16.1.9 Documentation of Statistical Methods and Analysis Output

16.1.9.1 Statistical Analysis Plan

16.1.9.1.1 Statistical Analysis Plan Version 2.0 (14 July 2021)

Statistical Analysis Plan

Sponsor:	Momenta Pharmaceuticals, Inc.
Protocol No:	MOM-M254-001
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
PRA Project ID:	MMT102EC-170091
Version:	2.0
Version Date:	14-Jul-2021

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	PPD
Signature of Sponsor Representative / Date:	PPD PPD
Name of Sponsor Representative / Title:	PPD
Signature of Sponsor Representative / Date:	PPD PPD
Name of Author / Title:	PPD
Signature of Author / Date:	

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Momenta Pharmaceuticals, Inc. Protocol MOM-M254-001.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 24 April 2020 (including all amendments up to this protocol date).

An approved and signed SAP is a requirement for database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the pharmacokinetic (PK), pharmacodynamic (PD) and safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in Section 9.8.2 of the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR, if significant.

4.0 Changes from Previous Version of Approved SAP

This is the second version of the SAP.

5.0 Study Objectives

5.1 Primary

Part A:

- To assess the safety and tolerability of a single ascending dose of intravenous administration of M254 in healthy volunteers

Part B:

- To assess the safety and tolerability of a single intravenous administration of M254 in immune thrombocytopenia (previously called idiopathic thrombocytopenic purpura; ITP) patients compared to 1000 mg/kg intravenous immunoglobulin (IVIg)

Part C:

- To assess the safety of a single intravenous administration of M254 compared to 1000 mg/kg of IVIg
- To characterize the PD of single intravenous administration of M254 compared to 1000 mg/kg IVIg

Part D:

- To assess the safety and tolerability of repeated intravenous administration of M254 in ITP patients

5.1.1 Primary Endpoint

Part A:

- 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

Part B:

- Incidence and severity of AEs following administration of M254 at single dose levels and 1000 mg/kg IVIg
- Clinically significant changes in clinical safety labs, vital signs, and ECGs following M254 administration and 1000 mg/kg IVIg

Part C:

- Incidence and severity of AEs of M254 and 1000 mg/kg IVIg
- Clinically significant changes in clinical safety labs, vital signs, and ECGs following M254 administration and 1000 mg/kg IVIg
- Platelet response after M254 administration compared to IVIg

Part D:

- Incidence and severity of AEs with repeated administration of M254
- Clinically significant changes in clinical safety labs, vital signs, and ECGs with M254 administration

5.2 Secondary

Part A:

- To characterize the PK of a single intravenous administration of M254 at different doses in healthy volunteers

Part B:

- To characterize the PK of a single intravenous administration of M254 at different doses in ITP patients

Part C:

- To characterize the PK of a single intravenous administration of M254 at different doses

Part D:

- To characterize the PK of repeated intravenous doses of M254 in ITP patients
- To assess PD of repeated intravenous doses of M254 in ITP patients

5.2.1 Secondary Endpoint

Part A, B and C:

- Measurements of PK parameters of M254 following the administration of a single intravenous dose

Part D:

- Measurements of PK parameters of M254 following the administration of a repeated intravenous doses
- Platelet response after repeated M254 administration

5.3 Exploratory

Part A:

- To characterize the PD of a single intravenous administration of M254 at different doses in healthy volunteers

Part B:

- To characterize the PD of a single intravenous administration of M254 at different doses in ITP patients compared to IVIg

Part C:

- To characterize the PD of single intravenous administration of M254 compared to 1000 mg/kg IVIg

5.3.1 Exploratory Endpoint

Part A, B and C:

- Exploratory biomarkers relating M254 exposure to potential efficacy in autoimmune diseases and the M254 mechanism of action may be analyzed

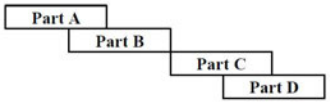
Additionally for Part B:

- Platelet response after M254 administration compared to IVIg

6.0 Study Design

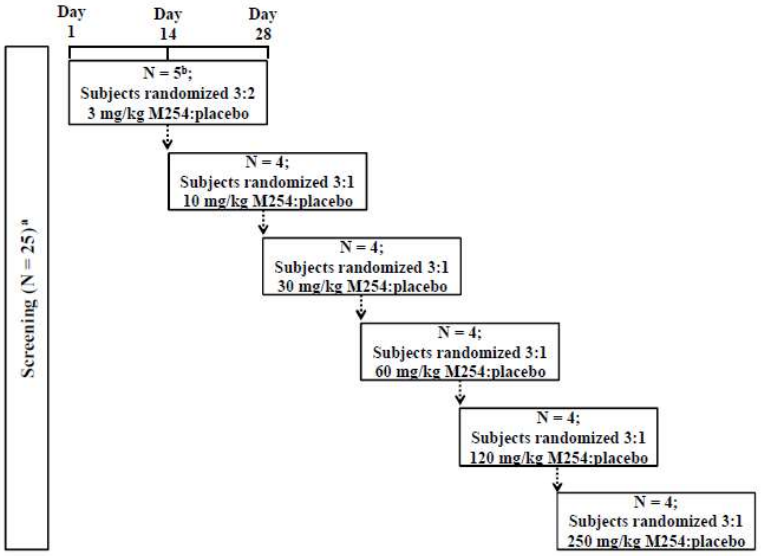
This is a Phase 1/2, study investigating single and repeated administration of M254 in a 4-part study.

Figure 1: Study Schema



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 mg/kg, 10 mg/kg, 30 mg/kg, 60 mg/kg, 120 mg/kg, 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 (Safety Review Committee). 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). There will be no additional sentinel groups in the study beyond this cohort (Cohort 1 Part A).

Figure 2: Part A Schema



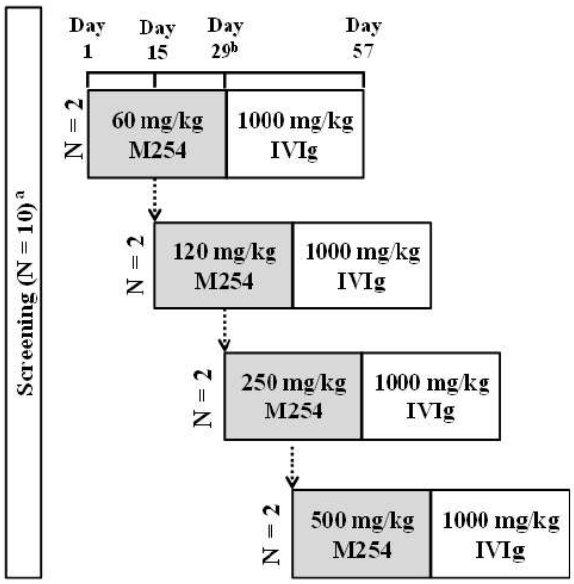
Note: Arrows represent dose escalation; Safety will be assessed prior to dose escalation.

[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.

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 mg/kg, 120 mg/kg, 250 mg/kg 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 NOAEL of 1000 mg/kg determined in the toxicology study in Cynomolgus monkeys). Additional patients to dosing cohorts may be added on the recommendation of the SRC. 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 post-dose. 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..

Figure 3: Part B Schema



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

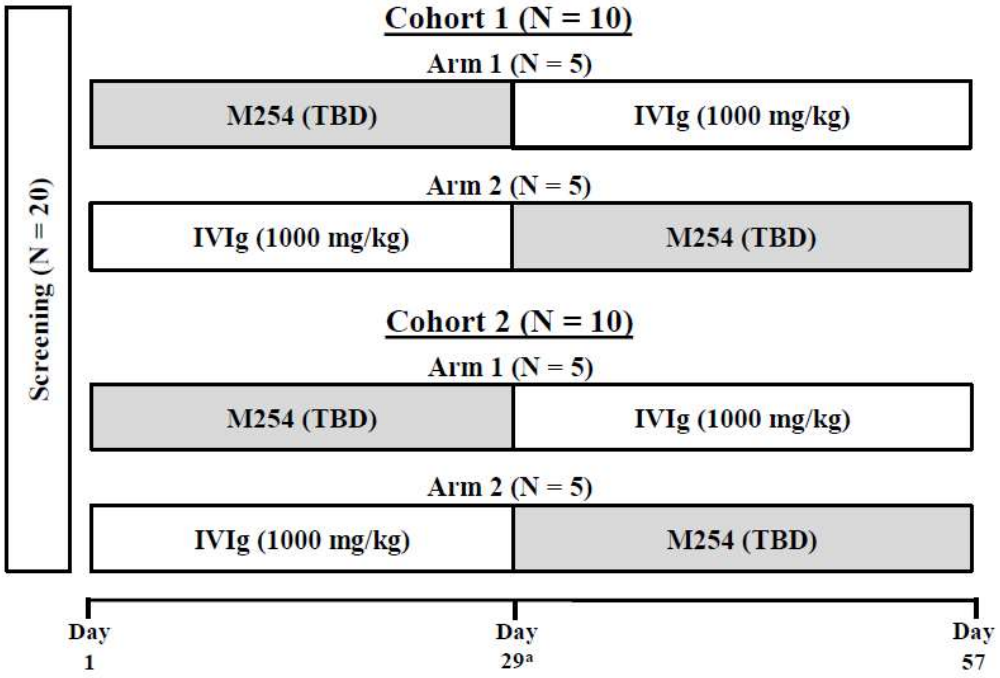
IVIg = Intravenous immunoglobulin; NOAEL = no-observed-adverse-event-level.

[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.

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. 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. 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.

Figure 4: Part C Schema



IVIg = Intravenous immunoglobulin; TBD = to be determined.

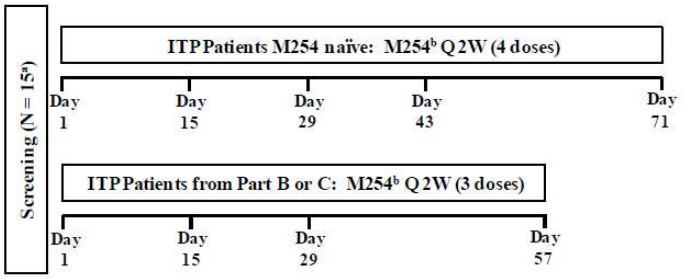
[a] Patients will be followed for 28 days or until their platelet counts have returned to ≤15% above baseline levels and then crossed to the second period. Patients will again be dosed and followed for an additional 28 days with safety and platelet assessments.

[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.

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. 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. If the patient's platelet count has not returned to ≤ 100 × 10^9/L, their platelet count will be monitored weekly until platelets return to ≤ 100 × 10^9/L. If these conditions are not met, M254 will not be administered further.

Figure 5: Part D Schema



ITP = Immune Thrombocytopenic Purpura; 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.

[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).

6.1 Sample Size Considerations

This is an exploratory trial for which no formal statistical hypothesis testing will be performed and therefore no formal sample size calculations have been done. For Part A, sample size of n=5 subjects in group 1 (3 active and 2 placebo) and n=4 in the following groups 1 (3 active and 1 placebo) are commonly accepted numbers of healthy volunteers for single ascending dose studies and are considered sufficient to achieve the objectives of the study. For the Part B a sample size of n=2 patients per dose level is also commonly accepted number for a single ascending dose patient study. In Part C a linear mixed effect model will be performed on the platelet data to calculate the confidence intervals for the ratio of effects between M254 and IVIg. Due to the exploratory nature of this part, no formal sample size calculation was performed here as well. A sample size of n=20 patients is considered sufficient to meet the objectives of this part of the study. A sample size of n=15-34 patients in Part D is also deemed acceptable for a repeated dose study and sufficient to achieve the objectives of this part as well.

6.2 Randomization

A randomization schema will be developed for Part A and Part C and managed by the pharmacy at PRA in Netherlands for the study. Subjects will be randomized according to a randomization code generated by the Biostatistics Department of PRA.

Part A is randomized and double blind (sponsor unblind). Following screening to confirm eligibility to participate, subjects will be randomized to receive M254 or placebo. In Cohort 1, 5 subjects will be enrolled with 3:2 (active: placebo) randomization. In this cohort 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). In all other cohorts, subjects will be randomized 3:1 (active: placebo) with total of 4 subjects in each cohort.

Part C consists of 2 randomized, unblinded crossover cohorts. 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 each cohort subjects will be allocated to treatment sequence (M254-IVIg or IVIg-M254) in a 1:1 ratio (5 subjects will be allocated to sequence M254/IVIg and 5 subjects will be allocated to sequence IVIg/M254).

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

To align with published reports of platelet response, an additional requirement of 'an increase from baseline of ≥20 × 109/L' was added to the definition of a therapeutic platelet count.

7.2 Interim Analysis and Key Results

After the completion of Part A the database was locked and unblinded and an interim reportprovided.

Dose escalation reports during Part A and B will be prepared by a process not covered by this SAP.

7.3 Final Analysis

Draft TFLs (Tables Figures and Listings) will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be incorporated in the first draft CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the PRA Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

Individual values and descriptive statistics of PK concentrations and PK parameters will generally be presented with 3 significant figures. Values greater than 999 will be presented as integers. The t_{max} will be reported with 2 decimals.

For all other summaries, all descriptive statistics will be presented with the same precision (number of decimals) as the data they are calculated from.

P-values will be reported to four decimal places; p-value less than 0.0001 will be reported as p <0.0001.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), minimum (min) value, median, and maximum (max) value. For PK and PD data, nblq (number of observations below the limit of quantification), CV, geometric mean, and coefficient of variation of the geometric mean (geoCV) will be presented additionally. If the total number of subjects per treatment is lower than 3 then the only descriptive statistics presented will be arithmetic mean, minimum and maximum.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the eCRF / Database.

9.1.4 Pooling

Summary statistics will be calculated by population (healthy volunteers or ITP), treatment (investigational product [placebo, M254, or IVIG], dose, and dose frequency) and time point (if applicable). Summary statistics in Part B and C will be calculated by cohort and treatment. Summary statistics in Part D will be calculated by total planned number of doses received, by total actual number of doses received and overall. Placebo data will be pooled for Part A. For the AEs presentation data from different dose levels per part will be summarized per dose and also different M254 doses will be pooled and summarized together (M254 overall). Data from the corresponding M254 dose levels in Parts B and C will be pooled together (in addition to presentation by part, cohort and treatment).

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. For Part A, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis (with the exception of unscheduled measurements used for baseline).

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the first study drug administration. In case of Part B, C and D, baseline will be the last observation recorded before the first study drug administration in each period. The last observation can be an unscheduled / repeated measurement. If a pre-treatment observation is missing in a given period then the screening value may be used.

9.2.2 Treatment/Subject Grouping

In tables the data will be presented by study part and treatment, and where applicable by sequence. Parts B and C will also have pooled analysis (see Section 9.5).

Label	Definition
Study Part	Part A – SAD HV, Part B – SAD ITP patients, Part C – cross over ITP patients, Part D – fixed dose ITP patients
Study Drug	M254, IVIg, Placebo
Treatment	Part A: Placebo, 3 mg/kg M254, 10 mg/kg M254, 30 mg/kg M254, 60 mg/kg M254, 120 mg/kg M254, and 250 mg/kg M254 Part B: 60 mg/kg M254, 120 mg/kg M254, 250 mg/kg M254, 500 mg/kg M254, 1000 mg/kg IVIg Part C: The dose of M254 will be determined after analysis of the data from Part A and Part B 1000mg/kg IVIg Part D: 3 or 4 doses of M254 (planned treatment) ; possibly more than one dose level of M254 as well

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation
Change from Baseline	All	Post-dose Observation minus Baseline Observation
Analysis Relative Day (Prior to Dose)	All	Date of Measurement minus Dose Date. In case of Part B and C it will be Date of Measurement minus Dose Date in a given treatment period.
Analysis Relative Day (Post-Dose)	All	Date of Measurement minus Dose Date +1. In case of Part B and C it will be Date of Measurement minus Dose Date in a given treatment period +1.

9.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the general PRA EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the primary objective of this study is to assess safety, tolerability and PD the datasets considered critical are subject level, AEs and PD (ADSL,

ADAE, ADPD). As these are related to the primary objectives these datasets will be double programmed per the QC plan.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1. At least the following datasets will be generated:

- Subject-Level Analysis Dataset (ADSL)
- Adverse Events Analysis Dataset (ADAE)
- Laboratory Analysis Dataset (ADLB)
- Vital Signs Analysis Dataset (ADVS)
- ECG Analysis Dataset (ADEG)
- Pharmacokinetic Concentrations Analysis Dataset (ADPC)
- Pharmacokinetic Parameters Analysis Dataset (ADPP)
- Pharmacodynamic Concentrations Analysis Dataset (ADPD)
- Pharmacodynamic Parameters Analysis Dataset (ADPDP)

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® version 8.1 or higher (Pharsight, Inc.). Additional PK computations may be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

In Part C there will be a subanalysis performed for patients with baseline platelet level of ≤30 vs >30×10^9/L.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Report layout will be according to the PRA EDS – ICH E3 compliant – CSR Template. The layout of TFLs will be according to the PRA EDS standards.

No table shells will be provided. The TFLs will be provided in Adobe PDF format.

Format:

- Page size: A4
- Data in listings will be sorted by study part, cohort, site number (if applicable: each site on a new page), subject number and time point.
- Data in tables will be sorted by study part, treatment and time point.

- Column titles will be in title case letters.
- All tables and listings will be in landscape format.
- The treatment labels listed below will be used in the TFLs. Treatments will be sorted by investigational product (placebo then M254 then IVIg) then dose level (increasing mg/kg) then number of doses. These labels will be modified to account for the dose selected as part of dose escalation and the initiation of each part:
-

  Part A:
  - Placebo
  - 3 mg/kg M254 HV (Healthy Volunteers)
  - 10 mg/kg M254 HV
  - 30 mg/kg M254 HV
  - 60 mg/kg M254 HV
  - 120 mg/kg M254 HV
  - 250 mg/kg M254 HV
  - M254 HV total

  Part B and C:
  Data will be first presented by cohort and within cohort by treatment period according to following layout:

60 mg/kg M254			120 mg/kg M254			Total		
M254 period	IVIg period	Diff	M254 period	IVIg period	Diff	M254 period	IVIg period	Diff
xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

  The following cohort labels will be used in Part B:
  - 60 mg/kg M254
  - 120 mg/kg M254
  - 250 mg/kg M254
  - 500 mg/kg M254
  - Total

  The following cohort labels will be used in Part C:
  - XXX mg/kg M254 (XXX will be replaced by the actual dose level)
  - Total

  Pooled Part B and C:
  - XXX mg/kg M254 (XXX will be replaced by the actual dose level)
  - M254 total
  - 1000 mg/kg IVIg

  Part D (planned treatment):
  - XXX mg/kg M254, 3 doses (XXX will be replaced by the selected mg/kg dose level)
  - XXX mg/kg M254, 4 doses (XXX will be replaced by the selected mg/kg dose level)
  - For the safety tables: XXX mg/kg M254 md (pooled)

  Treatments in Part D will also be presented by actual treatment – that is if the number of doses differs from planned a separate summary will be presented.

10.0 Analysis Sets

Analyses	Randomized Set	Safety Set	Pharmacokinetic Set	Full Analysis Set	Per Protocol Set
Disposition Summaries	✓				
Safety Assessments		✓			
Baseline Characteristics		✓			
PK Concentrations			✓		
PK Parameters			✓		
PD Concentrations				✓	✓
PD Parameters				✓	✓

10.1 Safety Set

The safety set will consist of subjects who receive at least one dose of M254 or IVIg or placebo. This set will be used for the safety data summaries and baseline characteristic summaries.

10.2 Pharmacokinetic Set

The PK set will consist of all subjects who receive at least 1 dose of M254 or IVIg with at least 4 evaluable data points adequate to create an evaluable serum concentration profile. This set will be used for PK concentration and parameter summaries.

10.3 Full Analysis Set

The FAS (Full Analysis Set) will consist of all subjects included in the safety set for whom at least 1 post-infusion PD assessment was completed.

10.4 Per Protocol Set

The PP (Per Protocol) set is a subset of the FAS 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.

10.5 Randomized Set

The Randomized Population set will include all subjects who were randomized (subjects who have received a randomization number). This set will be used for the disposition summaries.

11.0 Subject Disposition

The number and percentage of subjects randomized, dosed, and members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

12.0 Protocol Deviations and Violations

Protocol deviations/violations will be included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

All demographic data as collected during the screening visits will be listed by subject. Site identification number will be included in this listing.

Subject demographics will be summarized descriptively for all subjects by part and treatment or in case of Part C by treatment sequence. The summary will include the subjects' age (in years), gender, race, ethnicity, weight (in kg), height (in cm), and BMI (in kg/m^2). Demographics will be summarized for the safety and PP sets.

13.2 Medical History

Medical history will be listed. The medical history will be coded according to the latest version of the Medical Dictionary for Regulatory Activities. For Parts B,C and D, a separate listing of ITP history will be created, including date of diagnosis, platelet level at screening, information if splenectomy was performed and if patient has received IVIg therapy before.

13.3 Other Baseline Characteristics

Drug and alcohol screen results will be listed.

Serology results will be listed (hepatitis B surface antigen, Hepatitis C virus, and human immunodeficiency virus).

Pregnancy (β human chorionic gonadotropin [hCG]) results will be listed.

Non-compliance to inclusion or exclusion criteria (if any) will be listed.

14.0 Concomitant Medications

Medication and coding will be listed. There will be a separate listing of previous ITP medications for ITP patients in Parts B, C and D. The medications will be coded using the latest version of World Health Organization (WHO) Drug Dictionary Enhanced (DDE). Medications with an end date prior to the first dose of study drug will be considered prior medications and will be in a separate listing. If a partial date allows a medication to be considered concomitant, it will be categorized as such.

15.0 Treatment Compliance and Exposure

Study drug administration data will be listed, including date, start and end times of infusion, amount, volume, infusion completion / interruption details and comments.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

PK concentrations will be collected in serum and analyzed by PRA Bioanalytical Laboratory. The analysis described below will be performed at the end of the study.

16.1.1 Serum Variables

16.1.1.1 Concentrations

- Serum concentration of M254 (if receiving M254 in the current period)
- Total IgG serum levels and changes from baseline (if receiving IVIG in the current period)

16.1.1.2 Parameters

- PK Parameters for M254 as defined in Table 1: PK Parameters
- PK Parameters for total IgG (Immunoglubulin G) changes from baseline as defined in Table 1: PK Parameters

Table 1: PK Parameters

Parameter	Description	Part A	Part B	Part C	Part D	SAS Programming Notes
		In all parts WNL inputs are: • Absolute values for M254 • Changes from baseline for total IgG				
C_{max}	Maximum serum concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	x	x	x	x	Cmax from WNL
t_{max}	Time to maximum serum concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	x	x	x	x	Tmax from WNL
$AUC_{0\text{-last}}$	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	x	x	x		AUClast from WNL
$AUC_{0\text{-tau}}$	Area under the serum concentration-time curve over the dosing interval (time 0 to15 days).				x	AUC0-tau from WNL where tau is equal to 15 days.
$AUC_{0\text{-inf}}$	Area under the serum concentration-time	x	x	x		AUCINF_obs from WNL

Parameter	Description	Part A	Part B	Part C	Part D	SAS Programming Notes
		In all parts WNL inputs are: • Absolute values for M254 • Changes from baseline for total IgG				
	curve (time 0 to infinity).					If AUC_%Extrap_obs >20% then parameter will be flagged, but not excluded from descriptive statistics
$\%AUC_{extra}$	Percentage of estimated part for the calculation of $AUC_{0\text{-}inf}$. $((AUC_{0\text{-}inf}\text{-}AUC_{0\text{-}t})/AUC_{0\text{-}inf})*100\%$	x	x	x		AUC_%Extrap_obs from WNL
k_{el}	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least three points is required to obtain a reliable k_{el}.	x	x	x		Lambda_z from WNL If Rsq adjusted ≤ .80 then parameter will be flagged, but not excluded from descriptive statistics.
$t_{1/2}$	Terminal phase half-life expressed in time units..	x	x	x		HL_Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .80 then parameter will be flagged, but not excluded from descriptive statistics.
V_z	Volume of distribution at terminal phase, calculated as CL/k_{el}.	x (M254 only)	x (M254 only)	x (M254 only)		Vz_obs from WNL
CL	Clearance, calculated as dose/$AUC_{0\text{-}inf}$	x (M254 only)	x (M254 only)	x (M254 only)		CL_obs from WNL
MRT	Mean residence time will be approximated to constant infusion rate, $MRT = MRT_{total}\text{-}T_{iv}/2$	x (M254 only)	x (M254 only)	x (M254 only)	x (M254 only)	MRTINF_obs from WNL

Parameter	Description	Part A	Part B	Part C	Part D	SAS Programming Notes
		In all parts WNL inputs are: • Absolute values for M254 • Changes from baseline for total IgG				
	Where $T_{iv.}$ = infusion duration					

Note: AUCs will be calculated using linear up / log down, expressed in units of concentration x time.

16.2 Pharmacokinetic Summaries

16.2.1 Pharmacokinetic Concentrations

In calculation of total IgG changes from baseline the absolute BLQ values will be set to ½ LLOQ. Serum concentrations for M254 and absolute total IgG below the quantifiable limit (BQL) will be set to ½ lower limit of quantification (LLOQ) in the computation of mean concentration values. Continuous descriptive statistics (as defined in Section 9.1.3) will be used to summarize the serum concentrations of M254 (absolute values) and total IgG (absolute values and changes from baseline) . These data will be summarized as described in Section 9.1.4. CV will not be presented for changes from baseline summaries. If over ½ the subjects in a given cell in the absolute values table have values BQL then the descriptive statistics will not be presented for both the absolute values and the changes from baseline table and will instead display as BQL for the arithmetic mean, median and minimum. With the exception of maximum all other statistics will be missing.

Negative change from baseline values will not be imputed for the linear plots. For the semi-logarithmic plots negative change from baseline values will be considered nearly zero and show on the figure.

Linear and semi-logarithmic plots of the median M254 serum concentration (absolute values) and total IgG (absolute values and changes from baseline) by scheduled sampling time will be provided by study part and treatment with one panel per study part and one line per treatment. For Part D these plots will be provided for both planned and actual treatment summaries. These plots will show time in hours. The plots will match the summary table results and will not have an observation at a given time point if more than half of the subjects have values BQL.

Linear and semi-logarithmic plots of the combined individual serum concentration profiles by actual sampling time (spaghetti plots) will be provided for M254 (absolute values) and total IgG (absolute values and changes from baseline) by study part and treatment. For Part D these plots will be provided for both planned and actual treatment summaries.

Linear and semi-logarithmic plots of the individual M254 serum concentration (absolute values) and total IgG (absolute values and changes from baseline) by actual sampling time will be provided by part, treatment, analyte and subject. These plots will show time in hours. Individual plots will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

Individual M254 serum concentration (absolute values) and total IgG (absolute values and changes from baseline) data will be presented together with descriptive statistics by part and treatment.

16.2.2 Pharmacokinetic Parameters

PK parameters for M254 and total IgG changes from baseline will be estimated using non-compartmental methods.

The serum PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters for the M254, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. In estimating the PK parameters for the total IgG negative change from baseline values will be included in the calculation of AUC. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

Continuous descriptive statistics (as defined in Section 9.1.3) will be used to summarize the calculated PK parameters by study part and treatment. For t_{max}, only median, min and max will be presented. If the total number of subjects per treatment is lower than 3 then the only descriptive statistics presented will be arithmetic mean, median, minimum and maximum

The points to be included in the k_{el} range will be determined by the pharmacokineticist after inspection of the semi-log concentration-time profiles. At least 3 points will be required to be used. The C_{max} data point will not be included.

Parameters based on adjusted r^2 below 0.80 or $\%AUC_{extra}$ above 20% will be flagged but not excluded from descriptive statistics.

Additionally, plots of dose normalized Cmax, AUC0-inf (individual values and geometric mean) versus dose level will be provided to evaluate dose proportionality.

17.0 Pharmacodynamic Analysis

The platelet counts will be assessed in Part B, C and D. The analysis described below will be performed at the end of the study, it will not be included in the interim reports. This analysis will be performed on the FAS and repeated on the PP set.

17.1 Pharmacodynamic Variables

17.1.1 Platelet Counts

- Platelet counts

17.1.2 Platelet Parameters

A therapeutic platelet count is defined as ≥ 50 × 10^9/ L and an increase from baseline of ≥20 × 10^9/L (this will be referred to as threshold in Table 2: PD Parameters).

- Platelet parameters as defined in Table 2: PD Parameters

Table 2: Platelet PD Parameters calculated in WinNonLin.

Parameter	Description	Absolute values	Changes from baseline	% changes from baseline	SAS Programming Notes
t_{onset}	Time to onset of a therapeutic platelet count. Time that the response first crosses the threshold coming from the direction of the baseline value.	x			Tonset from WNL
R_{max}	Maximum platelet count following dosing, maximum and percentage platelet count change from baseline. Maximum observed response value.	x	x	x	Rmax from WNL
t_{max}	Time to maximum platelet count following dosing. Time of maximum observed response value.	x			Tmax from WNL
D_{aboveT}	Duration of a therapeutic platelet count. Total time that Response >= Threshold.	x			Time_Above_T from WNL
t_{offset}	Time greater than T_{onset} at which the curve first crosses back to the baseline side of threshold.	x			Toffset from WNL

$AUC_{0\text{-}14d}$	Area under the change from baseline platelet count-time curve for 14 days.		x		AUC0-14 from WNL
$AUC_{0\text{-}28d}$	Area under the change from baseline platelet count-time curve for 28 days.		x		AUC0-28 from WNL

17.2 Pharmacodynamic Summaries

17.2.1 Platelet Counts

Continuous descriptive statistics (as defined in Section 9.1.3) will be used to summarize the serum levels and changes from baseline (absolute values and percentages) by study part and treatment. Data from Part D will be summarized by planned and actual treatment (if the actual number of doses received differs from planned). CV will not be presented for changes from baseline summaries. If the total number of subjects per treatment is lower than 3 then the only descriptive statistics presented will be arithmetic mean, minimum and maximum

Linear plots of the arithmetic mean absolute values and changes from baseline (absolute and % change) by scheduled sampling time will be provided by part and treatment. For Part D these plots will be provided for both planned and actual treatment.

Linear plots of the combined individual serum levels (absolute values) and changes from baseline (absolute and % changes from baseline) by actual sampling time (spaghetti plots) will be provided by part and treatment. For Part D these plots will be provided for both planned and actual treatment.

Linear plots of the individual serum levels (absolute values) and changes from baseline (absolute and % changes from baseline) by actual time will be provided by subject.

All individual subject platelet counts and changes from baseline (absolute change and percentages) will be provided in the tables.

17.2.2 Platelet Parameters

Missing values in the calculation of any PD parameters will not be imputed and handled as missing values. The PD parameters for all subjects in the FAS set will be estimated from the platelet count-time profiles and platelet count change from baseline-time profiles (as specified in Table 2: PD Parameters). The calculation will be performed using the actual sampling times. If the actual time is missing, the scheduled time will be substituted in order to calculate the PD parameter.

Baseline is defined as the pre-dose sample of each period.

In calculation of AUC, the linear trapezoidal calculation method will be used. Descriptive statistics will be calculated and presented for all derived PD parameters by study part and treatment. In case of Part D by these data will be presented by planned and actual treatment (if the actual number of doses received differs from planned).

Individual PD parameters will be listed, and descriptive statistics will be summarized in tables.

17.2.2.1 Primary Statistical Analysis of Platelet Parameters

Efficacy analyses will be performed on Part C data using FAS. This is considered primary analysis. The ratio of effects between M254 and IVIg will be estimated from a linear mixed effect model on the natural

logarithms of absolute values R_{max} and change from baseline R_{max}, AUC_{0-14} and AUC_{0-28}, with factors for baseline platelet count, sequence, subject nested within sequence, period and treatment. 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. The ratios of geometric means and their 95% CIs will be presented. The same analysis will be performed for patients with baseline platelet level of ≤30 vs ≥30× 10^9/ L as exploratory analysis and only if there is sufficient number of patients in both groups. Otherwise the platelet baseline category and category covariate interaction term will be added to the model (as exploratory analysis).

17.2.2.2 Secondary Statistical Analysis of Platelet Parameters

For Part C the frequency counts of the responders and non-responders will be provided, according to the Table 3.

Table 3: Patient PD parameters.

Parameter	Description	SAS Programming Notes
Patients with response (R) for patients with baseline ≤30 × 10^9/ L	Platelet count of ≥30× 10^9/ L and at least 2-fold increase of the baseline count, confirmed on at least 2 separate occasions at least 7 days apart and the absence of bleeding during the 28 days after dose.	Count and count of patients with baseline ≤30× 10^9/ L
Patients with complete response (CR) for patients with baseline ≤30 × 10^9/ L	Platelet count of ≥100× 10^9/ L and at least 2-fold increase of the baseline count, confirmed on at least 2 separate occaions at least 7 days apart and the absence of bleeding during the 28 days after dose.	Count and count of patients with baseline ≤30× 10^9/ L
Patients with no response (NR) for patients with baseline ≤30 × 10^9/ L	Platelet count <30 × 10^9/ L or less than 2-fold increase of baseline platelet count, confirmed on at least 2 separate occasions approximately 1 day apart, or bleeding during the 28 days after dose.	Count and count of patients with baseline ≤30× 10^9/ L
Patients with loss of CR or R for patients with baseline ≤30 × 10^9/ L	Platelet count below 100 × 10^9/ L or bleeding (from CR) or below 30 × 10^9/ L or less than 2-fold increase from baseline platelet count or bleeding (from R). Platelet counts confirmed on at least 2 separate occasions at least 1 day apart.	Count and count of patients with baseline ≤30× 10^9/ L

For Part C overall platelet response rate and its 90% exact binomial CI in each treatment period will be presented for the FAS and PP set as secondary analysis. Overall platelet response rate is defined as reaching the therapeutic platelet count.

17.3 Exploratory biomarkers

Exploratory biomarkers will be reported under a separate report, if analyzed.

18.0 Safety Analyses

18.1 Safety Variables

The following safety variables will be summarized:

- AEs
- Vital Signs

    - Supine Blood Pressure
        - Systolic Blood Pressure (SBP)
        - Diastolic Blood Pressure (DBP)
    - Pulse Rate
    - Tympanic Body Temperature
    - Respiratory Rate
- Electrocardiograms (ECG)
    - Heart Rate
    - RR Interval
    - PR Interval
    - QRS-Duration
    - QTc (Fridericia) Interval
    - ST Segment Assessment
    - T-Wave Assessment
    - U-Wave Assessment
- Clinical Laboratory Evaluations
    - Clinical Chemistry
    - Hematology
    - Urinalysis
    - Coagulation
- Physical Examination
- Evaluation of Infusion Site

18.1.1 Adverse Events

All AE summaries will include only treatment-emergent adverse events (TEAE). TEAEs are those starting or increasing in severity on or after the first dose of study drug.

TEAEs occurring following dosing in a specific period but before dosing in the next period will be attributed to that specific period. If the time is missing for an AE on a dosing day then the AE will be attributed to the treatment given on that day.

A TEAE overview table will be included, presenting the number and percentage of subjects reporting TEAEs, subjects reporting TEAEs with outcome=Death, subjects reporting serious TEAEs, subjects who discontinue study drug due to a TEAE, subjects reporting treatment related TEAEs, subjects reporting injection site reactions.

A breakdown of the number of AEs, number and percentage of subjects reporting each AE, categorized by body system and preferred term coded according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA), will be presented by part, treatment and also M254 overall. Subjects will only be counted once within each body system or preferred term. There will be one such table presented for:

- All TEAEs
- TEAEs considered related to study drug
- Serious AEs (SAEs)
- AEs of Special Interest (AESI: systemic and local reactions, hemolysis, infections, flu-like symptoms, rash, myalgia and arthralgia, fever, chills)
- Severe AEs.

A summary of AEs reported, categorized by relationship (categories: related, not related) will also be provided by part, treatment and also M254 overall. AEs reported in the eCRF as 'Possibly', 'Likely' and 'Definitely' will be considered related to study drug, while categories 'None' and 'Unlikely' will be considered not related.

A summary of AEs reported, categorized by severity as recorded on eCRF, will also be provided by part, treatment and also M254 overall.

All AEs recorded on the eCRF will be listed together with MedDRA coding. One listing will contain TEAEs and one listing will contain non-treatment-emergent AEs.

A listing of AEs leading to study drug discontinuation will be provided ('Adverse Event' is reported as primary reason for early termination/study non-completion).

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date one minute after dosing
- Missing AE start date will be assumed to be after treatment for the determination of TEAE and on treatment for single treatment studies but will not be attributed to treatment in studies with multiple treatments

18.1.2 Deaths and Serious Adverse Events

If applicable, a listing of deaths and other SAEs will be provided by subject.

18.1.3 Laboratory Data

Safety laboratory data for Part A will be analyzed by PRA Clinical Laboratory, while the safety laboratory data for Part B, C and D will be analyzed by Medpace.

Clinical laboratory data will be presented using units from the study data tabulation model (SDTM) Controlled Terminology.

All laboratory data (absolute values and derived changes from baseline) will be listed, including laboratory variables not listed in the protocol. A separate listing, including out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology and coagulation (observed and derived changes from baseline) by treatment and scheduled time will be included.

Summary of clinically significant abnormalities using shift tables will be presented for safety laboratory tests. These tables will present shifts from baseline to all post-dose time points according to categories: Non-Clinically Significant vs Clinically Significant. It will only be prepared for parameters for which >25% of subjects have a clinically-significant shift from baseline.

18.1.4 Vital Signs

Vital signs data (absolute values and changes from baseline) will be listed and summarized descriptively.

Summary of clinically significant abnormalities using shift tables will be presented for vital signs. These tables will present shifts from baseline to all post-dose time points according to categories: Non-Clinically Significant vs Clinically Significant. It will only be prepared for parameters for which >25% of subjects have a clinically-significant shift from baseline.

18.1.5 Electrocardiograms

The observed measurements for all ECG parameters and the corresponding abnormalities will be listed for all timepoints. The means of triplicate measurements for continuous parameters and the change from baseline of the mean triplicate measurements at each scheduled timepoint will be listed by subject.

Descriptive statistics will be provided to summarize mean ECG parameters (observed and changes from baseline) by part, treatment and scheduled time.

Summary of clinically significant abnormalities using shift tables will be presented for ECGs. These tables will present shifts from baseline to all post-dose time points according to categories: Non-Clinically Significant vs Clinically Significant. It will only be prepared for parameters for which >25% of subjects have a clinically-significant shift from baseline.

18.1.6 Physical Examination

The findings (abnormalities) at screening and changes from/new findings since screening will be listed. If abnormalities in the physical examinations are reported, physical examinations will be summarized as shift tables (categories: Normal vs Abnormal).

19.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. 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. Version 8.0, Final, 24 Apr 2020.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ADaM	Analysis data model
ANOVA	Analysis of variance
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CSR	Clinical study report
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
FAS	Full Analysis Set
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
LLOQ	Lower limit of quantification
max	Maximum value
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum value
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PRA	PRA Health Sciences
QA'd	Quality assured
QC('d)	Quality control(led)
SAP	Statistical analysis plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study data tabulation model
TEAE	Treatment-emergent adverse event

TFL(s)	Tables, figures and listings
WNL	WinNonlin

Appendix 2: Schedule of Assessments

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°	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X
12-lead ECG		X	X		X°					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[a]	1[a]	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[a]
		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) All visit windows are relative to the most recent dose	1 [o]	1	1	1	1	1	2	3 [d]	4 [d]	5 [d]	8±1 [d]	10±3 [d]	12±3 [d]
	15±1 [o]	15	15	15	15	15	Skip [w]				22±1 [d]	Skip [w]	
	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) All visit windows are relative to the most recent dose	1 [a, o]	1	1	1	1	1	2	3 [d]	4 [d]	5 [d]	8±1 [d]	10±3 [d]	12±3 [d]
	15±1 [o]	15	15	15	15	15	Skip [w]				22±1 [d]	Skip [w]	
	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 [e] 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.

Appendix 3: List of In-Text Outputs

The planned tables, figures and subject data listings for the CSR are listed below. The placement and numbering presented is for tracking / development purpose and may deviate from the placement order and numbering listed in the CSR. This list defines the tables to be produced by programming. The Medical Writer can decide to insert any of the figures or create more tables for the CSR text independently of this plan.

List of CSR In-Text Tables and Figures:			
TFL Section	**Output Type**	**Title**	**Population Set**
14.1	Table	Subject Demographics and Characteristics	Randomized
	Table	Extent of Exposure	Safety
14.2	Figure	Arithmetic Mean PK Serum Concentrations	PK
	Table	Summary of PK Parameters	PK
	Figure	Dose normalized PK Parameters versus Dose	PK
	Table	Summary of Platelet Counts (Absolute Values and Changes from Baseline)	FAS/PP
	Figure	Arithmetic Platelet Counts (Absolute Values and Changes from Baseline)	FAS/PP
14.3	Table	Summary of all TEAEs by System Organ Class and Preferred Term	Safety/PP
	Table	Related TEAEs by System Organ Class and Preferred Term per Study Part and Treatment	Safety/PP
	Table	SAE by SOC, PT per Study Part and Treatment	Safety/PP
	Table	TEAEs of Special Interest by System Organ Class and Preferred Term per Study Part and Treatment	Safety/PP
	Table	Summary of TEAEs by Relationship, per Study Part and Treatment	Safety/PP
	Table	Summary of TEAEs by Severity, per Study Part and Treatment	Safety/PP

Appendix 4: List of End of Text Outputs

List of End of Text Tables and Figures:			
Output	**Title**	**Population Set**	**Interim (Y/N)**
Section 14.1 – Disposition and Demographic Data			
Table 14.1.1	Summary of Subject Disposition – Part A, B, C, D	Safety	
Table 14.1.2.1	Summary of Demographics – Part A, B, C, D	Safety/PP	
Section 14.2 – Pharmacokinetic Data and Pharmacodynamic Data			
14.2.1 Pharmacokinetic Data			
Table 14.2.1.1	Individual Values and Descriptive Statistics of M254 Serum Concentrations - Part A, B, C, D	PK	
Table 14.2.1.2	Individual Values and Descriptive Statistics of Total IgG Serum Levels Absolute Values - Part A, B, C, D	PK	
Table 14.2.1.3	Individual Values and Descriptive Statistics of Total IgG Serum Levels Changes from Baseline - Part A, B, C, D	PK	
Table 14.2.1.4	Individual Values and Descriptive Statistics of M254 Serum PK Parameters - Part A, B, C, D	PK	
Table 14.2.1.5	Individual Values and Descriptive Statistics of Total IgG Serum PK Parameters - Part A, B, C, D	PK	
Figure 14.2.1.6	Median M254 Serum Concentrations versus Time Profile (Linear and Semi-logarithmic) - Part A, B, C, D	PK	
Figure 14.2.1.7	Median Total IgG Serum Levels Absolute Values versus Time Profile (Linear and Semi-logarithmic) - Part A, B, C, D	PK	
Figure 14.2.1.8	Median Total IgG Serum Levels Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) - Part A, B, C, D	PK	
Figure 14.2.1.9	Combined Individual M254 Serum Concentrations versus Time Profile (Linear and Semi-logarithmic) – Part A, B, C, D	PK	
Figure 14.2.1.10	Combined Individual Total IgG Serum Levels Absolute Values versus Time Profile (Linear and Semi-logarithmic) – Part A, B, C, D	PK	
Figure 14.2.1.11	Combined Individual Total IgG Serum Levels Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) – Part A, B, C, D	PK	
Figure 14.2.1.12	Individual M254 Serum Concentrations versus Time Profile (Linear and Semi-logarithmic) - Part A, B, C, D	Safety	

Figure 14.2.1.13	Individual Total IgG Serum Levels Absolute Values versus Time Profile (Linear and Semi-logarithmic) - Part A, B, C, D	Safety	
Figure 14.2.1.14	Individual Total IgG Serum Levels Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) - Part A, B, C, D	Safety	
Figure 14.2.1.15	Dose Normalized (mg/kg) PK Serum Parameters vs Dose - Part A, B	PK	
Section 14.2.2 – Pharmacodynamic Data			
14.2.2.1 Platelet Counts			
Table 14. *2.2.1*.1	Individual Values and Descriptive Statistics of Platelet Counts – Part B, C, D	FAS/PP	
Table 14. *2.2.1*.2	Individual Values and Descriptive Statistics of Platelet PD Parameters – Part B, C, D	FAS/PP	
Table 14. *2.2.1*.3	Primary Statistical Platelet PD Parameters Analysis: Efficacy Analysis of M254 vs IVIg PD Parameters Ratios – Part C	FAS	
Table 14. *2.2.1*.4	Frequency counts of the responders and non responders	FAS/PP	
Table 14. *2.2.1*.5	Secondary Statistical Platelet PD Parameters Analysis: Overall Platelet Response Rate – Part B, C, D	FAS/PP	
Figure 14. *2.2.1*.6	Arithmetic Mean Platelet Counts Absolute Values versus Time Profile (Linear and Semi-logarithmic) - Part B, C, D	FAS/PP	
Figure 14. *2.2.1*.7	Arithmetic Mean Platelet Counts Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) - Part B, C, D	FAS/PP	
Figure 14. *2.2.1*.8	Arithmetic Mean Platelet Counts % Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) - Part B, C, D	FAS/PP	
Figure 14. *2.2.1*.9	Combined Individual Platelet Counts Absolute Values versus Time Profile (Linear and Semi-logarithmic) – Part B, C, D	FAS	
Figure 14. *2.2.1*.10	Combined Individual Platelet Counts Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) – Part B, C, D	FAS	
Figure 14. *2.2.1*.11	Combined Individual Platelet Counts % Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) – Part B, C, D	FAS	
Figure 14. *2.2.1*.12	Individual Platelet Counts Absolute Values versus Time Profile (Linear and Semi-logarithmic) - Part B, C, D	FAS	

Figure 14. *2.2.1.*13	Individual Platelet Counts Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) - Part B, C, D	FAS	
Figure 14. *2.2.1.*14	Individual Platelet Counts % Changes from Baseline versus Time Profile (Linear and Semi-logarithmic) - Part B, C, D	FAS	
Section 14.3 – Safety Data			
14.3.1 Adverse Events			
Table 14.3.1.1	Overview TEAE	Safety	Y[1]
Table 14.3.1.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Part A, B, C, D	Safety	Y[1]
Table 14.3.1.3	Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Part A, B, C, D	Safety	Y[1]
Table 14.3.1.4	Summary of Serious Adverse Events by System Organ Class and Preferred Term – Part A, B, C, D	Safety	Y[1]
Table 14.3.1.5	Summary of Adverse Events of Special Interest by System Organ Class and Preferred Term – Part A, B, C, D	Safety	Y[1]
Table 14.3.1.6	Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug – Part A, B, C, D	Safety	Y[1]
Table 14.3.1.7	Summary of Treatment-Emergent Adverse Events by Severity – Part A, B, C, D	Safety	Y[1]
14.3.2 Deaths, Other Serious And Significant Adverse Events			
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events		Y[1]
Table 14.3.3	Not part of TFL – Reserved for Narratives in CSR		
14.3.3 Clinical Laboratory			
Table 14.3.3.1	Listing of Abnormal Laboratory Values – Part A, B, C, D	Safety	
Table 14.3.3.2	Summary of Clinical Laboratory Data - Clinical Chemistry – Part A, B, C, D	Safety	
Table 14.3.3.3	Summary of Clinical Laboratory Data – Hematology – Part A, B, C, D	Safety	
Table 14.3.3.4	Summary of Clinical Laboratory Data – Coagulation – Part A, B, C, D	Safety	
Table 14.3.3.5	Shift Table Clinically Significant Results – Clinical Chemistry – Part A, B, C, D – if applicable	Safety	
Table 14.3.3.6	Shift Table Clinically Significant Results – Hematology – Part A, B, C, D – if applicable	Safety	
Table 14.3.3.7	Shift Table Clinically Significant Results – Coagulation – Part A, B, C, D – if applicable	Safety	

14.3.4 Other Safety Data			
Table 14.3.4.1	Summary of Vital Signs – Part A, B, C, D	Safety	
Table 14.3.4.2	Shift Table of Clinically Significant Vital Signs Results – Part A, B, C, D – if applicable	Safety	
Table 14.3.4.3	Summary of 12-Lead Electrocardiogram Part A, B, C, D	Safety	
Table 14.3.4.4	Shift Table of Clinically Significant ECG Results – Part A, B, C, D – if applicable	Safety	
Table 14.3.4.5	Shift Table of Physical Examination – Part A, B, C, D– if applicable	Safety	
[1] Table based on the safety set will be included in the interim report after Part B and interim report after cohort 1 of Part C.			

List of End of Text Listings:		
Output	**Title**	**Interim**
Section 16.2.1 – Disposition		
Listing 16.2.1.1	Subject Disposition - Part A, B, C, D	
Section 16.2.2 – Protocol Deviations		
Listing 16.2.2.1	Not part of TFL – Reserved for protocol deviations in CSR	
Section 16.2.3 – Excluded Subjects		
Listing 16.2.3.1	Overview of Analysis Sets - Part A, B, C, D	
Section 16.2.4 – Demographics and Baseline Characteristics		
Listing 16.2.4.1	Subject Demographics - Part A, B, C, D	
Listing 16.2.4.2	Medical History ITP - Part B, C, D	
Listing 16.2.4.3	Medical History Other – Part A, B, C, D	
Listing 16.2.4.4	Previous ITP Medications – Part B, C, D	
Listing 16.2.4.5	Previous Medications (non-ITP) - Part A, B, C, D	
Listing 16.2.4.6	Drug and Alcohol Screen - Part A, B, C, D	
Listing 16.2.4.7	Serology - Part A, B, C, D	
Listing 16.2.4.8	Pregnancy (beta-hCG) - Part A, B, C, D	
Listing 16.2.4.9	Deviations from In- and Exclusion Criteria - Part A, B, C, D	
Section 16.2.5 – Compliance and Serum Concentration Data		
Listing 16.2.5.1	Study Dates - Part A, B, C, D	
Listing 16.2.5.2	Study Drug Administration - Part A, B, C, D	
Listing 16.2.5.3	PK Time Deviations and Comments - Part A, B, C, D	
Listing 16.2.5.4	PD Time Deviations and Comments - Part B, C, D	

Section 16.2.6 – Adverse Events Data		
Listing 16.2.6.1	Treatment-Emergent Adverse Events - Part A, B, C, D	Y[1]
Listing 16.2.6.2	Non-Treatment-Emergent Adverse Events - Part A, B, C, D	Y[1]
Listing 16.2.6.3	Concomitant Medications - Part A, B, C, D	
Section 16.2.7 – Laboratory Data		
Listing 16.2.7.1	Clinical Laboratory Results – Chemistry - Part A, B, C, D	Y[2]
Listing 16.2.7.2	Clinical Laboratory Results – Hematology - Part A, B, C, D	Y[2]
Listing 16.2.7.3	Clinical Laboratory Results – Coagulation - Part A, B, C, D	Y[2]
Listing 16.2.7.4	Clinical Laboratory Results – Urinalysis - Part A, B, C, D	Y[2]
Listing 16.2.7.5	Clinical Laboratory Results – Reference Ranges - Part A, B, C, D	Y[2]
Listing 16.2.7.6	Clinical Laboratory Results – Comments - Part A, B, C, D	
Section 16.2.8 – Other Safety Data		
Listing 16.2.8.1	Vital Signs - Part A, B, C, D	Y[2]
Listing 16.2.8.2	12-Lead Electrocardiogram Results - Part A, B, C, D	Y[2]
Listing 16.2.8.3	Physical Examination Findings and Changes from Baseline- Part A, B, C, D	

[1] Listing will be included in the interim report after Part B and interim report after cohort 1 of Part C.
[2] Only clinically significant findings will be included in the interim report after Part B and interim report after Cohort 1 of Part C.

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.7	Randomization
Appendix 16.1.9.2	Statistical Appendices

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
21-12-2018	PPD	First draft
07-01-2019	PPD	Review comments Biostatistics, Science and Medical Writing addressed
25-03-2019	PPD	Sponsor review comments addressed
25-06-2019	PPD	Sponsor review comments addressed
28-06-2019	PPD	Sponsor review comments addressed
08-07-2019	PPD	Update due to protocol amendment and sponsor comments
29-06-2021	PPD	Update due to protocol amendment
14-07-2021	PPD	Sponsor review comments addressed

16.1.9.2 Statistical Methods and Analysis Output

STATISTICAL METHODS AND ANALYSIS OUTPUT

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

CONFIDENTIAL

PRA code: MMT102EC-170091
Sponsor code: MOM-M254-001

SPONSOR Momenta Pharmaceuticals, Inc.

AUTHOR PPD

TABLE OF CONTENTS

1. General

The safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) evaluation was conducted by the Biostatistics Department of PRA. This document describes deviations from the statistical analysis plan (SAP), additional decisions made during analysis and reporting and output of statistical analysis that were not included in the Tables, Figures or Listings.

Statistical analysis was performed using the computer program SAS® for Windows™ Version 9.4 (SAS Institute Inc.).

PK parameters were derived using validated Phoenix™ WinNonlin®, Version 8.1 (Certara USA Inc).

2. Deviations from the SAP

In section 16 of the SAP it was planned that the PK parameters of M254 will be calculated from the concentration profiles versus time. However during analysis predose concentrations were observed (as for the IgG). Therefore, the PK parameters calculation for M254 was also based on the changes from baseline of the plasma concentrations versus time profiles. In the M254 change from baseline calculations values below LLOQ were set to the LLOQ value. As the absolute concentration values for PK were not used in the analysis, the TFLs and CSR present figures with change from baseline data only. Section 9.2.1 plans to impute the missing baselines with screening values. In case baseline in period 2 was missing, baseline from period 1 was used instead of the screening value for the PK and PD data. Also: the SAP does not foresee how to treat negative AUC values in the statistical analysis of the platelet data (section 17.2.2.1 of the SAP). These values were not included in the analysis. The statistical analysis for platelet data was repeated for the subjects with baseline below or equal to 30, but in this model baseline as covariate was not included.

3. Statistical Analyses

Primary Statistical Analysis of Platelet Parameters

Statistical analysis of platelet parameters was performed according to the SAP and results of it are shown in Table 15.2.2-3. Negative AUC values were not included in this analysis. The statistical analysis for platelet data was repeated for the subjects with baseline below or equal to 30, but in this model baseline as covariate was not included. The raw statistical output for the comparison between test treatments versus reference treatment can be found in Section 4.1 of this document.

4. Raw Statistical Analysis Output

4.1 Statistical Analysis of Platelet Parameters

Summary of Primary Statistical Analysis of Platelet Parameters
Comparison: PD Variable Platelets, All subjects - Parameter: Max Response (10^9/L)

Parameter Category 1 (N)=10 Parameter Category 1=Platelets, All subjects Parameter (N)=1 Parameter Code=RMAX

The Mixed Procedure

Number of Observations

Number of Observations Read	21
Number of Observations Used	21
Number of Observations Not Used	0

Covariance Parameter Estimates

Cov Parm	Estimate
SUBJID(TRTSEQP)	0.1077
Residual	0.06513

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	9.23	36.28	0.0002
APERIOD	1	8.73	2.54	0.1467
TRTSEQP	1	8.32	3.10	0.1150
BL	1	11.4	0.32	0.5806

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
M254 vs IVIg	-0.7061	0.1172	9.23	-6.02	0.0002	0.05	-0.9702	-0.4419

Least Squares Means

Effect	Actual Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|
TRTA	IVIG	4.7980	0.1308	12.1	36.69	<.0001
TRTA	PT3	4.0919	0.1264	11.6	32.36	<.0001

Summary of Primary Statistical Analysis of Platelet Parameters
Comparison: PD Variable Platelets, All subjects - Parameter: Max CFB Response (10^9/L)

Parameter Category 1 (N)=10 Parameter Category 1=Platelets, All subjects Parameter (N)=2 Parameter Code=RMAXB

The Mixed Procedure

Number of Observations

Number of Observations Read	21
Number of Observations Used	21
Number of Observations Not Used	0

Covariance Parameter Estimates

Cov Parm	Estimate

SUBJID(TRTSEQP)	0.3740
Residual	0.1970

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	9.02	40.15	0.0001
APERIOD	1	8.46	1.14	0.3146
TRTSEQP	1	8.11	2.29	0.1685
BL	1	11.5	0.63	0.4432

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
M254 vs IVIg	-1.2981	0.2049	9.02	-6.34	0.0001	0.05	-1.7614	-0.8348

Least Squares Means

Effect	Actual Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|
TRTA	IVIG	4.4418	0.2374	11.7	18.71	<.0001
TRTA	PT3	3.1437	0.2299	11.1	13.68	<.0001

Summary of Primary Statistical Analysis of Platelet Parameters
Comparison: PD Variable Platelets, All subjects - Parameter: AUEC 0-14 Days CFB (10^9/L*h)

Parameter Category 1 (N)=10 Parameter Category 1=Platelets, All subjects Parameter (N)=15

The Mixed Procedure

Number of Observations

Number of Observations Read	21
Number of Observations Used	19
Number of Observations Not Used	2

Covariance Parameter Estimates

Cov Parm	Estimate
SUBJID(TRTSEQP)	0.3807
Residual	0.9899

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	8	9.00	0.0171
APERIOD	1	7.94	1.76	0.2213
TRTSEQP	1	7.06	3.03	0.1248
BL	1	8.21	2.16	0.1785

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
M254 vs IVIg	-1.4084	0.4696	8	-3.00	0.0171	0.05	-2.4914	-0.3255

Least Squares Means

Actual	Standard

Effect	Treatment	Estimate	Error	DF	t Value	Pr > |t|
TRTA	IVIG	9.3800	0.3972	13	23.62	<.0001
TRTA	PT3	7.9716	0.3709	12.7	21.49	<.0001

Summary of Primary Statistical Analysis of Platelet Parameters
Comparison: PD Variable Platelets, All subjects - Parameter: AUEC 0-28 Days CFB (10^9/L*h)

Parameter Category 1 (N)=10 Parameter Category 1=Platelets, All subjects Parameter (N)=16

The Mixed Procedure

Number of Observations

Number of Observations Read	21
Number of Observations Used	17
Number of Observations Not Used	4

Covariance Parameter Estimates

Cov Parm	Estimate
SUBJID(TRTSEQP)	0.3509
Residual	0.6203

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	6.8	13.58	0.0082
APERIOD	1	6.8	1.05	0.3397
TRTSEQP	1	7.16	0.89	0.3766
BL	1	8.8	0.51	0.4951

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
M254 vs IVIg	-1.5289	0.4149	6.8	-3.68	0.0082	0.05	-2.5158	-0.5419

Least Squares Means

Effect	Actual Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|
TRTA	IVIG	10.1392	0.3648	11.7	27.79	<.0001
TRTA	PT3	8.6103	0.3319	11.2	25.95	<.0001

Summary of Primary Statistical Analysis of Platelet Parameters
Comparison: PD Variable Platelets, Base <=30 - Parameter: Max Response (10^9/L)

Parameter Category 1 (N)=20 Parameter Category 1=Platelets, Base <=30 Parameter (N)=1 Parameter Code=RMAX

The Mixed Procedure

Number of Observations

Number of Observations Read	11
Number of Observations Used	11
Number of Observations Not Used	0

Covariance Parameter Estimates

Cov Parm	Estimate
SUBJID(TRTSEQP)	0.1688
Residual	0.1170

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	3.48	9.45	0.0447
APERIOD	1	3.48	0.19	0.6876
TRTSEQP	1	4.15	0.40	0.5597
BL	0			

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
M254 vs IVIg	-0.6844	0.2226	3.48	-3.07	0.0447	0.05	-1.3407	-0.02795

Least Squares Means

Effect	Actual Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|
TRTA	IVIG	4.7101	0.2412	6.28	19.52	<.0001
TRTA	PT3	4.0258	0.2182	5.6	18.45	<.0001

Summary of Primary Statistical Analysis of Platelet Parameters
Comparison: PD Variable Platelets, Base <=30 - Parameter: Max CFB Response (10^9/L)

Parameter Category 1 (N)=20 Parameter Category 1=Platelets, Base <=30 Parameter (N)=2 Parameter Code=RMAXB

The Mixed Procedure

Number of Observations

Number of Observations Read	11
Number of Observations Used	11
Number of Observations Not Used	0

Covariance Parameter Estimates

Cov Parm	Estimate
SUBJID(TRTSEQP)	0.8253
Residual	0.1436

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	3.11	22.87	0.0160
APERIOD	1	3.11	0.38	0.5815
TRTSEQP	1	4.01	0.19	0.6885
BL	0			

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
M254 vs IVIg	-1.1790	0.2465	3.11	-4.78	0.0160	0.05	-1.9483	-0.4098

Least Squares Means

Effect	Actual Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|

TRTA IVIG 4.4921 0.4176 4.99 10.76 0.0001
TRTA PT3 3.3131 0.4019 4.49 8.24 0.0007
Summary of Primary Statistical Analysis of Platelet Parameters
Comparison: PD Variable Platelets, Base <=30 - Parameter: AUEC 0-14 Days CFB (10^9/L*h)

Parameter Category 1 (N)=20 Parameter Category 1=Platelets, Base <=30 Parameter (N)=15 Parameter Code=AUEC14DB

The Mixed Procedure

Number of Observations

Number of Observations Read	11
Number of Observations Used	11
Number of Observations Not Used	0

Covariance Parameter Estimates

Cov Parm	Estimate
SUBJID(TRTSEQP)	0.9433
Residual	0.8034

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	3.58	2.52	0.1962
APERIOD	1	3.58	1.31	0.3225
TRTSEQP	1	4.19	0.85	0.4074
BL	0			

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
M254 vs IVIg	-0.9238	0.5824	3.58	-1.59	0.1962	0.05	-2.6192	0.7716

Least Squares Means

Effect	Actual Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|
TRTA	IVIG	9.3023	0.6021	6.45	15.45	<.0001
TRTA	PT3	8.3785	0.5396	5.81	15.53	<.0001

Summary of Primary Statistical Analysis of Platelet Parameters
Comparison: PD Variable Platelets, Base <=30 - Parameter: AUEC 0-28 Days CFB (10^9/L*h)

Parameter Category 1 (N)=20 Parameter Category 1=Platelets, Base <=30 Parameter (N)=16 Parameter Code=AUEC28DB

The Mixed Procedure

Number of Observations

Number of Observations Read	11
Number of Observations Used	10
Number of Observations Not Used	1

Covariance Parameter Estimates

Cov Parm	Estimate
SUBJID(TRTSEQP)	0.3200
Residual	1.3058

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	3.9	3.78	0.1254
APERIOD	1	3.9	0.05	0.8267
TRTSEQP	1	4.54	0.05	0.8375
BL	0			

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
M254 vs IVIg	-1.7917	0.9213	3.9	-1.94	0.1254	0.05	-4.3743	0.7909

Least Squares Means

Effect	Actual Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|
TRTA	IVIG	10.4641	0.8273	5.98	12.65	<.0001
TRTA	PT3	8.6724	0.5205	5.91	16.66	<.0001