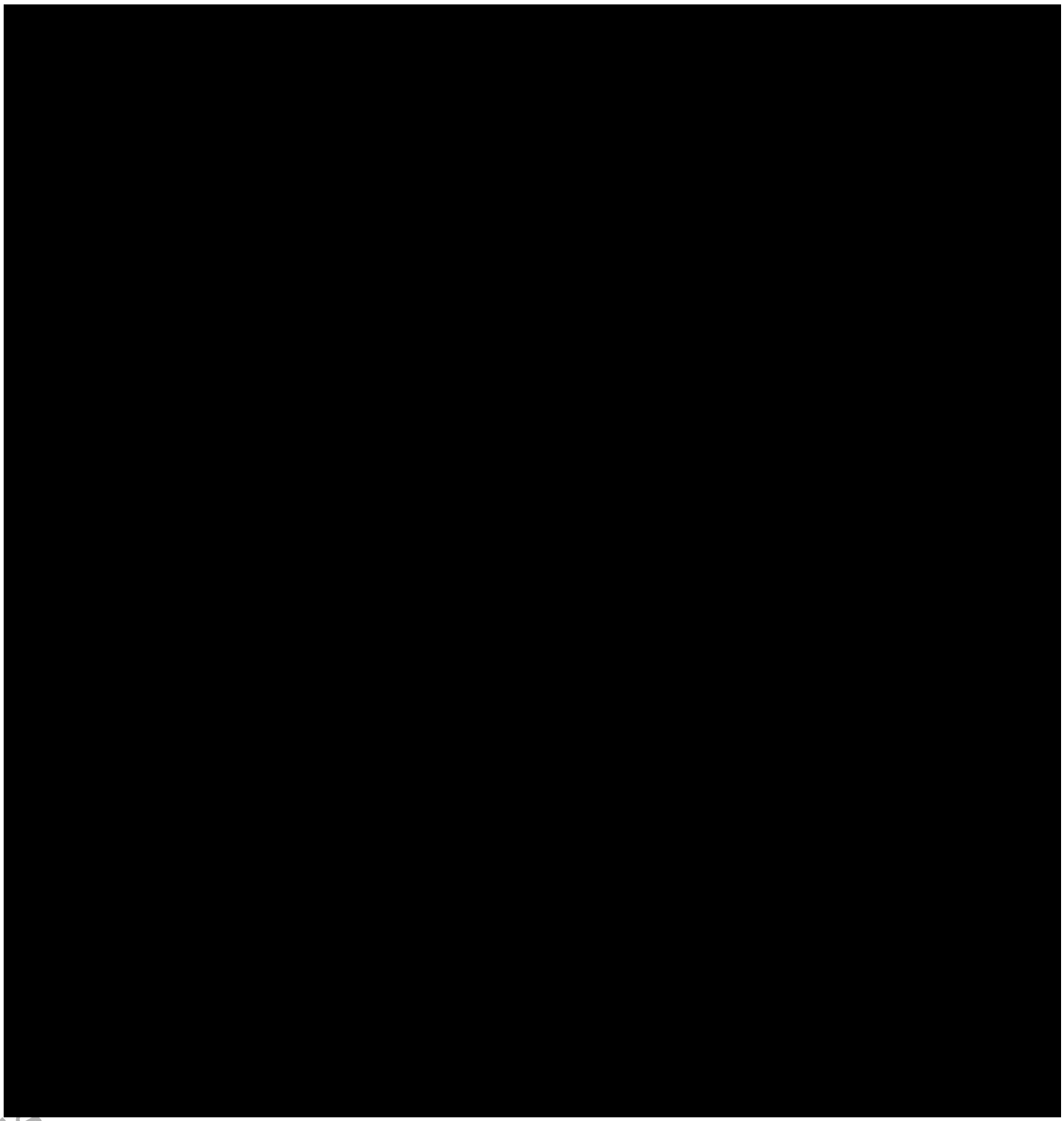




10.12 Appendix 12: SF-36 Form

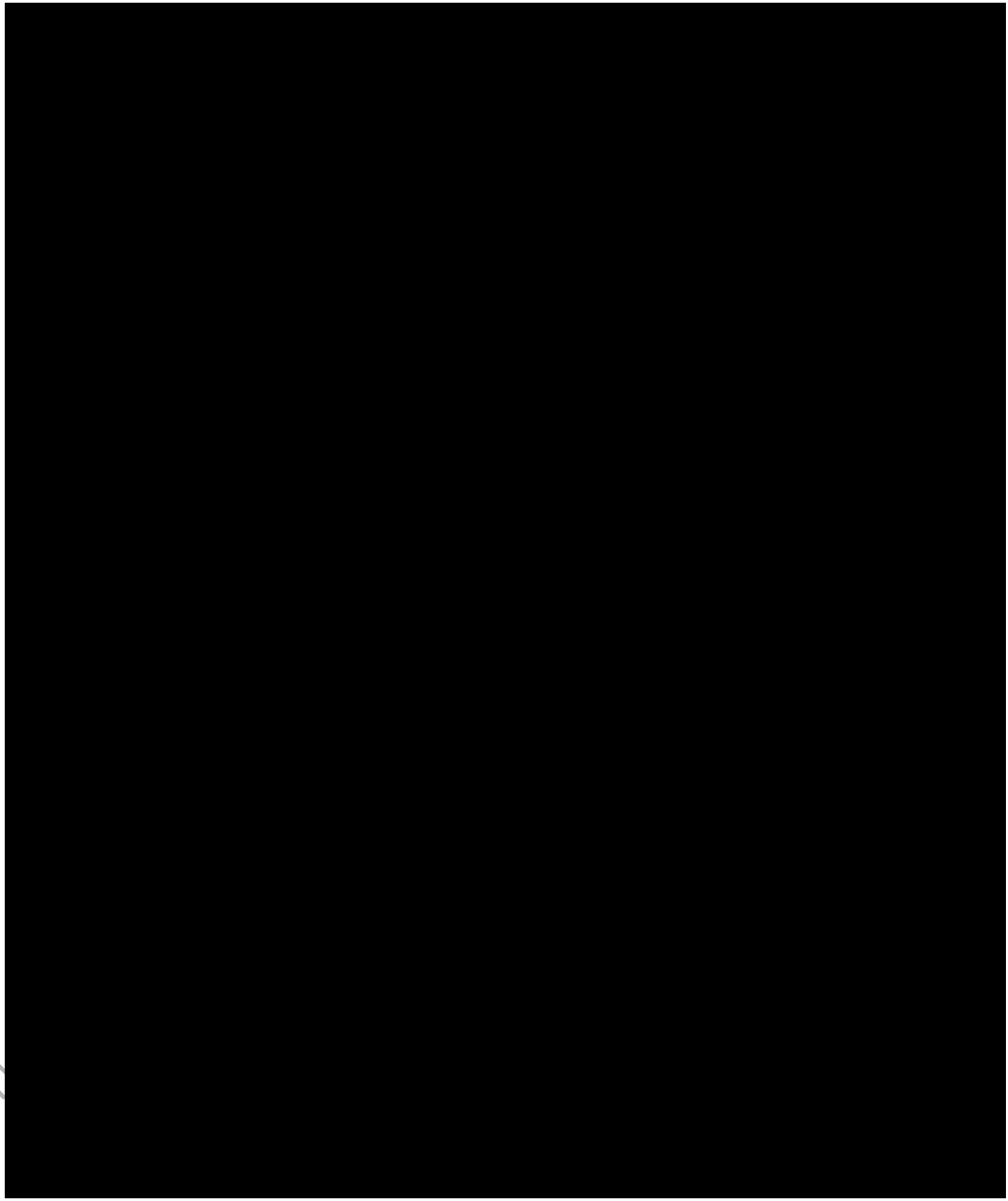
[redacted]



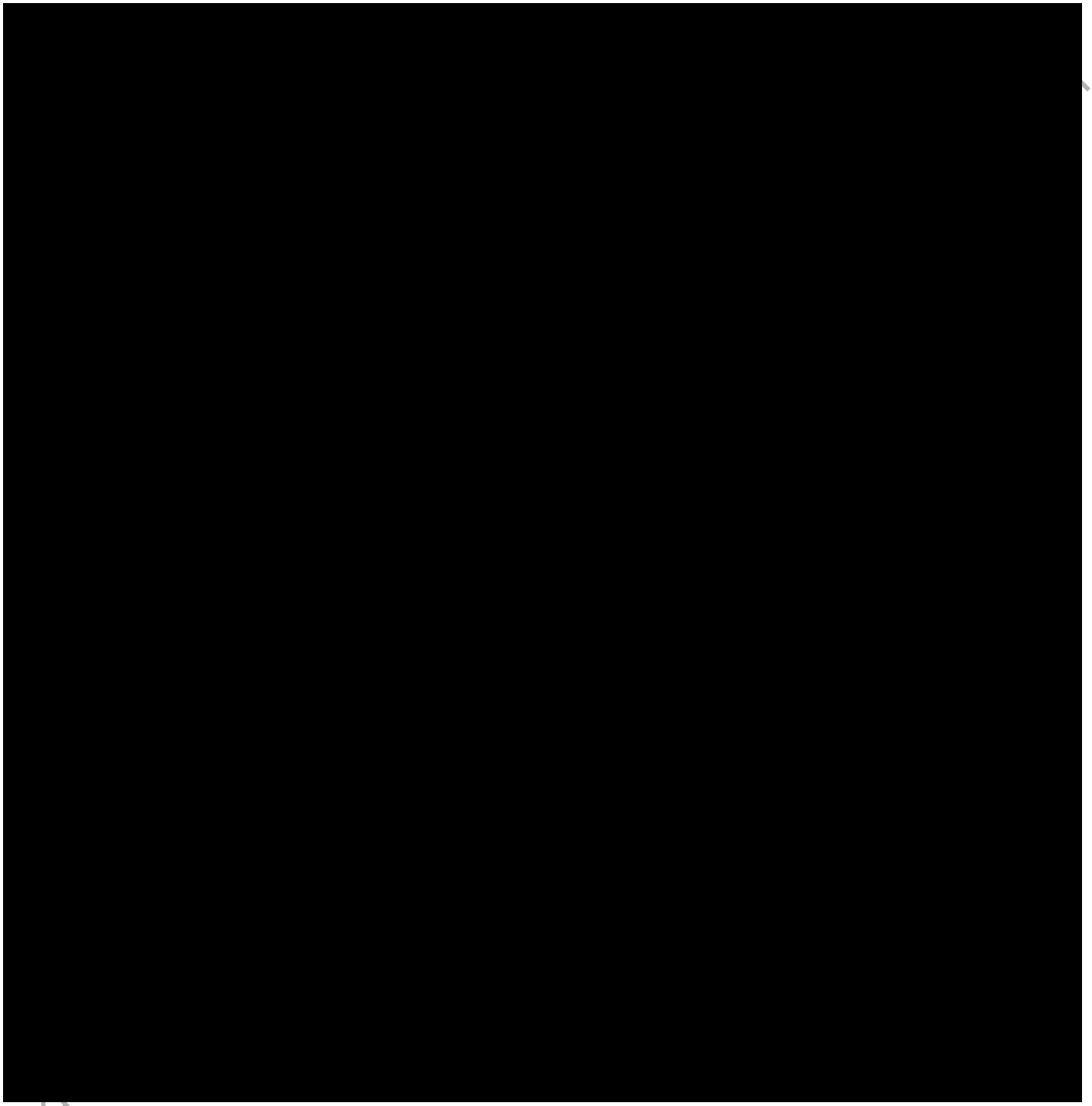


[redacted]

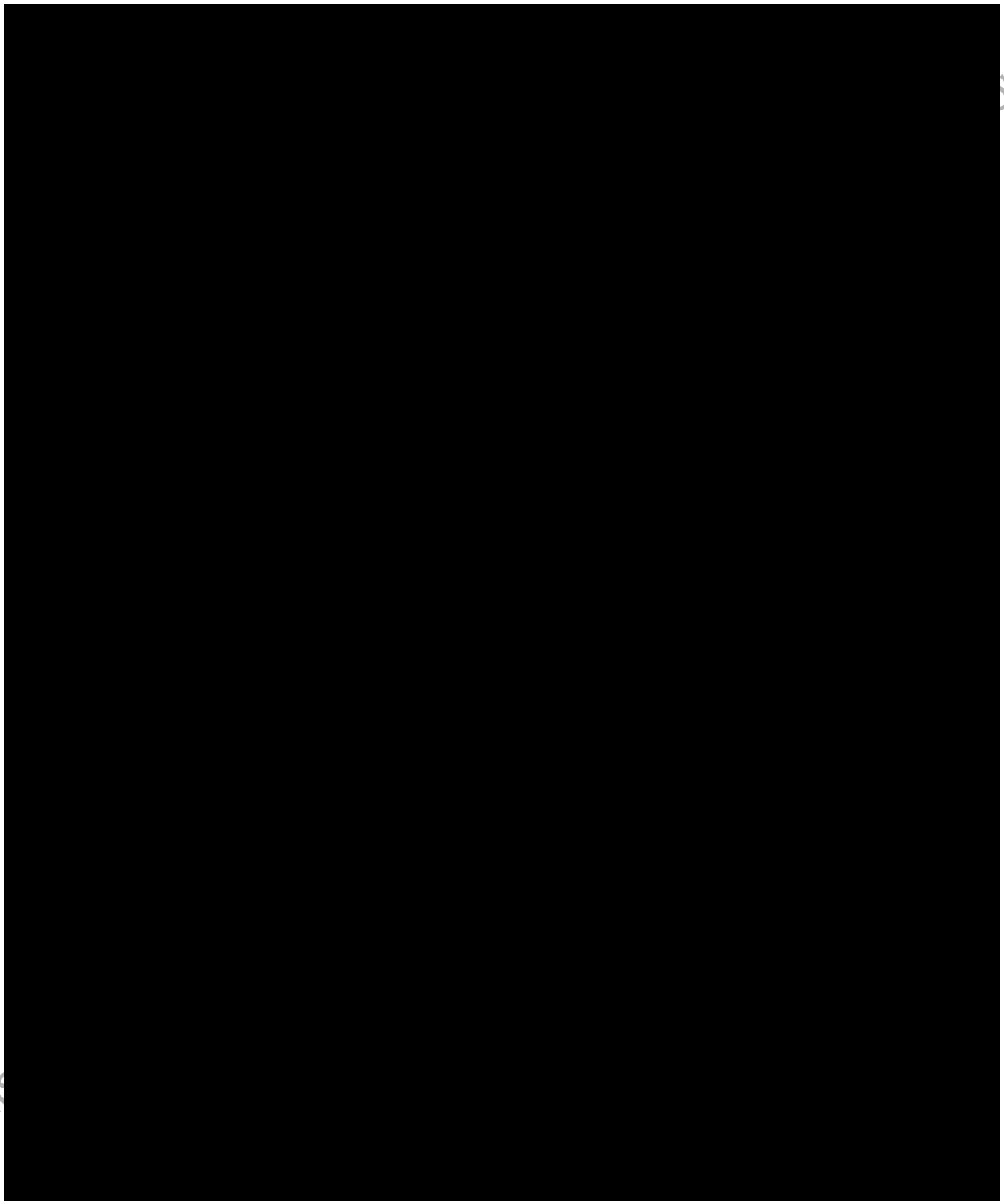
[redacted]

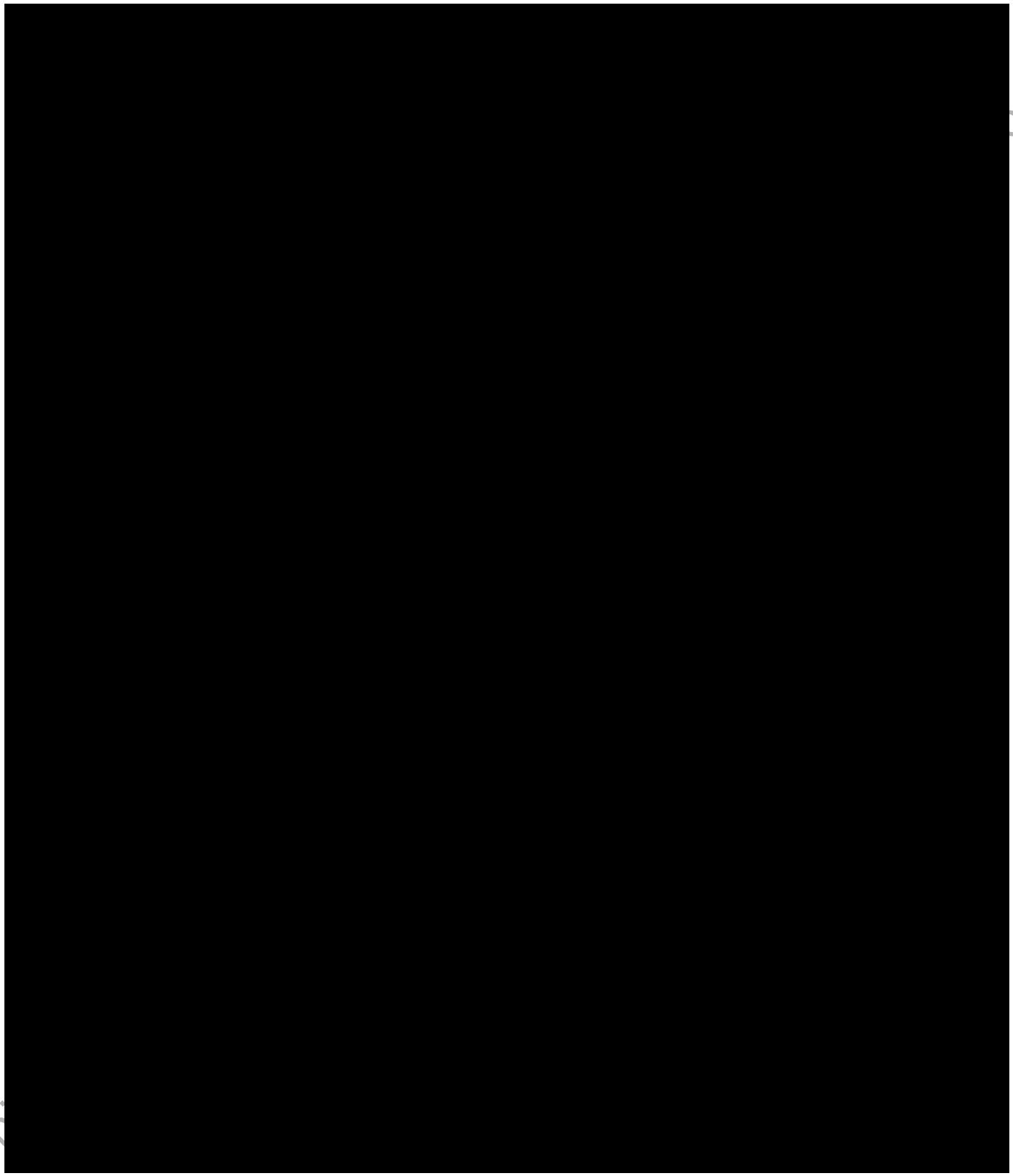


10.13 Appendix 13: FATIGUE-PRO Physical Fatigue Scale



10.14 Appendix 14: EQ-5D-5L





10.15 Appendix 15: PGI-S

The following question asks you about your current overall ITP symptoms.

Please check the box that best describes your current situation.

How would you describe your ITP symptoms during the past week?

	None
	Mild
	Moderate
	Severe
	Very severe

10.16 Appendix 16: PGI-C

The following question asks you about your overall symptoms now compared to before starting treatment within this clinical study.

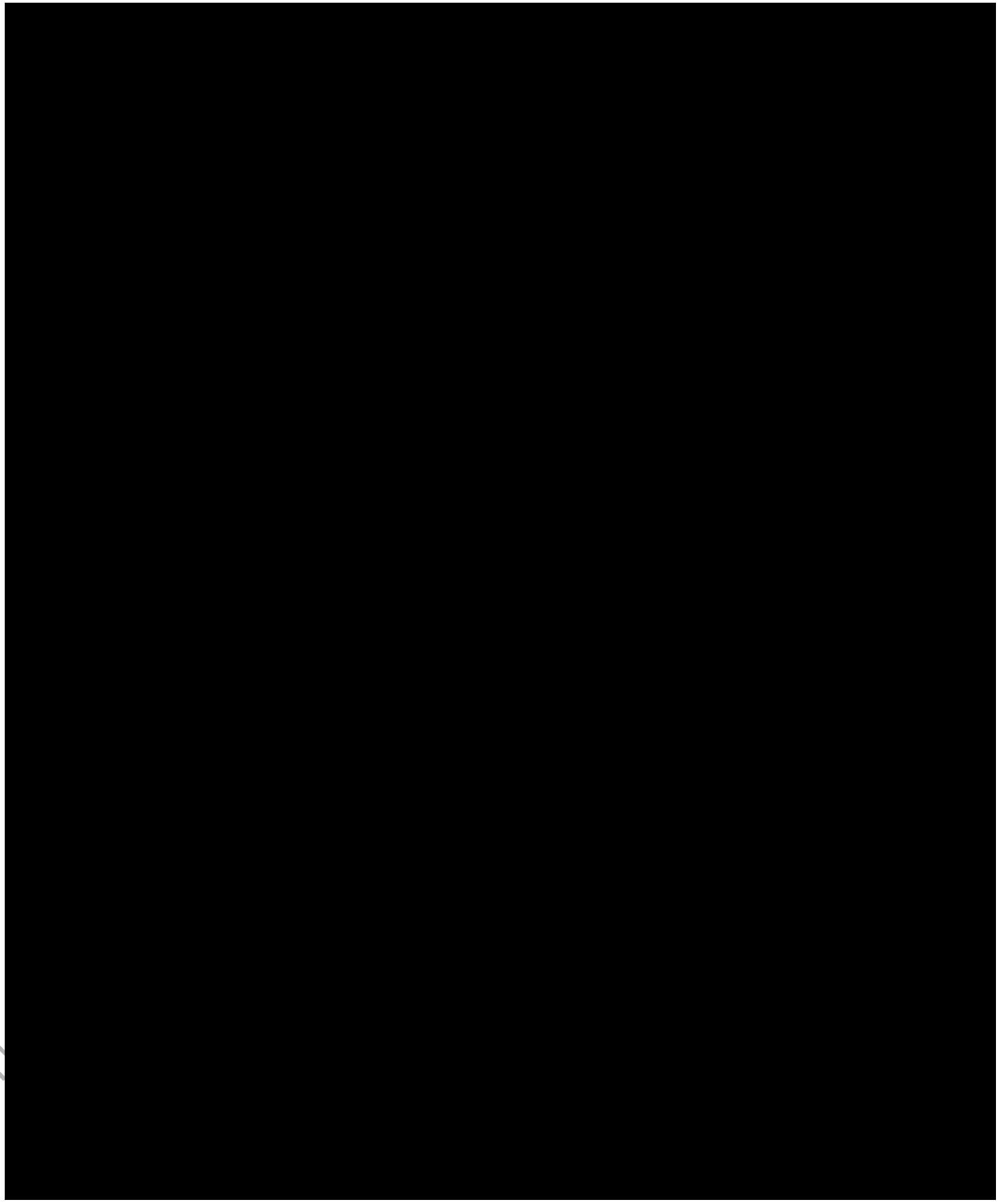
Please check the box that best describes your current situation.

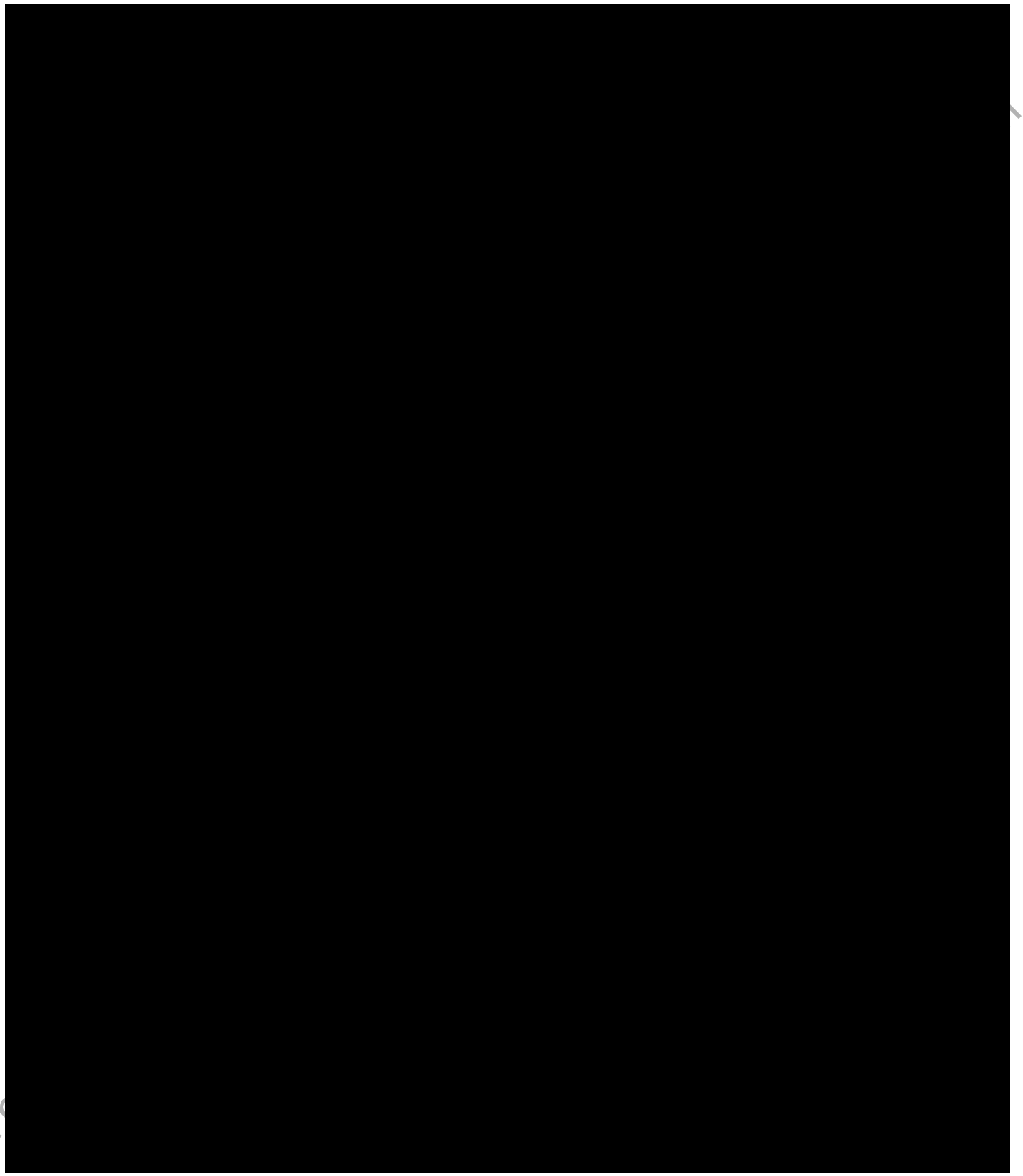
How would you describe your current ITP symptoms compared to before you started treatment in this clinical study?

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

10.17 Appendix 17: Headache Questionnaire

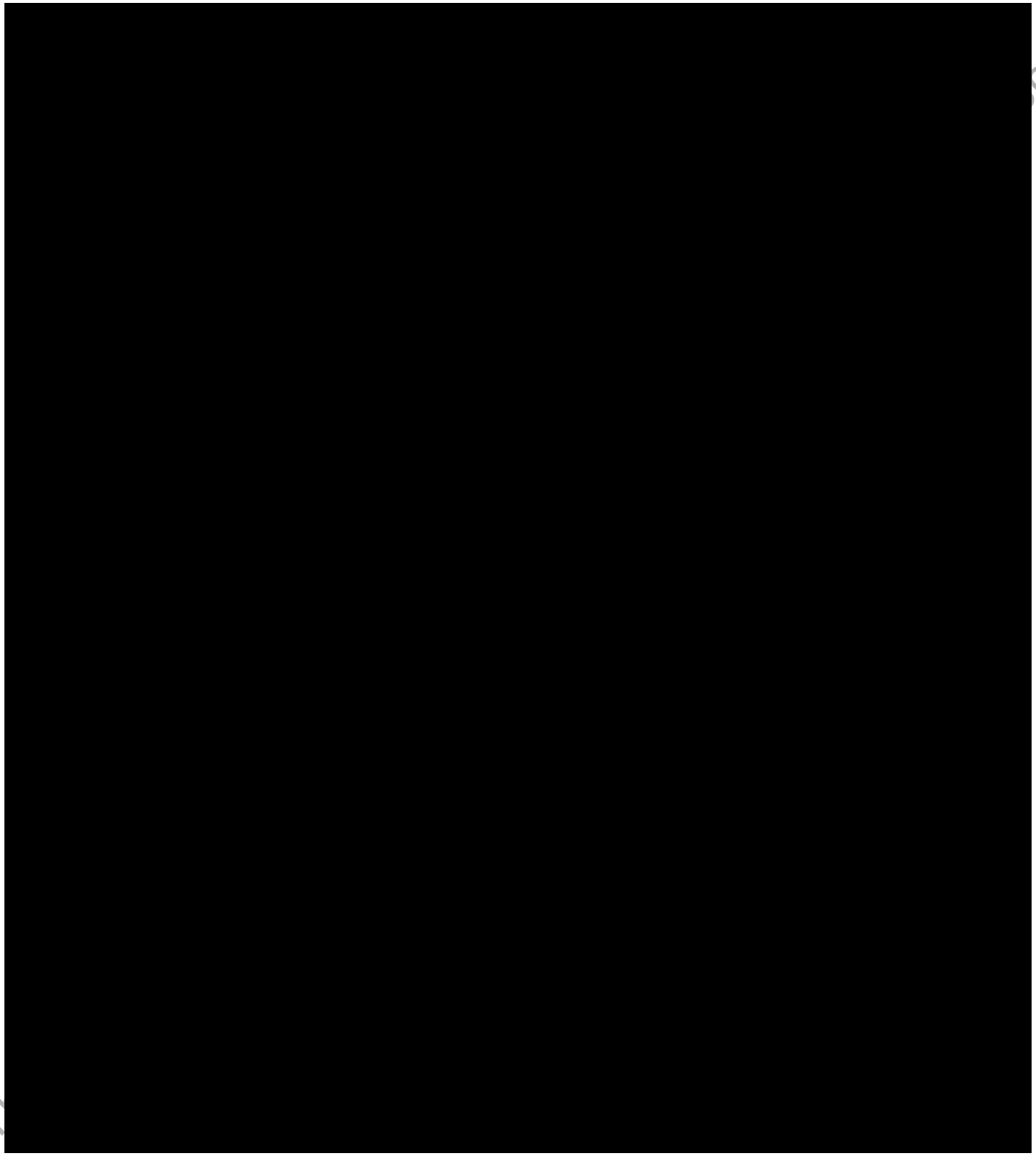
[redacted]





[redacted]

10.18 Appendix 18: Tuberculosis assessment



10.19 Appendix 19: 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

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

b. 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 BP 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.

10.20 Appendix 20: Management of headache

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

Determination of the severity of headache will be consistent with National Cancer Institute Terminology Criteria for Adverse Events (CTCAE) version 5.0 (see Appendix 3, Section 10.3). Severe headache is defined as severe pain limiting self-care activities 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.

The Headache Questionnaire (Appendix 17, Section 10.17) should be administered daily by a health care professional via an interview with any study participant experiencing moderate, severe and/or serious headache until resolving or resolution (ie, if headache becomes nonserious, mild, or completely resolved, whichever comes first). If the severe or serious headache is initially reported at a home visit or during a telephone call, the study participant should be seen at the study site as soon as is practically 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, meningitidis, 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 headaches or serious headaches when possible. These investigations will be performed to further understand the mechanism of headaches in the study participants.

Treatments must be permanently discontinued if a study participant has a serious headache (SAE of 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 the treatment has been put on hold and 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. However, if a participant experiences >2 severe headaches that is 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] to [redacted] or from [redacted] to [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 and risk of continuing treatment with IMP and chronic prophylactic treatment with analgesics must be carefully evaluated by the investigator.

10.21 Appendix 21: 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, for further details).

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] to [redacted] or from [redacted] to [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).

10.22 Appendix 22: 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 until Week 4 (Visit 5). However, to ensure study participants' safety, serum IgG level will be monitored by unblinded Medical Monitors external to UCB until Week 4 (Visit 5) and by the blinded Medical Monitors starting with the blood samples taken at Week 4 (Visit 5). In case the serum IgG level decreases <1g/L, as described below and in Table 10-7, the unblinded/blinded Medical Monitors will inform the investigator.

The most recently available IgG value is the trigger for discussions between the unblinded/blinded Medical Monitors and the investigator and for any decisions on changing/skipping the dose of IMP. All discussions and decisions related to the benefit-risk of dose change/skip 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 counts), current signs and symptoms of nonserious/serious infection, potential risk of acquiring a nonserious/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 10-7: Management of infections and hypogammaglobulinemia

IgG value	Actions	Outcome
IgG <1g/L[a]	Unblinded medical monitor informs the investigator	Investigator decides to either: • maintain the dose • reduce the dose • skip dose based on the study participant's status regarding platelets response, signs & symptoms of nonserious/ serious infection, potential risk of acquiring a nonserious/serious infection

AE=adverse event; eCRF=electronic case report form
[a] Events of hypogammaglobulinemia must not be captured as an AE in the eCRF, to protect the blind.

Dose adjustments/dose skipped

The dose of IMP can be reduced from [redacted] equivalent (eqv.) to [redacted] eqv., from [redacted] eqv. to [redacted] (approx. [redacted]), or directly from [redacted] eqv. to [redacted] (approximately [redacted]), as needed.

The IgG would be expected to return to values ≥1g/L in up to 3-4 weeks (after a dose decrease/skip). 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 it can be skipped, if needed.

In case a dose is skipped, 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

Splenectomised study participants are at a higher risk of infections, especially of overwhelming post-splenectomy infections. Irrespective of the IgG level, in case a splenectomised study participant develops a (persistent or re-occurring) 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/blinded Medical Monitors, as needed.

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

10.23 Appendix 23: Management of infusion-related 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 10-8. Definitions of the severity of the relevant events will be consistent with CTCAE version 5.0 (see Appendix 3, Section 10.3).

Table 10-8: Suggested management guidelines 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 min. 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); NSAIDs=Nonsteroidal anti-inflammatory drugs
Note: Management criteria were adapted from the CTCAE v5.0 (National Cancer Institute, 2017).

In case of suspected anaphylaxis, the Sampson Criteria (Sampson et al, 2006) should be accessed and Appendix 19 (Section 10.19, 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 s(C3, C4), plasma complements (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.

10.24 Appendix 24: SIAQ (infusion version)

PRE-SIAQ (Infusion version):

SELF-INJECTION ASSESSMENT QUESTIONNAIRE (SIAQ)

SELF-INFUSION VERSION

- PRE-Self-Infusion -

INTRODUCTION

The following questions ask about infusions in general and your feelings about giving yourself an infusion.

Please complete this questionnaire by yourself, preferably in a quiet environment. Take as much time as you need to complete it. There are no right or wrong answers. Your answers will remain strictly confidential and anonymous.

Please answer each question below by checking the box that best represents your opinion (Check only one box per question).

1. In general, how afraid are you of needles?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

2. In general, how afraid are you of having an infusion?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

3. How anxious do you feel about giving **yourself** an infusion?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

4. How confident are you about giving yourself an infusion in **the right way**?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

5. How confident are you about giving yourself an infusion in a **clean and sterile way**?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

6. How confident are you about giving yourself an infusion **safely**?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

7. Overall, how satisfied are you with your current way of taking your medication?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

POST-SIAQ (Infusion version):

SELF-INJECTION ASSESSMENT QUESTIONNAIRE (SIAQ)

SELF-INFUSION VERSION

- POST-Self-Infusion -

INTRODUCTION

The following questions concern the self-infusion of your medication and must be answered after giving yourself an infusion.

Please complete this questionnaire by yourself, preferably in a quiet environment. Take as much time as you need to complete it. There are no right or wrong answers. Your answers will remain strictly confidential and anonymous.

FEELINGS ABOUT INFUSIONS

The following questions concern your **feelings about infusions**.

Please answer each question below by checking the box that best represents your opinion (Check only one box per question).

1. In general, how afraid are you of needles?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

2. In general, how afraid are you of having an infusion?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

3. How anxious do you feel about giving **yourself** an infusion?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

SELF-IMAGE

The following question concerns your **self-image**.

Please answer the question below by checking the box that best represents your opinion (Check only one box).

4. How embarrassed would you feel if someone saw you with the self-infusion device?

Not at all	A little	Moderately	Very	Extremely
☐5	☐4	☐3	☐2	☐1

SELF-CONFIDENCE

The following questions concern your **confidence** about giving yourself an infusion.

Please answer each question below by checking the box that best represents your opinion (Check only one box per question).

5. How confident are you about giving yourself an infusion in **the right way**?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

6. How confident are you about giving yourself an infusion in a **clean and sterile** way?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

7. How confident are you about giving yourself an infusion **safely**?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

PAIN AND SKIN REACTIONS DURING OR AFTER THE INFUSION

The following questions ask about **pain and skin reactions** you may have experienced during or after the infusion.

Please answer each question below by checking the box that best represents your opinion (Check only one box per question).

8. During and/or after the infusion, how bothered were you by:	Not at all	A little	Moderately	Very	Extremely
a. **pain**?	☐5	☐4	☐3	☐2	☐1
b. **burning sensation**?	☐5	☐4	☐3	☐2	☐1
c. **cold sensation**?	☐5	☐4	☐3	☐2	☐1

9. During and/or after the infusion, how bothered were you by:	Not at all	A little	Moderately	Very	Extremely
a. **itching** at the infusion site?	☐5	☐4	☐3	☐2	☐1
b. **redness** at the infusion site?	☐5	☐4	☐3	☐2	☐1
c. **swelling** at the infusion site?	☐5	☐4	☐3	☐2	☐1
d. **bruising** at the infusion site?	☐5	☐4	☐3	☐2	☐1
e. **hardening** at the infusion site?	☐5	☐4	☐3	☐2	☐1

SATISFACTION WITH SELF-INFUSION

The following questions ask about your **satisfaction** with self-infusion.

Please answer each question below by checking the box that best represents your opinion (Check only one box per question).

10. How easy was it to give yourself an infusion?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

11. How satisfied are you with **how often** you give yourself an infusion?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
☐1	☐2	☐3	☐4	☐5

12. How satisfied are you with the **time it takes to infuse** the medication?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
☐1	☐2	☐3	☐4	☐5

13. Overall, how satisfied are you with your current way of taking your medication (self-infusion)?

Very dissatisfied	Dissatisfied	Neither dissatisfied nor satisfied	Satisfied	Very satisfied
☐1	☐2	☐3	☐4	☐5

14. Overall, how convenient is the self-infusion device?

Very inconvenient	Inconvenient	Neither inconvenient nor convenient	Convenient	Very convenient
☐1	☐2	☐3	☐4	☐5

15. After this study, would you choose to continue self-infusing your medication?

Definitely not	Probably not	I don't know	Yes, probably	Yes, definitely
☐1	☐2	☐3	☐4	☐5

16. After this study, how confident would you be to give yourself infusions at home?

Not at all	A little	Moderately	Very	Extremely
☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

10.25 Appendix 25: Protocol Amendment History

Amendment 3 (09 Dec 2021)

Overall Rationale for the Amendment

The primary reason for this protocol amendment is to correct errors in Table 1-1 Schedule of Assessment at Weeks 19, 23, 27 and 51.

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

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

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Objectives and Endpoints 3 Objectives and endpoints	Footnote "a" was added to the endpoints referring to "Baseline".	Updated for consistency.
1.1 Synopsis, Objectives and Endpoints 3 Objectives and endpoints	The following secondary objective and endpoint were removed: • To assess the pharmacodynamic (PD) effect of rozanolixizumab • Total serum IgG (absolute value) and change from Baselinea (absolute value and percentage) in serum IgG and in serum IgG subclass concentration at each scheduled assessment	To remove duplication as they will be assessed as an exploratory objective and endpoint.
1.1 Synopsis, Overall design 4.1 Overall design	The sentence "In case of a late rollover, platelet counts will need to be remeasured." was added.	The sentence was deleted in error in Protocol Amendment 2.
1.3 Schedule of activities, Table 1-1 Schedule of activities	The following assessments were added to Weeks 19, 23, 27 and 51: Platelet count, vital signs, recording of AEs (including hospitalizations), serum complements (C3 and C4) and plasma complements (C3a and C5a), blood collection for exploratory biomarker analysis, ITP bleeding scale and headache questionnaire.	Updated for consistency and to correct errors.

Section # and Name	Description of Change	Brief Rationale
	Assessments for pre-SIAQ and post-SIAQ were added at all dosing visits starting at Week 7.	
8.1.5.1 Tuberculosis assessment	A new subsection for monitoring for TB during the study was added.	Added for consistency across ITP protocols.

Amendment 2 (03 Dec 2021)

Overall Rationale for the Amendment

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

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	IMP dosing [redacted] was updated to [redacted].	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.
Global	Exploratory dosing was removed. Reference to maintenance dosing was removed.	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. Therefore, the exploratory arm intended to evaluate wider dosing intervals was removed as the scientific value is limited.
Global	54-week treatment period was updated to 52-week treatment period.	Updated to provide clarity and consistency with remainder of the protocol.
1.1 Synopsis Rationale	Reference to the starting dose of fixed dose equivalent of [redacted] was removed.	Deleted as the [redacted] equivalent starting dose is no longer applied in the parent studies TP0003 and TP0006.
1.1 Synopsis, Objectives and Endpoints 3 Objectives and endpoints	Objectives corresponding to the exploratory dosing were removed. Reference to maintenance dosing was removed.	Updated to provide consistency within the protocol due to the removal of the exploratory arm.

Section # and Name	Description of Change	Brief Rationale
	Objectives were reworded from "…starting after the second dose of rozanolixizumab (Week 4)" to "…starting at Week 4."	Updated to reflect the changes in the dosing frequency. Reference to the "second dose" was deleted and reference is only made to Week 4.
1.1 Synopsis, Objectives and endpoints 3 Objectives and endpoints	The other safety endpoints was updated to delete "α globulin and β globulin." 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 PD secondary endpoint was updated as follows: "Minimum value in total serum IgG and maximum decrease from Baseline in total serum IgG concentration" was changed 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"	Updated as this variable will be followed at every scheduled visit rather than only reporting the lowest value across the duration of the study.
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 over time" 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	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

Section # and Name	Description of Change	Brief Rationale
	(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.	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 3 Objectives and endpoints	The objective "To evaluate the effects of rozanolixizumab on exploratory biomarkers" and associated endpoints were removed.	Objective and endpoint were removed as the exploratory biomarker samples are taken for future analysis, with no predefined analysis objective and endpoints
1.1 Synopsis Overall design 4.1 Overall design	IMP dosing [redacted] was updated to [redacted] dosing. Rozanolixizumab dose administration was updated from Week 3, Visit 5 to Week 2, Visit 3.	Updated upon recommendation of the IDMC Updated to reflect the dosing frequency change from [redacted] to [redacted] dosing.
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 or platelet count measurement in case of late rollover, has been removed. The wording on rozanolixizumab infusion was updated. The timepoints for observation after the end of infusion were updated.	Updated for consistency with the [redacted] dosing regimen.
1.1 Synopsis, Overall design 4.1 Overall design	The following paragraph was added: "Based on feedback from the IDMC, [redacted] dosing was implemented in protocol amendment 2. Study participants being treated with the [redacted] dosing regimen will switch to the	To clarify the dosing for existing study participants receiving [redacted] dosing

Section # and Name	Description of Change	Brief Rationale
	[redacted] dosing regimen once protocol amendment 2 is approved at the respective study site."	
1.1 Synopsis Number of study participants	Reference to the interim analysis was removed.	To provide consistency with the feeder study protocols. The interim analysis in the feeder studies was removed.
1.1 Synopsis Treatment groups and duration 4.1 Overall design	The total maximum study duration per study participants was updated to 59 weeks.	To provide consistency within the protocol due to the change in dosing frequency.
1.2 Schema Figure 1-1 TP0004 study schematic	IMP dosing [redacted] was updated to [redacted] dosing. Reference to maintenance dosing was removed and changed to "treatment period." The treatment period was corrected to 52 weeks. Week 55 was updated to Week 53. The Safety Follow-up Period was updated to Week 60. The total maximum study duration per study participants was updated to 59 weeks.	To provide consistency within the protocol due to the change in dosing frequency and the removal of the exploratory arm.
1.3 Schedule of Activities Table 1-1 Schedule of activities	IMP dosing [redacted] was updated to [redacted] dosing. IRT contacts were updated accordingly. Columns related to home visits have been grayed out. Notes were added to clarify white columns are site visits and gray columns are 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" The safety follow-up period was amended from W61, Day 420 to W60, Day 414.	Updated to provide consistency within the protocol due to the change in dosing frequency, last dose being at Week 52 and the removal of the exploratory arm. Updated to harmonize the assessments and visits with the change in dosing regimen. The visit at Day 5 was removed

Section # and Name	Description of Change	Brief Rationale
	A +2 day time window for Week 1, Day 3 was added.	therefore the Visit at Day 3 was given a visit window.
	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."	To clarify the time window for assessments.
	Footnote a now b: was updated to clarify that home visits, if applicable are displayed in the grey columns. The following sentence was removed: "If applicable, home administration of IMP is to be conducted unless not approved by regulatory agencies."	Updated for clarity.
	Footnote f now g: was updated from "50 to 200×10^9/L" to "50 to 150×10^9/L and no dose change."	Updated for consistency across other sections of the protocol.
	Footnote g now h: visit window for rollover from TP0003 or TP0006 was updated to +3 days.	
	A new footnote "i" was added: "Platelet counts will be taken at the indicated home visits; however, the IMP dose will be based on the previous 4 platelet counts (must be stable between 50 to 150×10^9/L and no dose change). If criteria are not met, the visit must be conducted on site."	
	Footnote h now j: was updated to remove triplicate and three ECGs and the timepoints for ECG.	
	Footnote j now k: vital sign assessment timepoints were updated. Footnote p now q: relating to onsite observation was updated accordingly.	
	A new footnote "p" was added: "Prior to dosing, management of infections and hypogammaglobulinemia must be considered as per Appendix 22, Section 10.22."	Updated for clarity.
	Footnote q relating to the Exploratory Treatment Arm was deleted.	

Section # and Name	Description of Change	Brief Rationale
	Footnote u now s: was updated to remove the 4 hour postdose assessments at Baseline and Week 33. Footnote "t" relating to 2 to 5 days postdose PK and ADA samples was deleted. Footnote "u" was updated to add "and/or serious." A new footnote "v" was added: 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 10.22. Footnote aa now z: was updated as follows: This assessment is applicable only to participants experiencing **moderate**, severe and/or serious headache (see Section 10.20), 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. The IGRA TB test and chest x-ray were deleted.	The 4 hour postdose sample is not required. These samples are not required. Updated for consistency across other sections of the protocol. Updated for consistency with Section 10.20. Updated for consistency with Section 8.1.5
Table 1-2 Schedule of activities – exploratory treatment arm (Weeks 25 to 41)	Table 1-2 was deleted.	Updated to provide consistency within the protocol due to the removal of the exploratory arm.
2.2. Background	The background was updated to state the removal of the starting dose from feeder studies TP0003 and TP0006. CIDP01 was added to the list of completed studies. Brief details about CIDP01 and CIDP04 were added. A note was added that in TP0003/TP0006 protocol amendment 3, the starting fixed dose equivalent to [redacted] sc was	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
	removed due to the change to [redacted] weekly dosing.	
2.3 Benefit/risk assessment	The following cross reference was corrected from Section 6.5.1 to Section 8.2.9: "If any AEs were to occur, they should be handled as described in (Section 8.2.9) with causality assessment provided for both IMP and vaccine."	Cross reference was corrected.
Table 4-1 TP0004 dose levels and weight tiers of IMP	The table title was updated from 'rozanolixizumab' to 'IMP'.	Updated to provide consistency within the protocol.
Table 4-2 Dose adjustments of rozanolixizumab for maintenance treatment arm Figure 4-1 Dose adjustments of rozanolixizumab	Additional instructions were added for platelet counts of $<10\times10^9$/L and between $\geq30\times10^9$/L to $<50\times10^9$/L.	Updated to provide further clarity on when rescue medication is to be used.
Table 4-2 Dose adjustments of rozanolixizumab for maintenance treatment arm Figure 4-1 Dose adjustments of rozanolixizumab	A clarification was added that rescue therapy is recommended when platelet count reaches $<30\times10^9$/L. An additional row/box was added to clarify that platelet count $<10\times10^9$/L instructions would be to administer rescue therapy. The text regarding interindividual variable platelet response previously in the section body was included as footnote 'b' to the table.	Updated for clarity
4.1 Overall design	Vital signs measurement time points for all visits were updated and clarified.	Updated for consistency with the change in dosing regimen.
4.1 Overall design, Table 4-2, Figure 4-1	The following text was updated: Platelet counts of $<10\times10^9$/L rescue therapy is highly recommended. Platelet counts of $\geq10\times10^9$/L to $<30\times10^9$/L (on at least two consecutive visits) rescue therapy is recommended.	Updated to permit reduction in dose earlier in the event of a platelet increase given the change to a [redacted] dosing regimen.

Section # and Name	Description of Change	Brief Rationale
	≥30×10^9/L to <50×10^9/L dose level can be increased unless the study participant is on a maintenance dose of [redacted]. Platelet count of ≥50×10^9/L to ≤200×10^9/L was updated to ≥50×10^9/L to 150×10^9/L. Platelet count of >200×10^9/L to <400 x10^9/L was updated to 150×10^9/L to <400 x10^9/L. For platelet counts of ≥400×10^9/L, instructions were updated to "Once the platelet count is ≤150×10^9/L, reinitiate treatment decreased by one dose level." The text regarding interindividual variable platelet response was moved as table footnote b.	
4.3 Justification for dose	A more frequent dosing regimen of [redacted] equivalent once per week is introduced in TP0003/TP0006 and the OLE study. The [redacted] equivalent starting dose in TP0003/6 is removed from the protocol.	Updated to follow the advice of the external IDMC on introducing a more frequent dosing regimen to reduce the potential risks of low platelet counts.
5.1 Inclusion criteria	Criterion #1a, now 1b, was updated to state Visit 27.	Updated as per updated visit numbering in studies TP0003/TP0006.
5.1 Inclusion criteria	Inclusion criteria #3 and #4 were removed.	Inclusion criteria 3 and 4 were deleted as the criteria are not related to eligibility. Inclusion criterion 3: Highest permitted concomitant treatments are listed in table 6-2 and a stable dose is not required as an inclusion criterion Inclusion criterion 4: Depending on the IgG level, the participant should be dosed in accordance to Appendix 22 and IgG levels are not an inclusion criterion.
5.1 Inclusion criteria	Inclusion criterion #5, now 5a, was updated to correct "or" to "and"	The sentence was corrected.

Section # and Name	Description of Change	Brief Rationale
	"as confirmed by a negative pregnancy test **and** not planning to get pregnant"	
5.2 Exclusion criteria	Exclusion criterion #6a, now 6b, was updated to remove the bullet point relating to ALT, AST, or ALP results up to 25% above the exclusion limit may be repeated once for confirmation.	Updated for providing additional clarity to this exclusion criterion.
5.2 Exclusion criteria	Exclusion criterion 12 was removed.	No longer required as Baseline values are taken from TP0003/TP0006.
6 Study treatments Table 6-1 Treatments administered	Exploratory dosing was removed. IMP dosing [redacted] was updated to [redacted] dosing. Dosing instructions were updated.	Updated to provide consistency within the protocol.
6 Study treatments Table 6-1 Treatments administered	Dosing instructions: "and Week 53 measurement" was removed.	Removed as the Week 53 body weight measurement is not used for the dose calculation.
6.2 Measures to minimize bias: randomization	Description of the Exploratory Arm was removed.	Updated to provide consistency within the protocol.
6.4.1 Permitted concomitant treatments (medications and therapies)	An additional paragraph regarding the management of the concomitant ITP treatment of the study participants rolling over from TP0003/TP0006 to TP0004.	To clarify the management of the concomitant ITP treatment of the study participants rolling over from TP0003/TP0006 to TP0004.
6.4.1 Permitted concomitant treatments (medications and therapies), Table 6-2 6.4.3.1 Rescue therapy not leading to discontinuation	Permitted oral corticosteroids dose was increased to 20mg/day.	Allowed dose of oral corticosteroids was increased to a maximum of 20mg/day for more flexibility in the managing the concomitant ITP treatment.
6.4.3.2 Rescue therapy leading to discontinuation	Oral steroids above 10mg/day was updated to 20mg/day.	Updated to provide consistency with other changes in the protocol.
6.5 Dose modification	Individual requirements for splenectomized patients were removed.	Updated for consistency with the changes in Section 10.22.
6.5 Dose modification	A sentence was added to state that Dose modifications or temporary IMP treatment discontinuation are permitted if serum IgG value are<1g/L (Section 10.22).	Updated for consistency with the changes in Section 10.22.

Section # and Name	Description of Change	Brief Rationale
6.6 Self-administration	A new subsection was added regarding details for self-administration	Updated and introduced as a separate section to provide more details on the optional IMP self-administration
6.7 Home visits	A new subsection was added regarding details for home visits	Updated to separate the optional self-administration from the home visits and to provide more details on the optional home visits
7.1.1 Liver chemistry stopping criteria Figure 7-1 Figure 7-2	Cross reference to Appendix 6 was corrected to Appendix 5.	Updated to provide the correct reference
7.1.2 QTc stopping criteria	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 clarify that the 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 provide clarity
7.1.4 Temporary IMP discontinuation	Text was updated to clarify that: A study participant may temporarily discontinue IMP if any of the following events occur: 3. A severe AE of headache that is considered related to the IMP in the opinion of the investigator (Section 10.20). 4. A splenectomised study participant develops a (persistent or re-occurring) nonserious infection, as per investigator's decision (Section 10.22). 5. Total serum IgG values goes <1g/L as per investigator's decision (Section 10.22). As IMP treatment is administered [redacted] the decision is based on the most recently available total IgG value. In order to maintain	To be consistent with Section 20.20. To reflect changes in the process of managing infections and events of hypogammaglobulinemia and for consistency with the changes in Section 10.22.

Section # and Name	Description of Change	Brief Rationale
	the blind from the parent studies, IgG, IgG subclasses, total protein, and albumin values will be unblinded starting with the blood samples taken at Week 4 (Visit 5).	
7.2 Participant discontinuation/withdrawal from the study	#3 was added as follows: 3. An adverse event or a medical condition as described in Section 7.1.1, Section 7.1.2 or Section 7.1.3 occur.	Added for consistency throughout the protocol.
7.3 Lost to follow-up	"to complete the final evaluation" was deleted from the last bulletpoint	No final evaluation is required for a study participant who is lost to follow-up.
8.1.2 Vital signs	Body temperature was added to the list of vital signs to be measured before blood samples are taken.	Updated for further clarity and consistency throughout the protocol.
8.1.3 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.
8.1.5 Assessment and management of TB and TB risk factors	The text was updated to remove "appropriate rigorous" and to add 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 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.

Section # and Name	Description of Change	Brief Rationale
8.1.5.1 Tuberculosis assessment	Sections on physical examination for TB, TB assessment by IGRA, and TB assessment by chest x-ray were removed.	Updated for consistency with Section 8.1.5
8.1.5.2 Tuberculosis management	Test conversion for IGRA was removed. Under Latent TB, text regarding 2 indeterminate IGRA test results as suggestive of TB infection was removed.	Updated for consistency with Section 8.1.5
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.
8.1.5.2 Tuberculosis management	Text pertaining to AE reporting for Latent TB was removed.	Updated for consistency in reporting any TB related AEs as per Section 8.1.5.1.
8.2.8 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 for consistency with the changes in Section 10.20.
8.4 Treatment of overdose	The numbered list was changed to bullet points.	Formatting correction.
8.5.1 Platelet counts	Reference to the maintenance treatment arm was removed. The endpoints related to the Exploratory Treatment Arm were removed. Platelet count endpoints were updated.	Updated to provide consistency within the protocol
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 Exploratory biomarkers	α- and β-globulinswere removed.	Sampling of α- and β-globulins was removed to decrease study complexity, as scientific value of the evaluation is limited.
8.8 Exploratory biomarkers	The text was updated to add “and/or serious.”	Updated to provide consistency within the protocol.

Section # and Name	Description of Change	Brief Rationale
8.9 Immunology biomarkers	The serum complements sample 4 hours postdose at Baseline and Visit 23 (Week 33) was removed.	Updated to provide consistency within the protocol.
8.9 Immunology biomarkers	Serum cytokines were deleted.	Blood sampling for cytokine analysis was removed in the ITP protocols as samples have been collected in other rozanolixizumab studies and no additional information is expected from the ITP population.
9.1 Definition of analysis sets	The Exploratory Treatment Arm Safety Set was removed.	Updated to provide consistency within the protocol.
9.3 Estimands	Safety Set and estimand was updated to state "who started TP0004 on [redacted] dosing."	Updated to reflect that estimand concerns subjects who started on [redacted] dosing.
9.3 Estimands	A further secondary safety estimand, also based on "treatment policy" was added.	Updated to reflect the two dosing regimens.
9.4 Planned safety analysis	The text was updated to add "started TP0004 on [redacted] or [redacted] dosing"	Updated to reflect change in dosing regimen.
9.5 Planned efficacy/outcome analyses	The text was updated to add "started TP0004 on [redacted] or [redacted] dosing"	Updated to reflect change in dosing regimen.
9.5 Planned efficacy/outcome analyses	The wording for the secondary efficacy endpoints were updated.	Updated to reflect change in dosing regimen and the removal of exploratory arm.
9.6.1 Analysis of pharmacodynamic endpoints	α- and β-globulins were removed.	Updated for consistency with Section 8.8. Sampling of α- and β-globulin biomarkers were removed to decrease study complexity, as scientific value of the evaluation is limited.
9.6.1 Analysis of pharmacodynamic endpoints 9.6.2 Analysis of pharmacokinetics endpoints	Text was updated to state "by dosing regimen"	Updated to reflect the change in dosing regimen. Analysis can be done based on [redacted] or [redacted] dosings.
9.10 Determination of sample size	The text was updated to state "up to a maximum of"	Updated to provide further clarity

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical laboratory tests Table 10-1 Protocol-required safety laboratory assessments	Assessment of % platelet reticulocytes and associated footnotes were removed.	Updated to reflect that the analysis will not be performed.
10.2 Appendix 2: Clinical laboratory tests Table 10-1 Protocol-required safety laboratory assessments	Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Total cholesterol and Triglycerides were moved under Clinical Chemistry.	Moved under clinical chemistry as these will be measured as part of clinical chemistry panel.
10.2 Appendix 2: Clinical laboratory tests Table 10-1 Protocol-required safety laboratory assessments	Footnote e was updated as follows: "Includes total IgG, IgG subclasses, IgA, IgM, and IgE. Results of the IgG testing will be unblinded starting with the blood samples taken at Week 4 (Visit 5) in TP0004 in order maintain blind of from the parent studies.	To be consistent with Section 22.
10.5 Appendix 5: Liver safety Table 10-4 Phase 3-4 liver chemistry increased monitoring criteria with continued IMP	The cross reference to the liver chemistry stopping criteria was corrected.	Updated to provide the correct reference.
10.7, Appendix 7: Country-specific requirements France	The visit window of +7 days was updated to +3 days.	Updated to align with the updated visit window.
10.7, Appendix 7: Country-specific requirements Japan	TB assessment and chest x-ray for TB were removed.	Updated for consistency throughout the protocol.
10.7, Appendix 7: Country-specific requirements Japan	A cross reference was added to Table 10-2 and the wording was updated.	Updated for clarity.
10.7, Appendix 7: Country-specific requirements	Section 10.7.1 was added to list the countries where self-administration will be offered as an option	Updated to provide further clarity on the countries where self-administration will be offered as an option
10.9 Appendix 9: Abbreviations and trademarks	Additional abbreviations and definitions were added for:	General update.

Section # and Name	Description of Change	Brief Rationale
	CDC, eqv, HCP, QW, RO, and WHO.	
10.20 Appendix 20: Management of headache	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.
10.22 Appendix 22: 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 & symptoms of nonserious/ serious infection, potential risk of acquiring a nonserious/ serious infection).
10.23 Appendix 23: 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 samples have been collected in other rozanolixizumab studies and no additional information is expected from the ITP population.
10.25. Appendix 25: Protocol Amendment History	Protocol amendment 2 (global amendment) has been added. Appendix no. 26 was corrected to no. 25	General update.
Throughout	Minor editorial and formatting changes have been made.	Minor, therefore have not been summarized.

Amendment 1 (11 May 2021)

Overall Rationale for the Amendment

The primary reason for this protocol amendment was to incorporate changes in the objectives, endpoints, the statistical analysis section, as well as a specific study objective and endpoint on post-vaccination biomarkers in study participants who have received a COVID-19 vaccine. Other

changes include incorporating local protocol amendments (*0.1- Japan* and *0.2-France* only) 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. The duration for the treatment period was clarified from 52 weeks to 54 weeks.	Updated to provide clarity and be consistent with remainder of protocol. Updated to provide clarity, where the 54-week treatment period includes a 2-week observation period after Week 52.
Global	Japan-specific requirements have been highlighted throughout the protocol and added to Appendix 7, Section 10.7.	In accordance with local requirements and actual condition of medical treatment in Japan.
Serious adverse event reporting	For serious adverse event reporting (24h), the fax number for Japan has been removed. *For participants in Japan only*: Additional reporting instructions for SAE reporting (investigational device) and device deficiency reporting specific for Japan have been included.	In accordance with local requirements in Japan. Reporting instructions are included in the event the site uses devices that are not approved. [a]
1.1 Synopsis – Objectives and endpoints 3 Objectives and endpoints	For several objectives, wording on maintenance or exploratory dosing has been included.	Updated to provide clarity on which study population the objective applies to.
1.1 Synopsis – Objectives and endpoints 3 Objectives and endpoints	The primary objective has been changed to remove the following word, "*repeated*." The following text has been added to the safety endpoint: Occurrence of TEAEs leading to *permanent* withdrawal of investigational medicinal product (IMP) *(ie, study discontinuation)* The other safety endpoint specific to occurrence of AESM was updated to read as "*treatment-emergent AESM*"	Updated to provide further clarity.

Section # and Name	Description of Change	Brief Rationale
	The following word, "*repeated*" has been removed from the secondary and exploratory objectives relating to assessment the long-term clinical efficacy.	
1.1 Synopsis – Objectives and endpoints 3 Objectives and endpoints	For several endpoints, "*first Complete Response*" has been removed and "*during both maintenance dosing and exploratory dosing*" has been added.	Updated to provide clarity with the data collected for the study.
1.1 Synopsis – Objectives and endpoints 3 Objectives and endpoints	The secondary efficacy endpoint was amended to include "*over the planned 54-week Treatment Period*"	Updated to allow flexibility for potential calculation based on available visits for participants prematurely withdrawn from the study.
1.1 Synopsis – Objectives and endpoints 3 Objectives and endpoints	Footnotes have been updated: Footnote b, now a: Treatment cycle is defined as the period between two consecutive doses, unless otherwise noted in the Statistical Analysis Plan. Footnote b: Baseline definitions for the maintenance and exploratory arm treatment cycles will be detailed in the SAP.	Updated to provide definitions for Treatment cycle and Baseline for the Maintenance and Exploratory Treatment arms (maintenance and exploratory dosing).
1.1 Synopsis – Objectives and endpoints 3 Objectives and endpoints	The other efficacy endpoints have been updated to include several changes, and two new endpoints, as listed below: - Stable Response defined as platelet count $\geq 30x10^9$/L and absence of bleeding without rescue therapy at ≥70% of the visits over the planned 54-week Treatment Period starting after the second dose of rozanolixizumab (Week 4) - Cumulative number of weeks with platelet counts $\geq 30x10^9$/L over the planned 54-week Treatment Period - Mean Change from Baseline in platelet count at each visit - The rescue medication endpoint was changed from *Time to first*	Updated as per query from the FDA on endpoints related to efficacy.

Section # and Name	Description of Change	Brief Rationale
	rescue medication to "*Use of rescue medication by visit"* Additionally, the following endpoints were removed: - Complete Response, defined as platelet count ≥100x10^9/L, confirmed on at least 2 consecutive occasions, and absence of bleeding - Usage of rescue therapy	
1.1 Synopsis – Objectives and Endpoints 3 Objectives and endpoints	The following 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	A new secondary objective has been added: To assess the effect of rozanolixizumab on study participant perceived symptoms	Updated to reflect that only the ITP-PAQ Symptoms domain score will be assessed for the secondary HRQoL objective.
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. The secondary objective related to HRQoL has moved to be an exploratory objective. The following endpoint, *Response defined as change from Baseline at or above the defined threshold for ITP-PAQ Symptoms domain score* has been deleted. *"Change from baseline endpoint*" was moved to the exploratory PRO objective.	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 secondary endpoints for change from Baseline in serum IgG subclasses and concentrations have been moved to exploratory endpoints.	Minimum absolute IgG value and maximum decrease from Baseline in total serum IgG concentration over time are kept as secondary endpoints. Change from baseline in total IgG, IgG- subclasses and IgA, IgE and IgM over time are as other endpoints.
1.1 Synopsis – Objectives and endpoints 3 Objectives and endpoints	The secondary objective related to reduction in use of steroid has been updated to include also other concurrent ITP medications, and the associated endpoint has been	Updated to reflect that the analysis of changes in concomitant ITP therapies will not be limited only to corticosteroids.

Section # and Name	Description of Change	Brief Rationale
	modified to replace "*reduction"* with "*change*""	
1.1 Synopsis – Objectives and Endpoints 3 Objectives and endpoints 1.3 Schedule of Activities, Tables 1-1 and 1-2	The PRO name for 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 – Objectives and Endpoints 3 Objectives and Endpoints	Secondary and exploratory: Additional wording has been provided for clarification that the minimum value from Baseline in total serum IgG concentration refers to the absolute IgG value. Updated wording to clarify that total serum IgG will be measured in addition to the IgG subclasses.	Updated to provide further clarity. [a]
1.1 Synopsis – Objectives and Endpoints 3 Objectives and endpoints	Two new exploratory endpoints related to clinical efficacy in study participants with first exposure to rozanolixizumab have been added.	Added to specifically analyze efficacy in participants that switched from placebo to rozanolixizumab treatment in the OLE study.
1.1 Synopsis – Objectives and Endpoints 3 Objectives and endpoints	Exploratory endpoints: In relation to Complete Response by visit within 1 treatment cycle without rescue, the endpoint has been amended to "*Platelet count ≥30x10^9/L by visit within 1 treatment cycle without rescue therapy per treatment cycle*"	Updated for consistency to delete Complete Response endpoints and to focus on platelet counts ≥30x10^9/L and Clinically Meaningful Response.
1.1 Synopsis – Objectives and Endpoints 3 Objectives and endpoints	A new objective and the associated endpoints related to study participants experience with subcutaneous self-administration have been included.	For participants that are eligible to use self-administration this questionnaire was added to capture their experience.
1.1 Synopsis – Objectives and Endpoints	Exploratory: Changed pneumococci to *Streptococcus pneumoniae and* meningococci to *Neisseria meningitidis* Corrected spelling of *Haemophilus influenzae*	Updated for consistency with the table in Section 3. [a] Error in original protocol. [a]
1.1 Synopsis – Objectives and Endpoints 3 Objectives and endpoints	The following exploratory endpoint has been removed: "*Percent change from Baseline in vaccination titers*	Vaccination titers against tetanus will not be measured in this study.

Section # and Name	Description of Change	Brief Rationale
	against tetanus in all study participants"	
1.1 Synopsis – Objectives and Endpoints 3 Objectives and endpoints	The objective on assessing clinical efficacy in the Exploratory Treatment Arm has been amended to remove "*long-term*" and include "*intermittent*." The associated endpoint has been updated to remove "average"	Updated to be consistent with study design. Updated to ensure clarity with the associated objective.
1.1 Synopsis 3 Objectives and Endpoints	An additional objective and associated endpoint specific to the effect of rozanolixizumab on COVID-19 biomarkers the has been included.	New objective and endpoint is 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	Additional wording on which treatment will the study participants receive upon entering the Maintenance Treatment arm has been included.	Updated to provide further clarity.
1.1 Synopsis, Overall Design 4.1.2 Exploratory treatment arm	The following wording "*a proportion of*" and "*most recently*" have been added in reference to participants paused from treatment in the Maintenance Treatment Arm and randomized to the Exploratory Treatment Arm.	Updated to provide further 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 further clarity.
1.1 Synopsis – Overall Design 4.1.2 Exploratory treatment arm	Additional wording added ("*ie, no need for rescue therapy*") to clarify criteria for study participant to return to Maintenance Treatment Arm.	Updated to provide further clarity. [a]
1.1 Synopsis, Overall Design 4.1.1 Maintenance treatment arm 4.1.2 Exploratory treatment arm 6.4.3 Rescue therapy	The following wording "*dose and/or type*" has been added in reference to study participants possibly being withdrawn if they receive rescue therapy.	Updated to provide further clarity.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Overall Design	In relation to tolerability issues, the following term "side effects" has been amended to replace "*side*" with "*adverse*."	Updated to provide clarity and be consistent with remainder of the protocol.
1.1 Synopsis, Overall Design 4.1 Overall design 9.9.2 Data monitoring	The following sentence has been removed: "*the IDMC will be the same as used for the parent studies TP0003 and TP0006, but data from each study will be presented separately*"	Updated to be consistent with the IDMC Charter.
1.1 Synopsis, Number of Participants 9.10 Determination of sample size	The maximum number of participants completing TP0003 or TP0006 planned for enrollment into TP0004 has reduced from 210 to 180.	Number of participants has been changed based on revised sample size calculation method and assumptions in the parent studies, TP0003 and TP0006 leading to reduction of participants in TP0004.
1.1 Synopsis, Treatment Groups and Duration 4.1 Overall Design	The following wording has been added "*includes a 2-week observation period after Week 52*"	Updated to provide further clarity on the total duration of the maintenance treatment period.
1.3 Schedule of Activities, Table 1-1 (Maintenance treatment arm)	**For participants in Japan only:** IGRA TB test has been added to EOS/EW Visit.	To confirm safety at study termination. [a]
1.3 Schedule of Activities, Table 1-1 (Maintenance treatment arm)	New assessments specific to COVID-19 vaccination samples and the associated footnotes have been added. New details on platelet count assessments have been added as a new footnote (f). Subsequent footnotes have been reordered.	Included as part of the objective on post-vaccination biomarkers for participants who have received the COVID-19 vaccination.
1.3 Schedule of Activities, Table 1-1 (Maintenance treatment arm)	Tetanus titer has been removed.	Vaccination titers against tetanus will not be measured in this study.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 1-1 (Maintenance treatment arm)	Additional activities have been added: Pre-SIAQ and Post-SIAQ (Infusion version). The following footnotes have been added: y For study participants who self-infuse, to be completed once, prior to first self-infusion z To be completed within 1 hour after the first self-infusion and the next consecutive self-infusion	Added participant self-administration questionnaire to capture their experience.
1.3 Schedule of Activities, Table 1-1 (Maintenance treatment arm)	Footnote d: Reworded to state that the data will be transferred from the Week 25 (Visit 28) from TP0003 or TP0006.	Updated to correct timepoint when data will be taken from the parent studies. [a]
	Footnote f now g: Updated to clarify participants will need a new platelet count.	Updated to provide further clarity.
	Footnote g, now h: The following wording has been removed: "*1 to 2 minutes*"	Updated to provide further clarity.
	Footnote i, now j: Updated to include "*and prior to discharge from clinic/departure of home healthcare professional*"	Updated to provide further clarity.
	Footnote j, now k: Additional laboratory samples (total cholesterol, LDL, HDL, and triglycerides) will be collected at Week 13 and Week 25 only.	Lipid profile will be assessed during the study.
	For participants in Japan only: Footnote o: 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]
	Footnote t, now aa: updated to include cross-reference to the management of headaches	Updated to provide further clarity.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 1-1 (Maintenance treatment arm)	Footnote n, now q: Corrected footnote to state that observation time of 1 hour is required for the next 2 IMP infusions after Visits 1 and 5, and additional wording was added to specify that the infusions need to be well tolerated by the study participant to reduce observation time to 15 minutes for the remaining visits until Week 25. Additional wording specific to the criteria for no post-infusion observation periods after Week 25 has been included.	Updated to remain consistent with the observation requirements and the overall study design (Section 4.1).
1.3 Schedule of Activities, Table 1-2 (Exploratory treatment arm)	Table header was updated to include the correct visit numbers to correlate with the weeks. Correction of error in footnote b to correlate with updates to header correction.	Error in original protocol. [a]
1.3 Schedule of Activities, Table 1-2 (Exploratory treatment arm)	Added a scheduled visit for platelet count (local laboratory) at Week 35. For laboratory parameters, "local" was replaced with "central."	Error in original protocol. [a]
1.3 Schedule of Activities, Table 1-2 (Exploratory treatment arm)	Collection of anti-rozanolixizumab antibodies (ADA) samples was removed at Weeks 29, 37 and 41.	Additional ADA samples will already be collected at scheduled visits for plasma concentration of rozanolixizumab samples.
1.3 Schedule of Activities, Table 1-2 (Exploratory treatment arm)	Correction of typographical error in footnote b, $\geq 50 \times 10^9$/L and added "to $\leq 200 \times 10^9$/L." Footnote e: Replaced "*final*" with "*each*" dose of IMP. Footnote f now g: The following wording has been removed: "1 to 2 minutes" Footnote f: A new footnote specific to withdrawal criteria has been added. Footnote g now h: The following wording was added: "and prior to discharge from clinic/departure of home healthcare professional."	Updated for consistency with Overall Design in Section 1.1. [a] Updated to correct an error. [a] Updated to provide further clarity. Updated for consistency with the protocol. Updated to remain consistent with the post-infusion observation requirements and the overall study design (Section 4.1).

Section # and Name	Description of Change	Brief Rationale
	Footnote j: A new footnote specific to instructions if study participant requires IMP dosing. Footnote k and m: New footnotes specific to platelet count at the time of the visit. Footnote l: Durations of the post-dosing observation period have been updated.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program for an OLE study.
1.3 Schedule of Activities, Table 1-2 (Exploratory treatment arm)	Footnotes l and k, now o and p, respectively: postdose has been replaced with postevent.	Updated to correct an error.
1.3 Schedule of Activities, Table 1-2 (Exploratory treatment arm)	Added the following footnote (l) to the administration of IMP: "Study participants are to stay at the study site for 4 hours after the first IMP infusion. The observation will be 2 hours after the second dose, and 1 hour for the remaining dosing visits" Reordering of footnotes was required.	To provide details of post-infusion observation time for consistency with Section 4.1.[a]
1.3 Schedule of Activities, Table 1-2 (Exploratory treatment arm)	Additional activities have been added: Pre-SIAQ and Post-SIAQ (Infusion version). The following footnotes have been added: q For study participants who self-infuse, to be completed once, prior to first self-infusion r To be completed within 1 hour after the first and second consecutive self-infusion	Added participant self-administration questionnaire to capture their experience.
2.2 Background	Additional studies have been included to this section. "Ongoing" has been removed from Study UP0060.	Updated to be consistent. The study is complete.
2.3 Benefit/risk assessment	Text on potential risks associated with administration of rozanolixizumab has been updated. New wording on COVID-19 vaccines has been added.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
4.1 Overall Design	Wording referring to the medical monitor decision on whether	This deletion has been made due to the medical monitor's role in

Section # and Name	Description of Change	Brief Rationale
	participants can be enrolled has been removed.	determining a study participant's eligibility in TP0004 not being considered valid.
4.1 Overall Design	Several minor edits were made for consistency with other sections in the protocol. Wording referring to the medical monitor's decision on whether participants can be enrolled and participants receiving a vaccination titer for tetanus have been removed. Wording pertaining to the next step for to study participants previously randomized to placebo has been added. Post-infusion observation timings and instructions for the maintenance and exploratory treatment arms have been updated.	 Update due to the medical monitor's role in determining a study participant's eligibility not considered valid. Updated for consistency with footnote m in Table 1-1. [a] Updated to be consistent across the Phase 3 rozanolixizumab clinical program for an OLE study.
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, Table 4-1, footer 4.1.1 Maintenance treatment arm	Table header updated to replace "starting" with "*Exploratory arm*." Additional wording has been provided for clarification on the action taken for study participants with 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. [a]
4.1.2 Exploratory treatment arm	This section has been updated to include: "or the investigator deems not to be suitable" in reference to entry to the Exploratory Arm, and additional information on based on rescue therapy. Week 23 and Visit 18 have been included.	Updated to provide further clarity.
4.3 Justification for dose	The following wording, "*then quickly reset platelets to the desired levels as faster onset of*	Updated to provide further clarity.

Section # and Name	Description of Change	Brief Rationale
	response" has been replaced with "*is anticipated to increase platelet count to ≥50x10 within a week as*." In addition the following sentence has been included: "*However, if any safety concerns are identified in the parent studies, TP0003 and TP0006, corresponding changes will be made in the TP0004 dosing scheme*"	
5.1 Inclusion criteria	Criterion #1, now 1a, has been modified to remove "*and sponsor*" from the criterion.	This deletion has been made as the sponsor cannot be involved in deciding a study participant's eligibility in TP0004.
5.2 Exclusion criteria	Criterion #2 has been removed.	This deletion has been made due to the medical monitor's role in determining a study participant's eligibility in TP0004 not being considered valid.
5.2 Exclusion criteria	Criterion #6, now 6a: The following text has been removed: "In case of a clinically relevant increase, inclusion of the study participant must be discussed with the Medical Monitor or designee." Criterion #7, now 7a: the criterion has been updated to include a timepoint.	This deletion has been made due to the medical monitor's role in determining a study participant's eligibility in TP0004 not being considered valid. Updated to provide clarity on bilirubin values used at the time of eligibility.
5.2 Exclusion criteria	Criterion #9, now 9a: the criterion has been updated to include "*major*" in reference to planned surgery and the duration of 14 months has been replaced by study period. Criterion #10, now 10a: the criterion has been updated to include "*at the last available assessment in TP0003/TP0006*"	Updated to remain consistent with the parent studies. Updated to provide clarity on lab values used at the time of eligibility.
5.2 Exclusion criteria	Criterion #11, now 11a: The following text has been removed: "and any queries regarding continuation of the study participants will have to be addressed with the medical monitor."	This deletion has been made due to the medical monitor's role in determining a study participant's eligibility in TP0004.

Section # and Name	Description of Change	Brief Rationale
	"The ECG contains findings that may represent a significant abnormality"	This is not applicable and remains consistent with the parent studies.
5.2 Exclusion criteria	New criteria on renal impairment and QT interval (#12 and #13), and live vaccination prior to, during or after the study (#14) have been included.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program for an OLE study.
5.2 Exclusion criteria	New wording on France-specific requirements has been included.	Updated to align with French Ethics Committee query on exclusion criteria pertaining the French Public Health Code and participant's age at Baseline. [b]
6 Study treatments, Table 6-1	The description for unit doses, and packaging and labelling for the maintenance and exploratory arms has been updated to delete: "6mL" and "no less than 4.0mL extractable volume of."	Update to reflect the foreseeable changes in vial size.
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.
6.4.1 Permitted concomitant treatments (medications and therapies)	Added "above Baseline (Visit 1, TP0004)" to the following sentence: Any increase in concomitant ITP medication above Baseline *(Visit 1, TP0004)* is regarded as rescue therapy. New text has been added in specific to the requirement to collect information on COVID-19 vaccinations in the eCRF.	Updated to provide further clarity. [a] Information on COVID-19 vaccination will be required.
6.4.1 Permitted concomitant treatments (medications and therapies), Table 6-2	"Prednisolone" changed to "prednisone." Clarification of dose for oral corticosteroid. Dosing for cyclosporin was updated to include modified and unmodified doses. Addition of Eltrombopag, Avatrombopag and Fostamatinib at any dose as permitted concomitant treatments.	Updated to clarify permitted concomitant medications. [a]

Section # and Name	Description of Change	Brief Rationale
6.4.1 Permitted concomitant treatments (medications and therapies)	The following wording has been removed: "When applicable, the study participant must be on a stable dose of cannabidiols and/or medicinal marijuana for Visit 1 (Day 1)"	No fixed period of stable dose before Baseline for this study.
6.4.2 Prohibited concomitant treatments (medications and therapies)	Removal of Dexamethasone, and addition of Romiplostim as a prohibited treatment, and clarification for corticosteroids.	Updated to clarify prohibited concomitant medications. [a]
6.4.2 Prohibited concomitant treatments (medications and therapies)	Removal of TPO-RAs 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.	Updated for clarification of prohibited medications.
6.4.3 Rescue therapy	Additional wording to following sentence has been included: Any increase in concomitant ITP medication "*above Baseline (Visit 1, TP0004)*" is regarded as rescue therapy. Additional wording in relation to systemically administered corticosteroids has been included: "*ie, pulse, oral and iv steroids*" as well as "*are also considered rescue therapy*."	Updated to clarify rescue therapy. [a]
6.4.3.1 Rescue therapy not leading to discontinuation	Platelet count measurement was corrected from ≥ to <. Additional wording in reference to the measures of starting rozanolixizumab treatment and defining a high dose of corticosteroids have been included. The increase amount for permitted concomitant immunosuppressants has been corrected from 5% to 25%.	Updated to clarify rescue therapy. [a]
6.4.3.2 Rescue therapy leading to discontinuation	TPO-RAs was removed, and "initiation" was added in reference to additional ITP therapy.	Updated to clarify rescue therapy. [a]

Section # and Name	Description of Change	Brief Rationale
6.5 Dose modification	The following recommended dose modifications were updated/added: - 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. Wording on potential changes in the dosing scheme based on safety concerns identified in the parent studies has been included.	Updated to remain consistent across the rozanolixizumab program.
6.6 Home visits and home/self-dosing	Sub-heading was changed to "Home visits and self-administration" and additional wording has been included pertaining to self-administration requirements as well as the timing of administration. The conditions for conducting home visits/self-administration have been amended.	Updated to provide clarity and remain consistent with study design.
6.7 Treatment after the end of the study	New wording on access to a Managed Access Program has been included.	Updated to provide clarity.
7.1.3 Discontinuation of IMP due to other adverse events or medical condition	New section was included to detail criterion and procedure for any discontinuation of IMP due to other AEs or medical condition	Updated to remain consistent with Phase 3 ITP clinical program.
7.1.4 Temporary IMP discontinuation	Section was previously 7.1.3. All criteria were amended. Additional parameters to be unblinded following the second dose have been included. In addition, details have been added for participants that have suspected or confirmed COVID-19.	Updated to provide clarity and remain consistent with study design and remainder of protocol. Criteria #2 #3, and #5 were previously updated in protocol amendment 0.1.
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.

Section # and Name	Description of Change	Brief Rationale
7.2 Participant discontinuation/withdrawal from the study	This section was reordered and updated to remove repetitive information highlighted in Section 7.1.4.	Updated to provide clarity and be consistent with study design and remainder of protocol. Correction of error and for consistency with parent studies.
7.3 Lost to follow up	This section was updated to remove repetitive information in relation to evaluations and observations.	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.
8.1.3 Electrocardiograms	The following wording has been removed: "1 to 2 minutes"	Updated to provide further clarity.
8.1.5.1 Tuberculosis assessment	TB signs and symptoms questionnaire: "and must receive prophylactic LTB infection therapy" and "must be withdrawn" have been deleted.	To provide further clarity.
8.1.5.1 Tuberculosis assessment	If reference to determining if a participant has LTBI, wording on receiving prophylactic LTBI therapy has been removed.	To provide further clarity on the assessment of TB.
8.1.5.1 Tuberculosis assessment	TB assessment by IGRA: Wording on requirements for positive or indeterminate IGRA tests result has been updated.	To provide further clarity on the assessment of TB.
8.1.5.2 Tuberculosis management	New text on the recommendation for withdrawn participants with active TB or NTMB infection to enter the SFU Period and attend Visit 35 has been included.	To provide further clarity in line with the protocol.
8.1.6 Splenectomized study participants	The following wording "*for the whole duration of the study*" was added in reference to the requirement of carrying a splenectomy card. New wording on the requirement for splenectomized study participants to have documented evidence of vaccinations from parent studies has been included.	Updated to provide further clarity.

Section # and Name	Description of Change	Brief Rationale
8.2.5 Pregnancy	Instructional wording for participants with confirmed pregnancy has been reordered.	Updated to provide further clarity.
8.2.8 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 is met.	Updated to provide further clarity.
8.2.9 COVID-19 vaccination	New subsection has been included to ensure AEs considered related to COVID-19 are captured.	Implemented to ensure study participant safety in response to the COVID-19 pandemic.
8.5.1 Platelet counts	Wording on platelet count-related endpoints has been updated.	Updated to be consistent with the protocol and reflect the changes made for the endpoints.
8.5.3 Patient Reported Outcomes	The list of PROs has been updated to replace the "Physical Fatigue Instrument" by the "FATIGUE-PRO Physical Fatigue scale" and "EQ-5D" to "EQ-5D-5L."	To indicate the correct name of the PRO.
8.5.3.1 ITP-PAQ	Additional text on the choice of selection as a secondary endpoint has been included.	Updated to be consistent with the protocol and reflect the changes made for the endpoints
8.5.3.3 FATIGUE-PRO Physical Fatigue Scale	The "Physical Fatigue Instrument" has been replaced by the "FATIGUE-PRO Physical Fatigue scale." Additional changes were made to the description of the FATIGUE-PRO Physical Fatigue scale.	To indicate the correct name of the PRO.
8.5.3.7 SIAQ (Infusion version)	An new subsection for an additional patient reported outcome tool "SIAQ (Infusion version)" has been included.	Added to capture the participants experience of IMP self-administration.
8.8 Exploratory biomarkers	Duplicate details pertaining to sample collection, processing, storage, labeling, and shipping have been deleted.	To remove repetition.
8.9 Immunological biomarkers	New text has been added in specific to blood sampling for the measurement of COVID-19 antibodies.	COVID-19 antibodies will be collected in this study for all participants who have received a COVID-19 vaccine.

Section # and Name	Description of Change	Brief Rationale
9.1 Definition of analysis sets	Definition of analysis sets: The Safety Set and Exploratory Treatment Arm Set have been updated. The Pharmacokinetic Per-Protocol Set was updated to remove "*and no important protocol deviations affecting the PK variable, as confirmed during a pre-analysis review of the data prior to database lock*"	Updated for further clarity.
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.
9.4 Planned safety analyses	This section has been amended to remove "*8 weeks after the end of the Treatment Period*" and "*in study participants who discontinue the study or IMP*" in reference to follow up of exposure to treatment, and to include details specific to safety analyses.	Updated for further clarity.
9.5 Planned efficacy/outcome analyses	Changed "feeder" to "*parent*" when describing TP0003/TP0006 studies. New wording has been included to provide details and clarification on efficacy/outcome analyses.	Updated for consistency in terminology within protocol. [a] Clarification has been provided on how assessments will be conducted for key efficacy endpoints in study TP0004 for patients who received rescue medication, especially, near the end of the parent studies. [a]
9.6.1 Analysis of pharmacodynamics endpoints	Total IgG was added to the list of included analyses to be considered.	Updated for to be consistent with endpoints listed in the protocol.
9.6.2 Analysis of pharmacokinetics endpoints	The following wording has been removed: "stratified by dose regimen" and "stratified by treatment arm."	Updated for further clarity.
9.7 Handling of protocol deviations	The following wording has been removed: "exclusion of participants from analysis populations"	Updated to be consistent with the data cleaning plan.
9.9.1 Interim analysis	New wording on data cutoffs has been included.	Updated for further clarity.

Section # and Name	Description of Change	Brief Rationale
9.9.2 Data monitoring	Wording on reviewing safety data at periodic data reviews has been removed.	Updated to be consistent with the IDMC Charter.
10.1.3 Informed consent process	New wording has been included in reference to Japan-specific requirements.	In accordance with local requirements in Japan. [a]
10.1.5 Committees structure	The following new wording was added: "The IDMC will have the possibility to unblind the data"	To be consistent with the rest of the protocol.
10.1.6 Data quality assurance	Additional wording on quality tolerance limits has been included.	Correcting an error as this information was previously omitted from the protocol.
10.2, Appendix 2: Clinical laboratory tests	Table 10-1: Footnotes have been reordered due to addition of footnotes b, c, d, e, and g to clarify collection timepoints and requirements for protocol-required safety laboratory assessments.	Updated for clarification. [a]
10.2, Appendix 2: Clinical laboratory tests	Total cholesterol, LDL, HDL and triglycerides have been added. Table 10-1: Updated wording for immunoglobulin footnote g to clarify when results are unblinded. Glycosylated hemoglobin (HbA1c) has been removed.	Lipid profile will be assessed in the study. To ensure blinding is consistent throughout all studies in the rozanolixizumab clinical program.[a] Removed wording to maintain consistency within the protocol.
10.3, Appendix 3: Adverse events – definitions and procedures for recording, evaluating, follow-up, and reporting	Additional wording for follow-up of AEs and SAEs has been included.	Updated to ensure guidance for AE follow up is consistent with the Phase 3 rozanolixizumab clinical program.
10.4, Appendix 4: Contraceptive guidance and collection of pregnancy information, Table 10-2	Wording for vasectomized partner has been updated. Footnote c has been removed.	To remain consistent with the Phase 3 rozanolixizumab clinical program.
10.5 Appendix 5: Liver safety – suggested actions and follow-up assessments Table 10-3	Clarification of language related to acetaminophen contribution to liver injury and removal of wording pertaining to requirements in China. The following reference was removed: James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson	To remove wording that was left from a previous version and to clarify the language for suggested actions. [a] Updated to maintain consistency within the protocol. [a]

Section # and Name	Description of Change	Brief Rationale
	JA, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009; 37:1779-84	
10.7, Appendix 7: Country-specific requirements	New wording on specific requirements for France have been included.	Updated in accordance with include local requirements. [b]
10.7, Appendix 7: Country-specific requirements	New wording on specific requirements for Japan have been added, including section-specific updates and new wording on specific requirements for AEs, ADEs, SAEs, SADEs, and Device Deficiencies associated with an investigational/medical device, have been added.	In accordance with local requirements and actual condition of medical care, as well as sponsor requirements and procedures for any study using a medical or investigational device. [a]
10.9 Appendix 9: Abbreviations and trademarks	Additional abbreviations and definitions were added: ADE, PEX and SADE.	Updated to reflect the parameters measured in the study. [a]
10.11, Appendix 11: ITP-PAQ	Removed an additional version of the ITP-PAQ questionnaire.	Updated to remove an additional version of the questionnaire that was accidentally included. [a]
10.13, Appendix 13: FATIGUE-PRO Physical Fatigue scale	The "Physical Fatigue Instrument" has been replaced by the "FATIGUE-PRO Physical Fatigue scale."	Updated name for PRO.
10.20, Appendix 20: Management of headaches	Text added to clarify that the Headache Questionnaire should be completed by an HCP via an interview with the study participant, and 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 is not resolved prior to the next scheduled IMP.	To add further clarity.
10.21, Appendix 21: Management of diarrhea	Definition of severe (grade 3) diarrhea has been updated. Modification of language regarding stool sample collection for participants reporting severe diarrhea.	To add further clarity. To clarify when stool samples may be collected. [a]

Section # and Name	Description of Change	Brief Rationale
10.22 Appendix 22: Management of Infections and Hypogammaglobulinemia	Modification of language regarding the Medical Monitor to clarify they may be unblinded. [a] Additionally, the following has been included in reference to study sites and study team: "remain blinded to IgG levels until after the first two dose of IMP." In the event of a nonserious infection, the unblinded or blinded (after the second dose of IMP) medical monitor may be consulted. 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.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.23 Appendix 23: Management of infusion reactions or hypersensitivity reactions	Modification of language regarding potential infusion related reactions.	Updated to provide further clarity.
10.24 Appendix 24: SIAQ (infusion version)	A new appendix to include examples of the SIAQ questionnaires has been added.	Included for additional clarity and details on the questionnaire.
11 References	A new reference specific to SIAQ has been included.	General update.

[a] This update was previously incorporated to local protocol amendment 0.1 (Japan)

[b] This update was previously incorporated to local protocol amendment 0.2 (France)

11 REFERENCES

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.

Keininger D and Coteur F. Assessment of self-injection experience in patients with rheumatoid arthritis: psychometric validation of the Self-Injection Assessment Questionnaire (SIAQ). Health Qual Life Outcomes. 2011;9:2.

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;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;25(2):375-83.

Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117:4190-207.

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

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

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

SPONSOR DECLARATION

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

Approval Signatures

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