TITLE PAGE

Protocol Title:		A 4-part Phase 1/2 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of M254 in healthy volunteers and in patients with immune thrombocytopenic purpura	
Protocol Number:		MOM-M254-001	
Compound Number:		M254	
Study Phase:		Phase 1/2	
Short Title:		Safety and tolerability of M254 in healthy volunteers and immune thrombocytopenic purpura (ITP) patients	
Sponsor	**Sponsor Name**	Momenta Pharmaceuticals, Inc.	
	Legal Registered Address	301 Binney Street Cambridge, MA 02142, USA	
Regulatory Agency Identifier Number(s)		NCT: 03866577 EudraCT: 2018-003534-32	
Protocol Date:		Document Version	Date
		v 8 Global	28 April 2020

This study will be conducted, recorded, and reported in accordance with the Protocol and in compliance with the principles of Good Clinical Practice (GCP). These are stated in "Guidance for Good Clinical Practice," International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki, and any other applicable regulatory requirements.

CONFIDENTIALITY NOTICE

The information contained in this protocol and all other information relevant to M254 are the confidential and proprietary information of Momenta Pharmaceuticals, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Momenta Pharmaceuticals, Inc.

SPONSOR SIGNATORY:

MOM-M254-001: A 4-part Phase 1/2 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of M254 in healthy volunteers and in patients with immune thrombocytopenic purpura

I, the undersigned, have approved Version 8 Global of the clinical trial protocol with the date of 28 April 2020.

PPD Signature PPD PPD	PPD Date

Investigator Protocol Agreement

Study Title:	A 4-part Phase 1/2 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of M254 in healthy volunteers and in patients with immune thrombocytopenic purpura
Study Number:	MOM-M254-001
Version:	8 Global
Date:	28 April 2020

I will provide access to the study protocol and access to all study-related information to the study personnel at my site who are involved with this protocol. I will discuss with them this material and the material in the Investigator's Brochure to ensure that they are fully informed about the investigational drug and understand the protocol. All documents will be kept in the strictest confidence.

I confirm that my core staff and I have carefully read and understand this protocol. I agree to conduct this study according to the attached protocol. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) and all applicable national and local laws and regulations, as well as with the requirements of the appropriate Institutional Review Board or independent Ethics Committee (IRB/EC) and any other institutional requirements. These are stated in "Guidance for Good Clinical Practice," International Council for Harmonisation (ICH) guideline E6(R2) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki, and any other applicable regulatory requirements. No changes will be made to the study protocol without prior written approval of the Sponsor and the IRB/EC.

I have read, understand, and agree to abide by all conditions and instructions contained in this protocol.

_____ _____

Principal Investigator's Signature Date

Name (print): _____

Clinical Site/Institution: _____

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A 4-part Phase 1/2 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of M254 in healthy volunteers and in patients with immune thrombocytopenic purpura. This study was opened in Europe in 2018 (EudraCT: 2018-003534-32) as a 4-part study. Part A enrolled 25 healthy volunteers at a single site in the Netherlands and has been completed. This study will open in the United States (US) as a 3-part study with Parts B, C, and D; no subjects in the USA will be enrolled in Part A.

Short Title: Safety and tolerability of M254 in healthy volunteers and immune thrombocytopenic purpura (ITP) patients

Rationale:

Alterations in endogenous immunoglobulin G (IgG) sialylation have been reported to be associated with treatment response in inflammatory/autoimmune diseases [1, 4]. M254 is a hypersialylated immunoglobulin engineered from commercially available intravenous immunoglobulin (IVIg; [redacted]). M254 has demonstrated increased anti-inflammatory activity over IVIg in several animal models, including collagen antibody-induced arthritis and pemphigoid skin blistering [23], K/BxN – sera-induced arthritis model and an immune thrombocytopenia (previously called immune thrombocytopenic purpura; ITP) mouse model [23]. These findings support the clinical development of M254 for ITP and (antibody-induced) inflammatory diseases.

Intravenous immunoglobulin has been used for the treatment of a variety of acute and chronic autoimmune and systemic inflammatory diseases for decades [1, 3, 15, 13]. At the current maximal dosing regimens, only partial and transient responses are obtained in many clinical instances [3, 15]. In addition, the long infusion times (4 to 6 hours) associated with the high volume of IVIg treatment consume significant resources at infusion centers [6] and negatively affect patient-reported outcomes, such as convenience and quality of life [9]. M254 is expected to be many fold more potent compared to commercially available IVIg based on preclinical pharmacological experiments. This may lead to reduced infusion time for patients compared to commercially available IVIg. Hypersialylation may increase IVIg-related anti-inflammatory and immune-modulating activities.

Intravenous immunoglobulin is an approved therapy for the treatment of ITP with prompt increases in platelet counts as early as a day after treatment with peak platelet response occurring within 2 to 7 days. This known treatment effect with easily measurable pharmacodynamics (PD) endpoint of increasing platelet count makes ITP patients a suitable population for investigation of M254. The present 4-part (each part will be initiated sequentially), first in-human study will be conducted first in healthy subjects and subsequently in ITP patients to evaluate the safety, tolerability, pharmacokinetics (PK), and PD platelet response of M254 administered as single followed by multiple intravenous (IV) doses.

The study will be executed in 4 distinct parts. Part A will assess safety, tolerability, and PK of M254 after administration of a single ascending dose in healthy volunteers (no subjects in the USA will be enrolled in Part A). Part B will assess safety, tolerability, and PK of M254 after administration of a single ascending dose of M254 followed by 1000 mg/kg IVIg administration in ITP patients. Part C will be a 2-arm, crossover design comparing the PD platelet response of M254 with IVIg in patients with ITP. Part C will have 2 cohorts with doses to be determined following analysis of data from Parts A and B. Part D will be a repeat dose study of M254 for the evaluation of safety, tolerability, PK, and PD platelet response in patients with ITP.

Objectives and Endpoints

Part A (Netherlands only)

OBJECTIVES	ENDPOINTS
Primary	
• To assess the safety and tolerability of a single ascending dose of intravenous administration of M254 in healthy volunteers	• Incidence and severity of adverse events (AEs) following administration of M254 at single dose levels • Clinically significant changes in clinical safety labs, vital signs, and electrocardiograms (ECGs) with M254 administration
Secondary	
• To characterize the pharmacokinetics (PK) of a single intravenous administration of M254 at different doses in healthy volunteers	• Measurements of PK parameters of M254 following the administration of a single intravenous dose
Exploratory	
• To characterize the pharmacodynamics (PD) of a single intravenous administration of M254 at different doses in healthy volunteers	• Exploratory biomarkers relating M254 exposure to potential efficacy in autoimmune diseases and the M254 mechanism of action may be analyzed

Part B (USA sites included)

OBJECTIVES	ENDPOINTS
Primary	
• To assess the safety and tolerability of a single intravenous administration of M254 in immune thrombocytopenia (ITP) patients compared to 1000 mg/kg intravenous immunoglobulin (IVIg)	• Incidence and severity of adverse events (AEs) following administration of M254 at single dose levels and 1000 mg/kg IVIg • Clinically significant changes in clinical safety labs, vital signs, and electrocardiograms (ECGs) following M254 administration and 1000 mg/kg IVIg
Secondary	
• To characterize the pharmacokinetics (PK) of a single intravenous administration of M254 at different doses in ITP patients	• Measurements of PK parameters of M254 following the administration of a single intravenous dose
Exploratory	
• To characterize the pharmacodynamics (PD) of a single intravenous administration of M254 at different doses in ITP patients compared to IVIg	• Platelet response after M254 administration compared to IVIg • Exploratory biomarkers relating M254 exposure to potential efficacy in autoimmune diseases and the M254 mechanism of action may be analyzed

Part C (USA sites included)

OBJECTIVES	ENDPOINTS
Primary	
• To assess the safety of a single intravenous administration of M254 compared to 1000 mg/kg of intravenous immunoglobulin (IVIg) • To characterize the pharmacodynamics (PD) of single intravenous administration of M254 compared to 1000 mg/kg IVIg	• Incidence and severity of adverse events (AEs) of M254 and 1000 mg/kg IVIg • Clinically significant changes in clinical safety labs, vital signs, and electrocardiograms (ECGs) following M254 administration and 1000 mg/kg IVIg • Platelet response after M254 administration compared to IVIg
Secondary	
• To characterize the pharmacokinetics (PK) of a single intravenous administration of M254 at different doses	• Measurements of PK parameters of M254 following the administration of a single intravenous dose
Exploratory	
• To characterize the PD of single intravenous administration of M254 compared to 1000 mg/kg IVIg	• Exploratory biomarkers relating M254 exposure to potential efficacy in autoimmune diseases and the M254 mechanism of action may be analyzed

Part D (USA sites included)

OBJECTIVES	ENDPOINTS
Primary	
• To assess the safety and tolerability of repeated intravenous administration of M254 in immune thrombocytopenia (ITP) patients	• Incidence and severity of adverse events (AEs) with repeated administration of M254 • Clinically significant changes in clinical safety labs, vital signs, and electrocardiograms (ECGs) with M254 administration
Secondary	
• To characterize the pharmacokinetics (PK) of repeated intravenous doses of M254 in ITP patients	• Measurements of PK parameters of M254 following the administration of a repeated intravenous doses

• To assess PD of repeated intravenous doses of M254 in ITP patients	• Platelet response after repeated M254 administration

Hypothesis:

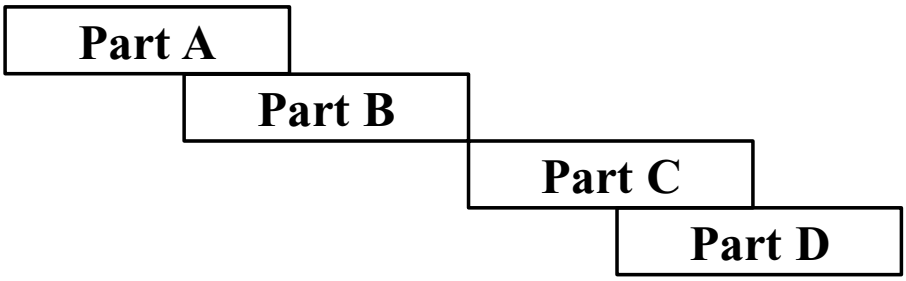
No formal hypothesis testing will be used.

Overall Design:

This is a Phase 1/2, study investigating single and repeated administration of M254 in a 4-part study. The overall design of each part (A, B, C, and D) is summarized below (Figure 1-1). A Scientific Review Committee (SRC) will review safety data as described in each of the parts below. Adverse events (AEs) will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. For all healthy volunteers and patients with ITP, a 28-day duration of safety monitoring following dosing of either M254 or IVIg has been selected based on nonclinical comparability of PK between M254 and IVIg, and clinical observations with IVIg where platelets return to ≤15% above baseline within 28 days.

For Parts B, C, and D of the study, during the follow-up period, participants may have laboratory assessments, vital signs, electrocardiogram (ECG), and PK samples assessed at home or another location mutually agreed with the site, but can be seen by the study staff if complications arise or for participant comfort.

Figure 1-1. Overall Schematic of 4-part Study Design Versus Timing



Part A (Netherlands only)

Part A is a single-ascending-dose, randomized, double-blinded sponsor unblind, safety, tolerability, and PK assessment of M254 or placebo in 6 cohorts of healthy volunteers. Planned doses include 3, 10, 30, 60, 120, and 250 mg/kg. In Cohort 1, 5 subjects will be enrolled with 3:2 (active:placebo) randomization. In all other cohorts, subjects will be randomized 3:1 (active:placebo) with total of 4 subjects in each cohort. There will be approximately 25 subjects in Part A. Up to 2 additional cohorts may be added based on

findings in prior cohorts. Additional dosing cohorts may be added on the recommendation of the SRC.

Following screening to confirm eligibility to participate, subjects will be randomized to receive M254 or placebo. Please refer to Section 4.3.1 and Figure 1-2 for dosing details.

At the first dose level (3 mg/kg), a sentinel group of 2 subjects (1 M254, 1 placebo) will be dosed and closely monitored for 48 hours before dosing the remainder of the cohort (2 M254, 1 placebo). The subjects in this sentinel group will be closely observed by the Investigator for any safety signals for the first 48 hours following drug administration. The general tolerability of the study drug will be monitored during this time and the ECG recordings and vital signs data will be reviewed. In addition, any reported AEs will be considered by the Investigator. If the safety and tolerability results of the first 48 hours following dosing for the initial subjects are acceptable to the Investigator, the other subjects in Cohort 1 of Part A may be dosed. There will be no additional sentinel groups in the study beyond this cohort (Cohort 1 Part A).

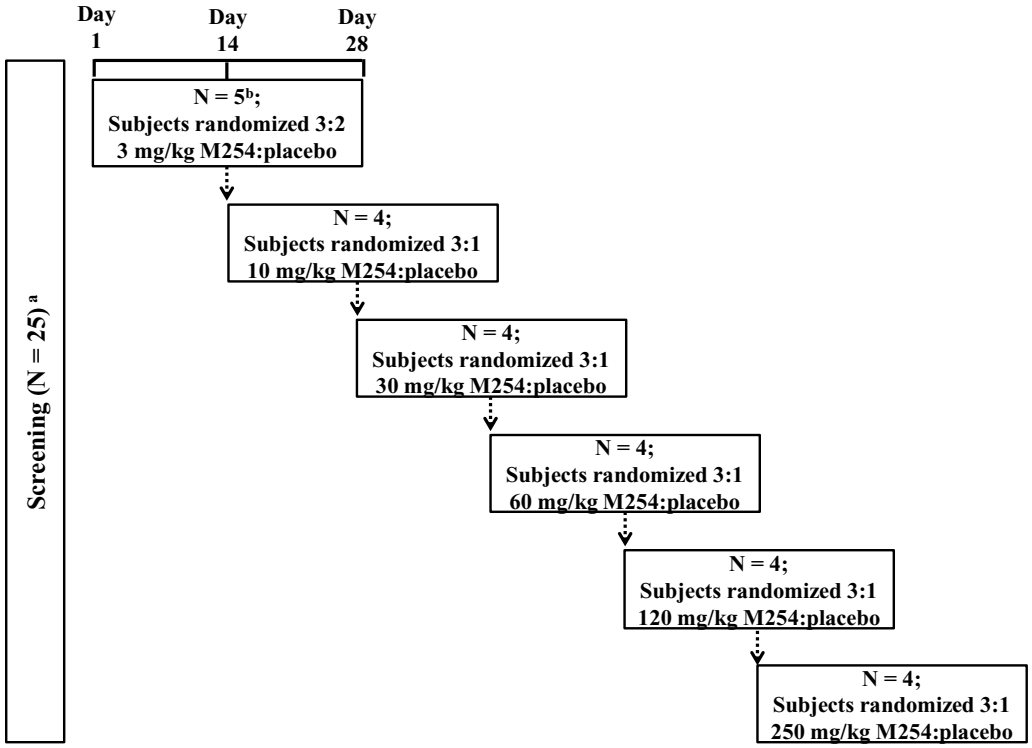
Safety assessments will be conducted out to Day 28 post M254 dosing. The SRC will review all available safety data after each cohort has completed at least 10 days of assessments after the single dose of M254. Dose escalation will only proceed after the recommendation of the SRC.

The SRC will review all safety data for all subjects in Part A out to Day 28.

Cohorts in Part B may start before the completion of Part A; however, prior to initiation of any cohort in Part B, either the same or a higher dose level will have been given in Part A and have a positive recommendation by the SRC, with the exception of doses greater than 250 mg/kg.

Dose escalation and continuation to the next study part may only occur when the SRC has given a positive recommendation and the Ethical Committee has given a statement of no objection, as per local requirement (where required).

Figure 1-2. Part A Study Schema



Note: Arrows represent dose escalation; Safety will be assessed prior to dose escalation.

[a] Up to 2 additional cohorts may be added based on findings in prior cohorts.

[b] In Cohort 1, dosing will be initially limited to a sentinel group (1 active, 1 placebo) that will be monitored for at least 48 hours before the remainder of the cohort is dosed.

Part B (USA sites included)

Initiation of any cohort in Part B will only proceed on the recommendation of the SRC after safety data from Part A Cohort 4 at the 60-mg/kg dose level has been reviewed and confirmed by SRC.

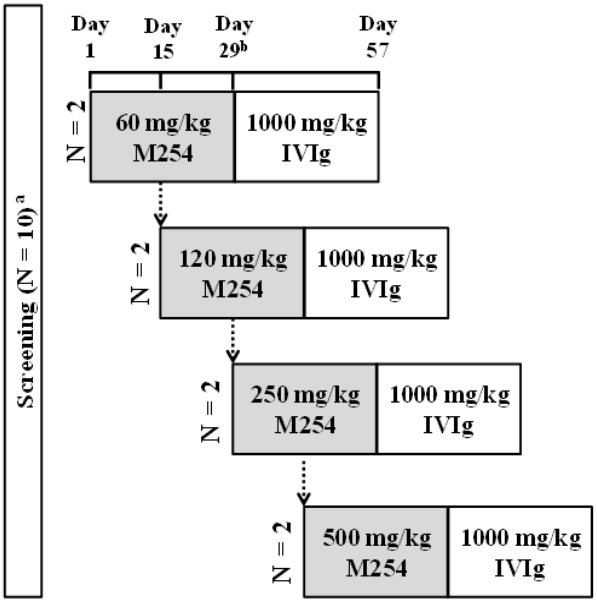
Part B is a single-ascending-dose, fixed-sequence, open-label part to assess safety, tolerability, PK, and PD of M254 followed by 1000 mg/kg IVIg in 4 cohorts of 2 ITP patients per cohort. Planned doses include 60, 120, 250, and 500 mg/kg. Up to 2 additional cohorts may be added based on findings in prior cohorts to better understand the safety of M254 and/or to better understand the efficacy to assist with dose selection for Part C. The maximum dose for Part B will not exceed 500 mg/kg (the no-observed-adverse-event-level [NOAEL] of 1000 mg/kg was determined in the toxicology study in cynomolgus monkeys). Additional patients may be added to dosing cohorts, including prior dose level cohorts, on the recommendation of the SRC.

Following screening to confirm eligibility to participate, patients will be dosed with M254. Please refer to Section 4.3.1 and Figure 1-3 for dosing details. There will be a 14-day safety monitoring period between enrollment of the first and second patients in the 500 mg/kg cohort.

Safety and platelet assessments will be conducted initially out to Day 28 post M254 administration. Patients will receive a fixed dose of IVIg at 1000 mg/kg on Day 29 if the patients' platelet count returns to ≤15% above baseline level. Patients whose platelets have not returned to ≤15% above baseline dosing level by Day 28 will have platelet determinations weekly until platelets return to ≤15% above baseline, up to 56 days postdose. If these conditions are not met by Day 57, IVIg will be administered, as long as the patients' platelets have returned to $<50 \times 10^9$/L. If the platelets have not returned to ≤15% above baseline and are $>50 \times 10^9$/L, the patient will complete Follow-Up assessments and be discharged from Part B. After dosing with IVIg, safety and the other assessments listed in the Schedule of Activities will be conducted for 28 days following IVIg administration.

The SRC will review all safety data for all patients in Part B up to at least 28 days following M254 administration for the last patient. Initiation of Part C will only proceed on the recommendation of the SRC. Dose escalation and continuation to the next study part may only occur when the SRC has given a positive recommendation and the Ethical Committee has given a statement of no objection, as per local requirement (where required).

Figure 1-3. Part B Study Schema



Note: Arrows represent dose escalation; Safety will be assessed prior to dose escalation.

IVIg = Intravenous immunoglobulin; NOAEL = no-observed-adverse-event-level.

[a] Up to 2 additional cohorts may be added based on findings in prior cohorts. Additional patients may be added to cohorts, including prior dose level cohorts. Maximum dose will not exceed 500 mg/kg (a NOAEL of 1000 mg/kg determined in the toxicology study in cynomolgus monkeys).

[b] All patients will receive a dose of IVIg (1000 mg/kg) at approximately Day 29.

Part C (USA sites included)

Part C consists of 2 randomized, unblinded crossover cohorts, to assess safety and PD of a single dose of M254 compared to a single dose of IVIg in ITP patients. The dose of M254 for each of these 2 cohorts will be determined after analysis of the data from Part A and Part B. Each cohort consists of 10 patients with 2 arms in each cohort consisting of 5 patients in each arm, for an overall total of 20 patients in Part C.

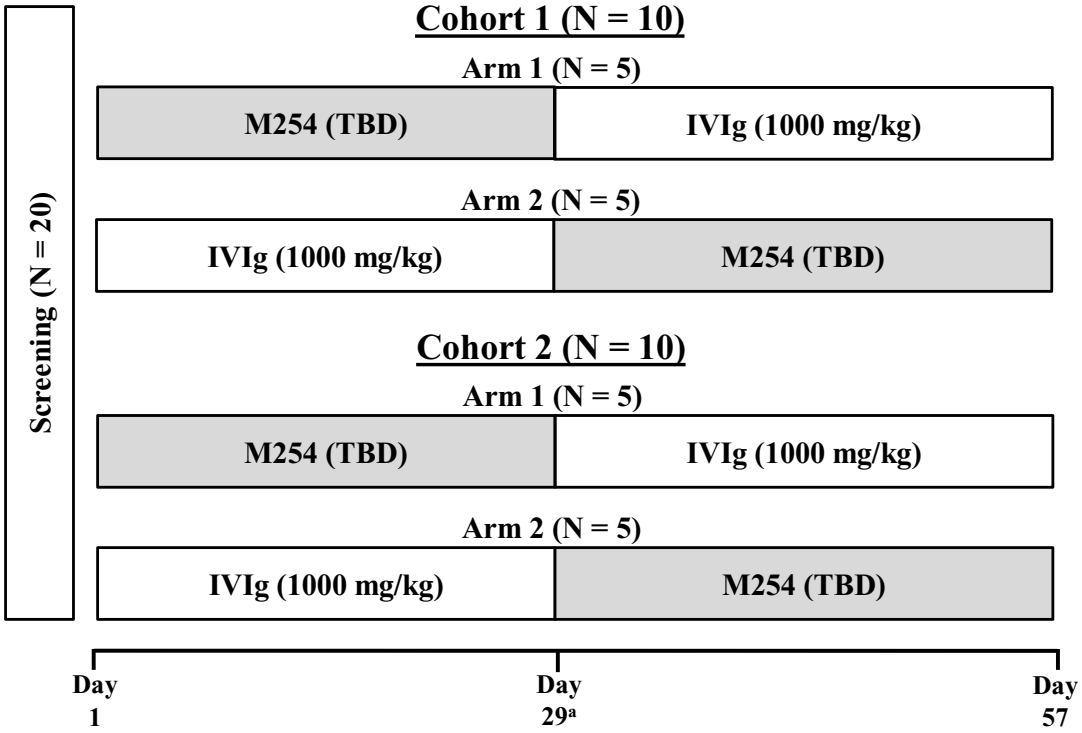
Following screening to confirm eligibility to participate, in crossover Cohort 1 or Cohort 2, 5 patients in each cohort will be randomized to M254 by IV administration and 5 patients will be randomized to 1000 mg/kg IVIg. Please refer to Section 4.3.1 and Figure 1-4 for dosing details.

Safety and platelet assessments will be conducted initially out to Day 28 post M254 or IVIg administration. Patients will receive 1 dose of either M254 or IVIg, depending on their assigned arm within the cohort on Day 29 if the patients' platelet count returns to ≤15% above baseline level. Patients whose platelets have not returned to ≤15% above baseline dosing level by Day 28 will have platelet determinations weekly until platelets return to ≤15% above baseline up to 56 days post the first M254 or IVIg administration. Patients who do not meet this criteria will receive the second administration of M254 or IVIg, as long as

the platelets have returned to <50 × 10^9/L. If the platelets have not returned to ≤15% above baseline and are ≥50 × 10^9/L, the patient will complete Follow-Up assessments on or around Day 57 post first infusion and be discharged from Part C; and the patient may be replaced. After patients are crossed over to M254 or IVIg, they are followed for an additional 28 days with safety and platelet assessments or until platelet counts return to ≤15% above their baseline level following similar rules to the first dose in Part C.

The SRC will review all safety data from both crossover cohorts in Part C; however the initiation of Part D will proceed after the SRC reviews all safety data from Cohort 1 and the recommendation is to proceed with Part D. Dose escalation and continuation to the next study part may only occur when the SRC has given a positive recommendation and the Ethical Committee has given a statement of no objection, as per local requirement (where required).

Figure 1-4. Part C Study Schema



IVIg = Intravenous immunoglobulin; TBD = to be determined.

[a] Patients will be followed for 28 days or until their platelet counts have returned to ≤15% above baseline levels and then crossed to the second period. Patients will again be dosed and followed for an additional 28 days with safety and platelet assessments.

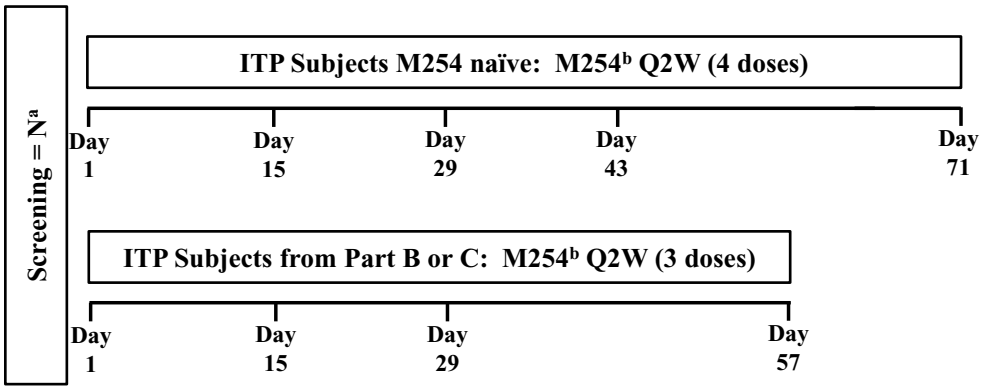
Part D (USA sites included)

Part D is a repeated, fixed-dose, open-label study of M254. Any patients who participate in Parts B or C are allowed to participate in Part D if they meet the eligibility criteria during screening for Part D. Part D may have up to 2 dose levels with up to approximately 15 to 34 ITP patients in total. The initial dose level for Part D will be less than or equal to the maximum tolerated dose, and it will be selected based on review of Part B data and available data from Part C. Following completion of Part C, the dose for new patients in Part D may be revised (the dose level will not be modified for patients who have already received at least 1 dose). Patients who have participated in Part B or C may be allowed to participate in Part D, prior to completion of randomization in Part C. New patients not in Part B or C may participate in Part D following complete randomization in Part C. The dose levels of M254 for Part D will be determined after analysis of available data from Part A, Part B, and Part C.

Following screening to confirm eligibility to participate (including rescreening patients who participated in Part B or C), M254 naïve patients will receive 4 doses of M254, and patients from Part B or C will receive 3 doses of M254 every 14 days. Patients in Part C may roll over into Part D by including any data after the last dose of IVIg or M254 in Part C for assessment of screening in Part D as long as those data are within the screening window specified. Please refer to Section 4.3.1 and Figure 1-5 for dosing details.

During Part D, if the patient's platelet count has not returned to $\leq 100 \times 10^9$/L, their platelet count will be monitored weekly until platelets return to $\leq 100 \times 10^9$/L. If these conditions are not met, M254 will not be administered further. Patients will be followed for safety assessments and platelet counts up to at least 28 days post their last dose of M254. Safety will be reviewed by the SRC quarterly (or more often as required).

Figure 1-5. Part D Study Schema



ITP = Immune Thrombocytopenia; Q2W = every 2 weeks.

Note: Days with tick marks before the timeline break (before Day 71 or Day 57) indicate dosing days.

[a] Patients may either be new to the study (M254 naïve) or have previously received M254 in Part B or C. This part will include up to approximately 15 to 34 patients.

[b] Dose of M254 to be ≤500 mg/kg (dose to be confirmed based on review of Parts A, B, and C and not to exceed the maximum dose tolerated in the prior study parts to date).

Number of Participants:

In Part A (Netherlands only), approximately 25 healthy volunteers will be included, 18 subjects will receive M254 and 7 will receive placebo. In Part B, up to approximately 20 patients will receive 1 dose of M254 and 1 dose of IVIg (2 each in 4 planned cohorts; 2 each in 2 optional cohorts; and 8 in optional expansions of existing cohorts or the optional cohorts). In Part C, 20 patients will receive 1 dose of M254 and 1 dose of IVIg. In Part D, up to approximately 15 to 34 patients will receive repeated doses of M254. Patients from Part B and C can continue to Part D. In total for Parts B, C, and D, there will be up to 74 patients who will receive at least 1 dose of M254 or IVIg.

Intervention Groups and Duration:

The total duration of study participation for each cohort in Part A (Netherlands only) will be up to 8 weeks; up to 4 weeks for screening and 4 weeks observation and follow-up. The total duration of participation in Parts B and C will be 12 to 20 weeks: up to 4 weeks for screening and 4 to 8 weeks for M254 period and 4 to 8 weeks for IVIg period based on platelet measurements returning to baseline as described above. The total duration of study participation in Part D will be 12 to 14 weeks: 4 weeks for screening and 8 (patients from Parts B or C) or 10 (M254-naïve patients) weeks observation and follow-up.

1.2 Schedule of Activities

Table 1-1. Part A Schedule of Activities (Netherlands only)

Day	-28 to -2	-1	1	1	1	1	1	1	1	1	1	1	2	3	4	5	8 ±1	10[n] ±1	12[n] ±1	15 ±1	18[n] ±1	22 ±1	29 ±2
	Screening	Pre-infusion	Infusion	Post-infusion																			Follow-up
Procedure[a] Hour	--	0	0	0 (end of infusion)	0.08 (5 min)	0.25	0.5	1	2	4	8	12	0	0	0	0	0	0	0	0	0	0	0
Unit Admit		X																					
Informed Consent	X																						
Demographics	X																						
Prior/Concomitant Medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X																						
Inclusion/Exclusion Criteria[b]	X	X																					
Physical Examination	X	X[p]								X													X[p]
Drug Screening	X																						
Body Weight	X	X																					X
Height and Body Mass Index	X																						
Vital signs[c]	X	X	X	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X
12-lead ECG	X	X		X[o]					X	X	X	X	X										X
Safety Labs[f]	X[f]	X	X									X	X	X		X	X			X		X	X

Table 1-1. Part A Schedule of Activities (Netherlands only)

Day	-28 to -2	-1	1	1	1	1	1	1	1	1	1	1	2	3	4	5	8 ±1	10[n] ±1	12[n] ±1	15 ±1	18[n] ±1	22 ±1	29 ±2
	Screening	Pre-infusion	Infusion	Post-infusion																			Follow-up
Procedure[a] Hour	--	0	0	0 (end of infusion)	0.08 (5 min)	0.25	0.5	1	2	4	8	12	0	0	0	0	0	0	0	0	0	0	0
Serology: HBsAg, anti-HCV, anti-HIV 1 and 2	X																						
Total IgG[h]		X	X	X		X	X		X	X		X	X	X		X	X			X		X	X
Blood Samples for PK[h, i]			X[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X
Blood Samples for Biomarkers		X											X				X						
Urinalysis	X	X	X									X	X	X		X	X			X		X	X
Pregnancy Test[g]	X	X																					X
Telemetry (set on alarm)[d]			X	X																			
M254 IV Infusion[j]			X (start)	X[k] (end)																			
Infusion Reaction[l]		X	X	X		X	X	X	X	X	X	X	X	X	X	X							
Unit Discharge																X							
Discharge from Study																							X[m]

AE = adverse event; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IV = intravenous; PK = pharmacokinetics.

[a] Procedures should occur in the order presented above from top to bottom if more than 1 procedure occurs at the same nominal time Urine sampling or anything with a specific footnote may be done out of order.

[c] Inclusion/exclusion criteria does not need to be redone for subsequent dose of IVIg, but follow other pre-infusion assessments.

[d] Vital signs includes tympanic body temperature, supine (after 5 minutes) blood pressure, pulse rate, and respiratory rate. Vital signs will be assessed every 30 minutes during an infusion with a window +3 minutes. For infusions <35 minutes, vital signs assessments may occur just after starting the infusion and just prior to the end of the infusion. Refer to Footnote O for exception.

[e] Telemetry should start at or before beginning of infusion and stop at or after end of infusion.

[f] Concomitant Medications and AEs will be assessed throughout the infusion and the study. Subjects will be queried and observed for AEs daily during the confinement period, then at each subsequent clinic visit.

[g] Safety labs will include complete blood count (CBC), hematology, serum chemistry, coagulation, and coagulation screening lab (at screening only) (see Table 10-1).

[h] Women of childbearing potential, only. Urine test on Day -1; serum test during Screening and on Day 29.

[i] Samples should be analyzed in a blinded fashion in Part A – see Part A lab manual for additional details.

[j] Samples drawn 15 minutes after in supine position at in-house visits. For ambulatory visits, samples drawn 15 minutes after sitting.

[k] Duration of infusion is based on dosing instructions (details provided in the pharmacy manual). Patients will be required to drink 2 glasses of liquid in the morning before the start of infusion. Just before infusion, patients will be provided the opportunity to urinate.

[l] If infusion duration is <20 minutes, end of infusion activities may be scheduled as logistically feasible with the PK sample drawn from 1 minute before the end of infusion to 2 minutes after the end of infusion. For infusion durations ≥20 minutes, activities should occur in the order of the table (top to bottom) unless a footnote indicates otherwise.

[m] Subjects will assessed for 2 types of infusion reactions: 1) cutaneous infusion reaction 2) systemic reactions. For either types of infusion reactions and AE must be recorded. In the event of systemic reactions, a sample of blood will be drawn to measure histamine, anaphylatoxin (C5a), IgE, and tryptase and will be compared with the baseline sample drawn prior to the first dose of study drug.

[n] Discharge from study after final study period unless further follow-up of open AEs is deemed necessary by the Investigator.

[o] Follow-up may be conducted by telephone for these visits

[p] ECG and vital signs assessments required at the end of the infusion may be initiated 15 minutes prior to the end of infusion

[q] These should be conducted as abbreviated physical exams

[r] PK sample is required prior to the start of infusion (on the day of the infusion).

Table 1-2. Part B Schedule of Activities (USA sites included)

(Schedule of Activities below is repeated when the patient receives their second infusion, which will be IVIg)

Day	-28 to -2	-1 [n]	1 [n]	1	1	1	1	1	2	3[b]	4[b]	5[b]	8±1[b]	10 ±3	12 ±3[b]	15 ±3[b]	18 ±3[b]	22 ±3[b]	29 ±3[n]
	Screening	Pre-infusion	Infusion	Post-infusion															Follow-up
Procedure[a] Hour	--	0	0	0 (end of infusion)	0.25	0.5	2	4	0	0	0	0	0	0	0	0	0	0	0
Unit Admit			X																
Informed Consent	X																		
Demographics	X																		
Prior/Concomitant Medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ITP-BAT		X																	X[s]
Medical History	X																		
Inclusion/Exclusion Criteria	X																		
Physical Examination	X	X[u]																	X[u]
Drug Screening	X																		
Body Weight[c]	X	X																	X
Height and Body Mass Index	X																		
Vital Signs[d]	X	X	X	X[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X		X[t]		X	X	X											X
Safety Labs[g]	X[g]	X						X	X		X		X			X		X	X

Table 1-2. Part B Schedule of Activities (USA sites included)

(Schedule of Activities below is repeated when the patient receives their second infusion, which will be IVIg)

Day	-28 to -2	-1 [n]	1 [n]	1	1	1	1	1	2	3[b]	4[b]	5[b]	8±1[b]	10 ±3	12 ±3[b]	15 ±3[b]	18 ±3[b]	22 ±3[b]	29 ±3[n]
	Screening	Pre-infusion	Infusion	Post-infusion															Follow-up
Procedure[a] Hour	--	0	0	0 (end of infusion)	0.25	0.5	2	4	0	0	0	0	0	0	0	0	0	0	0
Serology: HBsAg, anti-HCV, anti-HIV 1 and 2	X																		
Platelet Count[h]	X	X						X	X	X	X	X	X	X	X	X	X	X	X
Blood type, if unknown	X																		
Platelet Autoantibodies, if unknown	X																		
Total IgG[j]	X	X		X	X	X	X	X	X	X	X	X	X			X		X	X
Blood Samples for PK[r]			X[v]	X	X	X	X	X	X	X	X	X	X			X		X	X
Blood Samples for Biomarkers and ADA[w]		X							X				X						X
Urinalysis	X	X							X				X			X		X	X
Pregnancy Test[i]	X	X																	X
Telemetry (set on alarm)[e]			X																
M254 or IVIg IV Infusion[k]			X (start)	X[l] (end)															X[q]
Infusion Reaction[m]		X	X	X	X	X	X	X	X										X
Unit Discharge								X[o]											

Table 1-2. Part B Schedule of Activities (USA sites included)

(Schedule of Activities below is repeated when the patient receives their second infusion, which will be IVIg)

Day	-28 to -2	-1 [n]	1 [n]	1	1	1	1	1	2	3[b]	4[b]	5[b]	8±1[b]	10 ±3	12 ±3[b]	15 ±3[b]	18 ±3[b]	22 ±3[b]	29 ±3[n]
	Screening	Pre-infusion	Infusion	Post-infusion															Follow-up
Procedure[a] Hour	--	0	0	0 (end of infusion)	0.25	0.5	2	4	0	0	0	0	0	0	0	0	0	0	0
Discharge from Study																			X[p]

ADA = anti-drug antibody; AE = adverse event; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; ITP-BAT = immune thrombocytopenic purpura bleeding assessment tool; IV = intravenous; PK = pharmacokinetics.

[a] Procedures should occur in the order presented above from top to bottom if more than 1 procedure occurs at the same nominal time. Urine sampling or anything with a specific footnote may be done out of order.

[b] Only visits required to be at the study site are screening, infusions, the day after infusion, Day 10 after M254 infusion (as this is last safety visit prior to dose escalation decision), and Day 29, all others can be done by visiting nurse if patient prefers this option. Visit windows of ±1 day should be used whenever possible; ±3 day windows shouldonly be used when required due to clinical site closures (eg, for holidays or COVID-19-related limited schedules). When visit windows overlap, they must not be combined into a single actual day. Note: the first patient in the 500 mg/kg cohort must be seen in clinic at the Day 15 visit as there will be a 14-day safety monitoring period between enrollment of the first and second patients in the 500 mg/kg cohort.

[c] Screening weight will be used to determine eligibility and dosing, and will allow up to 1 month for weight variability.

[d] Vital signs includes body temperature, supine (after 5 minutes) blood pressure, pulse rate, and respiratory rate. Vital signs will be assessed every 30 minutes during an infusion. For infusions <35 minutes, vital signs assessments may occur just after starting the infusion and just prior to the end of the infusion. Refer to Footnote t for exception.

[e] Telemetry should start at or before beginning of the M254 infusion and stop at or after end of infusion. Telemetry does not need to be performed during the IVIg infusion.

[f] Concomitant Medications and AEs will be assessed throughout the infusion and the study. Subjects will be queried and observed for AEs daily during the confinement period, then at each subsequent clinic visit. Should there be a bleeding event reported by the patient or observed by the physician during examination, the ITP-BAT must be completed, see ITP-BAT in Appendix 6, as well as an AE form.

[g] Safety labs will include complete blood count (CBC), serum chemistry, coagulation, and coagulation screening lab (at screening only) (see Table 10-1). All safety labs will be assessed by the Central lab except for platelet counts, which should be done locally at all the visits where they are scheduled. In case of an AE that requires additional sampling and the Investigator needs to review the results to determine patient care, additional safety labs can be assessed by the local lab.

[h] The platelet measurement for eligibility must be taken within 96 hours of start of infusion. Platelet sample may be combined with safety labs if sample is taken at the same time. All scheduled platelet measurements must be sent to the central lab. If there is insufficient time to review the central lab results an additional local lab sample may be obtained in order to assess eligibility for infusion.

[i] Women of childbearing potential, only. Urine test on Day -1 for Day 1 prior to infusion; serum test during Screening and on Day 29. Central lab should assess serum sample collected at screening and on Day 29, but the local lab can assess the urine test on Day -1/Day 1 prior to the infusion.

[j] Duplicate samples for IgG should not be drawn if sample was already taken with safety labs collection.

[k] Duration of infusion is based on dosing instructions (details provided in the pharmacy manual). Patients will be required to drink 2 glasses of liquid in the morning before the start of infusion. Just before infusion, patients will be provided the opportunity to urinate. Patients receiving M254 or IVIg can be discharged 4 hours post-infusion.

[l] If infusion duration is <20 minutes, end of infusion activities may be scheduled as logistically feasible with the PK sample drawn from 1 minute before the end of infusion to 2 minutes after the end of infusion. For infusion durations ≥20 minutes, activities should occur in the order of the table (top to bottom) unless a footnote indicates otherwise.

[m] All systemic infusion reactions and associated AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE)

[n] Patients with ITP may be admitted to the unit the morning of Day 1so any procedure specified on Day -1 can occur on Day 1, but all results must be back before infusion begins. Likewise, any pre-infusion assessment specified on Day 1 can occur on Day -1 and does not need to be duplicated.

[o] Study staff should follow-up with the patient approximately 12 hours post-discharge for safety via phone call.

[p] Discharge from study after final study period unless further follow-up of open AEs is deemed necessary by the Investigator.

[q] IVIg infusion will occur on this day if patient's platelet count meets criteria, and then the Schedule of Activities should be followed starting at Day 1. For Period 2, Day 1, any assessments completed on the same date for Period 1 follow-up do not need to be duplicated.

[r] Blood sample for PK is required during the M254 treatment period only. It is NOT needed for the IVIg treatment period.

[s] ITP-BAT to be completed separately at Day 1 and 29 of each period (M254- and IVIg-treatment). Only 1 ITP-BAT assessment is needed if Day 29 of the first period is the same as Day 1 of the second period.

[t] ECG and vital signs assessments required at the end of the infusion may be initiated 15 minutes prior to the end of infusion

[u] These should be conducted as abbreviated physical exams

[v] PK sample is required prior to the start of infusion (on the day of the infusion).

[w] Biomarker samples are collected at pre-infusion, Day 2, and Day 8; ADA samples are collected at pre-infusion and Day 29 follow-up. Please refer to the lab manual for specific instructions.

Table 1-3. Part C Schedule of Activities (USA sites included)

(Schedule of Activities below is repeated when the patient receives their second infusion, which will be either M254 or IVIg)

Day	-28 to -2	-1 [m]	1 [m]	1	1	1	1	1	2	3[b]	4[b]	5[b]	8±1[b]	10 ±3 [b]	12 ±3[b]	15 ±3[b]	18 ±3[b]	22 ±3[b]	29 ±3[n]
	Screening	Pre-infusion	Infusion	Post-infusion															Follow-up
Procedure[a] Hour	--	0	0	0 (end of infusion)	0.25	0.5	2	4	0	0	0	0	0	0	0	0	0	0	0
Informed Consent	X																		
Demographics	X																		
Prior/Concomitant Medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ITP-BAT		X																	X[r]
Medical History	X																		
Inclusion/Exclusion Criteria	X																		
Physical Examination	X	X[t]																	X[t]
Drug Screening	X																		
Body Weight[c]	X	X																	X
Height and Body Mass Index	X																		
Vital Signs[d]	X	X	X	X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X		X[s]		X	X	X											X
Safety Labs[f]	X[g]	X						X	X		X		X			X		X	X

Table 1-3. Part C Schedule of Activities (USA sites included)

(Schedule of Activities below is repeated when the patient receives their second infusion, which will be either M254 or IVIg)

Day	-28 to -2	-1 [m]	1 [m]	1	1	1	1	1	2	3[b]	4[b]	5[b]	8±1[b]	10 ±3 [b]	12 ±3[b]	15 ±3[b]	18 ±3[b]	22 ±3[b]	29 ±3[n]
	Screening	Pre-infusion	Infusion	Post-infusion															Follow-up
Procedure[a] Hour	--	0	0	0 (end of infusion)	0.25	0.5	2	4	0	0	0	0	0	0	0	0	0	0	0
Serology: HBsAg, anti-HCV, anti-HIV 1 and 2	X																		
Platelet Count[g]	X	X						X	X	X	X	X	X	X	X	X	X	X	X
Bloodtype, if unknown	X																		
Platelet Autoantibodies, if unknown	X																		
Total IgG[i]	X	X	X	X	X			X	X			X	X			X		X	X
Blood Samples for PK[q]			X[u]	X	X			X	X			X	X			X		X	X
Blood Samples for Biomarkers and ADA[v]		X							X				X						X
Urinalysis	X	X						X	X				X			X		X	X
Pregnancy Test[h]	X	X																	X
M254 or IVIg IV Infusion[j]			X (start)	X[k] (end)															X[p]
Infusion Reaction[l]		X	X	X	X	X	X	X	X										X
Unit Discharge								X[n]											
Discharge from Study																			X[o]

ADA = anti-drug antibody; AE = adverse event; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; ITP-BAT = immune thrombocytopenic purpura bleeding assessment tool; IV = intravenous; PK = pharmacokinetics.

[a] Procedures should occur in the order presented above from top to bottom if more than 1 procedure occurs at the same nominal time. Urine sampling or anything with a specific footnote may be done out of order.

[b] Only visits required to be at the study site are screening, infusions, the day after an infusion, and Day 29, all others can be done by visiting nurse if patient prefers this option. Visit windows of ±1 day should be used whenever possible; ±3 day windows should only be used when required due to clinical site closures (eg, for holidays or COVID-19-related limited schedules). When visit windows overlap, they must not be combined into a single actual day.

[c] Screening weight will be used to determine eligibility and dosing, and will allow up to 1 month for weight variability.

[d] Vital signs includes body temperature, supine (after 5 minutes) blood pressure, pulse rate, and respiratory rate. Vital signs will be assessed every 30 minutes during an infusion. For infusions <35 minutes, vital signs assessments may occur just after starting the infusion and just prior to the end of the infusion. Refer to Footnote s for exception.

[e] Concomitant Medications and AEs will be assessed throughout the infusion and the study. Subjects will be queried and observed for AEs daily during the confinement period, then at each subsequent clinic visit. Should there be a bleeding event reported by the patient or observed by the physician during examination, the ITP-BAT must be completed, see ITP-BAT in Appendix 6, as well as an AE form.

[f] Safety labs will include complete blood count (CBC), serum chemistry, coagulation, and coagulation screening lab (at screening only) (see Table 10-1). All safety labs will be assessed by the central lab, except for platelet counts, which should be done locally at all the visits where they are scheduled. In case of an AE that requires additional sampling and the Investigator needs to review the results to determine patient care additional safety labs can be assessed by the local lab.

[g] The platelet measurement for eligibility must be taken within 96 hours of start of infusion. Platelet sample may be combined with safety labs if sample is taken at the same time. All scheduled platelet measurements must be sent to the central and local lab. If there is insufficient time to review the central lab results an additional local lab sample may be obtained in order to assess eligibility for infusion.

[h] Women of childbearing potential, only. Urine test on Day -1 for Day 1 prior to infusion; serum test during Screening and on Day 29. Central lab should assess serum sample collected at screening and on Day 29, but the local lab can assess the urine test on Day -1/Day 1 prior to the infusion.

[i] Duplicate samples for IgG should not be drawn if sample was already taken with safety labs collection.

[j] Duration of infusion is based on dosing instructions (details provided in the pharmacy manual). Patients will be required to drink 2 glasses of liquid in the morning before the start of infusion. Just before infusion, patients will be provided the opportunity to urinate. Patients receiving M254 or IVIg can be discharged 4 hours post-infusion.

[k] If infusion duration is <20 minutes, end of infusion activities may be scheduled as logistically feasible with the PK sample drawn from 1 minute before the end of infusion to 2 minutes after the end of infusion. For infusion durations ≥20 minutes, activities should occur in the order of the table (top to bottom) unless a footnote indicates otherwise.

[l] All systemic infusion reactions and associated AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE).

[m] Patients with ITP may admit to the unit the morning of Day 1so any procedure specified on Day -1 can occur on Day 1, but all results must be back before infusion begins. Likewise, any pre-infusion assessment specified on Day 1 can occur on Day -1 and does not need to be duplicated.

[n] Study staff should follow-up with the patient approximately 12 hours post-discharge for safety via phone call.

[o] Discharge from study after final study period unless further follow-up of open AEs is deemed necessary by the Investigator.

[p] M254 or IVIg infusion will occur on this day if patient's platelet count meets criteria, and then the Schedule of Activities should be followed starting at Day 1. For Period 2, Day 1, any assessments completed on the same date for Period 1 follow-up do not need to be duplicated.

[q] Blood sample for PK is required during the M254 treatment period only. It is NOT needed for the IVIg treatment period.

[r] ITP-BAT to be completed separately at Day 1 and 29 of each period (M254- and IVIg-treatment). Only 1 ITP-BAT assessment is needed if Day 29 of the first period is the same as Day 1 of the second period.

[s] ECG and vital signs assessments required at the end of the infusion may be initiated 15 minutes prior to the end of infusion

[t] These should be conducted as abbreviated physical exams

[u] PK sample is required prior to the start of infusion (on the day of the infusion).

[v] Biomarker samples are collected at pre-infusion, Day 2, and Day 8; ADA samples are collected at pre-infusion and Day 29 follow-up. Please refer to the lab manual for specific instructions.

Table 1-4. Part D Schedule of Activities (USA sites included)

Day (M254 Naïve)	-28 to -2	-1 [o]	1-54	57 ±3	71 ±3
Day (Part B/C Patients)	-28 to -2	-1[a, o]	1-40	43 ±3	57 ±3
Procedure[c] / Hour	Screening[b] --	Pre-infusion 0		Post-infusion 0	Follow-up 0
Informed Consent	X		See Table D2		
Demographics	X				
Prior/Concomitant Medications[g]	X	X		X	X
AE Assessment[g]	X	X		X	X
ITP-BAT[s]		X			
Medical History	X				
Inclusion/Exclusion Criteria	X	X			
Physical Examination	X	X[u]			X[u]
Drug Screening	X				
Body Weight[e]	X	X			X
Height and Body Mass Index	X				
Vital signs[f, t]	X	X		X	X
12-lead ECG [t]	X	X			X
Safety Labs[h]	X	X		X	X
Serology: HBsAg, anti-HCV, anti-HIV 1 and 2	X				
Platelet Count[i]	X	X		X	X
Bloodtype, if unknown	X				

Table 1-4. Part D Schedule of Activities (USA sites included)

Day (M254 Naïve)	-28 to -2	-1 [o]	1-54	57 ±3	71 ±3
Day (Part B/C Patients)	-28 to -2	-1[a, o]	1-40	43 ±3	57 ±3
	Screening[b]	Pre-infusion		Post-infusion	Follow-up
Procedure[c] Hour	--	0		0	0
Platelet Autoantibodies, if unknown	X				
Total IgG[k]	X	X		X	X
Blood Samples for PK[l]				X	X
Blood Samples for ADA[x]		X			X
Urinalysis	X	X		X	X
Pregnancy Test[j]	X	X			X
Infusion Reaction[n]		X			X
Discharge from Study					X[q]

Footnotes are described on the last page of Table D2.

Table D2 (USA sites included)

Day (M254 Naïve)	**1 [o]**	**1**	**1**	**1**	**1**	**1**	**2**	**3[d]**	**4 [d]**	**5 [d]**	**8±1 [d]**	**10±3 [d]**	**12±3 [d]**
All visit windows are relative	**15±1 [o]**	**15**	**15**	**15**	**15**	**15**	**Skip [w]**				**22±1 [d]**	**Skip[w]**	
to the most recent dose	**29±1 [o]**	**29**	**29**	**29**	**29**	**29**	**Skip[w]**				**36±1 [d]**	**Skip[w]**	
	43±1 [o]	**43**	**43**	**43**	**43**	**43**	**44**	**45[d]**	**46 [d]**	**47 [d]**	**50±1 [d]**	**52±3 [d]**	**54±3 [d]**
Day (Part B/C Patients)	**1[a, o]**	**1**	**1**	**1**	**1**	**1**	**2**	**3 [d]**	**4 [d]**	**5 [d]**	**8±1 [d]**	**10±3 [d]**	**12±3 [d]**
All visit windows are relative	**15±1 [o]**	**15**	**15**	**15**	**15**	**15**	**Skip[w]**				**22±1 [d]**	**Skip[w]**	
to the most recent dose	**29±1 [o]**	**29**	**29**	**29**	**29**	**29**	**30**	**31 [d]**	**32 [d]**	**33 [d]**	**36±1 [d]**	**38±3 [d]**	**40±3 [d]**
	Infusion	**Post-infusion**											
Procedure[c] Hour	**0**	**0 (end of infusion)**	**0.25**	**0.5**	**2**	**4**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Unit Admit	X												
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[f, t]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[t]		X	X	X	X	X							
Safety Labs[h]	X					X	X				X		
Platelet Count[i]	X					X	X	X	X	X	X	X	X
Total IgG[k]	X		X			X	X			X	X		
Blood Samples for PK[l]	X[v]	X	X			X	X			X	X		
Urinalysis	X					X	X				X		
M254 IV Infusion[l]	X[r] (start)	X[m] (end)											
Infusion Reaction[n]	X	X	X	X	X	X	X						
Unit Discharge						X[p]							

ADA = anti-drug antibody; AE = adverse event; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; ITP-BAT = immune thrombocytopenic purpura bleeding assessment tool; IV = intravenous; PK = pharmacokinetics.

[a] Patients continuing from Part C may have the procedures from Part C, Period 2, Day 29 (or the last day of Part C, Period 2 if follow-up is extended for any reason); Part D, Day -1, and Part D, Day 1 combined into a single visit, if preferred and if logistics for assessment allow.

[b] See Section 5 for the screening requirements for patients transitioning from Part B or C to Part D.

[c] Procedures should occur in the order presented above from top to bottom if more than 1 procedure occurs at the same nominal time. Urine sampling or anything with a specific footnote may be done out of order.

[d] Only visits required to be at the study site are screening, infusions, the day after an infusion, and the last follow-up, all others can be done by visiting nurse if patient prefers this option. Visit windows of ±1 day should be used whenever possible; ±3 day windows should only be used when required due to clinical site closures (eg, for holidays or COVID-19-related limited schedules). When visit windows overlap, they must not be combined into a single actual day.

[e] Screening weight will be used to determine eligibility and dosing, and will allow up to 1 month for weight variability.

[f] Vital signs includes body temperature, supine (after 5 minutes) blood pressure, pulse rate, and respiratory rate. Vital signs will be assessed every 30 minutes during an infusion. For infusions <35 minutes, vital signs assessments may occur just after starting the infusion and just prior to the end of the infusion. Refer to Footnote t for exception.

[g] Concomitant Medications and AEs will be assessed throughout the infusion and the study. Subjects will be queried and observed for AEs daily during the confinement period, then at each subsequent clinic visit. Should there be a bleeding event reported by the patient or observed by the physician during examination, the ITP-BAT must be completed, see ITP-BAT in Appendix 6, as well as an AE form.

[h] Safety labs will include complete blood count (CBC), serum chemistry, coagulation, and coagulation screening lab (at screening only) (see Table 10-1). All safety labs will assessed by the Central lab, except for platelet counts, which should be done locally at all the visits where they are scheduled. In case of an AE that requires additional sampling and the Investigator needs to review the results to determine patient care, additional safety labs can be assessed by the local lab.

[i] The platelet measurement for eligibility must be taken within 96 hours of start of infusion. Platelet sample may be combined with safety labs if sample is taken at the same time. All scheduled platelet measurements must be sent to the local and central lab. If there is insufficient time to review the central lab results an additional local lab sample may be obtained in order to assess eligibility for infusion.

[j] Women of childbearing potential, only. Urine test on Day -1; serum test during Screening and on Day 29. Central lab should assess serum sample collected at screening and on final follow-up, but the local lab can assess the urine test on Day -1/Day 1 prior to the infusion.

[k] Duplicate samples for IgG should not be drawn if sample was already taken with safety labs collection.

[l] Duration of infusion is based on dosing instructions (details provided in the pharmacy manual). Patients will be required to drink 2 glasses of liquid in the morning before the start of infusion. Just before infusion, patients will be provided the opportunity to urinate. Patients receiving M254 can be discharged 4 hours post-infusion.

[m] If infusion duration is <20 minutes, end of infusion activities may be scheduled as logistically feasible with the PK sample drawn from 1 minute before the end of infusion to 2 minutes after the end of infusion. For infusion durations ≥20 minutes, activities should occur in the order of the table (top to bottom).

[n] All systemic infusion reactions and associated AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE).

[o] Patients with ITP may be admitted to the unit the morning of Day 1 instead of Day -1. Any procedure specified on Day -1 can occur on Day 1, but all results must be back before infusion begins. Likewise, any pre-infusion assessment specified on Day 1 can occur on Day -1 and does not need to be duplicated.

[p] Study staff should follow-up with the patient approximately 12 hours post-discharge for safety via phone call.

[q] Discharge from study after final study period unless further follow-up of open AEs is deemed necessary by the Investigator.

[r] M254 infusion will occur on this day if patient's platelet count meets criteria, and then the Schedule of Activities should be followed starting from whichever infusion the patient is scheduled for in Part D, ie, 2nd, 3rd, or 4th. Any assessments completed on the same date from the prior infusion period follow-up do not need to be duplicated.

[s] ITP-BAT to be completed at Day 1 prior to infusion.

[t] ECG and vital sign assessments required at the end of the infusion may be initiated 15 minutes prior to the end of infusion

[u] These should be conducted as abbreviated physical exams

[v] PK sample is required prior to the start of infusion (on the day of the infusion).

[w] Skip indicates that no assessments occur on these days.

[x] ADA samples are collected at each pre-infusion and the final follow-up visit. Please refer to the lab manual for specific instructions.

2 INTRODUCTION

2.1 Study Rationale

Intravenous immunoglobulin (IVIg) is a therapeutic blood product prepared from the pooled plasma of 3,000 to 60,000 healthy donors per batch [1, 3, 7]. It is a complex heterogeneous mixture of immunoglobulin (Ig) G subclasses and low amounts of immunoglobulin A (IgA), immunoglobulin M (IgM), and other plasma proteins [15]. Intravenous immunoglobulin contains a variety of antibodies present in human serum, and the large number of donors ensures diversity in the Ig repertoire that far exceeds that of an individual donor [13].

Intravenous immunoglobulin has been used for the treatment of a variety of acute and chronic autoimmune and systemic inflammatory diseases for decades [1, 3, 15, 13]. At the current maximal dosing regimens, only partial and transient responses are obtained in many clinical instances [3, 15]. In addition, the long infusion times (4 to 6 hours) associated with the high volume of IVIg treatment consume significant resources at infusion centers [6] and negatively affect patient-reported outcomes, such as convenience and quality of life [9]. M254 is expected to be many fold more potent compared to commercially available IVIg based on preclinical pharmacological experiments. This may lead to reduced infusion time for patients compared to commercially available IVIg. Hypersialylation may increase IVIg-related anti-inflammatory and immune-modulating activities.

Alterations in endogenous IgG sialylation have been reported to be associated with treatment response in inflammatory/autoimmune diseases [1, 4]. M254 is a hypersialylated immunoglobulin engineered from commercially available IVIg ([redacted]). M254 has demonstrated increased anti-inflammatory activity over IVIg in several animal models, including collagen antibody-induced arthritis and pemphigoid skin blistering [23], K/BxN – sera-induced arthritis model and an immune thrombocytopenia (ITP) mouse model [23]. These findings support the clinical development of M254 for ITP and (antibody-induced) inflammatory diseases.

Intravenous immunoglobulin is an approved therapy for the treatment of ITP with prompt increases in platelet counts as early as a day after treatment with peak platelet response occurring within 2 to 7 days. This known treatment effect with easily measurable pharmacodynamics (PD) endpoint of increasing platelet count makes ITP patients a suitable population for investigation of M254. The present 4-part (each part will be initiated sequentially), first in-human study will be conducted first in healthy subjects and subsequently in ITP patients to evaluate the safety, tolerability, pharmacokinetics (PK), and PD platelet response of M254 administered as single followed by multiple intravenous (IV) doses.

The study will be executed in 4 distinct parts. Part A (Netherlands only) will assess safety, tolerability, and PK of M254 after administration of a single ascending dose in healthy volunteers. Part B will assess safety, tolerability, and PK of M254 after administration of a single ascending dose followed by 1000 mg/kg IVIg administration in ITP patients. Part C will be a 2 arm, crossover design comparing the PD platelet response of M254 with IVIg in

patients with ITP. Part C will have 2 cohorts at M254 dose levels to be selected from Part A and Part B. Part D will be a repeat dose study of M254 for the evaluation of safety, tolerability, PK, and PD platelet response in patients with ITP.

2.2 Background

2.2.1 Disease Background

Primary ITP is an acquired autoimmune disorder affecting both children and adults, characterized by a platelet count below 100×10^9/L. The incidence of ITP in adults is around 4 per 100,000 people per year. Clinical manifestations include petechiae, purpura, bruising, and overt bleeding. Previously, 'acute ITP' was used to describe a self-limited form of disease and 'chronic ITP' thrombocytopenia described the disease if it lasted for more than 6 months. In 2009, new terminology for ITP was agreed upon based on the duration of the disease. The new terms for ITP are: 'newly diagnosed' (from diagnosis until 3 months), 'persistent ITP' (3 to 12 months) and 'chronic ITP' (ITP lasting for more than 12 months) [21, 20].

Bleeding is highly variable and there is great heterogeneity in primary ITP. Bleeding is most commonly mucocutaneous, involving gum bleeding, blood blisters in the mouth and menorrhagia. Major bleeding is not common if the platelet count is above 30×10^9/L. The most serious form of bleeding, intracranial hemorrhage, is rare and is most often seen in older patients who have additional comorbidities and in patients who fail to respond to therapy [20].

Diagnosis of ITP is mainly based on exclusion, when the history, physical examination, complete blood count (CBC) and examination of peripheral blood smear do not suggest other etiology for the thrombocytopenia. The low peripheral blood platelet count is caused by premature platelet destruction by self-reacting antibodies in addition to an impairment of platelet production. Autoantibodies reacting with glycoprotein (GP) IIb/IIIa may affect platelet aggregation; these are the most common autoantibodies seen in primary ITP [17].

The disease is heterogeneous in its pathophysiology, clinical features, and responses to treatment. To date, most of the treatments used have been immune-modulating drugs. Initial first-line treatment has remained unchanged for decades and comprises corticosteroids, IVIg, and less commonly anti-D in countries where the anti-D is available [18]. There have been several trials of IVIg in ITP since its first use in the mid-1980s. Intravenous immunoglobulins are sterile, purified IgG products manufactured from pooled human plasma and typically contain more than 95% unmodified IgG, which has intact fragment crystallizable (Fc)-dependent effector functions and only trace amounts of IgA or IgM. The recommended dose for commercially available approved IVIg is 1 g/kg (10 mL/kg) for 2 consecutive days. The response rate in ITP is similar to that of corticosteroids but the time to response is shorter, with a response normally seen within 24 hours although most are transient rarely exceeding 3 to 4 weeks. Toxicities include headache, renal impairment and thrombosis.

2.2.2 Background of Investigational Product, M254

M254 is a novel hypersialylated IgG therapeutic candidate derived from commercially available IVIg, with potentially greater potency when compared to IVIg. In M254, the IgG fraction containing sialic acids has been increased. The design of M254 is based on scientific evidence illustrating the relevance of glycosylation on immunoglobulin function. In particular, it has been shown that the anti-inflammatory activity of IVIg is dependent on Fc-sialylation [18, 5].

To generate M254, IVIg is exposed to a sequential enzymatic reaction CCI [redacted] For IVIg, the sum of the all the nonsialylated glycans is >80% and the sum of all sialylated glycans is <20% [11]. For M254, the CCI [redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of M254 is provided in the Investigator's Brochure [11].

2.2.3 Background of Study Product, [redacted]IVIg

[redacted] IVIg is commercially available. It is usually prepared from pooled plasma from not fewer than 1,000 donors. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range.

The mechanism of action in disease indications other than replacement therapy is not fully elucidated but includes immunomodulatory effects.

The safety and efficacy of IVIg was evaluated in 6 prospective, open-label, single-arm, multicenter studies performed in Europe (ITP [16, 19], primary immunodeficiency [PID] [16], and chronic inflammatory demyelinating polyneuropathy [CIDP] [16, 22, 10] studies) and the United States of America (USA) (PID [16] study). The safety and efficacy profile of IVIg can be found in the respective European Medicines Agency (EMA) and Food and Drug Administration (FDA) prescribing information [16, 2].

2.3 Benefit/Risk Assessment

M254 is predominantly a hyper-sialylated immunoglobulin (CCI [redacted] engineered from commercially available IVIg. This increase in sialyation was demonstrated to increase anti-autoimmune and anti-inflammatory activity in preclinical pharmacological experiments. M254 has been evaluated in preclinical pharmacology and nonclinical toxicology studies. Intravenous immunoglobulin is considered standard of care in multiple disease settings notably in ITP. This study has been designed to start with Part A (Netherlands only) where ascending single doses of M254 will be evaluated for safety and tolerability in healthy individuals with all doses of M254 lower than doses considered safe in nonclinical toxicological studies. In Part B, patients with ITP will be administered a dose of M254, which has expected minimum biological activity, escalating up to clinical efficacious doses of increasing platelet counts. Part C will evaluate efficacious

doses of M254 with crossover to standard of care IVIg. Patients in Part B and C will be assessed for the clinically relevant PD marker of increase in platelet count to identify dose to be evaluated in Part D.

It is expected that M254 will be biologically active at significantly lower doses compared to IVIg, so it is likely to shorten the infusion period without impacting expected efficacy when compared to IVIg in patients with ITP. All participants will be monitored for safety and tolerability as well as for efficacy (in parts with ITP patients) and only those ITP patients who are not at risk of life threatening bleeding with a platelet count $\geq 15 \times 10^9$/L will be selected.

Given the dose selection rationale described above, eligibility criteria, and active safety monitoring (including but not limited to platelet count assessment with potential of benefit of receiving same or more efficacious dose level), the study will not introduce unfavorable risk:benefit for the study participants.

For more detailed information on the potential risks and treatment of adverse events (AEs), please refer to the Investigator's Brochure [11].

3 OBJECTIVES AND ENDPOINTS

3.1 Part A (Netherlands only)

OBJECTIVES	ENDPOINTS
Primary	
• To assess the safety and tolerability of a single ascending dose of intravenous administration of M254 in healthy volunteers	• Incidence and severity of adverse events (AEs) following administration of M254 at single dose levels • Clinically significant changes in clinical safety labs, vital signs, and electrocardiograms (ECGs) with M254 administration
Secondary	
• To characterize the pharmacokinetics (PK) of a single intravenous administration of M254 at different doses in healthy volunteers	• Measurements of PK parameters of M254 following the administration of a single intravenous dose
Exploratory	
• To characterize the pharmacodynamics (PD) of a single intravenous administration of M254 at different doses in healthy volunteers	• Exploratory biomarkers relating M254 exposure to potential efficacy in autoimmune diseases and the M254 mechanism of action may be analyzed

3.2 Part B (USA sites included)

OBJECTIVES	ENDPOINTS
Primary	
• To assess the safety and tolerability of a single intravenous administration of M254 in immune thrombocytopenia (ITP) patients compared to 1000 mg/kg intravenous immunoglobulin (IVIg)	• Incidence and severity of adverse events (AEs) following administration of M254 at single dose levels and 1000 mg/kg IVIg • Clinically significant changes in clinical safety labs, vital signs, and electrocardiograms (ECGs) following M254 administration and 1000 mg/kg IVIg
Secondary	
• To characterize the pharmacokinetics (PK) of a single intravenous administration of M254 at different doses in ITP patients	• Measurements of PK parameters of M254 following the administration of a single intravenous dose
Exploratory	
• To characterize the pharmacodynamics (PD) of a single intravenous administration of M254 at different doses in ITP patients compared to IVIg	• Platelet response after M254 administration compared to IVIg • Exploratory biomarkers relating M254 exposure to potential efficacy in autoimmune diseases and the M254 mechanism of action may be analyzed

3.3 Part C (USA sites included)

OBJECTIVES	ENDPOINTS
Primary	
• To assess the safety of a single intravenous administration of M254 compared to 1000 mg/kg of intravenous immunoglobulin (IVIg) • To characterize the PD of single intravenous administration of M254 compared to 1000 mg/kg IVIg	• Incidence and severity of adverse events (AEs) of M254 and 1000 mg/kg IVIg • Clinically significant changes in clinical safety labs, vital signs, and electrocardiograms (ECGs) following M254 administration and 1000 mg/kg IVIg • Platelet response after M254 administration compared to IVIg
Secondary	
• To characterize the pharmacokinetics (PK) of a single intravenous administration of M254 at different doses	• Measurements of PK parameters of M254 following the administration of a single intravenous dose
Exploratory	
• To characterize the pharmacodynamics (PD) of single intravenous administration of M254 compared to 1000 mg/kg IVIg	• Exploratory biomarkers relating M254 exposure to potential efficacy in autoimmune diseases and the M254 mechanism of action may be analyzed

3.4 Part D (USA sites included)

OBJECTIVES	ENDPOINTS
Primary	
• To assess the safety and tolerability of repeated intravenous administration of M254 in immune thrombocytopenia (ITP) patients	• Incidence and severity of adverse events (AEs) with repeated administration of M254 • Clinically significant changes in clinical safety labs, vital signs, and electrocardiograms (ECGs) with M254 administration
Secondary	
• To characterize the pharmacokinetics (PK) of repeated intravenous doses of M254 in ITP patients • To assess pharmacodynamics (PD) of repeated intravenous doses of M254 in ITP patients	• Measurements of PK parameters of M254 following the administration of a repeated intravenous doses • Platelet response after repeated M254 administration

3.5 Hypothesis

No formal hypothesis testing will be used.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1/2, study investigating single and repeated administration of M254 in a 4-part design (Figure 1-1). The overall design of each part (A, B, C, and D) is summarized below. A Scientific Review Committee (SRC) will review safety data as described in each of the parts below. The SRC will consist of, at a minimum, a therapeutic expert in hematology, the Sponsor Medical Monitor, and a Sponsor Clinical Operations representative. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5. For all healthy volunteers and patients with ITP, a 28-day duration of safety monitoring following dosing of either M254 or IVIg has been selected based on nonclinical comparability of PK between M254 and IVIg, and clinical observations with IVIg where platelets return to baseline within 28 days [24]. M254 and IVIg doses in all cohorts will be administered at an IV infusion rate of CCI [redacted], which is less than infusion rates recommended for IVIg [16, 2], though the infusion rate may differ between cohorts. Doses in Parts C and D will be less than or equal to the maximum dose found previously tolerated. A table containing detailed information about infusion rate and duration

for each cohort is provided in the pharmacy manual. More information can also be found in Section 6.1.1.1.

For Parts B, C, and D of the study, during the post-discharge follow-up period, participants may have laboratory assessments, vital signs, electrocardiogram (ECG), and PK samples assessed at home or another location mutually agreed with the site, but can be seen by the study staff if complications arise or for participant comfortability.

Subject enrollment in the USA will begin with Part B of this study. No subjects from the USA will be enrolled in Part A.

4.1.1 Part A (Netherlands only)

Part A is a single-ascending-dose, randomized, double blinded sponsor unblind, safety, tolerability, and PK assessment of M254 or placebo in 6 cohorts of healthy volunteers. Planned doses include 3, 10, 30, 60, 120, and 250 mg/kg. In Cohort 1, 5 subjects will be enrolled with 3:2 (active:placebo) randomization. In all other cohorts, subjects will be randomized 3:1 (active:placebo) with total of 4 subjects in each cohort. There will be approximately 25 subjects in Part A. Up to 2 additional cohorts may be added based on findings in prior cohorts. Additional dosing cohorts may be added on the recommendation of the SRC.

Following screening to confirm eligibility to participate, subjects will be randomized to receive M254 or placebo. Please refer to Section 4.3.1 and Figure 1-2 for dosing details.

At the first dose level (3 mg/kg), a sentinel group of 2 subjects (1 M254, 1 placebo) will be dosed and closely monitored for 48 hours before dosing the remainder of the cohort (2 M254, 1 placebo). The subjects in this sentinel group will be closely observed by the Investigator for any safety signals for the first 48 hours following drug administration. The general tolerability of the study drug will be monitored during this time and the ECG recordings and vital signs data will be reviewed. In addition, any reported AEs will be considered by the Investigator. If the safety and tolerability results of the first 48 hours following dosing for the initial subjects are acceptable to the Investigator, the other subjects of Cohort 1 of Part A may be dosed. There will be no additional sentinel groups in the study beyond this cohort (Cohort 1 Part A)

Safety assessments will be conducted out to Day 28 post M254 dosing. The SRC will review all available safety data after each cohort has completed at least 10 days of assessments after the single dose of M254. Dose escalation will only proceed after the recommendation of the SRC.

The SRC will review all safety data for all subjects in Part A out to Day 28. Cohorts in Part B may start before the completion of Part A; however, prior to initiation of any cohort in Part B, either the same or a higher dose level will have been given in Part A and have a positive recommendation by the SRC, with the exception of doses greater than 250 mg/kg.

Dose escalation and continuation to the next study part may only occur when the SRC has given a positive recommendation and the Ethical Committee has given a statement of no objection, as per local requirement (where required).

Blood for safety labs and PK will be collected as defined in the Schedule of Activities (Table 1-1).

4.1.2 Part B (USA sites included)

Initiation of any cohort in Part B will only proceed on the recommendation of the SRC after safety data from Part A Cohort 4 at the 60-mg/kg dose level has been reviewed and confirmed by SRC.

Part B is a single-ascending-dose, fixed-sequence, open-label part to assess safety, tolerability, PK, and PD of M254 followed by 1000 mg/kg IVIg in approximately 4 cohorts of 2 ITP patients per cohort. Planned doses include 60, 120, 250, and 500 mg/kg. Up to 2 additional cohorts may be added based on findings in prior cohorts to better understand the safety of M254 and/or to better understand the efficacy to assist with dose selection for Part C. The maximum dose for Part B will not exceed 500 mg/kg. (The no-observed-adverse-event-level [NOAEL] of 1000 mg/kg was determined in the toxicology study in cynomolgus monkeys.) Additional patients to dosing cohorts may be added on the recommendation of the SRC.

Following screening to confirm eligibility to participate, patients will be dosed with M254. Please refer to Section 4.3.1 and Figure 1-3 for dosing details. There will be a 14-day safety monitoring period between enrollment of the first and second patients in the 500 mg/kg cohort.

Safety and platelet assessments will be conducted initially out to Day 28 post M254 administration. Patients will receive a fixed dose of IVIg at 1000 mg/kg on Day 29 if the patients' platelet count returns to ≤15% above baseline level. Patients whose platelets have not returned to ≤15% above baseline dosing level by Day 28 will have platelet determinations weekly until platelets return to ≤15% above baseline, up to 56 days postdose. If these conditions are not met by Day 57, IVIg will be administered, as long as the patients' platelets have returned to $<50 \times 10^9$/L. If the platelets have not returned to ≤15% above baseline and are $\geq 50 \times 10^9$/L, the patient will complete Follow-Up assessments and be discharged from Part B. After dosing with IVIg, safety and the other assessments listed in the Schedule of Activities will be conducted for 28 days following IVIg administration.

The SRC will review all available safety data after each cohort has completed at least 10 days of assessments after the single dose of M254. Dose escalation will only proceed on the recommendation of the SRC after review of the safety data for each cohort (see Section 6.6). If 1 of the 2 ITP patients experiences any dose-limiting toxicity (DLT), the cohort will be repeated with 2 additional ITP patients either at the same or lower dose per the recommendation of the SRC. If at a given dose level, 2 patients (either 2 of 2 or 2 of 4) experience a DLT, that dose level will not be repeated, though a lower dose may be selected by the SRC.

The SRC will review all safety data for all patients in Part B up to at least 28 days following M254 administration for the last patient. Initiation to Part C will only proceed on the recommendation of the SRC. Dose escalation and continuation to the next study part may only occur when the SRC has given a positive recommendation and the Ethical Committee has given a statement of no objection, as per local requirement (where required).

Blood for safety labs, PK, and PD will be collected as defined in the Schedule of Activities (Table 1-2).

4.1.3 Part C (including sites within the USA)

Part C consists of 2 randomized, unblinded crossover cohorts to assess safety and PD of a single dose of M254 compared to a single dose of IVIg in ITP patients. The dose of M254 for each of these 2 cohorts will be determined after analysis of the data from Part A and Part B. Each cohort consists of 10 patients with 2 arms in each cohort consisting of 5 patients in each arm, for an overall total of 20 patients in Part C.

Following screening to confirm eligibility to participate, in crossover Cohort 1 or Cohort 2, 5 patients in each cohort will be randomized to M254 by IV administration and 5 patients will be randomized to 1000 mg/kg IVIg. Please refer to Section 4.3.1 and Figure 1-4 for dosing details.

Safety and platelet assessments will be conducted initially out to Day 28 post M254 or IVIg administration. Patients will receive their dose of either M254 or IVIg, depending on their assigned arm within the cohort, on Day 29 if the patients' platelet count returns to ≤15% above baseline level. Patients whose platelets have not returned to ≤15% above baseline dosing level by Day 28 will have platelet determinations weekly until platelets return to ≤15% above baseline up to 56 days post the first M254 or IVIg administration. Patients who do not meet this criteria will receive the second administration of M254 or IVIg, as long as the platelets have returned to $<50 \times 10^9$/L. If the platelets have not returned to ≤15% above baseline and are $\geq 50 \times 10^9$/L, the patient will complete Follow-Up assessments on or around Day 57 post first infusion and be discharged from Part C; and the patient may be replaced. After patients are crossed over to the second administration of M254 or IVIg, they are followed for an additional 28 days with safety and platelet assessments or until platelet counts return to ≤15% above their baseline level following similar rules to the first dose in Part C.

The SRC will review all safety data from both crossover cohorts in Part C; however, the initiation of Part D will proceed after the SRC reviews all safety data from Cohort 1 and the recommendation is to proceed with Part D. Dose escalation and continuation to the next study part may only occur when the SRC has given a positive recommendation and the Ethical Committee has given a statement of no objection, as per local requirement (where required).

Blood for safety labs, PK, and PD will be collected as defined in the Schedule of Activities (Table 1-3).

4.1.4 Part D (USA sites included)

Part D is a repeated, fixed-dose, open-label study of M254. Any patients who participate in Parts B or C are allowed to participate in Part D if they meet inclusion criteria during screening for Part D. Part D may have up to 2 dose levels with up to approximately 15 to 34 ITP patients in total. The initial dose level for Part D will be less than or equal to the maximum tolerated dose, and it will be selected based on review of Part B data and available data from Part C. Following completion of Part C, the dose for new patients in Part D may be revised (the dose level will not be modified for patients who have already received at least 1 dose). Patients who have participated in Part B or C may be allowed to participate in Part D, prior to completion of randomization in Part C. New patients not in Part B or C may participate in Part D following complete randomization in Part C. The dose levels of M254 for Part D will be determined after analysis of available data from Part A, Part B, and Part C.

Following screening to confirm eligibility to participate (including rescreening patients who participated in Part B or C), M254 naïve patients will receive 4 doses of M254, and patients from Part B or C will receive 3 doses of M254 every 14 days. Patients in Part C may roll over into Part D by including any data after the last dose of IVIg or M254 in Part C for assessment of screening in Part D as long as those data are within the screening window specified. Please refer to Section 4.3.1 and Figure 1-5 for dosing details.

If the patient's platelet count has not returned to $\leq 100 \times 10^9$/L, their platelet count will be monitored weekly until platelets return to $\leq 100 \times 10^9$/L. If these conditions are not met, M254 will not be administered further. Patients will be followed for safety assessments and platelet counts up to at least 28 days post their last dose of M254. Safety will be reviewed by the SRC quarterly (or more often as required).

Blood for safety labs, PK, and PD will be collected as defined in the Schedule of Activities (Table 1-4).

4.1.5 Study Duration for Participants

The total duration of study participation for each cohort in Part A will be up to 8 weeks; up to 4 weeks for screening and 4 weeks observation and follow-up. The total duration of participation in Parts B and C will be 12 to 20 weeks: up to 4 weeks for screening and 4 to 8 weeks for M254 period and 4 to 8 weeks for IVIg period based on platelet measurements returning to baseline as described above. The total duration of study participation in Part D will be 12 to 14 weeks: 4 weeks for screening and 8 (patients from Parts B or C) or 10 (M254-naïve patients) weeks observation and follow-up.

4.1.6 Number of Participants

In Part A (Netherlands only), approximately 25 healthy volunteers will be included, 18 subjects will receive M254 and 7 will receive placebo. In Part B, up to approximately 20 patients will receive 1 dose of M254 and 1 dose of IVIg (2 each in 4 planned cohorts; 2 each in 2 optional cohorts; and 8 in optional expansions of existing cohorts). In Part C, 20 patients will receive a dose of M254 and IVIg. In Part D, up to approximately 15 to

34 patients will receive repeated doses of M254. Patients from Part B and C can continue to Part D. In total for Parts B, C, and D, there will be up to 74 patients who will receive at least 1 dose of M254 or IVIg.

4.1.7 Replacement of Participants

In this study, participants may be replaced in the Parts A, B, or C if they discontinue study treatment prior to completing the protocol defined safety observation period in absence of treatment-related toxicity.

4.1.8 Number of Sites

For Part A there will be 1 site in the Netherlands. Up to approximately 40 additional sites may be added for Parts B, C, and D.

4.2 Scientific Rationale for Study Design

The initial dose of M254 3 mg/kg in Part A given for the first time in adults is designed to provide a sentinel dose to assess initial safety and tolerability.

The subsequent doses of M254 in Part A Cohort 1 and increased doses in Parts A, B, C, and D is designed based on expected efficacious doses in adults.

4.3 Justification for Dose

4.3.1 Justification for M254 Dose

Doses are selected for safety, to allow for minimal biological activity for the starting dose, to reach the lower end of the potential efficacious dose range for the top dose in Part A, and to span the potential efficacious dose range for the top dose in Part B. Doses in Parts C and D will be determined based on safety and efficacy observed in the study to date. Doses will not exceed the NOAEL of 1000 mg/kg determined in the toxicology study in cynomolgus monkeys.

The initially planned dose levels for Part A are 3, 10, 30, 60, 120, and 250 mg/kg of M254 administered intravenously. The NOAEL (1000 mg/kg) as determined in preclinical toxicology studies is 4-fold higher than the highest dosing level in healthy volunteers. The starting dose is 330-fold below the NOAEL in cynomolgus monkeys and approximately 30-fold below the dose anticipated to potentially provide efficacy in patients with ITP. The maximum dose represents a dose expected to be efficacious in patients.

The initially-planned M254 dose levels for Part B are: 60, 120, 250, and 500 mg/kg administered intravenously. The starting dose will be less than or equal to a dose previously found tolerated in Part A, and the maximum dose will not exceed 500 mg/kg. A higher safety margin could not be evaluated in preclinical studies due to dosing volume limitations, so the maximum repeat-dose level tested (1000 mg/kg) was set as the NOAEL.

The M254 doses for Part C will be determined following analysis of data from Parts A and B.

The M254 dose for Part D will be determined following review of available data from Parts A, B, and C.

Doses may be adjusted from the planned doses without exceeding limits defined in Section 6.7.2 and without exceeding a dose previously found not to be tolerated.

4.3.2 Justification for IVIg Dose

The IVIg dose administered in Parts B and C will be 1000 mg/kg. It was selected based on the approved and commonly used dose level of IVIg for the treatment of ITP [16, 2, 14].

4.4 End of Study

4.4.1 End of Study Definition

End of Study (Individual Participant): A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

Primary Completion: The primary completion date is defined as the date when the last participant is assessed or receives an intervention for the final collection of data for the primary endpoint(s) for the purposes of conducting the primary analysis (ie, Part C, Cohort 1).

End of Study (End of trial): The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

4.5 Patient Input on Study Design

Subject input was not obtained while designing this protocol.

5 STUDY POPULATION

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 1).

Eligibility criteria will be evaluated during screening. For patients continuing from Part C to Part D, the most recent available assessments that are both after the last dose of M254 or IVIg in Part C, Period 2 and within the screening interval for Part D (as defined in the Schedule of Activities, Section 1.2) may be used for screening into Part D.

5.1 Eligibility Criteria for Healthy Volunteers (Netherlands only)

5.1.1 Inclusion Criteria for Healthy Volunteers

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

1. Participant must be ≥18 and ≤55 years of age inclusive, at the time of signing the informed consent form (ICF).
2. Good health as indicated by medical history (without hemolysis or thrombosis that may impact current study), physical examination, vital signs (with systolic blood pressure below 140 mmHg), clinical laboratory tests, and 12-lead ECG, and all abnormal findings are assessed as not clinically significant by the Investigator.
3. Body weight must be between 50 and 110 kg, inclusive, and body mass index (BMI) between 18.5 and 30 kg/m^2, inclusive, at screening.
4. Healthy male and females are eligible.
   a. Male participants:
      - If male, surgically or biologically sterile. If not sterile, agreement to use an acceptable form of birth control with sexual partner (as described in Appendix 4) or abstain from sexual relations for 100 days following the last treatment.

   b. Female participants:
      - A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least 1 of the following conditions applies:
        - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (surgically sterilized via hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or of nonchildbearing potential (ie, postmenopausal for at least 1 year).

      OR

        - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 90 days after the last dose of study intervention.

      - Of childbearing potential, with a fertile male sexual partner, willing to use 2 adequate methods of contraception from 30 days prior to dosing until 90 days after the last dose of study treatment. Adequate contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.
5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

6. Ability to speak, read, and understand primary medical care language(s) at the site.
7. If female, a negative serum pregnancy test at screening and a negative urine or serum pregnancy test at check-in to the clinic for the baseline visit, and not nursing or planning a pregnancy through 90 days following the last dose of study medication.

5.1.2 Exclusion Criteria for Healthy Volunteers

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

1. Previously received M254.
2. History of any drug allergy, hypersensitivity, or intolerance to any drug product that in the opinion of the Investigator would place the subject at particular risk and compromise the safety of the subject in the study.
3. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, psychiatric disease, or any other condition, that in the opinion of the Investigator would jeopardize the safety of the subject or the validity of the study results.
4. History of splenectomy, asthma (with the exception of childhood asthma that has resolved), chronic obstructive pulmonary disease, or recurrent or current gastrointestinal or respiratory infections.
5. Any illness within 5 days, or clinically significant airway infections within 30 days, prior to first study drug dosing.
6. On fluid restriction.
7. Any prescription medication(s) within 14 days of dose administration (or 5 half-lives, whichever is longer) or any nonprescribed systemic or topical medication (including any herbal product) within 7 days prior to dose administration.
8. Plans to participate in another clinical trial while enrolled in this study and/or received an investigational drug and/or device within 60 days prior to dose administration.
9. Positive urine drug screen at screening.
10. Positivity for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) at screening.
11. History or current diagnosis of substance dependence (except nicotine and caffeine) or alcohol abuse over the past 2 years, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR).
12. Smokes or has smoked more than 5 cigarettes per day in the last 90 days and is unable to stop smoking during in-patient observation period in clinic.
13. Unwilling to abstain from alcohol for at least 24 hours prior to dosing with study medication until the time of discharge from the study unit and at least 24 hours prior to each ambulatory visit.
14. Donation or significant loss of whole blood (480 mL or more) within 30 days or plasma within 14 days prior to admission.

15. Vaccination within 1 month before dosing, or plans to receive vaccination within 3 months after the last dose.
16. Veins unsuitable for cannulation or multiple venipunctures on either arm.
17. Patients with any prior history of arterial or venous thrombosis, AND ≥2 of the following risk factors: hormone replacement therapy, systemic contraception (containing estrogen), smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilic disorders (eg, Factor V Leiden, antithrombin III deficiency, antiphospholipid syndrome, etc), hyperviscosity (cryoglobulines and chylomicronemia)
18. Patients with selective IgA deficiency with known anti-IgA antibodies.

5.2 Eligibility Criteria for ITP Patients

5.2.1 Inclusion Criteria for ITP Patients (USA sites included)

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

1. Participant must be 18 years of age or greater at the time of signing the ICF.
2. Diagnosed with primary ITP (with or without splenectomy) according to the Hematology Guidelines for at least 3 months prior to screening.
3. Must have received at least 1 prior treatment for ITP

   NOTE: if received prior treatment with IVIg, and if known from medical history, must have responded as defined by an increase of platelet count above 50×10^9/L within 14 days of IVIg treatment.
4. Platelet count $\geq 15 \times 10^9$/L and $< 50 \times 10^9$/L within 96 hours prior to start of study drug infusion on Day 1.
5. Body weight must be within a range that allows for the planned M254 infusion time to be completed in ≤4 hours. Please refer to the infusion rate schedule in the Infusion Manual and Section 6.1.1.1.M254
6. Maintenance immunosuppressive therapy, steroid therapy, cyclosporine A, mycophenolate mofetil, azathioprine, thrombopoietin receptor agonists, or danazol are allowed, but the dosages of all these medications must be stable for at least 4 weeks prior to Visit 1 (Day 1).
7. No history of clotting disorder other than ITP including no myocardial infarction within the last 6 months. No arrhythmia known to increase the risk of thrombotic events (eg, atrial fibrillation).
8. Male and females are eligible.
   a. Male participants:
      - If male, surgically or biologically sterile. If not sterile, agreement to use an acceptable form of birth control with sexual partner (as described in Appendix 4) for 2 weeks prior to administration of study medication, during study treatment, and for 100 days following the last treatment (ie, study

completion or premature discontinuation from the study), or abstain from sexual relations for the same duration.

b. Female participants:

- A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least 1 of the following conditions applies:
  - Not a WOCBP as defined in Appendix 4 (surgically sterilized via hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or of nonchildbearing potential (ie, postmenopausal for at least 1 year).

  OR

  - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 90 days after the last dose of study intervention (ie, study completion or premature discontinuation from the study).
- Of childbearing potential, with a fertile male sexual partner, willing to use 2 adequate methods of contraception for 2 weeks prior to administration of study medication, during study treatment, and for 90 days following the last treatment (ie, study completion or premature discontinuation from the study). Adequate contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.

9. If female, a negative serum pregnancy test at screening and a negative urine pregnancy test at check-in to the clinic for the baseline visit, and not nursing or planning a pregnancy through 90 days following the last dose of study medication.
10. Subject is capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
11. Prothrombin time (PT) and activated partial thromboplastin time ≤1.4-fold above the upper limit of normal.

5.2.2 Exclusion Criteria for ITP Patients (USA sites included)

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

1. Patients with any prior history of arterial or venous thrombosis, AND ≥2 of the following risk factors: hormone replacement therapy, systemic contraception (containing estrogen), smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilic disorders (eg, Factor V Leiden, antithrombin III deficiency, antiphospholipid syndrome, etc), hyperviscosity (cryoglobulines and chylomicronemia)

2. Any clinically relevant abnormality, other than ITP, which in the opinion of the Investigator makes the patient unsuitable for participation in the study.
3. Female patients who are nursing or pregnant at screening or predose on Day 1.
4. History of alcohol/drug abuse or dependence within 12 months of the study.
5. Rituximab within 3 months of screening.
6. Patient has consumed aspirin, aspirin-containing compounds, salicylates, anticoagulants, quinine or nonsteroidal anti-inflammatories (NSAIDs) for >3 consecutive days within 2 weeks of the study start and until the end of the study.
7. Consumption of any herbal or dietary supplements, excluding vitamin or mineral supplements, within 1 week of the study start.
8. History of platelet agglutination that prevents reliable measurement of platelet counts.
9. Any laboratory or clinical evidence for HIV infection.
10. Any clinical history for hepatitis C infection, chronic hepatitis B infection, or any evidence for active hepatitis at the time of patient screening. Laboratory test shows positive serology for hepatitis C or hepatitis B defined as a positive test for HBsAg. Patients who have been treated for HCV and demonstrate a negative serum HCV RNA level at 12 weeks or longer after the completion of HCV therapy may be included in the study after consultation with the Medical Monitor.
11. Patients with known history of chronic kidney disease.
12. Patients with primary immunodeficiency.
13. Patients with selective IgA deficiency with known anti-IgA antibodies.
14. Patients who have had an anaphylactic or severe systemic reaction to the administration of human immunoglobulins.
15. Patients with hyperprolinaemia Type I or II or hypersensitivity to proline in Parts B and C only as CCI will be administered.
16. Patients with a history of myocardial infarction, ischemic stroke, pulmonary embolism and deep vein thrombosis within 6 months.
17. Patients with a history of hemorrhagic stroke.
18. Patients expected to require rescue on Day 1 of the study.
19. Patients with severe or clinically significant bleeding (eg, Grade 3 for skin, ≥ Grade 2 for mucosal domains, or ≥ Grade 1 for organ domain) using the ITP bleeding assessment tool (ITP-BAT).
20. Patients taking thrombopoietin receptor agonist AND have albumin ≤35 g/L.

5.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening. See Section 10.1.3 for Informed Consent Process details.

6 STUDY INTERVENTION

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

Refer to the Investigator's Brochure for more detailed information regarding the storage, preparation, destruction, and administration of each treatment.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

M254 will be supplied to the study site by Momenta or its agent for dosing by IV administration. Details of dose preparation will be provided in the Pharmacy Manual.

All participants will receive study drug as an IV infusion. A peripheral IV catheter will be inserted before dosing for administration of study drug. M254 is administered by IV infusion at a rate of up to a maximum of [redacted] (see Section 6.1.1.1 for more details).

Subjects and patients should be hydrated prior to the start of infusion with approximately 2 glasses of liquid to avoid a possible thromboembolic event. Additionally, subjects and patients should be mobilized immediately following the end of infusion to decrease the risk of thromboembolic events.

The date, time, and volume of administration of all doses are to be recorded.

For Part A, the placebo to be used is commercially available Glucose 5% solution for injection.

For Part B and C, [redacted] IVIg will be supplied to the study site by Momenta or its agent for dosing by IV administration. IVIg is a liquid solution administered via IV infusion. Additional information on dosage and administration can be found in the [redacted]

6.1.1.1 M254 and IVIg Infusion Rate

M254 and IVIg is administered by IV infusion at a rate of up to a maximum of [redacted], whichever is lower ([redacted] is less than infusion rates recommended for

IVIg). After completion of the infusion, the IV line should be flushed with approximately 50 mL of 5% dextrose in water (D5W) within 10 minutes of completion of the infusion to ensure that the entire intended dose of drug product has been infused and none is retained in the IV tubing; other methods for ensuring accurate dosing may be used upon agreement of the Sponsor. Additional dosing information is provided in the study Infusion Manual.

The initially-planned infusion rate schedule is described in Table 6-1; the infusion rate and duration at an infusion rate may be increased or decreased as part of the dose escalation decision with the restriction that it may not be >4 mg/kg/min.

Table 6-1. M254 and IVIg Infusion Rate

Start Time (minutes relative to Infusion Start)	End Time (minutes relative to Infusion Start)	Infusion Rate (mg/kg/minute)
0	30	0.5
30	60	1
60	90	2
90	360	4

Two specific examples of implementing the above infusion rate table for the CCI rate are:

- CCI

6.1.2 Non-investigational Products

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Study Drug Packaging and Storage

Study drugs must be stored in a secure area (eg, a locked refrigerator or locked cabinet within a refrigerator), protected from moisture and light, and be stored at CCI CCI Further instructions regarding storage and handling, dose preparation, and administration of study drugs are detailed in the Pharmacy Manual.

6.2.2 Study Drug Accountability

In accordance with Good Clinical Practices (GCP), each study site will account for all study drug supplies. The pharmacy will maintain accurate records, including information regarding the receipt and subject administration of all test articles. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled. Drug will be retained and returned to the drug distribution center. Destruction at site may be considered per site standard operating procedures (SOPs) and approval of the Sponsor. The arrangement for destruction must be communicated to the Sponsor or delegated contract research organization (CRO). Refer to the Pharmacy Manual for further information.

6.3 Measures to Minimize Bias: Randomization and Blinding

Part A is double-blind, sponsor open; subjects and the Investigator will be blinded to individual subjects' treatment throughout this part. The sponsor will be unblinded throughout this part (and throughout the study). Specified individuals at the Investigator site (such as the unblinded pharmacist) will be unblinded throughout this part (and throughout the study). When interacting with the Investigator or site personnel, the sponsor will maintain care in the communication not to unblind.

Parts B, C, and D are open-label investigations; patients and Investigators will not be blinded throughout these parts of the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that dispensing has been done accurately.

A randomization schema will be developed for Part A and Part C and managed by the pharmacy at PRA in Netherlands for the study. The process will be described in detail in the applicable study plan.

6.4 Study Intervention Compliance

Administration of each IV infusion of study drug and all assessments will be performed by qualified personnel under the direction of the Investigator. Clinic personnel will confirm that study drug was administered and record start and end time of each infusion. Deviation(s) from the prescribed dosage regimen will be recorded in the electronic case report form (eCRF).

6.5 Concomitant Therapy

Subjects participating in the study should avoid concomitant administration of any new medications other than antihistamine or acetaminophen (or corticosteroids for moderately severe acute reactions) during the course of the study, except as prescribed for newly-emerging AEs. Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) throughout the study, unless, in the opinion of the Investigator and sponsor, the medication will not interfere with the study.

Premedication should not be administered systematically. If a patient develops an infusion reaction related to the M254 or IVIg infusion, standard management should be applied (see the Infusion Manual for detail).

During the study subjects should remain on the dose of the ITP medications they were on at screening.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the subject's eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
-

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6 Dose-Cohort Study Escalation Rules

In this study, Parts A and B are dose-escalating; Parts C and D are not dose-escalating.

A dose escalation report (DER) will be provided by the Investigator to the Independent Ethics Committee (IEC) (where required) following completion of each dose level. The SRC will approve escalation to the next dose only if none of the stopping criteria have been reached, the safety and tolerability (and PD for Part B) out to Day 10 are acceptable, and there are no concerns regarding delayed significant AEs in earlier cohorts.

The minimum number of participants required to decide on dose escalation is 2 participants on active treatment (ie, a total of at least 3 subjects in Part A at all dose levels; and 2 patients in Part B); in Part B for dose levels precedented as tolerated with safety reviewed in Part A, only 1 subject is required for dose escalation though 2 will remain planned for the cohort.

Based on absence of significant toxicity in the Good Laboratory Practice (GLP) toxicity studies, escalation to the next higher dose will be up to approximately CCI . Based on emerging safety data (and PD data in Part B), lower or other intermediate dose(s) may be used, for instance when anticipated that after a planned dose escalation stopping criteria will be met. Pharmacokinetic data is not deemed necessary for dose escalation since IV dosing of this modified IgG has predictive exposures (100% bioavailability, volume of distribution [Vd] and clearance expected to be similar to endogenous IgG). There are no significant toxicity findings in the preclinical studies, and the maximum exposure in healthy volunteers is expected to remain well below exposures of the high dose (1000 mg/kg) used in GLP toxicity studies. In patients the maximum exposure is not expected to be above the high dose (1000 mg/kg) used in GLP toxicity studies.

A more conventional 3+3 escalation design was considered but not employed in this study. A notable difference between the expectation of the design in the current study with 2 patients compared to a 3+3 design in literature is how the dose is used in the future. In the current study, CCI [redacted] In a more conventional 3+3 design, a dose that triggers the 3+3 rule would be considered **tolerable**, and would be used for future study.

6.7 Stopping Rules

6.7.1 Dose-Cohort Study Stopping Rules

Dosing within a cohort and dose escalation to a next cohort will be halted pending evaluation by Sponsor and SRC recommendation if 1 of the following circumstances occurs and it is determined by the Investigator that the occurrence is possibly related to the administration of study drug:

- A serious adverse reaction (ie, a SAE considered at least possibly related to the study drug administration) in 1 subject.
- Grade 3 or higher AE per National Cancer Institute (NCI) CTCAE version 5.0 criteria (ie, severe nonserious AEs considered at least possibly related to the study drug administration) in 2 participants in the same cohort, or in 1 subject in the sentinel cohort.
- Grade 4 or higher grade AE per NCI CTCAE version 5.0 criteria.
- Other findings that, at the discretion of the Investigator in consultation with Sponsor's Medical Monitor and SRC recommendation, indicate that further dosing should be stopped.

When stopping rules for a cohort are met, the randomization code for participants meeting the stopping rules will be unblinded. If after de-blinding it is concluded that participants on active medication meet the stopping rules, dosing in the cohort will be stopped and no further dose escalation will be performed.

6.7.2 Dose Limiting Toxicities

Dose-limiting toxicities will include any NCI CTCAE v.5 Grade 3 or higher adverse reaction occurring within 4 weeks following the administration of M254.

Note: Events considered by the sponsor as clearly unrelated to the study drug will not be considered a DLT, eg, thrombocytopenia related to ITP, accidents, and lab results attributed to other therapies or illnesses.

6.7.3 Rules for Dosing Adjustments, Withholding or Restarting, Permanent Discontinuation

Unless participant safety precludes doing so, the Medical Monitor should be consulted prior to stopping or modifying the dosing schedule of study drug.

If more than 1 subject or patient with CTCAE Grade 3 or 4, not reasonably related to an alternative etiology (eg, motor vehicle accident-related injury or gunshot wound) the sponsor will discuss already collected data from the healthy subjects in Part A prior to discontinuation for the Part A (if already more than 1 dose level has been evaluated prior to the Part A being discontinued) with the Investigators and may modify other parts of the study as needed.

If 1 of the 2 ITP patients in Part B experiences any DLT, the cohort may be repeated with 2 additional ITP patients either at the same or lower dose per the recommendation of the SRC. If at a given dose level, 2 patients (either 2 of 2 or 2 of 4) experience a DLT that dose level will not be repeated, though a lower dose may be selected by the SRC.

6.7.4 Study Stopping Rules

Dosing in the study will be halted pending evaluation by Sponsor and SRC recommendation if one of the following circumstances occurs:

- Grade 5 AE considered related to study treatment, in which case the review process will also include regulatory agencies and IRBs/Ethics Committees
- The following Grade 3 or greater treatment-related AE in 2 or more patients:
  - thromboembolic AE
  - renal impairment AE
  - hemolysis AE
  - creatinine elevation

NOTE: Events that are definitely not related to study treatment (eg, accidents or other external causes) will not trigger study-stopping rules.

6.8 Intervention After the End of the Study

There is no intervention planned after participants complete the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

In accordance with the Declaration of Helsinki, International Council for Harmonisation (ICH) GCP Guidelines, and the US FDA Regulations, a research subject has the right to withdraw at any time for any reason without prejudice to future medical care. However, in the absence of a medical contraindication, the Investigator should encourage the subject to remain in the study and, at a minimum, follow the subject for safety data collection.

The Sponsor and Investigator also have the right to withdraw participants. Subjects or patients may be discontinued from study treatment if they experience intolerable toxicity related to any study treatment despite dose reduction, or for any of the following reasons:

- Withdrawal of subject informed consent
- AE
- Significant noncompliance with protocol requirements
- Need for prohibited therapy
- Termination of the study
- Any other reason which, in the opinion of the Investigator or Sponsor, would justify the subject's removal
- Subject lost to follow-up

All reasons for early termination or withdrawal will be documented in the eCRF.

The Sponsor and the Investigator may decide to halt dosing for safety reasons, including emerging nonclinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns.

Termination of the study by the Sponsor may take place upon written notice to PRA Netherlands for the following reasons: 1) if the Ethics Committee irrevocably revokes approval for the study; 2) if it is necessary to protect the safety, health, or welfare of participants; 3) if it transpires that continuation of the study cannot serve any scientific purpose, and this is confirmed by the Ethics Committee; 4) if conducting the study becomes prohibitive by law, rule, regulation, or any amendment thereof; or 5) if the Investigator is no longer capable of performing the tasks of the Investigator, and no replacement agreeable to both parties can be found.

7.2 Discontinuation/Withdrawal From the Study

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

An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Any treatment-related Grade 3 or higher AE per NCI CTCAE version 5.0 criteria
- Pregnancy (see Appendix 4 and Section 8.4.5)
- If in the opinion of the Investigator, patient with ITP is not responding adequately or for adequate duration in Part D (ie, no platelet count increase from baseline or return to

baseline within 1 weeks), subject should be discontinued from the study to timely administer treatment per local standard of care.

- Protocol deviation
  - Noncompliance to intervention
  - Requires treatment not allowed in the protocol for disease flare
  - If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Sponsor decision
- Participant request to discontinue study intervention

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Activities (Section 1.2). See activities for the final follow-up to be performed.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

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

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8 STUDY ASSESSMENTS AND PROCEDURES

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.2), is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

All patients must personally sign and date the IRB/IEC approved informed consent before any study-specific procedure can be performed. All screening evaluations (see Schedule of Activities [Section 1.2]) must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. During screening, a complete medical history will be obtained from each subject/patient. Demographic data will also be collected in order to examine their possible association with patient safety and treatment effectiveness during initial screening.

Screening in Part B will proceed only when all single ascending dose cohorts in healthy volunteers up to 60 mg/kg have been reviewed for safety by the SRC, and if according to the Investigator and SRC, an interim summary of all safety data from Part A, through the 60 mg/kg cohort, concludes that the anticipated exposure in the first cohort of Part B does not impose unnecessary risk. The interim summary will be sent to the IEC, where required.

The SRC will review all safety data for all patients in Part B up to at least 28 days following M254 administration for the last patient. Initiation to Part C will only proceed on the recommendation of the SRC.

The SRC will review all safety data from both crossover cohorts in Part C; however, the initiation of Part D will proceed after the SRC reviews all safety database from Cohort 1 and the recommendation is to proceed with Part D with approval of the Investigator.

8.1.2 Treatment Period

Individual study assessments are presented in Schedule of Activities (Section 1.2). Where possible, a window for each study visit is described in the Schedule of Activities. Visit windows noted in the Schedule of Activities apply throughout all sections of the protocol. Subjects and patients should remain with a similar level of physical activity during the study and not initiate new or strenuous exercise from randomization to the final follow-up. Subjects and patients should be hydrated prior to the start of infusion with approximately 2 glasses of liquid to avoid a possible thromboembolic event. Additionally, subjects and patients should

be mobilized immediately following the end of infusion to decrease the risk of thromboembolic events.

If 1 assessment in a series is missed, "not done" should be recorded in the clinic record and eCRF. The original schedule for postdose sample collection will be adhered to rather than adjusting the postdose scheduling from the point of the missed sample.

All collected data will be attributed to the closest nominal/scheduled time point for analysis; unscheduled assessments will be collected separately. The Sponsor does accept any institution-specific time allowances that are documented as part of the local standard operating procedures.

8.1.3 Follow-up

A follow-up visit will be completed 29 ± 2 days after the last dose of study drug for Parts A, B, and C. For Part D, the follow-up visit will be completed 71 ± 3 days (M254 naïve patients) or 57 ± 3 days (Part B/C patients). Refer to the Schedule of Activities (Section 1.2) for required procedures during this visit.

8.2 Efficacy Assessments

Efficacy endpoints are based on platelet levels and are collected at times described in the Schedule of Activities (Section 1.2).

8.3 Safety Assessments

Safety endpoints will be summarized using the Safety Analysis Set (SAF) and are collected at times described in the Schedule of Activities (Section 1.2).

Clinical significance for safety assessments is defined as any variation in assessment results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from screening values is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the subject's eCRF. The Investigator will continue to monitor the subject with additional assessments until the values have reached reference range and/or the values at Screening, or until the Investigator determines that follow-up is no longer medically necessary.

8.3.1 Adverse Events

Adverse events will be assessed and recorded by the study staff. If an AE requires medical attention, it should be reported to the Investigator immediately. The Investigator must meet with the subject to assess all medical and psychiatric AEs reported by the subject, as well as those recorded by the study staff. After current AEs are assessed, the Investigator must review with the subject and assess any AEs unresolved from the previous assessment. After each AE assessment, the Investigator will record in the subject's source document and AE eCRF, according to the procedures described in Section 10.3, the type of AE and whether

serious or nonserious, severity of each AE, and the relationship to the study agent. These categories are asking for the Investigator's best judgment of the severity and relatedness of each AE.

Any study subject with a related AE will be followed by the Investigator until the event is resolved to the satisfaction of the Site Investigator and Medical Monitor. During Part A, if the AE is unrelated, the subject will not be discharged until medically stable, and then will be referred, at the subject's sole expense, for ongoing care and/or treatment, which may include psychological and lifestyle counseling, support groups, or pharmacological and medical treatment.

Refer to Section 8.4 for information regarding AEs.

8.3.2 Vital Signs

Vital signs measurements will include supine blood pressure (after 5 minutes in supine position), pulse rate, respiratory rate, and body temperature.

The Investigator will determine if any of the vital signs measurements are clinically significant or not clinically significant.

See Schedule of Activities (Section 1.2) for the timing and frequency. Vital signs will be assessed every 30 minutes during an infusion. For infusions <35 minutes, vital signs assessments may occur at the beginning and end of infusion.

8.3.3 12-Lead ECG

Triplicate (3 ECGs within a 10-minute period) 12-lead ECGs will be obtained after the subject has been in the supine position for at least 5 minutes. Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T Wave, and U Wave abnormalities. In addition, the following intervals will be measured and reported: RR, PR, QRS, and QTc.

The Investigator will determine if the ECG results are clinically significant or not clinically significant.

See Schedule of Activities (Section 1.2) for the timing and frequency.

8.3.4 Physical Examinations

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities. Height and weight will also be measured.

An abbreviated physical examination will include assessments of skin, lungs, cardiovascular system, and abdomen (liver and spleen).

See Schedule of Activities (Section 1.2) for the timing and frequency.

8.3.5 Infusion Reaction Evaluation

Systemic infusion reactions are not uncommon with administration of biologics and in particular with therapeutic antibodies, including IVIg, as described below.

The Investigator will evaluate and record the signs and symptoms of infusion reactions as individual AEs. All systemic infusion reactions and associated AEs will be graded using CTCAE. The occurrence of a moderate or severe systemic infusion reaction should prompt a meeting of the SRC to review the clinical circumstances and make a determination as to whether dosing should continue.

Premedication prior to M254 administration should not be administered systematically.

Most systemic infusion reactions are either acute or subacute, occurring within 24 hours of the infusion. Delayed reactions are less common; by definition these occur more than 24 hours after the infusion; in practice most occur 5 to 10 days after the infusion [25]. Infusion reactions are often described in terms that are related to a presumed mechanism (eg, allergic, IgE mediated, immune complex mediated, target-engagement mediated, cytokine release, anaphylactic, anaphylactoid); in practice, determination of mechanism is often challenging and based on observation, course, laboratory assessments, and expertise.Acute infusions should be classified as mild moderate or severe. Mild reactions may present with flushing, dizziness, diaphoresis, nausea, palpitations, and hyperemia. Moderate reactions may present with chest pain, hypertension, hypotension, fever, urticaria, dyspnea, chills, and/or rash. Severe reactions may present with marked hypertension or hypotension, severe dyspnea, bronchospasm, stridor, wheezing, and rigors. Most reactions tend to be mild, and related to the rate of the infusion [25], and can be managed by slowing or temporarily stopping the infusion. If necessary, antihistamines or acetaminophen may be given according to the clinical judgment of the Investigator. With moderately severe acute reactions, the infusion should be discontinued, and the subject should be treated with acetaminophen and antihistamines, and if necessary with corticosteroids. Once the reaction has been arrested, the infusion may be cautiously restarted, if deemed appropriate by the Investigator. With severe reactions the infusion should be discontinued, and the subject should be treated immediately with acetaminophen, antihistamines, and systemic corticosteroids. If anaphylaxis if present, epinephrine should be administered before the corticosteroids. The infusion should not be restarted even if the reaction is brought under control.

Delayed reactions (after 24 hours) most likely represent a mild type III immune complex reaction, typically secondary to anti-drug antibodies. The most common symptoms that have been reported associated with delayed reactions include joint pains, rash, arthritis, myalgia, jaw pain, fatigue, headaches, edema, sore throat, and fever. If the symptoms are mild, acetaminophen alone may be sufficient. Persistent severe symptoms may require a short course of corticosteroids, and discontinuation of further study drug administration.

8.3.6 Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.2) for the timing and frequency.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.

Subjects will be in a seated or supine position during blood collection. Instructions for blood collection, processing, storage, and shipping are described in the Laboratory Manual.

8.3.7 Pregnancy Screen

A serum pregnancy test will be conducted at screening and on Day 29 for all female participants of childbearing potential. A urine pregnancy test will be conducted on Day -1.

8.4 Adverse Events and Serious Adverse Events

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

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

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

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the time of consent until the end of study at the time points specified in the Schedule of Activities (Section 1.2).

All AE will be collected from the time of consent until the end of study at the time points specified in the Schedule of Activities (Section 1.2).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from becoming aware of the event, as indicated in Appendix 3. The Investigator will submit any updated SAE data including but not limited to previously missing information, corrections, or additional details of the event, to the sponsor or designee within 24 hours of the Investigator becoming aware.

Investigators are not obligated to actively seek information about AEs or SAEs occurring after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

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.

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

8.4.3 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 (systemic infusion reactions, hemolysis, infections, flu-like symptoms, rash, myalgia and arthralgia, fever, chills), will be followed until resolution, stabilization, 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.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of an SAE is essential so that regulatory obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will

review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 30 days after the final study visit.
- If a pregnancy is reported, the Investigator should inform the sponsor or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.5 Treatment of Overdose

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until M254 can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis 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 case report form (CRF).

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

All participants will undergo blood sampling at designated time points to determine serum M254 concentration following a single dose of blinded study drug. Instructions for blood collection, processing, storage, and shipping are described in the Laboratory Manual. Serial blood sampling for PK will be done after the participants have remained in the same posture (supine or sitting) for at least 15 minutes and will be obtained at the time points listed in the Schedule of Activities (Section 1.2). Posture per time point will be identical between participants.

PK parameters (maximum plasma concentration [C_{max}], time to maximum plasma concentration [t_{max}], area under the concentration–time curve from zero to time of last

measurable concentration area [$AUC_{(0\text{-last})}$], area under the concentration-time curve from zero to infinity [$AUC_{(0\text{-}\infty)}$], Vd, clearance of drug [CL], mean residence time [MRT], and apparent terminal-phase half-life [$t_{½}$]) will be computed using noncompartmental methods.

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

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

8.7 Pharmacodynamics

Blood sampling for PD will be done after the participants have remained in the same posture (supine or sitting) for at least 15 minutes. Posture per time point will be identical between participants.

For the purpose of PD parameters, a "therapeutic platelet count" will be defined as $\geq 50 \times 10^9$/L.

The PD parameters will include:

- Time to onset of a therapeutic platelet count
- Maximum platelet count following dosing
- Time to maximum platelet count following dosing
- Maximum and percentage platelet count change from baseline
- Duration of a therapeutic platelet count
- Time to therapeutic platelet count
- Area under the change from baseline platelet count-time curve for 14 and 28 days

8.8 Exploratory Biomarkers and Anti-drug Antibodies

Approximately 16 mL of blood will be collected and processed to both plasma and serum for assessment of biomarkers associated with inflammation and for assessment of anti-drug antibodies (ADA) to residual enzymes from exposure to M254. Instructions for blood collection, processing, storage, and shipping are described in the Laboratory Manual.

8.9 Health Economics/Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

The sample size has been chosen to provide adequate numbers of subjects and patients to characterize the safety, tolerability, PK, and PD of M254 and the study has not been formally powered.

No formal sample size calculation was performed for this study (Parts A, B, and D).

Part C is an exploratory study designed to obtain preliminary information on the safety and efficacy of M254 for the treatment of ITP.

Assuming ratio of M254 to IVIg in maximum change from baseline of platelet counts as CCI [redacted].

9.2 Populations for Analyses

For purposes of analysis, the following 4 population sets are defined:

- The SAF will include all participants who received at least 1 dose of study drug.
- The PK Set will include all randomized participants who received at least 1 dose of study drug with at least 4 evaluable data points adequate to create an evaluable plasma concentration profile of M254.
- The Full Analysis Set (FAS) population will include all randomized participants in the SAF for whom at least 1 PD assessment was completed.
- The Per Protocol Set (PP) is a subset of the intent-to-treat (ITT) population and will include participants who complete the study with all planned safety, PD, and PK assessments and no major protocol deviations impacting safety or PD assessments. Assignment to the PP population will be determined prior to unblinding the study.

Categorical variables will be summarized by the number and percentage of participants in each category. Continuous variables will be analyzed in terms of summary statistics.

Summaries will separate the populations by study part (A, B, C, or D), by dose level, and by dose regimen (single or repeated dose).

9.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for

accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All demographic, safety, PK, and PD data will be listed and summarized in tabular and graphical formats using descriptive statistics for continuous variables and frequency and percentages for discrete variables. Missing data will not be imputed.

9.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Efficacy analyses will be performed using Full Analysis Set (FAS). For Part C, for the ratio of effects between M254 and IVIg, a linear mixed effect model will be performed on the natural logarithms of maximum platelet counts, maximum change from baseline, and area under the curve (AUC), with factors for baseline platelet count, sequence, subject nested within sequence, period, and regimen. The factor of subject nested within sequence will be random effect and others are fixed effects. The estimated ratio will be obtained by exponentiation of the difference of least squares means in natural log-transformed parameters between M254 and IVIg.
Secondary	Overall platelet response rate and its 90% exact binomial confidence interval in each treatment period will be presented. Duration of a clinically significant platelet response will be presented descriptively.
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

9.3.2 Safety Analyses

All safety analyses will be performed on the SAF.

Endpoint	Statistical Analysis Methods
Primary	Analysis of all safety data will be performed on the Safety Analysis Set (SAF) and will be presented by the treatment received. Adverse events will be coded using Medical Dictionary for Regulatory Authorities (MedDRA). The occurrence of adverse events (AEs), serious AEs (SAEs), and AEs of Special Interest will be summarized in terms of incidence, as well as in terms of total number of AEs. Analysis of AEs in terms of incidence by severity and by relatedness will also be provided. Prior and concomitant medications will be coded by the World Health Organization Drug Dictionary Enhanced and will be listed. Medical history will be listed by subject and coded using the MedDRA. Descriptive statistics and a summary of clinically significant abnormalities using shift tables will be presented for safety laboratory tests, vital signs, electrocardiogram (ECGs), and other laboratory parameters. For vital signs and ECGs, descriptive statistics at each visit and change from baseline at each visit will be provided. Physical examinations will be summarized as shift tables. Listings will also be provided for each type of safety data.
Secondary	Not applicable.
Exploratory	Not applicable.

9.3.3 Other Analyses

Pharmacodynamic exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

9.4 Interim Analyses

There will be 3 interim analyses in this study: Part A (after CCI End of Part B, and End of Cohort 1 Part C.

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

9.5 Handling of Missing Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the CRF will be included in data listings that will accompany the CSR.

For AEs, missing dates will not be imputed; however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs

will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

No other data imputation will be performed.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (eg, participant recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- An initial sample ICF is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Sponsor Trial Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential patient population.
  - For those enrolling in Part A (Netherlands only), there will be 1 consent form for the healthy volunteers.
  - For those enrolling in Part B, there will be 1 consent form.
  - For those enrolling in Part C, there will be 1 consent form.
  - For those enrolling in Part D, there will be 1 consent form. Patients from Parts B or C will need to sign a new consent form for participation in Part D.
- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants (and/or legally authorized representative if the subject is mentally incompetent or physically incapacitated) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- 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.
- The Investigator must ensure that the participant's confidentiality is maintained for documents submitted to Sponsor.
- For SAEs reported to Sponsor or designee, participants are to be identified by their unique participant identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).
- Documents that are not submitted to Sponsor (eg, signed ICFs) are to be kept in confidence by the Investigator, except as described below.
- In compliance with governmental regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the participant's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.
- The Investigator is obligated to inform and obtain the consent of the participant to permit such individuals to have access to his/her study-related records, including personal information.

10.1.5 Committees Structure

The Safety Review Committee (SRC) will, at a minimum, consist of a therapeutic expert in hematology, the Sponsor Medical Monitor, and a Sponsor Clinical Operations representative.

10.1.6 Dissemination of Clinical Study Data

A clinical study report (CSR) will be prepared in accordance with the ICH guideline on structure and contents of CSRs and any applicable regulatory and legal requirements.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic case report form (eCRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

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

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

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

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

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory. No more than 500 mL of blood will be collected for any distinct study part and for any patient from Part B or C who also participates in Part D will not have greater than 500 mL of blood taken in a 2 month time frame.

Local laboratory results are required for platelet counts and pregnancy testing. Results of all local labs preformed during the study must be entered in the CRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Investigators must document their review of each laboratory report by signing and dating the lab report.

For Part A, laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Table 10-1. Protocol-required Laboratory Assessments Parts A and B

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- pH
- Protein
- Specific gravity
- Urobilinogen

Serum Chemistry:

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Chloride (Cl)
- Creatinine
- Creatine kinase (CK) and subtypes (MB [muscle/brain] fraction – if CK is elevated)
- Gamma-glutamyl transferase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Inorganic phosphate
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Troponin I
- Uric acid

Coagulation Screening Labs:

- Antithrombin III (ATIII) deficiency
- Factor V Leiden
- Protein S deficiency
- Protein C deficiency

Serology:

- HBsAg, HCV, and HIV

Coagulation:

- Activated partial thromboplastin time (PTT)
- D-dimer
- Prothrombin time (PT)

Immunoglobulins:

- Total IgG
- IgG Subclasses: IgG1, IgG2, IgG3, IgG4

Platelet autoantibodies

Serum and urine human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal)

HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G

Table 10-2. Protocol-required Laboratory Assessments Part C and Part D

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Urinalysis (dipstick):

- Glucose
- Hemoglobin
- Leukocytes
- Protein

Serum Chemistry:

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Chloride (Cl)
- Creatinine
- Gamma-glutamyl transferase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Inorganic phosphate
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total protein

Coagulation Screening Labs:

(only for patients with a history of thrombosis):

- Antithrombin III (ATIII) deficiency
- Factor V Leiden
- Protein S deficiency
- Protein C deficiency

Serology:

- HBsAg, HCV, and HIV

Coagulation:

- Activated partial thromboplastin time (PTT)
- Prothrombin time (PT)

Immunoglobulins:

- Total IgG
- IgG Subclasses: IgG1, IgG2, IgG3, IgG4

Platelet autoantibodies

Serum and urine human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal)

HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An adverse event (AE) is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or serious adverse event (SAE) if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the 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 or other criteria being met). For any SAE, refer to the Safety Management Plan for further details of recording and reporting.

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Immediately 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, 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. Other medically important serious event: • 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 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include 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 case report form (CRF).
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. 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 Sponsor.
- 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.
- The Investigator must assign the following AE attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Intensity (or toxicity defined below);
  - Assessment of relatedness to investigational product; and
  - Action taken.Changes in AE severity are to be recorded as a single event worst severity.

Assessment of Intensity

The Investigator will grade severity of AEs in accordance with Common Terminology Criteria for Adverse Event (CTCAE) Version 5.0 (web page: https://evs.nci.nih.gov/ftp1/CTCAE/About.html). AEs not listed in the CTCAE should be graded as follows:

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined criterion as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure 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 Sponsor. 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 Sponsor.**
- 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 1 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 Sponsor 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.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Sponsor 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 the medical monitor by telephone. • Contacts for SAE reporting can be found in the Safety Management Plan.
SAE Reporting to Sponsor via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor. • 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 Safety Management Plan.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

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

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

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 level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 follicle stimulating hormone measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 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 are eligible to participate if they agree to the following during the intervention period and for at least 100 days after the last dose of study intervention:

- Refrain from donating sperm

Plus either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
  - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

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 below.

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b. Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 1 highly effective method of contraception and 1 barrier method (ie, condom, cervical cap, diaphragm) should be utilized during the treatment period and for at least 90 days after the last dose of study intervention

Pregnancy Testing:

- Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing is required during Day 1 of the treatment period and at follow-up visit, corresponding to protocol-defined time frame in Section 5.1 after the last dose of study intervention and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

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 intervention.
- 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 24 hours 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 no longer than 6 to 8 weeks following the estimated 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

- 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 24 hours 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, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated 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 intervention by the Investigator will be reported to the sponsor as described in

Section 8.4.5. 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.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

Phase I liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>Alanine aminotransferase (ALT) ≥3 x ULN
If ALT ≥3 x upper limit of normal (ULN) AND bilirubin ≥ 2 x ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, report as a serious adverse event (SAE)[a,b]
See additional actions and follow-up assessments below</td></tr>
<tr><th colspan="2">Required Actions and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to the sponsor within 24 hours
• Complete the liver event case report form (CRF), and complete an SAE data collection tool if the event also met the criteria for an SAE[b]
• Perform liver function follow-up assessments
• Monitor the participant until liver function test abnormalities resolve, stabilize, or return to baseline (see MONITORING)

MONITORING:
If ALT ≥3 x ULN AND bilirubin ≥2 x ULN or INR >1.5
• Repeat liver function tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver function follow-up assessments within 24 hours.
• Monitor participant twice weekly until liver function test abnormalities resolve, stabilize, or return to baseline.
• A specialist or hepatology consultation is recommended.</td><td>• Viral hepatitis serology[c]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis after the most recent dose[d]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
• Fractionate bilirubin, if total bilirubin ≥ 2 x ULN
• 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) CRF
• 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</td></tr>
</table>

If ALT ≥3 x ULN AND bilirubin <2 x ULN and INR ≤1.5:	**If ALT ≥3 x ULN AND bilirubin ≥2 x ULN or INR >1.5:**
• Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver function follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver function abnormalities resolve, stabilize, or return to baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [8]) • 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 study intervention if ALT ≥3 x ULN and bilirubin ≥ 2 x ULN. 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 ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct bilirubin) or ALT ≥3 x ULN 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] Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (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.

[d] PK sample may not be required for participants known to be receiving placebo or noncomparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.6 Appendix 6: ITP-BAT

ITP-BAT

1.	Skin: Petechiae (excluding steroid-induced or senile purpura)

1.1	Has the patient had petechiae? (see pictures)	☐ Yes	☐ No
1.2	Are petechiae present at this visit?	☐ Yes	☐ No
1.3	If answer to 1.2 is yes, please select the body area where the petechiae are most prevalent. How many petechiae do you count in an area the size of the patient's palm?	☐ 1 to 10 ☐ More than 10 or more than 5 in at least 2 palm areas located in at least 2 different body areas (one above and one below the belt) ☐ More than 50, scattered above and below the belt	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Petechiae (does not include steroid–induced or senile purpura)	☐ No	☐ Less than or equal to 10 in a patient's palm-sized area in the most affected body area ☐ 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, one above and one below the belt (in the most affected body areas)	☐ More than 50, if scattered both above and below the belt	

2.	**Skin: Ecchymoses**

2.1	Has the patient had ecchymoses? (see pictures)	☐ Yes	☐ No
2.2	Ecchymoses present at this visit	☐ Yes	☐ No
2.3	If answer to 2.2 is yes, please specify how many	☐ 1-2 in the same body area, smaller than a patient's palm-sized area, spontaneous or disproportionate to trauma/constriction ☐ 3 or more in the same body area, smaller than a patient's palm-sized area, spontaneous or disproportionate to trauma/constriction ☐ At least 2 in two different body regions, smaller than a patient's palm-sized area, spontaneous or disproportionate to trauma/constriction ☐ 1 to 5 larger than a patient's palm-sized area, spontaneous or disproportionate to trauma/constriction, with or without smaller ones ☐ More than 5 larger than a patient's palm-sized area, spontaneous or disproportionate to trauma/constriction,	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Ecchymoses	☐ None or up to 2 in the same body area, but smaller than a patient's palm-sized area, if a) spontaneous **or** b)disproportionate to trauma / constriction*	☐ 3 or more in the same body area, but all smaller than a patient's palm-sized area, if a) spontaneous **or** b) disproportionate to trauma/ constriction* ☐ At least 2 in two different body areas, smaller than a patient's palm-sized area, if a) spontaneous **or** b) disproportionate to trauma/ constriction* ☐ Any number and size if reported by the patient	☐ From 1 to 5 larger than a patient's palm-sized area, if a) spontaneous **or** b) disproportionate to trauma / constriction* 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*	

* Bleedings considered proportionate to trauma/constriction on a clinical ground should not be reported for skin domain

3. Skin: Subcutaneous Hematomas

3.1	Has the patient had subcutaneous hematomas? (see pictures)	☐ Yes	☐ No
3.2	Subcutaneous hematomas present at this visit	☐ Yes	☐ No
3.3	If answer to 3.2 is yes, please specify how many	☐ 1 smaller than a patient's palm-sized area ☐ 2 smaller than a patient's palm-sized area, spontaneous ☐ 2 smaller than a patient's palm-sized area, disproportionate to trauma ☐ More than 2 smaller or at least 1 larger than the patient's palm-sized area, spontaneous ☐ More than 2 smaller or at least 1 larger than the patient's palm-sized area, disproportionate to trauma	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Subcutaneous hematomas	☐ No	☐ 1 smaller than a patient's palm-sized area ☐ Any number and size if reported by the patient	☐ 2 smaller than a patient's palm-sized area, spontaneous ☐ 2 smaller than the size of the patient's palm, disproportionate to trauma	☐ 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	

4. Skin: Bleeding from minor wounds

4.1	Has the patient had prolonged bleeding from minor wounds?	☐ Yes	☐ No
4.2	Bleeding from minor wounds present at this visit	☐ Yes	☐ No
4.3	If answer to 4.2 is yes, please specify the duration (min.)	☐ Less than 5 minutes ☐ More than 5 minutes or interfering with daily activities	
4.4	Treatment: please specify	☐ Requiring protracted medical observation at the time of this visit ☐ Medical report provided by the patient describing his/her evaluation by a physician	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Bleeding from minor wounds*	☐ 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	

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

FINAL SKIN SCORE	

5. Mucosal: Epistaxis

5.1	Has the patient had spontaneous epistaxis?	☐ Yes	☐ No
5.2	Epistaxis present at this visit	☐ Yes	☐ No
5.3	If answer to 5.2 is yes, please specify the duration	☐ Less than 5 minutes ☐ More than 5 minutes ☐ Interfering with daily activities	
5.4	Treatment: please specify	☐ Packing or cauterization or in-hospital evaluation at the time of this visit ☐ Medical report provided by the patient describing packing or cauterization or in-hospital evaluation ☐ RBC transfusion	
5.5	Hb drop >2 g/dL	☐ Yes	☐ No

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Epistaxis*	☐ 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 >2 g/dL

* Epistaxis is also reported in some normal subjects. Thus, a critical judgment is required in grading this manifestation: it should be reported only if judged more severe when compared with pre-ITP bleeding, if any.

6. Mucosal (oral cavity): Gum bleeding

6.1	Has the patient had gum bleeding?	☐ Yes	☐ No
6.2	Gum bleeding present at this visit	☐ Yes	☐ No
6.3	If answer to 6.2 is yes, please specify the duration	☐ Less than 5 minutes ☐ More than 5 minutes or interfering with daily activities	
6.4	Treatment: please specify	☐ Requiring protracted medical observation at the time of this visit ☐ Medical report provided by the patient describing his/her evaluation by a physician	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Oral cavity – gum bleeding*	☐ 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	

* Gum bleeding is also reported in some normal subjects. Thus, a critical judgment is required in grading this manifestation: it should be reported only if judged more severe when compared with pre-ITP bleeding, if any.

7. Mucosal (oral cavity): Hemorrhagic bullae or blisters

7.1	Has the patient had hemorrhagic bullae or blisters?	☐ Yes	☐ No
7.2	Hemorrhagic bullae present at this visit	☐ Yes	☐ No
7.3	If answer to 7.2 is yes, please specify how many	☐ Less than 3 ☐ From 3 to 10 and no difficulty with mastication ☐ More than 10 or more than 5 if difficulty with mastication	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
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	

8. Mucosal (oral cavity): Bleeding after bites to lip & tongue or after deciduous teeth loss

8.1	Has the patient had bleeding after bites to lip and tongue?	☐ Yes	☐ No
8.2	Bleeding after bites to lips and tongue wounds present at this visit	☐ Yes	☐ No
8.3	If answer to 8.2 is yes, please specify the duration	☐ Less than 5 minutes ☐ More than 5 minutes or interfering with daily activities	
8.4	Treatment: please specify	☐ Interventions to ensure hemostasis or in-hospital evaluation at the time of this visit ☐ Medical report provided by the patient describing interventions to ensure hemostasis or in-hospital evaluation	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	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	

9. Mucosal: Subconjunctival hemorrhage (not due to conjunctival disease)

9.1	Has the patient had subconjunctival hemorrhage? (see pictures)	☐ Yes	☐ No
9.2	Subconjunctival hemorrhage present at this visit	☐ Yes	☐ No
9.3	If answer to 9.2 is yes, please specify	☐ Petechiae/hemorrhage partially involving one eye ☐ Petechiae/hemorrhage partially involving both eyes or diffuse hemorrhage in one eye ☐ Diffuse hemorrhage in both eyes	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
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	

FINAL MUCOSAL SCORE	

10. Organ: Gastrointestinal bleeding not explained by visible mucosal bleeding or lesion (Hematemesis, Melena, Hematochezia, Rectorrhagia)

10.1	Has the patient had gastrointestinal bleeding?	☐ Yes	☐ No
10.2	Gastrointestinal bleeding at this visit or described in a medical report exhibited by the patient	☐ Yes	☐ No
10.3	If answer to 10.2 is yes, please specify		
	Type of bleeding	☐ Hematemesis ☐ Melena ☐ Hematochezia ☐ Rectorrhagia	
10.4	Has the symptom ever required medical attention?	☐ Yes	☐ No
10.5	If answer to 10.4 is yes, please specify	☐ Prescription of endoscopy or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ Medical report provided by the patient prescribing endoscopy or other therapeutic procedures or in-hospital evaluation ☐ RBC transfusion ☐ Hb drop >2 g/dL	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
GI 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* or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ Medical report prescribing endoscopy* or other therapeutic procedures or in-hospital evaluation	☐ RBC transfusion or Hb drop >2 g/dL

* Any endoscopic investigations should be considered for grading only if performed for therapeutic purpose and not solely for diagnostic purpose.

11. Organ: Lung bleeding (Hemoptysis, Tracheobronchial bleeding)

11.1	Has the patient had lung bleeding?	☐ Yes	☐ No
11.2	Lung bleeding present at this visit or described in a medical report exhibited by the patient	☐ Yes	☐ No
11.3	If answer to 11.2 is yes, please specify		
	Type of bleeding	☐ Hemoptysis	
		☐ Tracheobronchial bleeding	
11.4	Has the symptom ever required medical attention?	☐ Yes	☐ No
11.5	If answer to 11.4 is yes, please specify	☐ Requiring bronchoscopy or other therapeutic procedures or in-hospital evaluation at the time of this visit	
		☐ An equivalent episode if described in a medical report exhibited by the patient	
		☐ RBC transfusion	
		☐ Hb drop >2 g/dL	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	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* or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ An equivalent episode if described in a medical report ☐ Medical report exhibited by the patient prescribing bronchoscopy* or other procedures or in-hospital evaluation	☐ RBC transfusion or Hb drop >2 g/dL

* Any endoscopic investigations should be considered for grading only if performed for therapeutic purpose and not solely for diagnostic purpose.

12. Organ: Hematuria

12.1	Has the patient had hematuria?	☐ Yes	☐ No
12.2	Hematuria present at this visit	☐ Yes	☐ No
12.3	If answer to 12.2 is yes, please specify	☐ Microscopic (lab analysis exhibited) ☐ Macroscopic or described in a medical report exhibited by the patient	
12.4	Has the symptom ever required medical attention?	☐ Yes	☐ No
12.5	If answer to 12.4 is yes, please specify	☐ Requiring cystoscopy or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ An equivalent episode if described in a medical report exhibited by the patient ☐ RBC transfusion ☐ Hb drop >2 g/dL	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Hematuria	☐ No	☐ Any episode if reported by the patient ☐ Microscopic (lab analysis)	☐ Macroscopic ☐ Described in a medical report	☐ Macroscopic, and requiring cystoscopy* 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 >2 g/dL

* Any endoscopic investigations should be considered for grading only if performed for therapeutic purpose and not solely for diagnostic purpose.

13. Organ: Menorrhagia (compared with pre-ITP or with a phase of disease with normal platelet count)

13.1	Has the patient had very heavy menstrual bleeding (menorrhagia)?	☐ Yes ☐ No
13.2	If answer to 13.1 is yes, please describe your last cycle	☐ Doubling nr. of pads/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 hours or clot and flooding
13.3	Has the symptom required medical attention?	☐ Yes ☐ No
13.4	If answer to 13.3 is yes, please specify	☐ Requiring combined treatment with antifibrinolytics and hormonal therapy or gynecological investigation (either at this visit or described in a medical report exhibited by the patient) ☐ Acute menorrhagia requiring hospital admission or endometrial ablation (either at this visit or described in a medical report exhibited by the patient) ☐ RBC transfusion ☐ Hb drop >2 g/dL

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1*	2	3	4
Menorrhagia **(compared to pre-ITP or to a phase of disease with normal platelet count)**	☐ 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 >2 g/dL

* In girls at menarche grade 1 cannot be assigned, lacking comparison with previous cycles.

14. Organ: Intramuscular hematomas (only if diagnosed by a physician with an objective method)

14.1	Intramuscular hematomas present at this visit	☐ Yes	☐ No
	If yes, please specify	☐ Post trauma, if judged disproportionate to trauma	
		☐ Spontaneous	
14.2	Have the symptom required medical attention?	☐ Yes	☐ No
	If yes, please specify	☐ Requiring hospital admission or surgical intervention	
		☐ RBC transfusion	
14.3	Intramuscular hematomas described in a medical report exhibited by the patient	☐ Yes	☐ No
	If yes, please specify	☐ Post trauma, if judged disproportionate to trauma	
		☐ Spontaneous	
14.4	Has the symptom required medical attention?	☐ Yes	☐ No
	If yes, please specify	☐ Requiring hospital admission or surgical intervention	
		☐ RBC transfusion	
		☐ Hb drop >2 g/dL	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
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 >2 g/dL

15. Organ: Hemarthrosis (only if diagnosed by a physician with an objective method)

15.1	Hemarthrosis present at this visit	☐ Yes	☐ No
	If yes, please specify	☐ Post trauma, function conserved or minimally impaired, if judged disproportionate to trauma	
		☐ Spontaneous, function conserved	
15.2	Have the symptom required medical attention?	☐ Yes	☐ No
	If yes, please specify	☐ Requiring immobilization or joint aspiration	
		☐ Requiring surgical intervention	
15.3	Hemarthrosis described in a medical report exhibited by the patient, function conserved	☐ Yes	☐ No
	If yes, please specify	☐ Post trauma, function conserved or minimally impaired, if judged disproportionate to trauma	
		☐ Spontaneous, function conserved	
15.4	Has the symptom required medical attention?	☐ Yes	☐ No
	If yes, please specify	☐ Requiring immobilization or joint aspiration	
		☐ Requiring surgical intervention	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
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 disproportionate to trauma ☐ An equivalent episode if described in a medical report	☐ Spontaneous, diagnosed at this visit, function conserved or minimally impaired ☐ An equivalent episode if described in a medical report	☐ Spontaneous or post-trauma (if judged disproportionate to trauma) diagnosed at this visit and requiring immobilization or joint aspiration ☐ An equivalent episode if described in a medical report	☐ Spontaneous or post-trauma (if judged disproportionate to trauma) diagnosed at this visit and requiring surgical intervention ☐ An equivalent episode if described in a medical report

16. Organ: Ocular bleeding (for subconjunctival hemorrhage see mucosal section)
(only if diagnosed by a physician with an objective method)

16.1	Ocular bleeding present at this visit	☐ Yes ☐ No
	If yes, please specify	☐ Any post-trauma, vitreous or retinal hemorrhage, involving one or both eyes with or without impaired/blurred vision if judged disproportionate to trauma ☐ Spontaneous, vitreous or retinal, involving one eye without impaired/blurred vision ☐ Spontaneous, vitreous or retinal, with impaired/blurred vision, involving one or both eyes
16.2	Ocular bleeding described in a medical report exhibited by the patient	☐ Yes ☐ No
	If yes, please specify	☐ Any post-trauma, vitreous or retinal hemorrhage, in one or both eyes with or without impaired/blurred vision if judged disproportionate to trauma ☐ Spontaneous, vitreous or retinal hemorrhage, involving one or both eyes with impaired/blurred vision ☐ Spontaneous, vitreous or retinal hemorrhage, with loss of vision in one or both eyes

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
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

17. Organ: Intracranial bleeding (intracerebral, intraventricular, subarachnoidal, subdural, extradural) (only if diagnosed by a physician with an objective method)

17.1	Intracranial bleeding, either present at this visit or described in a medical report exhibited by the patient	☐ Yes	☐ No
17.2	If yes, please specify	☐ Post trauma, requiring hospitalization ☐ Spontaneous, requiring hospitalization, in presence of an underlying intracranial lesion ☐ Spontaneous, requiring hospitalization, without an underlying intracranial lesion	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Intracranial bleeding*: 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

* 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 patient also had intracranial bleeding Grade 3, the SMOG index is S2M2O3 (intracranial 3) (see text).

18. Organ: Other internal bleedings (only if diagnosed by a physician with an objective method)

18.1	Other internal bleeding, either present at this visit or described in a medical report exhibited by the patient	☐ Yes	☐ No
18.2	If yes, please specify	☐ Hemoperitoneum ☐ Hemopericardium ☐ Hemothorax ☐ Retroperitoneal bleeding ☐ Hepatic peliosis (with organ rupture) ☐ Splenic peliosis (with organ rupture) ☐ Retroorbital bleeding ☐ Metrorrhagia ☐ Other	
18.3	Have the symptoms required medical attention?	☐ Yes	☐ No
	If yes, please specify	☐ Hospitalization <48 hrs ☐ Hospitalization >48 hrs ☐ RBC transfusion ☐ Hb drop >2 g/dL	

Comments

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Other internal bleeding: Hemoperitoneum, Hemopericardium hemothorax retroperitoneal bleeding hepatic and splenic peliosis with organ rupture retro-orbital bleeding metrorrhagia (in postmenopausal women), etc. **(only if diagnosed with an objective method at the visit or described in a medical report provided by the patient)**				☐ Any event requiring hospitalization <48 hrs.	☐ Any event requiring hospitalization >48 hrs. or RBC transfusion or Hb drop >2 g/dL

FINAL ORGAN SCORE Remember to separately report in brackets intracranial bleeding, if any (see note at page 17)	

FINAL SMOG (Fatal bleeding is always assigned grade 5)	

19. Organ: Bleeding after Surgery, invasive procedures (biopsy, epidural anesthesia, catheter insertion), hemostatic challenges (extraction of a permanent or deciduous tooth, or parturition)

19.1	Have you ever had bleeding after surgery, invasive procedures, parturition or tooth extraction?	☐ Yes	☐ No
19.2	If yes, please specify	☐ Tooth extraction ☐ Tonsillectomy/Adenoidectomy ☐ Pharynx/Nose surgery ☐ Vaginal parturition ☐ Major-abdominal surgery ☐ Major-thoracic surgery ☐ Major-gynecology and cesarean section ☐ Biopsy ☐ Epidural anesthesia ☐ Catheter insertion ☐ Arthroscopy ☐ Other	
19.3	Have the symptoms required medical attention?	☐ Yes	☐ No
	If yes, please specify	☐ Revisiting ☐ Antifibrinolytics ☐ Prolonged in-hospital stay ☐ Iron therapy ☐ Resuturing or packing ☐ Return to operating room ☐ Caused organ damage ☐ Occurred in critical areas (eg, CNS) ☐ RBC transfusion ☐ Hb drop >2 g/dL ☐ Requiring critical care or surgical intervention ☐ Directly contributing to death	

Comments

		Grades of bleeding°				
Type and date of intervention/ procedure	**Platelet counts before and during**	**0**	**1**	**2**	**3**	**4**
Permanent or deciduous tooth extraction^ **Date**	Date Plt count /10^9/L Date Plt count /10^9/L Date Plt count /10^9/L	☐ No	☐ Present	☐ Requiring revisiting or antifibrinolytics	☐ Resuturing or packing	☐ RBC transfusion or Hb drop >2 g/dL
Invasive procedures*/ Surgery **Date**	Date Plt count /10^9/L Date Plt count /10^9/L Date Plt count /10^9/L	☐ No	☐ Present but not requiring revisiting or protracted observation	☐ Requiring revisiting or prolonged in-hospital stay	☐ Requiring return to operating room or causing organ damage or occurring in critical areas (eg, CNS)	☐ Requiring critical care or directly contributing to death
Parturition **Date**	Date Plt count /10^9/L Date Plt count /10^9/L Date Plt count /10^9/L	☐ No	☐ Present	☐ Requiring iron therapy or prolonged in hospital stay	☐ RBC transfusion or Hb drop >2 g/dL	☐ Requiring critical care or surgical intervention

° These criteria are proposed as provisional and are not used to calculate the patient's SMOG and are provided to help in the description of bleeding after hemostatic challenges.

^ Spontaneous loss of a deciduous tooth is considered in Table 2.

* Biopsy, epidural anesthesia, catheter insertion, etc. https://zoom.us/j/333539415

10.7 Appendix 7: Abbreviations

Abbreviation or Term	Definition
ADA	Anti-drug Antibody
AE	Adverse event
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATIII	Antithrombin III
AUC	Area above the curve
AUC (0-last)	Area under the concentration–time curve from zero to time of last measurable concentration area
AUC (0-∞)	Area under the concentration–time curve from zero to infinity
BAT	Bleeding assessment tool
BMI	Body mass index
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CIDP	Chronic inflammatory demyelinating polyneuropathy
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
Cl	Chloride
CL	Clearance
C_{max}	Maximum concentration in plasma
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
D5W	5% dextrose injection
DER	Dose escalation report
DLT	Dose-limiting toxicity

Abbreviation or Term	Definition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
Fc	Fragment crystallizable
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GP	Glycoprotein
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
Hct	Hematocrit
HCV	Hepatitis C virus;
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgA, IgG, IgM	Immunoglobulin A, immunoglobulin G, immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
ITP	Immune thrombocytopenic purpura; Immune thrombocytopenia
ITT	Intent-to-treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
K	Potassium

Abbreviation or Term	Definition
LDH	Lactate dehydrogenase
MB	Muscle/brain
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
Na	Sodium
NCI	National Cancer Institute
NOAEL	No-observed-adverse-event-level
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamics
PID	Primary immunodeficiency
PK	Pharmacokinetics
PP	Per protocol set
PR interval	Interval that begins at the onset of the P wave and ends at the onset of the QRS complex; represents the time the impulse takes to reach the ventricles from the sinus node
PRA	Pharmaceutical Research Associates Inc
PT	prothrombin time
PTT	Activated partial thromboplastin time
Q2W	Every 2 weeks
QRS interval	Interval corresponding to the depolarization of the right and left heart ventricles
QT interval	Measure of time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT interval corrected
RBC	Red blood cell
RR interval	Time interval between the R wave of 1 heartbeat and the R wave of the preceding heartbeat; measures heart rate
SAE	Serious adverse event
SAF	Safety analysis set
SGOT	Aspartate aminotransferase
SGPT	Alanine aminotransferase
SOP	Standard operating procedure
SRC	Scientific Review Committee

Abbreviation or Term	Definition
$t_{½}$	Terminal elimination half-life
t_{max}	Time to reach maximum plasma concentration
ULN	Upper limit of normal
USA	United States of America
Vd	Volume of distribution
WBC	White blood cell
WOCBP	Women of childbearing potential

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