NCT: NCT03395210

STATISTICAL ANALYSIS PLAN

Protocol PRN1008-010 – Part A

An Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study Investigating the Safety, Pharmacokinetics, and Clinical Activity of Rilzabrutinib (PRN1008), an Oral BTK Inhibitor, in Patients with Relapsed Immune Thrombocytopenia

Development Phase: Phase 1/2

Analysis Stage: Final

Sponsor

Principia Biopharma

Document Version

Final v2.0, 03-Mar-2021

Prepared by

SCIAN
THERAPEUTIC EXPERIENCE
CDM & BIOSTATISTICS

[Filename: dfi17124-prn1008-010-part-a-16-1-9-sap.docx]

SIGNATURES
Statistical Analysis Plan

Version: Final v2.0

03-Mar-2021

for PRN1008-010 – Part A - Final

Prepared by

[redacted]

Approval

[redacted]

Approval [redacted]

Approval [redacted]

Version History:

Version No.	Version Date (dd-MMM-yyyy)	Description of Changes
1.0	04-Nov-2020	Not applicable
2.0	03-Mar-2021	1. Editorial changes 2. Add protocol version 14. 3. Removed Section 7 "Mock Shells for Tables, Listings and Figures (TLF shells)". Shells will be included in a separate document. 4. Added Observation Period and Analysis Period. 5. Updated definition for prior and concomitant medications. 6. Added details for patients to be included in each dose level in Section 3.3.1 Treatment Label. 7. Added the following subgroup to subgroup analyses: o TPO-RA naïve patients o Never respond to fostamatinib o Never respond to rituximab 8. Added the following exploratory endpoints: o Proportion of patients with at least 4 out of the final 6 platelet counts ≥ 50,000/µL across all dose levels; o Proportion of patients with at least 8 out of the final 12 platelet counts ≥ 50,000/µL across all dose levels 9. Added EQ-5D index score as an EQ-5D endpoint 10. Section 5.5.1 Adverse Events: o Add summary during main + LTE for patients who entered into LTE: TEAEs, related TEAEs, TEAEs by severity, SAE, TEAEs leading to treatment discontinuation, bleeding events: o Add post-treatment AEs 11. Categorization of lab tests 12. Update rules for handling Lab values below or above a threshold (Section 3.6.3) 13. Fisher's exact method for CI is replaced with Clopper Pearson method. 14. Removed scatter plots for lab parameters

ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BID	bis in die (twice a day)
BMI	Body Mass Index
BP	Blood Pressures
bpm	Beats per Minute
CDISC	Clinical Data Interchange Standards consortium
CI	Confidence Interval
CPK	Creatinine phosphokinase
CRF	Case Report Form
CS	Clinically Significant
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
EOT	End of Treatment
EQ-5D VAS	Euro-QoL 5-Dimension Visual Analog Scale
EOT	End of Treatment
FSH	Follicle Stimulating Hormone
FU	Follow Up
GLP	Good Laboratory Practice
Hep	Hepatitis
HIV	Human Immunodeficiency Viruses
IDSM	Independent Data Safety Monitor
IP	Investigational Product
ITP	Immune Thrombocytopenia
ITP-BAT	Immune Thrombocytopenic Purpura Bleeding Assessment Tool

Abbreviation	Definition
ITT	Intent-to-Treat
LTE	Long Term Extension
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
NPV	Negative Predictive Value
PK	Pharmacokinetic
PPV	Positive Predictive Value
PT	Preferred Term
QD	quaque die (once a day)
QOL	Quality of Life
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings and Figures
TPO	Thrombopoietin
ULN	Upper Limit of Normal
WHODRUG	World Health Organization Drug
WHO DDE	World Health Organization Drug Dictionary

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of this document is to describe the final statistical analysis for Part A of the PRN1008-010 study. This statistical analysis plan (SAP) is a based on the protocol version 14.0 dated 12 Aug 2020 and case report form dated 23 SEP 2019.

2 SYNOPSIS OF STUDY DESIGN & PROCEDURES

2.1 Study Objectives

2.1.1 Safety Objective

- To characterize the safety and tolerability of up to four dose levels of rilzabrutinib in patients with Immune Thrombocytopenia (ITP)

2.1.2 Efficacy Objectives

- To explore the clinical activity of up to four dose levels of rilzabrutinib in relapsed/refractory patients with ITP
- To identify a potential dose regimen to use in future studies of rilzabrutinib in patients with ITP

2.1.3 Pharmacokinetics Objective

- To characterize the pharmacokinetics of rilzabrutinib in patients with ITP

2.1.4 Exploratory Objectives

[redacted]

2.2 Study Design

This is an adaptive, open-label, dose-finding study of rilzabrutinib in patients with ITP who are refractory or relapsed with no available and approved therapeutic options, with a platelet count <30,000/µL on two counts no sooner than 7 days apart in the 15 days before treatment begins.

Protocol amendments changed the active treatment period from 12 weeks to 24 weeks to >=24 weeks as follows:

- In protocol version 7.0 (01 December 2017) the active treatment period is 12 weeks with a

post-treatment safety follow up for a period of 12 weeks.

- In protocol version 8.0 (24 August 2018) the active treatment period is 24 weeks with a post-treatment safety follow up for a period of 4 weeks.
- In protocol version 9.0 (06 May 2019), patients who complete the active treatment period and demonstrate a platelet response defined as platelet counts ≥ 50,000/µL at ≥ 50% of the visits during the last 8 weeks of the active treatment would be allowed to enter the Long Term Extension (LTE) to receive study drug at the 400 mg BID dose. Patients may continue in the LTE until the patient is:
  a) no longer responding per the LTE-defined platelet response and/or experiences dose limiting toxicities
  b) the drug is no longer being developed by the Sponsor
  c) the program is stopped for safety reasons or
  d) the drug becomes commercially available in the patient's country

  Patients who had previously completed the study prior to this amendment, were responders per the LTE requirement and did not experience a Dose-Limiting Toxicity (DLT) were allowed to enroll into the LTE. To qualify for the LTE patients would still need to satisfy the protocol inclusion and exclusion criteria.

Each patient is enrolled in the study and allowed to up-titrate their dose after 28 days of rilzabrutinib therapy, at each dose level, if they do not experience a platelet response (as defined in section 6.2 of the protocol) or a DLT at the last dose level. If the patient experiences a platelet response in the first 28-day cycle, at any one dose level but does not have a platelet response in the second cycle at that dose, they may dose escalate at the end of the second cycle. Patients experiencing a platelet response (as defined for the primary endpoint) will not have their dose escalated at the next cycle.

The "sentinel cohorts" at each dose level consist of the first 3 patients, or 6, if 3 extra are added for a DLT or platelet response. To be evaluable in a sentinel cohort, patients must have ≥ 75% compliance over the first 28-day dosing period. The sentinel cohort data is reviewed by the Independent Data Safety Monitor (IDSM), in order to choose the starting dose for additional, new patients entering the study. After review, the IDSM may determine that a starting dose for new patients should be dropped for futility (lack of platelet response), increased to the next planned dosing level, kept the same or reduced.

Doses levels will be: 200 mg QD; 400 mg QD; 600 mg per day (300 mg BID); 800 mg per day (400 mg BID) (see Table 1 and Table 2 Table 1 below). Due to the design, not all patients will necessarily be dosed at all dose levels.

Table 1 Adaptive Cohort Dosing Table – protocol version 7.0

Cohort	Starting dose level (n*) 4 weeks	Next dose level** 4 weeks	Next dose level** 4 weeks
1	200 mg QD (3-6)	400 mg QD	300 mg BID
2	400 mg QD (≤ 6)	300 mg BID	400 mg BID
3	300 mg BID (≤ 6)	400 mg BID	400 mg BID
4	400 mg BID (≤ 6)	400 mg BID	400 mg BID

Table 2 Adaptive Cohort Dosing Table – protocol version 8.0 and 9.0

Cohort	Starting dose level (n*) 4 weeks	Next dose level** 4 weeks	Next dose level** 4 weeks	Next dose level** 4 weeks	Next dose level** 4 weeks	Next dose level** 4 weeks
1	200 mg QD (3-6)	400 mg QD	300 mg BID	400 mg BID	400 mg BID	400 mg BID
2	400 mg QD (≤ 6)	300 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID
3	300 mg BID (≤ 6)	400 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID
4	400 mg BID (≤ 6)	400 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID

* Unless a sustained platelet response is seen or a DLT, in which case 3 extra patients are added to that group. A starting dose level may be dropped for futility after 3 or 6 patients are evaluated, or retained if efficacy is observed.

** Individual patients will not dose-escalate when there is a platelet response at a lower dose level or toxicity (see dose-escalation rules). If several dose levels are therapeutic, some or all patients may not reach the higher dose levels.

2.3 Expected Sample Size

Approximately 60 patients with ITP will be enrolled such that approximately 15 patients complete 24 weeks of dosing and at least 10 patients complete 24 weeks of treatment at a starting dose of 400 mg BID. Patients who drop out for reasons other than treatment-emergent adverse events (TEAEs) during the treatment period may be replaced.

2.4 Randomization and Blinding

This is an open-label study.

2.5 Protocol Versions

Study enrollment started on protocol version 7.0 and the current protocol version is version 14.0 dated 12 Aug 2020.

Protocol Version	Version Date
Version 7	01 Dec 2017
Version 8	24 Aug 2018
Version 9	06 May 2019
Version 10	27 Sep 2019
Version 11	24 Oct 2019
Version 12	05 Dec 2019
Version 13	05 Mar 2020
Version 14	12 Aug 2020

2.6 Protocol Amendments

In version 8.0 of the protocol, the study drug treatment and post treatment follow-up were changed from 12 weeks to 24 weeks, and 12 weeks to 4 weeks, respectively.

[redacted]

A 24-week treatment period is supported by completed long term good laboratory practice (GLP) animal safety toxicology studies (Investigator Brochure Version 9.)

In version 9.0 of the protocol, patients who entered into LTE will be monitored weekly for 6 months, then monthly for six months ad every three months thereafter.

In version 10.0 of the protocol, the 400 mg tablet was introduced for patients who enter the long term extension and definition of abstinence was added to inclusion criterion #6 a.

Cogstate testing was removed from protocol version 11.0.

In version 12.0 of the protocol, the planned number of patients was increased from 40 to 60 patients.

In version 13.0 of the protocol, Part B, an expansion of the study that will investigate the safety and efficacy of only the selected dose of 400 mg BID was added. Part B will enroll patients with ITP who have relapsed or have an insufficient response to prior therapies.

In version 14.0 of the protocol, the response criteria for entrance into the LTE from Part A were further defined. Part B stopping rules and study endpoints were updated to reflect discussion with FDA. Part A unneeded weighted logistic regression analysis was removed.

2.7 Schedule of Assessments

Table 3 Schedule of Assessments (protocol version 7.0)

	Screening (D-28 to D-1)	On-treatment clinic visits, treatment cycles of 28days, X≤3								Weekly lab visit between clinic visits[14]	Early Withdrawal/ Unscheduled visit
		C1D1 only	CXD1 (first day of each cycle)[13]	CXD8	CXD15	D85 (last day of active rilzabrutinib (PRN1008) treatment)	D113	D141	End of Study D169		
Clinic visits[1]	X		X	X	X	X	X	X	X		X
Laboratory Only Visits for Hematology, differential & retics	X									X	
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
AEs	X	X	X	X	X	X	X	X	X		X
Concomitant Medications	X		X	X	X	X	X	X	X		X
Dose-escalation points[2]			X								
Height	X										
Weight	X		X			X	X	X	X		X
Physical exam/med history[3]	X		X	X	X	X	X	X	X		X
Online cognitive testing	X		X		X	X	X	X	X		X
ECG (12-lead, single)	X										X[3]
ECG (12-lead, triplicate)[4]			X								
Vital Signs	X		X	X	X	X	X	X	X		X
Urinalysis	X		X	X	X	X	X	X	X		X
Hep B &C, HIV	X										
Pregnancy test[5]	X		X			X	X	X	X		X
FSH[6]	X										
ABO and Rh Blood Type	X										
Serum Chem	X		X	X		X	X	X	X		X
Hematology, differential, retics.	X		X	X	X	X	X	X	X		X
T/B/NK/monocyte counts[7]			X			X	X	X	X		
PT/INR PTT	X		X	X		X	X	X	X		
[redacted]											

	Screening (D-28 to D-1)	On-treatment clinic visits, treatment cycles of 28days, X≤3								Weekly lab visit between clinic visits[14]	Early Withdrawal/ Unscheduled visit
		C1D1 only	CXD1 (first day of each cycle)[13]	CXD8	CXD15	D85 (last day of active rilzabrutinib (PRN1008) treatment)	D113	D141	End of Study D169		
[redacted]											
Mean platelet volume			X								
Immature platelet fraction			X								
[redacted]											
ITP-BAT Bleeding Scale[12]	X		X		X	X	X	X	X		X

1. Clinic/laboratory visit windows are ± 3 days for all dosing period and lab visits and ± 5 days for clinic follow up visits.
2. See protocol section 4.3 of the protocol dose-escalation rules
3. Full physical examination at screening, abbreviated physical examination at other visits.
4. Triplicate ECG pre-dose and at 2 hours post-dose (± 15 minutes) on the first day of dosing at each new dose level.
5. For women of childbearing potential only. Serum pregnancy tests are performed at screening, urine pregnancy tests are performed at other visits.
6. To confirm postmenopausal status for women who are not surgically sterile and of reproductive potential
7. T/B/NK/monocyte counts (i.e., CD3, CD4, CD8, CD14, CD19, CD16/56), and B cell subsets (i.e., naïve, memory and plasmablasts)
8. [redacted]
9. [redacted]
10. *On Day 1 of each new dose level cycle, patients will take their dose in the clinic* and remain in the clinic for intensive PK sampling for 6 hours following the first dose at time points: 0, 0.5, 1, 1.5, 2 (time windows for first 2 hours are ± 2 minutes) , 3, 4, and 6 hr (time windows for > 2 hr samples are ±5 minutes). *On subsequent clinic visits of each dosing cycle, patient should take their dose in the morning before the clinic visit (whether dosing is QD or BID)*, and the PK sample is taken at random times after last dose (with time of last dose recorded on CRF, no time window).
11. If still taking rilzabrutinib (PRN1008)
12. ITP-BAT scale performed at all clinic visits but not laboratory-only visits
13. Assessments on Day 1 of each 28-day treatment Cycle are performed pre-dose; ECGs and PK samples are also collected at additional times post-dose per Footnote 4 (ECGs) and Footnote 10 (PK samples).
14. Weekly lab visits between the in clinic visits occur each cycle at Day 22 (CXD22) and weekly between Day 85 and Day 169 on Days 92, 99, 106, 120, 127, 134, 148, 155 and 162. The lab visits have a visit window of ± 3 days.

Table 4 Schedule of Assessments (protocol version 8.0 to version 14.0)

	Screening (D-28 to D-1)	On-treatment clinic visits, treatment cycles of 28days, X≤6[16]					Weekly lab visit between clinic visits[14]	Early Withdrawal/ Unscheduled visit
		C1D1 only	CXD1 (first day of each cycle)[13]	CXD15	D169 (last day of active rilzabrutinib (PRN1008) treatment)	End of Study D197		
Clinic visits[1]	X		X	X	X	X		X
Laboratory Only Visits for Hematology, differential & retics							X	
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X[1]						
AEs	X	X	X	X	X	X		X
Concomitant Medications	X		X	X	X	X		X
Dose-escalation points[2]			X					
Height	X							
Weight	X		X		X	X		X
Physical exam/med history[3]	X		X	X	X	X		X
Online cognitive testing[18]	X[15]		X		X	X		X
ECG (12-lead, single)	X							X[3]
ECG (12-lead, triplicate)[4]			X			X[17]		
Vital Signs	X		X	X	X	X		X
Urinalysis	X		X	X	X	X		X
Hep B &C, HIV	X							
Pregnancy test[5]	X		X		X	X		X
FSH[6]	X							
ABO and Rh Blood Type	X							
Serum Chem	X		X		X	X		X
Hematology, differential, retics.	X		X	X	X	X		X
T/B/NK/monocyte counts[7]			X		X	X		
PT/INR PTT	X		X		X	X		
[redacted]								
Mean platelet volume			X					
Immature platelet fraction			X					

	Screening (D-28 to D-1)	On-treatment clinic visits, treatment cycles of 28days, X≤6[16]					Weekly lab visit between clinic visits[14]	Early Withdrawal/ Unscheduled visit
		C1D1 only	CXD1 (first day of each cycle)[13]	CXD15	D169 (last day of active rilzabrutinib (PRN1008) treatment)	End of Study D197		
[redacted]								
ITP-BAT Bleeding Scale[12]	X		X	X	X	X		X

1. Clinic/laboratory visit windows are ± 3 days for all dosing period and lab visits. Labs to confirm eligibility prior to Cycle 1 Day 1 may be taken up to 3 days in advance of Cycle 1 Day 1.
2. See protocol section 4.3 of the protocol dose-escalation rules
3. Full physical examination at screening, abbreviated physical examination at other visits.
4. Triplicate ECG pre-dose and at 2 hours post-dose (± 15 minutes) on the first day of dosing at each new dose level. Where patients are continuing into a new cycle at the prior dose level, ECG is not required.
5. For women of childbearing potential only. Serum pregnancy tests are performed at screening, urine pregnancy tests are performed at other visits.
6. To confirm postmenopausal status for women who are not surgically sterile and of reproductive potential
7. T/B/NK/monocyte counts (i.e., CD3, CD4, CD8, CD14, CD19, CD16/56), and B cell subsets (i.e., naïve, memory and plasmablasts)
8. [redacted]
9. [redacted]
10. *On Day 1 of each new dose level cycle, patients will take their dose in the clinic* and remain in the clinic for intensive PK sampling for 6 hours following the first dose at time points: 0, 0.5, 1, 1.5, 2 (time windows for first 2 hours are ± 2 minutes) , 3, 4, and 6 hr (time windows for > 2 hr samples are ±5 minutes). *On subsequent clinic visits of each dosing cycle, patient should take their dose in the morning before the clinic visit (whether dosing is QD or BID)*, and the PK sample is taken at random times after last dose (with time of last dose recorded on CRF, no time window). Where patients are continuing into a new cycle at the prior dose level, PK sampling is not required.
11. If still taking rilzabrutinib (PRN1008)
12. ITP-BAT scale performed at all clinic visits but not laboratory-only visits
13. Assessments on Day 1 of each 28-day treatment Cycle are performed pre-dose; ECGs and PK samples are also collected at additional times post-dose per Footnote 4 (ECGs) and Footnote 10 (PK samples).
14. Weekly lab visits between the in clinic visits occur each cycle at Day 8 (CXD8) and Day 22 (CXD22) and weekly between Day 169 and Day 197 on Days 176, 183, and 190. The lab visits have a visit window of ± 3 days.
15. Cognitive testing is performed twice during Screening. This may be done consecutively or separately at any time during the screening period
16. For patients who receive additional cycles of 400 mg BID to a total of 6 full cycles – the visits and procedures will be exactly as in Cycles 1-6 (Day 1, Day 8 lab only, Day 15, Day 22 lab only)
17. Protocol version 9.0 only
18. Removed from protocol version 11.0 and on

Table 5 Schedule of Assessments (protocol version 9.0 to version 14.0 – Extension Period – First 6 Months)

	Day 169 Visit/rollover/C7D1	On-treatment clinic visits, treatment cycles of 28days, X≤6				Early Withdrawal/ Unscheduled visit
		CXD1 (first day of each cycle)	CXD8	CXD15	CXD22	
Clinic visits[1]	X					X
Laboratory Only Visits for Hematology, differential & retics			X	X	X	
Informed Consent extension	X					
AEs	X	X				X
Concomitant Medications	X	X				X
Weight	X	X				X
Physical Exam[7]	X	X				
Online cognitive testing[8]	X	X				X
Vital Signs	X	X				X
Urinalysis	X	X				X
Pregnancy test[2]	X	X				X
Serum Chem	X	X				X
Hematology, differential, retics.	X	X				X
T/B/NK/monocyte counts[3]	X	X				
PT/INR PTT	X	X				
[redacted]						
ITP-BAT Bleeding Scale	X	X				X

1. Clinic/laboratory visit windows are ± 7 days for all dosing period and lab visits.
2. Urine pregnancy test for women of childbearing potential only.
3. T/B/NK/monocyte counts (i.e., CD3, CD4, CD8, CD14, CD19, CD16/56), and B cell subsets (i.e., naïve, memory and plasmablasts), at D169, every 6 months during the active treatment period and at End of Study.
4. PT/INR, PTT: only if needed to follow up on bleeding adverse events.

[redacted]

6. *At each dosing cycle, patient should take their dose in the morning before the clinic visit*, and the PK sample is taken at random times after last dose (with time of last dose recorded on CRF, no time window).
7. Full physical exam at End of Study, abbreviated physical exam at all other visits.
8. Removed from protocol version 11.0 and on

Table 6 Schedule of Assessments (protocol version 9.0 to version 14.0 – Extension Period Continued)

	On-treatment clinic visits, visits every 28 days for 6 months, then every 3 months[8]				
	CXD1 (first day of each cycle) Every 28 days for 6 months	**Every 3 months**	**Last day of active rilzabrutinib (PRN1008) treatment**	**End of Study (4 week post last dose)**	**Early Withdrawal/ Unscheduled visit**
Clinic visits[1]	X	X	X	X	X
AEs	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
Weight	X	X	X	X	X
Physical Exam[7]	X	X	X	X	
Vital Signs	X	X	X	X	X
Urinalysis	X	X	X	X	X
Pregnancy test[2]	X	X	X	X	X
Serum Chem	X	X	X	X	X
Hematology, differential, retics.	X	X	X	X	X
T/B/NK/monocyte counts[3]	X	X	X	X	
PT/INR PTT	X	X	X	X	
[redacted]					
ITP-BAT Bleeding Scale	X	X	X	X	X

1. Clinic/laboratory visit windows are ± 7 days for all dosing period and lab visits.
2. Urine pregnancy test for women of childbearing potential only.
3. T/B/NK/monocyte counts (i.e., CD3, CD4, CD8, CD14, CD19, CD16/56), and B cell subsets (i.e., naïve, memory and plasmablasts), at D169, every 6 months during the active treatment period and at End of Study.
4. PT/INR, PTT: only if needed to follow up on bleeding adverse events.

[redacted]

6. *At each dosing cycle, patient should take their dose in the morning before the clinic visit*, and the PK sample is taken at random times after last dose (with time of last dose recorded on CRF, no time window).
7. Full physical exam at End of Study, abbreviated physical exam at all other visits.
8. After the initial 6 months of weekly LTE visits patients will visit monthly for an additional 6 months (total of 12 months of LTE) and then every three months until they are no longer on study.

3 ANALYSIS CONSIDERATIONS

3.1 Type of Analyses

The analyses and documentation described in this SAP are for the final analysis of the study.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

All patients who have enrolled into the study will be included in the Intent-to-Treat (ITT) population. Enrolled patient is defined as patient who signed the informed consent form and was not reported as a screen failure on the eCRF. Summaries of baseline characteristics and efficacy analyses will be done in the ITT population.

3.2.2 Safety Population

All patients who have received at least one dose of rilzabrutinib will be included in the Safety population. Summaries of adverse events and other safety parameters will be done in the Safety population.

3.3 Treatment Groups

3.3.1 Treatment Group Labels

The following treatment group labels will be used in the tables, listings and figures:

Treatment Group Label	Patients Included
Overall	All patients in the population will be included in this group.
Starting Dose 200 mg QD Starting Dose 400 mg QD Starting Dose 300 mg BID Starting Dose 400 mg BID	Patients will be classified to these groups according to the starting dose received. Each patient will be assigned to only one of these groups.
200 mg QD 400 mg QD 300 mg BID 400 mg BID	Patients are evaluable in the dose group(s) if the dose level was received during the defined period (Sections 3.4.1and 3.5.2). Since most patients received more than one dose, a given patient can be assigned to multiple dose levels. For each of the following type of analyses, patients will be classified to each dose level based on:

Treatment Group Label	Patients Included
	• Dose level received prior to the visit for responder analyses, time-to analyses and analyses of proportion of patients meeting an endpoint, i.e., percent of weeks with platelet counts ≥ 50,000/μL. • Dose level received at the onset of event for adverse events, and bleeding events analyses. Adverse events started after date of last dose of study drug will be attributed to the last dose level received. • Dose level received during the time the medication was taken for any medication analyses. Medications taken after date of last dose of study drug will be attributed to the last dose level received.

3.4 Analysis Timepoints and Definitions

3.4.1 Observation Period

The observation period will be divided into 3 segments:

1) The **pre-treatment period** is defined as the period to the date of first dose of study drug.
2) The **on-treatment period** is defined as the period from the first dose of study drug to the last dose of study drug + 1. The on-treatment period includes the main treatment period and the LTE period.
   - **Main on-treatment period** is defined as from the date of first dose of study drug
     - to the date of the last dose of study drug + 1, if the patient did not enter LTE.
     - to the date before the first dose of study drug during LTE, if the patient entered LTE. Date of first dose in LTE is based on the date of dosing reported on C1D1_LTE Study Drug Administration eCRF.
3) The **post-treatment period** is defined as the period from the end of the on-treatment period. That is, the 4-week post treatment follow up period per protocol.

3.4.2 Analysis Period

There are primarily 3 analysis periods for safety analyses:

1) Main period is
   - Main on-treatment period + FU, if the patient did not enter LTE
   - Main on-treatment period only, if the patient entered LTE
2) LTE period is LTE on-treatment period + FU
3) Main and LTE period combined, if the patient entered LTEs

Efficacy analyses will be based on on-treatment period (i.e., up to end of treatment +1 day), with the exception of descriptive analyses which will include post-treatment follow up visits.

3.4.3 Study Visits

For protocol version 7.0, the study visits are:

- Screening
- Cycle X Day 1, Cycle X Day 8, Cycle X Day 15 and Cycle X Day 22, where X <= 3
- Day 85 (Last day of active rilzabrutinib treatment)
- Day 113 (Follow-up visit)
- Day 141 (Follow-up visit)
- Day 169 (End of Study visit)
- Early Withdrawal
- Unscheduled visit
- Laboratory Only Visits for Hematology, differential & retics: Days 92, 99, 106, 120, 127, 134, 148, 155, 162 and 169) (Follow-up visit)

For protocol version 8.0, the study visits are:

- Screening
- Cycle X Day 1, Cycle X Day 8, Cycle X Day 15 and Cycle X Day 22, where X ≤ 6
- Day 169 (Last day of active rilzabrutinib treatment)
- Day 197 (End of Study visit)
- Early Withdrawal
- Unscheduled visit
- Laboratory Only Visits for Hematology, differential & retics: Days 176, 183 and 190) (Follow-up visit)

For protocol version 9.0 to version 14.0, the study visits are:

- Screening
- Cycle X Day 1, Cycle X Day 8, Cycle X Day 15 and Cycle X Day 22, where X ≤ 10
- LTE: LTE Cycle X Day 1, LTE Cycle X Day 8, LTE Cycle X Day 15 and LTE Cycle X Day 22, where X ≤ 6
- LTE – monthly visit: LTE Cycle X Day 1, where 7 ≤ X ≤ 12
- LTE – every 3 months visit: LTE Visit X, where X ≥ 1 (until patients no longer on study)
- Last day of active rilzabrutinib treatment
- End of Study
- Early Withdrawal
- Unscheduled visit
- Laboratory Only Visits for Hematology, differential & retics: Days 176, 183 and 190) (Follow-up visit)

All scheduled visits will be used for descriptive summary. Unscheduled visits will be included in the derivation of 'Last value on-treatment' defined in section 3.4.4.

3.4.4 Analysis Visits

In addition to study visits described above, analysis visits based on dosing cycle of each dose level will be derived for descriptive summary during the main treatment period as follows:

- 1st Cycle of Exposure: Day 1, Day 8, Day 15 and Day 22
- 2nd Cycle of Exposure: Day 1, Day 8, Day 15 and Day 22
- 3rd Cycle of Exposure: Day 1, Day 8, Day 15 and Day 22
- 4th Cycle of Exposure: Day 1, Day 8, Day 15 and Day 22
- 5th Cycle of Exposure: Day 1, Day 8, Day 15 and Day 22
- 6th Cycle of Exposure: Day 1, Day 8, Day 15 and Day 22
- Xth Cycle of Exposure: Day 1, Day 8, Day 15 and Day 22 – for patients who had treatment cycle(s) beyond Cycle 6
- Last value on-treatment (Last post-baseline visit during the main on-treatment period including unscheduled visits within each dose level)

For example, if a patient received 200 mg QD at Cycle 1, 400 mg QD at Cycle 2 and Cycle 3 and 300 mg BID at Cycle 4 and Cycle 5, the scheduled visits will be mapped to the analysis visits as follows:

Dose Level	Scheduled Visit	Analysis Visit
200 mg QD	Cycle 1 – Day 1, 8, 15 and 22	200 mg QD: 1st Cycle of Exposure – Day 1, 8, 15 and 22
400 mg QD	Cycle 2 – Day 1, 8, 15 and 22	400 mg QD: 1st Cycle of Exposure – Day 1, 8, 15 and 22
400 mg QD	Cycle 3 – Day 1, 8, 15 and 22	400 mg QD: 2nd Cycle of Exposure – Day 1, 8, 15 and 22
300 mg BID	Cycle 4 – Day 1, 8, 15 and 22	300 mg BID: 1st Cycle of Exposure – Day 1, 8, 15 and 22
300 mg BID	Cycle 5 – Day 1, 8, 15 and 22	300 mg BID: 2nd Cycle of Exposure – Day 1, 8, 15 and 22

Note: Visits occurred at and after the visit where dose reduction occurred will not be mapped.

3.4.5 Baseline for Platelet Count

The average of the 2 screening results and the Cycle 1 Day 1 result will be used as the Baseline value for platelet count. If at least one of the platelet counts is missing, the average of the non-missing platelet counts will be used. This baseline value will be used for the main treatment period and LTE period analyses.

3.4.6 Baseline for Lab and Vital Signs

If measurement date and time are available, the last value measured prior to the date and time of first rilzabrutinib treatment will be used as the Baseline value for labs and vital signs.

If only the measurement date is available but time is not available, the value measured at Cycle 1 Day 1 will be used as the Baseline value. If Cycle 1 Day 1 result is missing and the screening result is available,

then the screening result will be used as Baseline. This baseline value will be used for the main treatment period and LTE period analyses.

3.4.7 Baseline for ECG

The average of the non-missing triplicate ECG results measured at Cycle 1 Day 1 will be used as the Baseline value for the numerical ECG parameters. If all 3 results at Cycle 1 Day 1 are missing, the single value measured at Screening will be used as Baseline.

For the categorical result of overall ECG assessment, the worst finding of the triplicate assessments collected at Cycle 1 Day 1 will be used as the Baseline result. If all 3 results are missing, the overall ECG assessment collected at Screening will be used as Baseline.

3.4.8 Pre-treatment vs. treatment emergent adverse events

Pre-treatment events are the events that started prior to the first study drug dosing.

Treatment emergent adverse events (TEAEs) are the events started on or after the first study drug dosing. The CRF variable "Did this AE occur before the first dose?" will be used if the start date of the event is the same as the date of first study drug dosing.

3.4.9 Prior medications vs. concomitant medications

Medications will be classified as follows:

- Prior medications are those the participant used prior to first dose study drug. Prior medications can be discontinued before first dose of study drug or can be ongoing during treatment period.
- Concomitant medications are any interventions received by the patient concomitantly to study drug during the on-treatment period, i.e., from date of first dose of study drug to the date of last dose of study drug +1.

  Per protocol patients are not allowed to initiate new ITP medication after 1st dose of study drug unless it is a rescue medication. Thus, concomitant non-rescue ITP medication would include ITP medication started prior to the 1st dose and ongoing up to the date of last dose of study drug +1 only.
- Post-treatment medications are those the patient took in the period running from the end of the concomitant medications period up to the end of the study.

A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

3.4.10 Study Day

The date of first study drug dosing is considered as Study Day 1.

- Study Day = (Date of assessment – date of first dose + 1), if the assessment date is on or after the date of first dose.
- Study Day = (Date of assessment – date of first dose), if the assessment date is prior to the date of first dose.

3.4.11 Completed 24 Weeks of Main Treatment

Completed 24 weeks of main treatment = (Date of last dose in main study – Date of first dose + 1) >= 165 days, taking into consideration of +/- 3 days visit window

3.4.12 Duration of ITP (primary or secondary) (years)

Duration of disease (years) = ((Date of first study drug dosing – Date patient was diagnosed with ITP+ 1)/30.4375)/12

3.4.13 Time since Most recent prior therapy/Splenectomy (months)

Time since event (months) = (Date of first study drug dosing – Date of event + 1)/30.4375. For patients who are still on their most recent therapy, this will equal 0.

3.5 Data Handling

3.5.1 Partial dates

For the purpose of categorizing treatment emergent events or mediation period, imputation of day, month and/or year for partial or missing AE onset dates or medication start date will be performed as described below.

- Day, month and year missing
  - Leave as missing, no imputation. In this case, the adverse event will be considered as treatment emergent.
- Day and month missing
  - If year of start date is prior to the year of the 1st dose of rilzabrutinib, then impute day and month as 31-DEC, ELSE
  - If year of start date is the same as the year of the 1st dose of rilzabrutinib, then impute day and month as the day and month of 1st dose of rilzabrutinib, ELSE
  - If year of start date is after the year of the 1st dose of rilzabrutinib, then impute day and month as 01-JAN (Note that this situation is rare, and the sponsor will make every effort to obtain the actual month that the AE started.)
- Only day missing
  - If month and year of start date are prior to the month and year of the 1st dose of rilzabrutinib, then impute day as the last day of the month, ELSE
  - If month and year of start date are the same as the month and year of the 1st dose of rilzabrutinib, then impute day as day of 1st dose of rilzabrutinib, ELSE

- If month and year of start date are after the month and year of the 1st dose of rilzabrutinib, then impute day as 01.

Imputation of day, month and/or year for partial or missing medication stop dates will be performed as described below if the medication is not flagged as "Ongoing". If the imputed start date is after the imputed end date, then the imputed start date will be set to be the same as the imputed stop date.

- Day, month and year missing
  - Leave as missing, no imputation. In this case, the medication will be considered as concomitant.
- Day and month missing
  - If year of stop date is prior to the year of the 1st dose of rilzabrutinib, then impute day and month as the last day of the last month
  - If year of stop date is the same as the year of the 1st dose of rilzabrutinib, then impute day and month as the date prior to the day and month of 1st dose of rilzabrutinib,
- Only day missing
  - If month and year of stop date are prior to the month and year of the 1st dose of rilzabrutinib, then impute day as the last day of the month, ELSE
  - If month and year of stop date are the same as the month and year of the 1st dose of rilzabrutinib, then impute day as the date prior to the day of 1st dose of rilzabrutinib.
  - If month and year of stop date are after the month and year of the 1st dose of rilzabrutinib, then impute day as 01.

Imputation of day and month for other imprecise date such as Date of Diagnosis will be performed as described below.

- If only day is missing, impute as 01
- If day and month are missing, impute as 01-JUL

The imputation of missing or partial dates are for categorization purpose only and will not be used in the listings.

3.5.2 Missing data imputation

An unscheduled platelet count will be allocated to the scheduled visit if it is within the visit window of the scheduled visit with missing platelet count.

Other missing data will not be imputed.

3.5.3 Lab values below or above a threshold

For quantitative analyses, Lab values below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

3.6 Interim Analyses

No interim analysis is planned.

3.7 Handling of Study Center Effects

Study center effects will not be assessed.

3.8 Documentation & Other Considerations

Data are entered electronically into a clinical database built by Medidata RAVE and exported as SAS® datasets. SDTM and ADaM datasets will be generated following the Clinical Data Interchange Standards consortium (CDISC) conventions (SDTMIG v3.2 and ADaMIG v1.1). Summary tables and figures will be produced based on the ADaM datasets and patient data listings will be produced based on the SDTM datasets or raw clinical database. All tables, figures and listings will be produced using SAS® version 9.4.

Medical conditions and AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1, to assign a primary system organ class (SOC) and preferred term (PT) to each AE. Prior and concomitant medications are coded to preferred drug names using the World Health Organization Drug Dictionary (WHODRUG) version (WHO-DDE) B2, September 2017.

Continuous data will be summarized with the following descriptive statistics unless otherwise noted: number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized with frequencies and percentages.

No hypothesis testing will be performed. P-values may be generated for exploratory purpose.

For presentation of continuous data, the mean, median, SD and LS mean will be presented to 1 decimal place greater than the original data and the minimum and maximum will have the same number of decimal places as the original data. The format for minimum and maximum will be “Min, Max”. Standard deviation will be abbreviated as “SD” and standard error will be abbreviated as “SE”. For presentation of categorical data, percentage will be reported to 1 decimal place. Confidence Intervals (CI), difference in percentage and CI will be reported to 2 decimal places.

3.9 Data base lock

The database is planned to be locked approximately 4-6 weeks after all patients have completed or discontinued the main study period.

4 STATISTICAL METHODS

4.1 Primary Efficacy Endpoints

The primary efficacy endpoint is:

- Proportion of patients able to achieve two or more consecutive platelet counts, separated by at least 5 days, of ≥ 50,000/µL AND an increase of platelet count of ≥ 20,000/µL from baseline, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count.

4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

1) Percent of weeks with platelet counts ≥ 50,000/µL by dose level and overall
2) Proportion of patients with 4 out of the final 8 platelet counts ≥ 50,000/µL across all dose levels
3) Change from baseline to the average of the post Day 1 platelet counts by dose level and overall for patients had > 4 weeks of study drug on that given dose level
4) Number of weeks with platelet counts ≥ 50,000/µL across all dose levels
5) Number of weeks with platelet counts ≥ 30,000/µL across all dose levels
6) Time to first platelet count ≥ 50,000/µL across all dose levels

4.3 Exploratory Measures

4.4 Pharmacokinetic Outcome Measures

Plasma pharmacokinetic (PK) parameters (C_{max}, T_{max}, AUC, $t_{1/2}$, V/F, CL/F) of rilzabrutinib in ITP patients will be evaluated in each patient based on frequent sampling on Day 1 of a new, higher dosing level and

reported by dose and, if relevant, overall. Exploratory analyses will pool these data with the data from other studies of rilzabrutinib.

4.5 Changes to Planned Analyses from the protocol

Change	Description	See SAP section
Analysis populations	The Screening and ITT Exposed population defined in protocol sections 10.7.1 and 10.7.3 were replaced by: • Intent-to-Treat (ITT) population All summarises of baseline characteristics and efficacy analyses will be done in the ITT population.	3.2
Secondary endpoints	The following secondary endpoints defined in protocol section 10.3 are replaced: 1) Proportion of patients able to achieve two or more platelet counts of ≥ 50,000/µL AND increase of platelet count of ≥ 20,000/µL from baseline at any time (on treatment or during follow up) without use of rescue medication in the 4 weeks prior to the latest elevated platelet count 2) Proportion of patients able to achieve two or more platelet counts, separated by at least 5 days, representing an increase of platelet count of ≥ 20,000/µL from baseline, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count 3) Proportion of patients able to achieve two or more platelet counts, separated by at least 5 days, of ≥ 100,000/µL, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count 4) Change from baseline to the average of the last two platelet counts at each dosing level 5) Time to first platelet response (as defined in the primary endpoint) 6) Proportion of patients that completed 24 weeks of treatment and demonstrated a platelet response defined as platelet counts ≥ 50,000/µL at ≥ 50% of the visits during the last 8 weeks of the active treatment period With the following secondary endpoints: 1) Percent of weeks with platelet counts ≥ 50,000/µL by dose level and overall	4.2

Change	Description	See SAP section
	2) Proportion of patients with 4 out of the final 8 platelet counts ≥ 50,000/µL across all dose levels 3) Change from baseline to the average of the post Day 1 platelet counts by dose level and overall for patients had > 4 weeks of study drug on that given dose level 4) Number of weeks with platelet counts ≥ 50,000/µL across all dose levels 5) Number of weeks with platelet counts ≥ 30,000/µL across all dose levels 6) Time to first platelet count ≥ 50,000/µL across all dose levels The following secondary endpoints defined in protocol section 10.3 are defined as safety endpoints in section 5.5: 1) Percentage of participants receiving rescue medication at each dosing level and overall 2) Proportion of patients with a Grade 2 or higher bleeding event at each dosing level and overall 3) Bleeding scale (ITP Bleeding Assessment Tool [ITP-BAT]) at the end of treatment period for each dosing level	
Additional exploratory endpoints	[redacted]	4.3

Change	Description	See SAP section
Additional efficacy analyses	Subset analysis and predictive platelet count analysis are added for the primary efficacy endpoint.	5.4.1.1 and 5.4.1.2
Additional safety endpoints	The following new safety endpoints were defined as secondary efficacy endpoints in the protocol: 4) Percentage of participants receiving rescue medication at each dosing level and overall 5) Proportion of patients with a Grade 2 or higher bleeding event at each dosing level and overall 6) Bleeding scale (ITP Bleeding Assessment Tool [ITP-BAT]) at the end of treatment period for each dosing level	5.5

5 ANALYSIS DETAILS

All study visits including the LTE visits will be included for the patient disposition tables and listings when applicable. Data collected during the LTE period will be summarized for the efficacy and safety analyses as needed.

5.1 Patient Disposition, Demographics and Baseline Characteristics

The ITT population will be used for patient disposition, demographics and baseline characteristics. Descriptive statistics will be done by starting dose and overall, unless specified otherwise. Patient data listings will be listed by starting dose, patient ID and start date of event, if applicable.

5.1.1 Patient Disposition

The number and percentage of patients will be tabulated for patients who:

- Enrolled into the study
- Received at least one dose of study drug
- Completed the main study
    - Completed 24 weeks of treatment (defined in section 3.4.11)
- Entered into LTE
    - Ongoing in LTE
    - Withdraw from LTE
        - Primary reason for withdrawal
- Did not enter into the LTE period
- Early withdraw from main study
    - Primary reason for early discontinuation

The number of percentages of patients enrolled by country and study site will also be tabulated. Frequency table will also be created for the number and percentage of patients in each analysis populations.

Disposition information will be listed by starting dose.

Reason for Screen failures will be summarized.

5.1.2 Demographics and Baseline Characteristics

Demographics variables including age, age group (< 65 and >= 65 years; interquartile range), gender, method of birth control for female patients, race, ethnicity, height at screening, weight at screening and body mass index (BMI) at screening will be summarized by descriptive statistics.

5.1.3 ITP History

ITP history data including type of ITP (primary or secondary), duration of ITP (primary or secondary) (years), average of the most recent and second most recent screening platelet count, baseline platelet count, time since the most recent prior therapy resulted in a platelet response (months), splenectomy done (Y/N) , time since splenectomy (months), number of prior ITP therapies, number of prior corticosteroids ITP therapies, number of prior TPO-RAs ITP therapies, number of other ITP therapies, and the last treatment that the patient responded to will be summarized and listed.

The number of prior ITP therapies is based on the record identifier of ITP medications. Splenectomy will be counted as one prior ITP therapy.

5.1.4 Medical History

Medical history events will be coded using MedDRA version 20.1. The medical history events, other than ITP, will be summarized by primary system organ class (SOC) and preferred term (PT) for each starting dose and overall.

Medical history data will be listed.

5.1.5 Prior and Concomitant Medications

All medications will be coded according to the WHODRUG dictionary WHO-DDE B2, September 2017.

The following medications will be summarized by Level 4 classification and preferred name for ITP and rescue medications, and by Levels 2 and 3 classifications for other medications for each starting dose and overall:

- Prior ITP medications
- Other prior medications

Concomitant and post-treatment medications will be summarized for each dose level and overall:

- Non-rescue ITP medications taken during the main on-treatment period
- Non-rescue ITP medications taken during the LTE on-treatment period
- ITP medications taken post treatment period
- Rescue medications taken during the main period
- Rescue medications taken during the LTE period
- Other concomitant and post-treatment medications taken during the main period
- Other concomitant and post-treatment medications taken during the LTE period

Medications will be attributed to the dose level where the medication is taken during the dose level. The same medication may be attributed to more than one dose level. Medications started after the date of last dose of study drug will be attributed to the last dose level received.

Separate listings will be provided for each category of medications.

5.2 Protocol Deviations

Protocol deviations will be identified and classified into minor vs. major by the Sponsor prior to database lock. The categories of protocol deviations are: Concomitant Medication, IP and Dosing, Enrollment Criteria, Informed Consent, Laboratory/Procedures Required, Safety and Visit Schedule.

Major protocol deviations will be tabulated by the deviation categories, starting dose and overall for patients who are in the ITT population.

A patient data listing with deviation category and deviation details will be provided for patients with major protocol deviations.

Patients impacted by Covid-19 will be summarized upon data availability, such as discontinuation due to Covid-19, protocol deviation due to Covid-19, and visit(s) impacted by Covid-19 as collected in eCRF, etc.

5.3 Study Drug Treatment Exposure and Compliance

Study drug treatment information will be summarized and documented in the Safety Population. Descriptive statistics will be done for all patients in the main treatment period and in the LTE treatment period in separate tables, as well as for main + LTE period. Patient data listings will be listed by starting dose, patient and study visit.

5.3.1 Actual Duration of Study Drug Exposure (days)

- Actual duration of study drug exposure in main treatment period (days) = (Date of last dose in main treatment period – Date of first dose in main treatment period) + 1, regardless of unplanned intermittent interruption

- Actual duration of study drug exposure in LTE treatment period (days) = (Date of last dose in LTE treatment period – Date of first dose in LTE treatment period) + 1, regardless of unplanned intermittent interruption

In addition, duration of treatment exposure will also be summarized categorically by cycles.

5.3.2 Actual Total Cumulative Dose (mg)

Actual total cumulative dose in main treatment period (mg) = Sum of (Dose $Level_i$ (x2 if BID) x actual duration of study drug exposure in main treatment period for Dose $Level_i$ – total # of doses missed in Dose $Level_i$ during main treatment period))

Actual duration of study drug exposure in main treatment period for each dose level will be based on (Date of last dose in Dose $Level_i$ – Date of first dose in Dose $Level_i$) + 1, regardless of unplanned intermittent interruption

For patients who only had one dose level, the actual duration of Dose $Level_i$ is the same as duration of study drug exposure in Section 5.3.1.

For patients with more than one dose levels:

- Date of first dose for the starting dose level is date of first dose taken at Cycle 1 Day 1.
- Date of first dose for the subsequence dose levels is the date of dosing reported on the Study Drug Administration eCRF where a dose adjustment was made. If the date of dosing is missing, then the date of visit where dose adjustment made will be used.
- Date of last dose for Dose Level$_i$ is the date of first dose of the next dose level – 1..
- Date of last dose for the last dose level is the date of last dose reported on the End of Study form.

Actual total cumulative dose in LTE treatment period (mg) = 400 mg x2 if BID x actual duration of study drug exposure in LTE treatment period – total # of doses missed in LTE treatment period)

5.3.3 Actual Average Daily Dose (mg/day)

Actual average daily in main treatment period (mg/day) = Actual total cumulative dose in main treatment period (mg)/ Actual duration of study drug exposure in main treatment period (days)

Actual average daily in LTE treatment period (mg/day) = Actual total cumulative dose in LTE treatment period (mg)/ Actual duration of study drug exposure in LTE treatment period (days)

5.3.4 Study Drug Compliance (%)

Compliance with study drug will be calculated as the actual total cumulative dose (mg) taken divided by the planned number of doses (mg), i.e., do not adjust for missed doses, expressed as a percentage.

Compliance will be summarized by descriptive statistics for the main treatment period and LTE treatment period. The number and percentage of patients with 100% compliance, greater than 80% but less than 100% compliance and less than 80% compliance will be tabulated.

5.4 Efficacy Analyses

The ITT population will be used for all efficacy analyses. For analyses of a particular study drug dose level, all patients who received that dose at least once will be included.

Rescue medication is defined as any therapy used to rescue a patient (one of intravenous immunoglobulin [IVIG], high-dose steroids, platelet infusion or anti-D immunoglobulin infusion). A rescue therapy may be used if there is a significant safety event requiring 'rescue' from a deterioration in the patient's platelet count that in the opinion of the investigator puts the patient at significant risk of a safety event. Patients who take rescue while on study will be discontinued. Response status for patients who receive rescue therapy while on study will be evaluated using the platelet counts up until the time of rescue therapy.

The descriptive statistics for the main treatment period will be done by starting dose and overall for all study visits and by cycle of exposure (as appropriate), unless specified otherwise. All binomial confidence intervals for efficacy analyses will use the Clopper-Pearson method. Descriptive summary will be generated for data collected during the LTE period as needed. Patient data listings will be listed

by starting dose, patient, dose level and study visit, including both of the main treatment period and LTE period.

5.4.1 Primary Efficacy Endpoint

Platelet count is measured at visits as specified in the Schedule of Assessments (Table 3 to Table 6).

The primary efficacy endpoint is:

- Proportion of patients able to achieve two or more consecutive platelet counts, separated by at least 5 days, of ≥ 50,000/µL AND an increase of platelet count of ≥ 20,000/µL from baseline, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count.

The number and percentage of patients who meet the primary efficacy endpoint criteria in the main treatment period will be tabulated by dose level and overall. A 95% confidence interval will be calculated for the proportions using the Clopper-Pearson method. The response will be attributed to the dose level at the visit prior to the first of the two consecutive scheduled platelet counts occurred that are at least 5 days apart, see table below. A patient can have multiple responses within the same dose level and/or at different dose levels. This table will be repeated by starting dose.

Example 1: Patient had a response at 200 dose only

Visit	Dose dispensed at this visit	Platelets	Response	Dose that response is attributed to
C1D1	200	25		
C1D8	200	30		200
C1D15	200	35		200
C2D1	400	51	Y	200
C2D8	400	55		400
C2D15	400	42		400
C3D1	600	39		400
C3D8	600	40		600
C3D15	600	41		600

Example 2: Patient had a response at 200 and 400 doses.

Visit	Dose dispensed at this visit	Platelets	Response	Dose that response is attributed to
C1D1	200	25		
C1D8	200	30		200
C1D15	200	35		200
C2D1	400	51	Y	200
C2D8	400	55	Y	400
C2D15	400	53		400
C3D1	600	39		400
C3D8	600	40		600
C3D15	600	41		600

Example 3: Patient had a response at 200 and 600 doses.

Visit	Dose dispensed at this visit	Platelets	Response	Dose that response is attributed to
C1D1	200	25		
C1D8	200	30		200
C1D15	200	35		200
C2D1	400	51	Y	200
C2D8	400	55		400
C2D15	400	42		400
C3D1	600	43		400
C3D8	600	59	Y	600
C3D15	600	59		600

Example 4: Patient had a response at 200, 400 and 600 doses.

Visit	Dose dispensed at this visit	Platelets	Response	Dose that response is attributed to
C1D1	200	25		
C1D8	200	30		200
C1D15	200	35		200
C2D1	400	51	Y	200
C2D8	400	55	Y	400
C2D15	400	53		400
C3D1	600	39		400
C3D8	600	59	Y	600
C3D15	600	59		600

Time-series graphs will be provided for platelet counts over the duration of the study for each patient. This individual platelet profile will distinguish main, LTE and FU period, display the dose levels the

patient received, and indicate the clinically relevant responding platelet levels and when the patient received rescue therapy.

Descriptive summary will be generated for the main and LTE period.

Graphical presentation of the results (i.e., spaghetti plot, line plot, etc.) may also be explored.
Depending on the impacts of Covid-19, sensitivity analyses on the primary endpoint may be performed.

5.4.1.1 Subset Analyses

The robustness of the primary endpoint results will be explored by calculating the number and percent of patients meeting the primary efficacy endpoint overall (i.e., across all doses) within the following patient subsets:

1) Duration of ITP Disease: Persistent vs. Chronic
    a. Persistent: between 3-12 months from date of ITP diagnosis
    b. Chronic: >12 months from date of ITP diagnosis
2) Type of Prior ITP Therapy (TPO-RAs/Steroids)
    a. Patients on prior TPO-RAs but not on prior steroids
    b. Patients on prior corticosteroids but not on prior TPO-RAs
    c. Patients on prior TPO-RAs AND prior steroids
3) Patients with the following number of prior ITP therapies. The number of prior ITP therapies is based on the record identifier of ITP medications. Splenectomy will be counted as one prior ITP therapy.
    a. 1 prior ITP therapy
    b. 2 prior ITP therapies
    c. 3 prior ITP therapies
    d. 4 or more prior ITP therapies
4) Patients with at least 1 response to
    a. prior TPO-RAs
    b. prior corticosteroids
    c. prior fostamatinib
    d. prior rituximab
    e. prior IVIG
    f. Other prior immunosuppressive agents (i.e.: Dopsone, Azathioprine, Plaquenil, [hydroxychloroquine])
5) Patients who never responded to:
    a. TPO-RA,
    b. fostamatinib
    c. rituximab
6) Patients on rilzabrutinib monotherapy vs. Patients on ITP concomitant therapy (excluding rescue therapies as patients who need rescue therapy are discontinued from the study; status determined based on the patients' use of concomitant ITP therapy). Patients on rilzabrutinib

monotherapy are patients who were on rilzabrutinib only during study treatment period without any concomitant ITP medications.

7) Patients on concomitant ITP medication:
    a. TPO-RA alone
    b. Corticosteroids alone
    c. Both TPO-RA and steroids (with or without other ITP medications)
    d. No concomitant ITP medication
8) Baseline Platelet Count: ≤15,000/µL vs. >15,000-30,000/µL
9) Patients who had 24 weeks of study drug under protocol version 8 (see section 3.4.11).
10) Patients who were TPO-RA naïve, i.e., never received TPO-RA medications

All ITP therapies will be reviewed and categorized into different types of ITP therapies, i.e. TPO-RA, corticosteroids, fostamatinib, etc. manually by the medical reviewer and a look-up dataset will be created for the analyses.

Subset analyses will not be repeated for the LTE period.

5.4.1.2 Predictive Platelet Count Analysis

The following three (3) predictive values of platelet count will be crossed tabulated in a performance metrics with two platelet outcomes.

Predictive values of platelet count:

i. ≥ 30,000/µL on Study Day 8
ii. ≥ 20,000/µL above baseline on Study Day 8
iii. ≥ 50,000/µL at any time over the first 8 weeks of study drug treatment

Platelet outcome variables:

i. Primary efficacy response – Achieved primary efficacy platelet response (see Section 5.4.1)
ii. Durability of response – Achieved 8 out of final 12 platelet counts ≥ 50,000 µ/L (see Section 5.4.3.6)

The performance metrics will be constructed as follow:

	Achieved $outcome_i$	Did not achieved $outcome_i$	Total
Predictive $Value_i$ (Y)	a	b	a + b
Predictive $Value_i$ (N)	c	d	c + d
Total	a + c	b + d	a + b + c + d

The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) will be calculated as:

- Sensitivity = a/(a +c)
- Specificity = d/(b+d)

- PPV = a/(a+b)
- NPV = d/(c+d)

This analysis will be performed for ITT population overall and patients started with 400 mg BID. This analysis will not be repeated for the LTE period.

5.4.2 Secondary Efficacy Endpoints

The analyses of secondary efficacy endpoints will be performed for the main treatment period only.

The number and percent of weeks of platelet counts will based on the number of scheduled weekly platelet assessments (i.e., not by study day) and only weeks with non-missing platelet counts will be included in the calculations.

5.4.2.1 Percent of weeks with platelet counts ≥ 50,000/µL by dose level and overall

The percent of weeks that patients achieve platelet counts ≥ 50,000/µL in the main treatment period will be summarized across all dose levels. This table will be repeated by starting dose.

5.4.2.2 Proportion of patients with at least 4 out of the final 8 platelet counts ≥ 50,000/µL across all dose levels

The final 8 scheduled platelet counts are the measurements performed in the last 8 weeks of study treatment (depending on treatment duration, not necessarily from Week 17 to Week 24) in the main treatment period and including missing result(s). The number and percentage of patients who had at least 4 out of the final 8 platelet counts ≥ 50,000/µL will be tabulated across all dose levels. Patients with less than 4 platelet counts will be considered as non-responders. A 95% confidence interval will be calculated for the proportions using the Clopper-Pearson method. This summary will be repeated by Starting Dose.

As a sensitivity analysis, this endpoint will be repeated for patients who completed 24 weeks of main treatment where the final 8 scheduled platelet counts are the measurements performed from Week 17 to Week 24.

In addition, this endpoint will be analyzed for patients starting rilzabrutinib 400 BID where the final 8 scheduled platelet counts are the measurements performed from Week 17 to Week 24.

5.4.2.3 Change from baseline to the average of the post Day 1 platelet counts by dose level and overall for patients had > 4 weeks of study drug on that given dose level

The change from baseline to the average of the post Day 1 platelet counts by dose level and overall will be summarized by descriptive statistics for the observed values collected in the main treatment period for patients who had more than 4 weeks of study drug on that given dose level. The number of weeks of study drug will be determined by number of on-study drug visits, eg, Patients who attended Cycle 1 Day 1 and did not discontinue study drug on or before data of Cycle 2 Day 1 visits will be included.

5.4.2.4 Number of weeks with platelet counts ≥ 50,000/µL across all dose levels

The number of weeks that patients achieved platelet counts ≥ 50,000/µL in the main treatment period will be summarized across all dose levels. Summaries will be repeated in these 2 groups of patients: those that intended to finish the study drug at 12 weeks, i.e., patients who enrolled under protocol version v7.0and those that intended to finish at 24 weeks, i.e., patients who enrolled under protocol version 8.0 and up. This table will be repeated by Starting Dose.

5.4.2.5 Number of weeks with platelet counts ≥ 30,000/µL across all dose levels

The number of weeks that patients achieved platelet counts ≥ 30,000/µL in the main treatment period will be summarized across all dose levels. Summaries will be repeated in these 2 groups of patients: those that intended to finish the study drug at 12 weeks, i.e., patients who enrolled under protocol version v7.0 and those that intended to finish at 24 weeks i.e., patients who enrolled under protocol version 8.0 and up. This table will be repeated by Starting Dose.

5.4.2.6 Time to first platelet count ≥ 50,000/µL across all dose levels

Time to first platelet count ≥ 50,000/µL during the main treatment period in days will be calculated as:

(Date of first occurrence of platelet count ≥ 50,000/µL – Date of first study drug dosing) +1

Patients who did not experiencing platelet count ≥ 50,000/µL will be censored

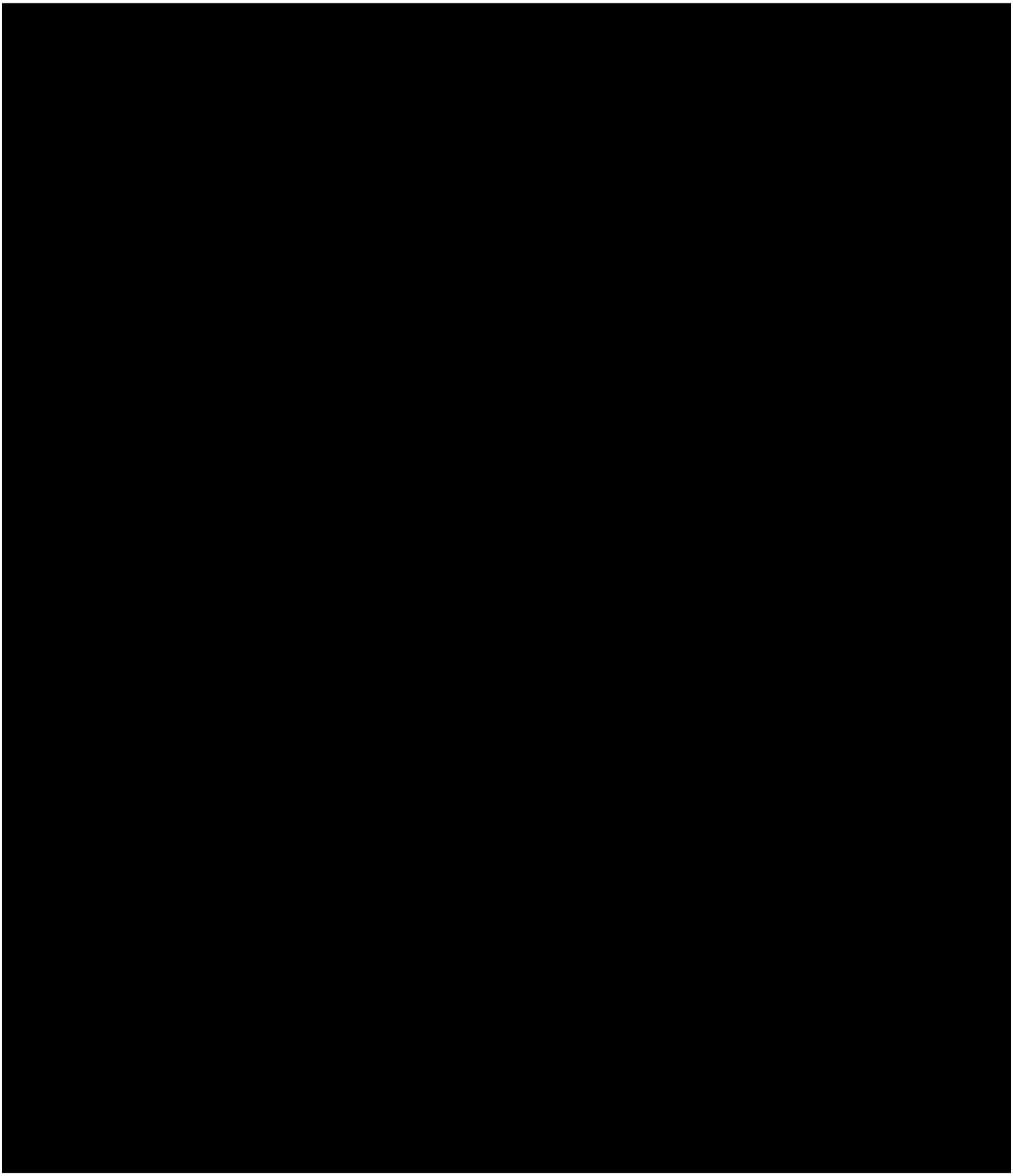
- at the end of the main on-treatment period for those who completed the main treatment period,
- at Week 25 (ie, 1 week after the protocol scheduled Week 24 visit) for those who prematurely discontinued the main treatment due to any AE or lack of response, and
- at the time of discontinuation for those who prematurely discontinued the main treatment due to other reasons.

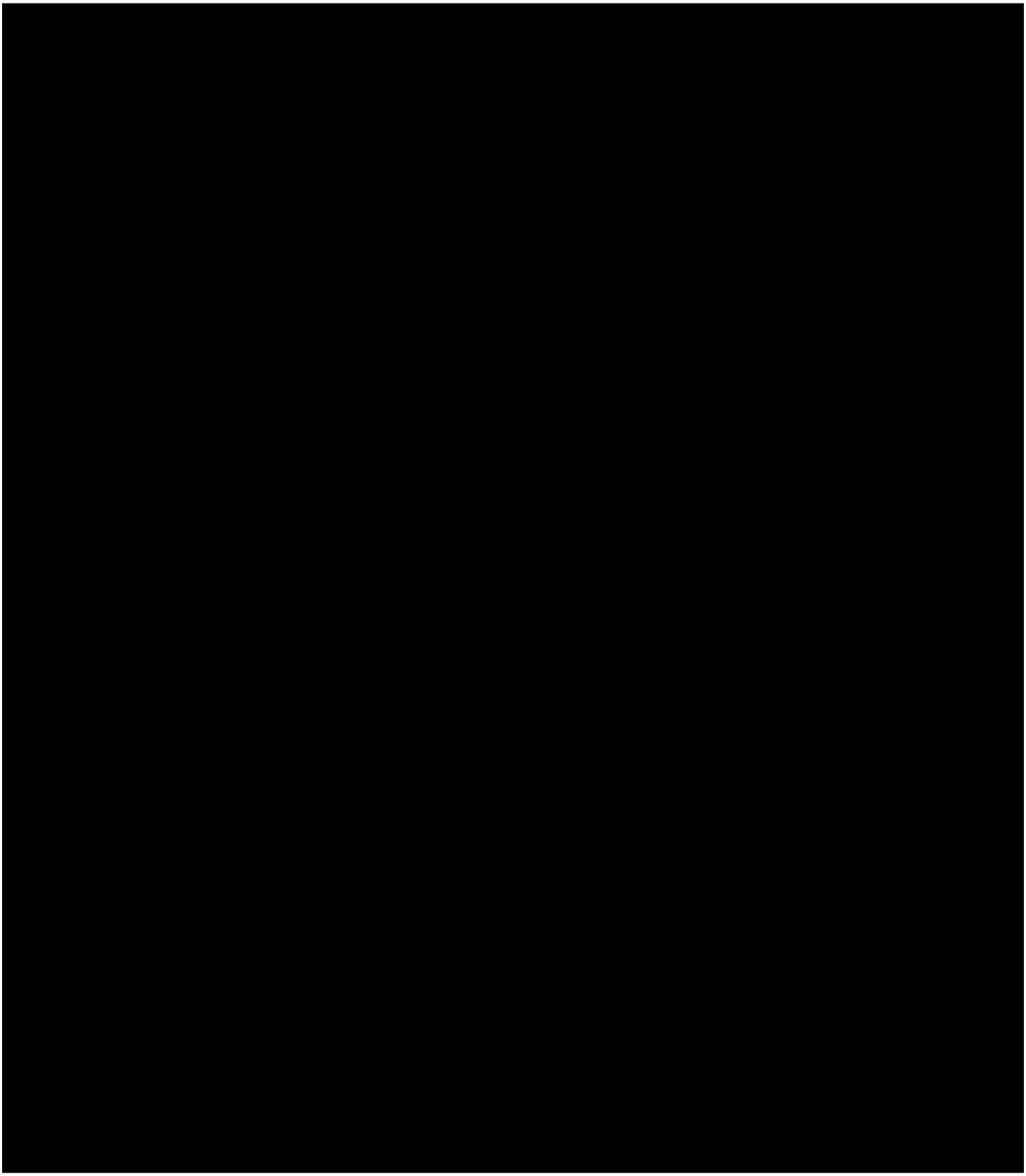
All platelet counts including unscheduled measurements will be included. The number of days to first platelet count ≥ 50,000/µL will be summarized by descriptive statistics for overall across all dose levels.

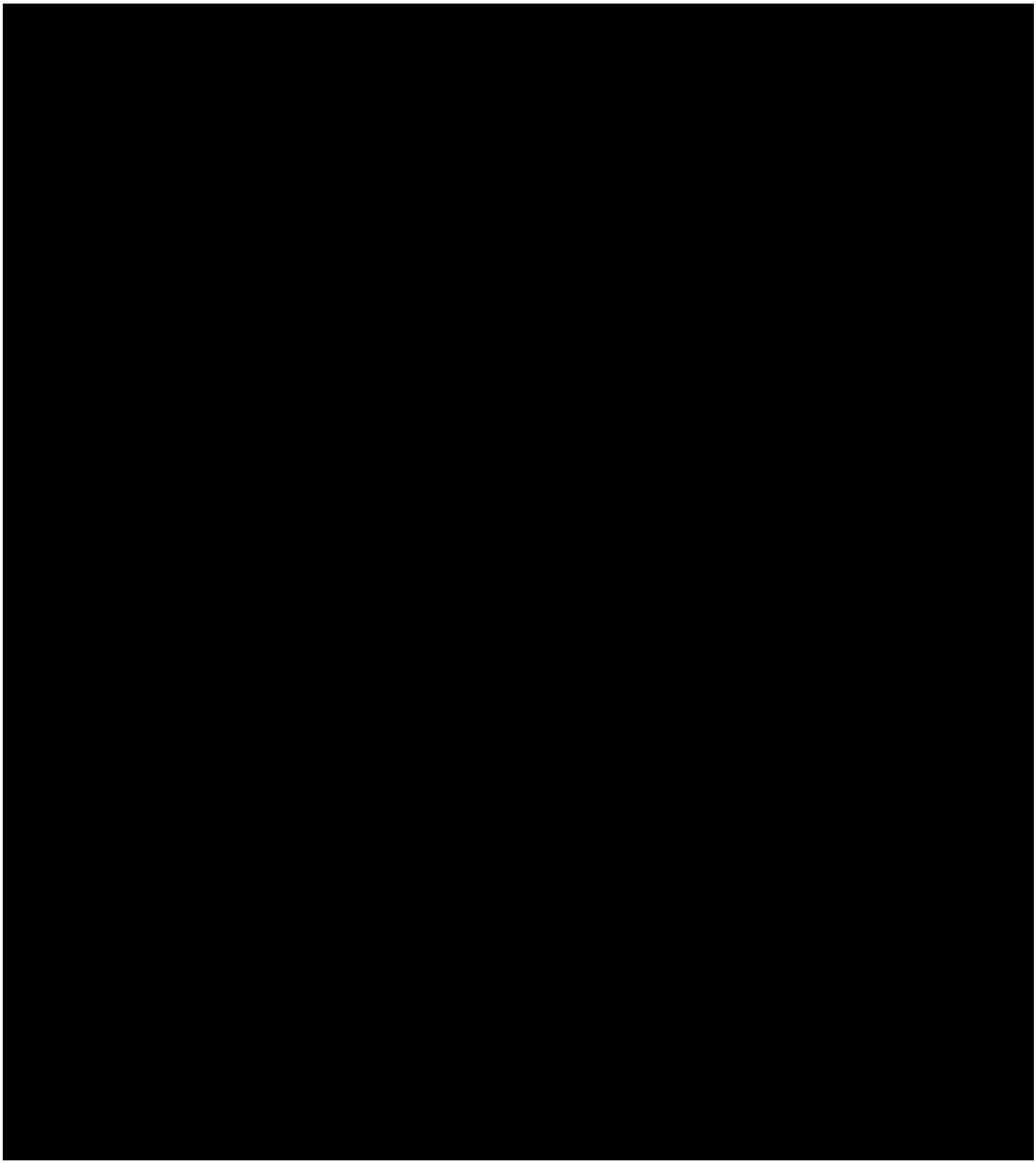
Kaplan-Meier estimates will be calculated for time to first platelet ≥ 50,000/µL. The 25%, median and 75% time to event will be produced with the corresponding 2-sided 95% confidence intervals. Kaplan-Meier plot will also be provided.

5.4.3 Exploratory Efficacy Endpoints

[redacted]







5.5 Safety Analyses

The Safety Population will be used for the safety analyses. The summary statistics for the main period will be done by starting dose and overall for all study visits and by cycle of exposure (as appropriate), unless specified otherwise. Descriptive summary will be generated for data collected during the LTE period as needed.

Patient data listings will be listed by starting dose, patient, dose level and study visit or start date of event if applicable, indicating on-treatment period or LTE on-treatment period.

In addition to standard analyses of all adverse events, dose limiting toxicities, laboratory tests, ECG data, and vital signs, the analyses of safety will include the following endpoints:

1) Percentage of participants receiving rescue medication at each dosing level and overall
2) Proportion of patients with an Intensity Grade 2 or higher bleeding event at each dosing level and overall
3) Bleeding scale (ITP Bleeding Assessment Tool [ITP-BAT]) at the end of treatment period for each dosing level and overall

5.5.1 Adverse Events

TEAEs will be attributed to the dose level where the AE start date is on or after the start date of that dose level and before the next dose level if applicable. TEAEs started after date of last study drug dosing will be attributed to the last dose level received.

The following summaries of adverse events will be provided:

Summary	All patients (By Dose Level and Overall)	LTE patients	
	Main Period	Main + LTE Period	LTE Period
Overview of adverse event profile: Treatment emergent adverse events	X	X	X
TEAEs by primary SOC and PT (number of patients, number of events and event rate)	X	X	X
TEAEs reported in >=5% patients by PT in descending order (number of patients)	X		
TEAE leading to study drug discontinuation by primary SOC and PT (number of patients)	X	X	X
TEAE leading to death by primary SOC and PT (number of patients)	X		
Treatment emergent SAE by primary SOC and PT (number of patients)	X	X	X
TEAEs by the maximum intensity, primary SOC and PT (number of patients)	X	X	X
Related TEAEs by primary SOC and PT (number of patients, number of events and event rate)	X	X	X
Related TEAEs by the maximum intensity grade, primary SOC and PT (number of patients)	X	X	X
TEAEs intensity Grade>=3 by primary SOC and PT (number of patients)	X	X	X
Bleeding events by primary SOC and PT (number of patients, number of events and event rate)	X (for overall only)	X	X
Related bleeding events by primary SOC and PT (number of patients, number of events and event rate)	X (for overall only)	X	X
Bleeding events (Intensity Grade 2 or higher) by primary SOC and PT (number of patients, number of events and event rate)	X	X	X
Related bleeding events (Intensity Grade 2 or higher) by primary SOC and PT (number of patients, number of events and event rate)	X	X	X
TEAEs by primary SOC and PT and by age group (<65, >=65 years) (number of patients)	X		

Summary	All patients (By Dose Level and Overall)	LTE patients	
	Main Period	Main + LTE Period	LTE Period
TEAEs by primary SOC and PT and interquartile age group (number of patients)	X		
TEAEs by primary SOC and PT and by gender (male, female) (number of patients)	X		
TEAEs by primary SOC and PT and by concomitant ITP medications (No concomitant ITP medication, Corticosteroids alone, TPO-RA alone, Corticosteroids + TPO-RA) (number of patients)	X		

"X" represents a summary table will be provided.

Patients with multiple events within a particular primary SOC or PT within each dose level/study period will be counted once within that dose level/study period. Adverse events will be sorted by primary SOC internationally agreed order and within each primary SOC, by overall descending frequency of PT. For primary SOC or PT with tied frequency, they will be sorted in alphabetical order.

Event rate is calculated as number of patients with an event divided by total patient year during the respective observation period.

For by maximum severity tables, patients with multiple events within a particular primary SOC or PT will be counted once under the maximum intensity grade.

The following AE tables will be created for the "overall" group:

- Pre-treatment AEs by primary SOC and PT (number of patients)
- Post-treatment AEs by primary SOC and PT (number of patients)

Patient data listings will be generated for:

- AEs
- SAEs
- AE leading to study drug discontinuation

5.5.2 Dose Limiting Toxicity (DLT)

The DLT definition is described in section 4.2 of the protocol. A patient data listing will be provided for all DLTs, if any.

5.5.3 Percentage of patients receiving Rescue Medication at each dose level and overall

The proportion of patients receiving rescue medications will be tabulated for each dose level and overall. 95% confidence interval will be calculated for the proportion using the Clopper-Pearson method.

A separate table will be generated for rescue medications taken during the LTE period.

Rescue medications taken will be listed in a patient data listing.

5.5.4 Proportion of patients with an Intensity Grade 2 or higher Bleeding Event at each dose levels and overall

Preferred terms of TEAEs that may be evidence of bleeding events will be identified by SMQ (broad search of SMQ = Haemorrhages) and then medically determined after final coding review and before database lock and a look-up dataset will be created for the analysis.

A bleeding event will be attributed to the dose level where the event start date is on or after the start date of that dose level and before the next dose level if applicable. The proportion of patients with at least one Intensity Grade 2 or higher bleeding event will be tabulated for each dose level and overall. A 95% confidence interval will be calculated for the proportion by using the Clopper-Pearson method.

A patient data listing will be provided for all bleeding events.

5.5.5 Bleeding scale (ITP Bleeding Assessment Tool (ITP-BAT) at the end of main treatment period for each dose level

ITP-BAT Scale (Rodeghiero 2013) is assessed at visits specified in the Schedule of assessments (Table 3 and Table 6).

The ITP-BAT Scale comprises of 11 grades from 0 (none) to 2 (marked bleeding) assessed at nine anatomical sites by history over the previous week (Hx). In addition, two of these sites, skin and oral, were also assessed by physical examination (PE). The 'worst ever' bleeding experienced at each site was graded using the same system.

For each anatomical site, shift from baseline tables will be provided for the worst post-baseline visits.

Summary statistics tables will be generated for the main and LTE period.

The ITP-BAT Scale assessments will be listed in a patient data listing.

5.5.6 Laboratory Data

The following laboratory parameters are measured at visits specified in the Schedule of Assessments (Table 3 and Table 6).

Laboratory Panel	Test Parameters
Hematology	**White Blood Cells:** White Blood Cells, Basophils Absolute, Basophils Percent, Eosinophils Absolute, Eosinophils Percent, Lymphocytes Absolute, Lymphocytes Percent, Monocytes Absolute, Monocytes Percent, Neutrophils Absolute, Neutrophils Percent, Bands Absolute*, Bands Percent*, Metamyelocytes Absolute*, Metamyelocytes Percent*, Myelocytes Absolute*, Myelocytes Percent*, Blasts Absolute*, Blasts Percent*, Lymphocytes Atypical Absolute, Lymphocytes Atypical Percent, Plasma Cells Absolute, Plasma Cells Percent, Promyelocytes Absolute*, Promyelocytes Percent*, WBC Morphology, **Red Blood cells:** Red Blood Cells, Hemoglobin, Hematocrit, Mean Cell Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hgb Concentration Red Cell Distribution Width, Nucleated RBC Manual Absolute*, Nucleated RBC Manual Percent*, Retic AA, Retic PA, RBC Morphology
Coagulation	PT, INR and aPTT
Serum Chemistry	**Liver function:** Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total bilirubin (TBL), Direct bilirubin, Indirect bilirubin, Alkaline phosphatase (ALP), Albumin, Total Protein, **Renal function:** Creatinine, Urea, **Electrolytes and minerals:** Sodium, Chloride, Calcium, Phosphate, Potassium, **Metabolism:** Glucose (random), Creatinine phosphokinase (CPK)
Urinalysis	pH, Specific gravity, Protein, Glucose, Ketones, Bilirubin, Blood, Nitrites, Urobilinogen, Leukocytes,
T/B/NK/monocyte counts	CD3, CD4, CD8, CD14, CD19, CD16/56 and B cell subsets (i.e. naïve, memory and plasmablasts)

*Summary statistics and shift tables will not be provided for the hematology parameters indicated because they were not consistently assessed for all patients

Shifts from baseline tables will be provided for the laboratory parameters where abnormality (ie, out of normal range) and/or clinically significant abnormality can be determined.

The maximum and minimum values of all post-baseline visits will be summarized.

A special group of clinical laboratory tests, including ALT, AST, TBL and ALP, which are believed to be the indicators for drug induced liver injury (DILI) will be assessed separately. Frequency tables will be used to summarize elevations in these parameters. The following criteria will be documented:

- AST > 3x, 5x, 10x and 20x Upper Limit of Normal (ULN)
- ALT > 3x, 5x, 10x, and 20x ULN
- Total Bilirubin > 1.5x and 2x ULN
- ALP > 1.5x ULN
- ALT or AST > 3x ULN and Total Bilirubin > 1.5x ULN
- ALT or AST > 3x ULN and Total Bilirubin > 2x ULN

Scatter plots of the peak TBL divided by the ULN will be plotted on a log scale against the peak ALT divided by the ULN. Reference lines will be plotted for the ULN for TBL and ALT, 2x ULN for TBL and 3x ULN for ALT. Any patients in the upper right quadrant, which is defined by 2x ULN for TBL and 3x ULN for ALT, would represent cases to be investigate for potential DILI.

Patient data listings will be provided for patients with abnormal CS values (or out-of-normal range values as needed) at any visits.

5.5.7 Vital Signs and Body Weight

Vital signs include blood pressures (BP), pulse, temperature and respiratory rate and body weight are measured at visits specified in the Schedule of assessments (Table 3 and Table 6).

The observed values and change from baseline values will be summarized by visit for each starting dose and overall.

The following ranges will be used to classified the BP and pulse measurements as Low/Normal/High:

- Systolic blood pressure (SBP): 90 to 140 mmHg, inclusive
- Diastolic blood pressure (DBP): 60 to 80 mmHg, inclusive
- Pulse: 50 to 100 bpm, inclusive

Shift from baseline tables will be produced by using the above criteria and the maximum post-baseline values.

Descriptive statistics tables will be generated for the vital sign measurements taken during the main and LTE period.

Patient data listings will be provided patients with out-of-range SBP, DBP or pulse results at any visits.

5.5.8 12-Lead ECG

Single ECG assessment is performed at the Screening, End of Study, Early Withdrawal and Unscheduled visit. Triplicate ECG assessments are performed at pre-dose and at 2 hours post-dose (+/- 15 minutes) on the first day of dosing at each new dose level. For patients continue into a new cycle at the prior dose level, ECG is not required.

The ECG parameters include: heart rate, QT interval, P-R interval, RR interval, QRS duration, QTcF interval and overall ECG assessments (normal, abnormal – not clinically significant (NCS) and abnormal – clinically significant (CS)).

For triplicate ECG assessments, the average of the three numerical values and the worst of the three overall ECG assessments will be used for the summary statistics.

For the numerical values, observed and change from baseline will be summarized by descriptive statistics.

For overall ECG assessments, shift from baseline tables will be for the worst post-baseline assessments.

Descriptive statistics tables will be generated for data collected during the main and LTE period.

A patient data listing will be provided for patients with abnormal CS ECG assessments at any visits.

5.5.9 Physical Examinations

Physical examinations are performed as specified in the Schedule of Assessments (Table 3 and Table 6 Table 4).

At the screening visit, a complete physical examination consists of checking the normality or abnormality of the following body systems: general appearance, skin, eyes, ears, nose, throat, heart, chest/breast, abdomen, neurological system, lymph nodes, spine (skeletal), and extremities.

At other visits, an abbreviated physical examination consists of checking the normality or abnormality of the following body systems: general appearance, skin, abdomen, and cardiorespiratory examination.

Shift from baseline tables will be provided for general appearance, skin, abdomen, and cardiorespiratory examination for the worst post-baseline finding.

Patient data listings will be provided for patients with abnormal CS findings at any visits.

5.5.10 Online Cognitive Testing

Online cognitive tests are performed by using the Cogstate computerized battery at visits as specified in the Schedule of Assessments (Table 3 and Table 6). The four test domains are: Detection test; Identification test; One Back Working Memory Test and One Card Learning Test.

A separate SAP will be created by Cogstate and the cognitive testing results will be summarized in a separate report.

6 SUPPORTING DOCUMENTS

ITP Disease Activity – ITP-BAT Bleeding Assessment

ITP-BAT BLEEDING SCALE

Assess how much bleeding the subject has at the following sites by physical examination and record the severity at each site below

Site	0	1	2
Skin (Physical Examination (PE))	☐ None ☐ Not Done	☐ 1–5 bruises and/or scattered petechiae	☐ >5 bruises with size >2 cm and/or diffuse petechiae
Oral (PE)	☐ None ☐ Not Done	☐ 1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	☐ Multiple blood blisters and/or gum bleeding

Ask the subject to assess how much bleeding they have experienced over the previous week at the following nine anatomical sites and check the box that represents each answer

Site	0	1	2
Skin (Hx)	☐ None ☐ Not Done	☐ 1–5 bruises and/or scattered petechiae	☐ >5 bruises with size >2 cm and/or diffuse petechiae
Oral (Hx)	☐ None ☐ Not Done	☐ 1 blood blister or >5 petechiae and/or gum bleeding <5 min	☐ Multiple blood blisters and/or gum bleeding >5 min
Epistaxis	☐ None ☐ Not Done	☐ Blood when blowing nose and/or epistaxis <5 min (per episode)	☐ Bleeding >5 min (per episode)
Gastrointestinal (GI)	☐ None ☐ Not Done	☐ Occult blood	☐ Gross blood
Urinary (U)	☐ None ☐ Not Done	☐ Microscopic (+ve dipstick)	☐ Macroscopic
Gynecological (GYN)	☐ None (normal period) ☐ Not Done	☐ Spotting not at time of normal period	☐ Bleeding >spotting not at time of period or very heavy period
Pulmonary	☐ None ☐ Not Done	☐ N/A	☐ Yes
Intracranial haemorrhage	☐ None ☐ Not Done	☐ N/A	☐ Yes
Subconjunctival haemorrhage	☐ None ☐ Not Done	☐ Yes	☐ N/A

General Quality of Life Evaluation: EQ-5D-5L

EuroQOL-5 Dimension 5 Level (EQ-5D-5L) (Feng 2015)

EQ-5D-5L descriptive system

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discom	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

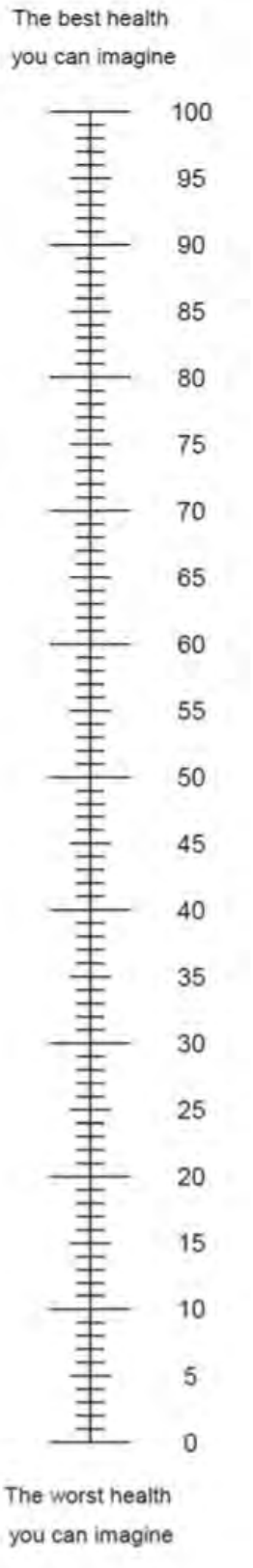
ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

The EQ-VAS in EQ-5D-5L [31]

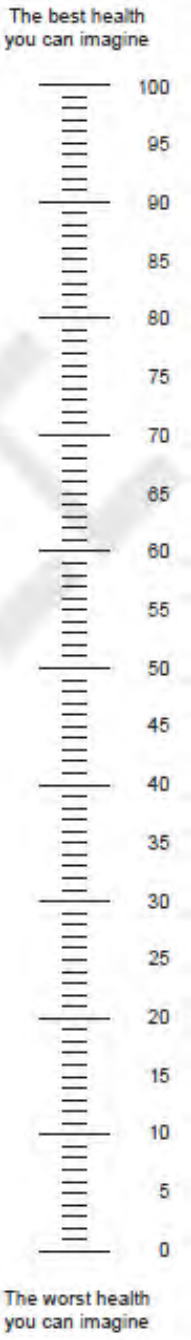
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



7 REFERENCES

Rodeghiero F, Michel M, Gernsheimer T, Ruggeri M, Blanchette V, et. al. Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group. Blood 2013 121: 2596-2606.

Feng Y, Devlin N, Herdman M. Assessing the health of the general population in England: how do the three- and five-level versions of EQ-5D compare? Health Qual Life Outcomes. 2015 Oct 21;13:171.

STATISTICAL ANALYSIS PLAN

Protocol title:	**An Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study Investigating the Safety, Pharmacokinetics, and Clinical Activity of Rilzabrutinib (PRN1008), an Oral BTK Inhibitor, in Patients with Relapsed Immune Thrombocytopenia**
Protocol number:	**DFI17124**
Compound number (INN/Trademark):	**SAR444671/PRN1008 (Rilzabrutinib)**
Study phase:	**Phase 1/2**
Short title:	**LUNA 2**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**28-Nov-2022**

Regulatory agency identifier number(s):

IND No. 132668

EudraCT: 2017-004012-19

NCT: NCT03395210

WHO: U1111-1203-3503

Total number of pages: 50

TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This statistical analysis plan (SAP) for study DFI17124 (PRN1008-010) part B is based on the protocol dated 19-Mar-2021. There are no major changes to the statistical analysis features in this SAP.

The first participant was enrolled on 18-Feb-2021. The SAP is approved before DBL, when all enrolled participants have concluded 24 weeks of treatment.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	28-Nov-2022	ITP-BAT in protocol corrected to IBLS in SAP	Correction

1 INTRODUCTION

1.1 STUDY DESIGN

Study PRN1008-010 (also known as DFI17124) is a 2-part, open-label Phase1/2 study investigating rilzabrutinib in participants with immune thrombocytopenia (ITP) who have relapsed or have an insufficient response to prior therapies. Part A (the dose finding part) of the main 24-week treatment period has been completed based on data cutoff date of 04 May 2021, and a clinical study report (CSR) has been prepared. Part B will investigate the safety and efficacy of rilzabrutinib 400 mg BID. Participants from both parts (A and B) may enter a common long-term extension (LTE). This SAP will cover Part B only.

Part B consists of a 28-day screening period, 24-week 400 mg BID rilzabrutinib active treatment period, and a long-term extension (LTE) period. There will be a 4-week safety follow-up period after the last dose of rilzabrutinib. All visits to be conducted are specified in the schedule of assessments of the protocol.

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
Efficacy	
• To further explore the clinical activity and durability of response of the selected dose of 400 mg BID of rilzabrutinib in participants with ITP who have relapsed or have an insufficient response to prior therapies	• Proportion of participants able to achieve platelet counts ≥50,000/μL on at least 8 out of the last 12 weeks of the 24-week treatment period without the use of rescue medication after 10 weeks of active treatment
Safety	
• To characterize the safety and tolerability of 400 mg BID dose of rilzabrutinib in participants with ITP	• The incidence, severity, and relationship of treatment-emergent adverse events (TEAEs), including clinically significant changes in physical examination, laboratory tests, electrocardiogram(s) (ECG(s)), and vital signs • TEAEs in the post treatment follow-up period and their possible relationship to prior rilzabrutinib treatment
Secondary	
Efficacy	
• To further explore the clinical activity and durability of response of the selected dose of 400 mg BID of rilzabrutinib in participants with ITP who have relapsed or have an insufficient response to prior therapies	• Number of weeks with platelet count ≥50,000/μL OR ≥30,000/μL and doubling the baseline in the absence of rescue therapy (platelet counts will be censored for 4 weeks after the use of rescue medication, if given) Proportion of all treated participants able to achieve two or more consecutive platelet counts, separated by at least 5 days of ≥50,000/μL AND an increase of

	platelet count of ≥20,000/μL from baseline without use of rescue medication in the 4 weeks prior to the latest elevated platelet count • Number of weeks with platelet counts ≥30,000/μL and doubling from baseline over the 24-week treatment period (platelet counts will be censored for 4 weeks after the use of rescue medication, if given) • Proportion of participants receiving rescue medication • Change from baseline in ITP Bleeding Scale (IBLS)
Pharmacokinetic (PK)	
• To characterize the pharmacokinetics of rilzabrutinib in participants with ITP	• Plasma PK parameters of rilzabrutinib in ITP participants will be evaluated in each participant based on sparse sampling and population PK modeling
Exploratory	
• To further explore the clinical activity and durability of response of the selected dose of 400 mg BID of rilzabrutinib in participants with ITP who have relapsed or have an insufficient response to prior therapies	• Proportion of participants who completed 24 weeks of treatment and demonstrated a platelet response defined as platelet counts ≥50,000/μL at 4 out of the last 8 weeks of the active treatment period
[redacted]	[redacted]

2 SAMPLE SIZE DETERMINATION

Part B will enroll approximately 23 participants. The sample size is designed to provide an estimate of the true response rate. If 5 responders are observed out of 23 treated participants, the observed response rate is 22% (90% CI: 9%, 40%), with the lower bound of the exact 90% CI exceeding 8%, which is the historical standard of care response rate estimated from a pooled analysis of 8 randomized studies in ITP participants.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Enrolled	All participants from screened population who have been allocated to an intervention regardless of whether the intervention was received or not.
Exposed	All screened participants who have taken study intervention, regardless of the amount administrated.
Intent-to-treat (ITT)	All enrolled participants.
Safety	All enrolled participants who have taken investigational medical product (IMP), regardless of the amount administered.
Pharmacokinetic (PK)	All enrolled participants from the safety population who have at least one post-baseline PK result.

4 STATISTICAL ANALYSES

This SAP is based on protocol Version 15, dated 19 March 2021.

4.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation, median, (Q1, Q3 if applicable), minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of investigational medicinal product (IMP). For participants enrolled, however not treated, the baseline value is defined as the last available value before enrollment.

Baseline of platelet count is defined as the average of three platelet counts: two qualified screening platelet counts collected in eCRF and Week 1 (study day 1) platelet count.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to date of first investigational medicinal product (IMP) administration.
- The **on-treatment period** is defined as the period from the first dose of IMP to the last dose of IMP + 1. The on-treatment period includes the main on-treatment period and the long-term extension (LTE) on-treatment period.
  - If the subject did not enter LTE, the **main on-treatment period** is defined as from the date of first dose of IMP to the date of the last dose of IMP + 1.
  - If the subject entered LTE, the **main on-treatment period** is defined as from the date of first dose of IMP to the date before the first dose of IMP during LTE. Date of first dose during LTE is based on the date of dosing reported on LTE Cycle 1 Day 1 (C1D1_LTE) in Study Drug Administration eCRF.
  - LTE on-treatment period is defined as from the date of first dose of IMP during LTE to the last dose of IMP + 1.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

The **treatment-emergent period** is any time after the first administration of rilzabrutinib. Treatment-emergent (TE) period includes both on-treatment period and post-treatment period. That is, **main treatment-emergent period** includes main on-treatment period and post-treatment period for those did not enter LTE; **LTE treatment-emergent period** includes LTE on-treatment period and post-treatment period.

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Enrolled participants
- Enrolled but not exposed participants
- Enrolled and exposed participants
- Participants who completed the main study period
  - Participants who completed 12 weeks of treatment
  - Participants who completed 24 weeks of treatment
- Participants who did not complete main 24-week study period and main reason for permanent IMP discontinuation
- Participants who entered LTE
  - Ongoing in LTE
  - Discontinued from LTE and main reason for discontinuation
- Status at the last contact (alive, dead).

In addition, the number (%) of participants screened, screened-failed, enrolled, entered LTE, with early study discontinuation will be provided by country and site.

Protocol deviations

Major protocol deviations will be tabulated by the deviation categories based on enrolled population.

Participants impacted by Covid-19 will be summarized upon data availability, such as discontinuation due to Covid-19, protocol deviation due to Covid-19, and visit(s) impacted by Covid-19 etc. as collected in eCRF.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint(s)

Proportion of participants able to achieve platelet counts ≥ 50,000/μL on at least 8 out of the last 12 weeks [Week 14 (Day 92) to Week 25 (Day 169)] of the 24-week treatment period without the use of rescue medication after 10 weeks of active treatment.

4.3.2 Main analytical approach

The responder of the primary endpoint must have met ALL of the following criteria:

- Platelet counts ≥ 50,000/μL for at least 8 out of the last 12 weeks [Week 14 (Day 92) to Week 25 (Day 169)] during the 24-week treatment period (or equivalently the on-treatment period for efficacy).

  The on-treatment period for efficacy is defined as the period from the date of the 1st IMP administration
  - up to 1 day after the last IMP administration for participants who did not enter LTE, or
  - Week 25 (Day 169) visit for participants who entered LTE.

  The on-treatment period for efficacy will be used for all efficacy analyses related to platelet counts.

  And,
- Not rescued after 10 weeks of treatment. “Rescued after 10 weeks of treatment” for efficacy analysis is defined as from Week 11 (Day 71) to the day prior to the last date of IMP administration for those do not enter LTE or the visit date of Week 25/C1D1_LTE (Day 169) for those entered LTE.
- Not discontinued before Week 25 due to related TEAE (per investigator’s assessment), lack of response, or need to rescue medication as recorded in eCRF, i.e., participants who discontinue before Week 25 and the discontinuation reasons are treatment related adverse event (AE), lack of response, or need of rescue medication will be considered as non-responders.

The response rate will be summarized for ITT population along with the 95% exact Clopper-Pearson Confidence Interval (CI).

Platelet counts and the change from baseline will be summarized by visit. The time course of platelet count will be described graphically, and the following plots will also be provided:

- Individual platelet count profile: line plot of platelet count by visit for each participant
- Spaghetti plot platelet count by participant in each study period (i.e., main and LTE)
- Median platelet count/change from baseline by visit in each study period

An unscheduled platelet count will be allocated to a scheduled visit if it is within the visit window of the scheduled visit where a platelet count is not available (see Section 5.3).

4.3.3 Sensitivity analysis

NA.

4.3.4 Supplementary analysis

The following supplementary analyses will be performed to further evaluate the durable platelet response during the 24-week treatment period. The proportion will be summarized along with the 95% exact Clopper-Pearson CI for the ITT population.

- Proportion of participants who have met the primary endpoint (Section 4.3.2) or entered LTE,
- Number/proportion of participants able to achieve platelet counts ≥ 50,000/μL for ≥two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week treatment period without the use of rescue medication after 10 weeks of active treatment, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/μL during the last 6 weeks of the 24-week treatment period.

  To qualify for a responder, a participant must have met the following criteria

  - At least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week treatment period, and
  - Platelet counts ≥50,000/μL for ≥ two-thirds of 8 non-missing weekly assessments, and
  - at least 2 platelet counts ≥50,000/μL occurred during the last 6 weeks of the 24-week treatment period, and
  - Not rescued after 10 weeks of treatment (see Section 4.3.2 for details), and
  - Not discontinued before Week 25 due to related TEAE (per investigator's assessment), lack of response, or need of rescue medication as recorded in eCRF.

  The last 6 weeks are Week 20 (Day 134) to Week 25 (Day 169).
- Number/proportion of participants able to achieve platelet counts ≥50,000/μL on at least 4 out of the last 6 biweekly platelet counts during the 24-week treatment period without the use of rescue medication after 10 weeks of active treatment.

  To qualify for a responder, a participant must have met the following criteria

  - Platelet counts ≥ 50,000/μL for at least 4 out of the last 6 biweekly platelet counts during the 24-week treatment period, and
  - Not rescued after 10 weeks of treatment (see Section 4.3.2 for details), and

- Not discontinued before Week 25 due to related TEAE (per investigator's assessment), lack of response, or need of rescue medication as recorded in eCRF.

The last 6 biweekly counts will be at Weeks 15, 17, 19, 21, 23, and 25.

4.3.5 Subgroup analyses

Analyses will be performed to assess the consistency on the primary endpoint (Section 4.3.2) across the following subgroups:

- Duration of ITP Disease: Persistent vs Chronic, where
  - Persistent: between 3-12 months from date of ITP diagnosis
  - Chronic: > 12 months from date of ITP diagnosis
- Duration of ITP: ≤ 3 years vs > 3 years
- Type of Prior ITP Therapy
  - Prior thrombopoietin receptor agonist (TPO-RA) but no prior corticosteroid (CS)
  - Prior CS but no prior TPO-RA
  - Prior TPO-RA and prior CS
  - Neither TPO-RA nor CS
- Prior TPO-RA
  - TPO-RA naïve, i.e., never received TPO-RA medications, Yes vs No
  - For non-TPO-RA naïve, responded to TPO-RA, Yes vs No

  Note: "responded" means "resulted in platelet count ≥50,000/μL" per eCRF.
- Prior CS
  - Prior CS, Yes vs No
  - For those who exposed to CS, responded to CS, Yes vs No
- Prior IVIg or Anti-D immunoglobulin
  - Prior IVIg or Anti-D immunoglobulin, Yes vs No
  - For those who exposed to IVIg or Anti-D immunoglobulin, responded to either, Yes vs No
- Prior Rituximab
  - Prior Rituximab, Yes vs No
  - For those who exposed to Rituximab, responded to Rituximab, Yes vs No
- Participants on rilzabrutinib monotherapy vs. Participants on ITP concomitant therapy
- Participants on concomitant ITP medication
  - TPO-RA but no CS

- CS but no TPO-RA
- TPO-RA and CS
- No concomitant TPO-RA nor CS

- Participants with unique number of prior ITP medications by category: <3 vs ≥3, and the unique ITP medications is identified by standardized medication name
- Baseline Platelet Count: <15,000/μL vs. ≥15,000/μL
- Splenectomy Yes vs splenectomy No
- Participants who had completed 24 weeks of treatment

95% confidence intervals will be calculated for the proportions using the Clopper-Pearson method.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Definition of endpoint(s)

The secondary endpoints are defined below:

- Number of weeks with platelet count ≥50,000/μL OR ≥30,000/μL and doubling the baseline in the absence of rescue therapy (platelet counts will be censored for 4 weeks after the use of rescue medication, if given)
- Proportion of all treated participants able to achieve two or more consecutive platelet counts, separated by at least 5 days of ≥50,000/μL AND an increase of platelet count of ≥20,000/μL from baseline without use of rescue medication in the 4 weeks prior to the latest elevated platelet count
- Number of weeks with platelet counts ≥30,000/μL and doubling from baseline over the 24-week treatment period (platelet counts will be censored for 4 weeks after the use of rescue medication, if given)
- Proportion of participants receiving rescue medication
- Change from baseline in ITP Bleeding Scale (IBLS)

4.4.2 Main analytical approach

All secondary endpoints will be assessed during the 24-week treatment period unless otherwise specified. The number (percent) will be summarized for the ITT population along with the 95% exact Clopper-Pearson CI for the categorical endpoints.

- Number of weeks with platelet count ≥50,000/μL OR ≥30,000/μL and doubling the baseline in the absence of rescue therapy (platelet counts will be censored for 4 weeks after the use of rescue medication, if given)

To qualify for the criteria specified in the endpoint at a given week, the participant must have met ALL the following criteria,

- Platelet count ≥50,000/μL OR ≥30,000/μL and doubling the baseline at a given week during the 24-week treatment period from Week 2 (Day 8) to Week 25 (Day 169),
- Not rescued within the 4 weeks prior to the elevated platelet count at the given week, that is, if the participants received rescue medication during the 24-week treatment, platelet counts will be censored from the date when the rescue medication is initiated up to 4 weeks after the use of rescue medication, i.e., any weeks that fall into this period will be considered as not qualifying for the criteria specified.

95% CI of mean using t-distribution will be provided.

- Number of weeks with platelet counts ≥30,000/μL and doubling from baseline over the 24-week treatment period: this endpoint will be derived similarly as the secondary endpoint above.

  95% CI of mean using t-distribution will be provided.

- Proportion of all treated participants able to achieve two or more consecutive platelet counts, separated by at least 5 days of ≥ 50,000/μL AND an increase of platelet count of ≥ 20,000/μL from baseline without use of rescue medication in the 4 weeks prior to the latest elevated platelet count

  To qualify for a responder, the participant must have met the following criteria

  - ≥2 consecutive platelet counts ≥50,000/μL, separated by at least 5 days, and
  - An increase of platelet count of ≥20,000/μL from baseline, and
  - Not rescued within the 4 weeks prior to the latest elevated platelet count

- Proportion of participants receiving rescue medications

  The number and proportion of participants receiving rescue medications will be tabulated respectively

  - during 24-week treatment period (from the date of first dose of IMP to the day prior to the last date of IMP administration for those do not enter LTE or the visit date of Week 25/C1D1_LTE (Day 169) for those entered LTE)
  - during LTE period (from the date of first dose of IMP during LTE to the date of the last dose of IMP - 1)

- Change from baseline in ITP Bleeding Scale (IBLS): see Section 4.8.3

4.5 EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

[redacted]

4.5.2 Main analytical approach

The general analysis is specified in Section 4.3.2. Necessary details for analyzing each endpoint are provided below.

[redacted]

[redacted]

- [redacted]

[redacted] (Section 4.3.1).

[redacted]

[redacted] Section 4.7.3.

[redacted] Section 4.7.3.

[redacted] Section 4.7.3.

[redacted] Section 4.8.3.

4.6 MULTIPLICITY ISSUES

NA.

4.7 SAFETY ANALYSES

All safety analysis will be performed on the safety population as defined in Table 3, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned unless otherwise specified.
- Safety data in participants who do not belong to the safety population (e.g., exposed but not enrolled) will be provided.

4.7.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and treatment compliance and summarized within the safety population. Duration of study drug exposure (days) and treatment compliance will be summarized for main 24-week treatment period and LTE treatment period, respectively.

Duration of IMP exposure

Duration of IMP exposure will be summarized based on treatment periods, which are defined below:

- Duration of study drug exposure in each treatment period (days) = (last IMP administration date during main or LTE treatment period - first IMP administration date in each treatment period) + 1, regardless of unplanned intermittent interruption.

Last dose date can be found in eCRF. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing. In cases where participants are still on-going in LTE when the data base lock (DBL) occurred, the data cut-off date (last participant last visit date in 24-week treatment period) will be used as the last dose date of LTE.

Duration of IMP exposure will be summarized quantitatively and categorically by month: 1 to 28 days (Week 1 to Week 4), 29 to 56 days (Week 5 to Week 8), …, 141 to 168 (Week 21 to Week 25), 169 to 196 days (Month 1 LTE), 197 to 224 days (Month 2 LTE) etc.

Additionally, the cumulative duration of treatment exposure (expressed in participant-months) will be provided.

Treatment compliance

A given administration will be considered noncompliant if the participant has dates indicating missing doses as recorded in eCRF.

Percentage of treatment compliance for a participant will be defined as the number of administration days that the participant was compliant divided by the total number of administration days (i.e., Duration of IMP) ×100%, during main 24-week treatment period and LTE treatment period, respectively.

Treatment compliance will be summarized quantitatively and categorically: < 80%, 80% to 100%, and ≥100%.

4.7.2 Adverse events

General common rules for adverse events

All AEs will be graded according to National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) version v5.0, and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of the database lock.

The AEs will be analyzed in the following 2 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period (including the on-treatment and post-treatment periods defined in Section 4.1).

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be flagged in the AE listing.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the CTCAE grade is missing for 1 of the treatment-emergent occurrences of an AE, the grade will be imputed with the maximal grade of the other occurrences. If the grade is missing for all the occurrences, the grade will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. Summaries will be provided for all grades combined and for grade ≥3 (including grade 5). Missing grades, if any, will be included in the "all grades" category.

The AE tables will be sorted as indicated in Table 4.

Table 4 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a]
PT	By decreasing frequency of PTs

a The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (e.g., treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any grade ≥ 3 TEAE
- Any treatment emergent SAE
- Treatment emergent SAE related to IMP as per Investigator's judgment
- TEAE leading to death
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period)
- Any TEAE leading to permanent IMP discontinuation
- TEAE related to IMP as per Investigator's judgment
- Bleeding events (Intensity Grade 2 or higher)
- Infection (Intensity Grade 2 or higher)

The AE summaries of Table 5 will be generated with number (%) of participants experiencing at least one event. TEAE will be provided for main treatment-emergent period, LTE treatment-emergent period respectively.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels	Main period	LTE
All TEAE	Overview[a]	✓	✓
	Primary SOC, HGLT, HLT and PT	✓	
	Primary SOC and PT	✓	✓
	PT	✓	
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT	✓	✓
TEAE by maximal intensity	Primary SOC and PT	✓	✓
TEAE Grade 3 or higher	Primary SOC and PT	✓	
Treatment emergent SAE	Primary SOC and PT	✓	✓
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT	✓	✓
TEAE leading to permanent discontinuation of intervention	Primary SOC and PT	✓	✓
Bleeding event by grade[b]	Primary SOC and PT	✓	✓
Bleeding events (Intensity Grade 2 or higher)[b]	Primary SOC and PT	✓	✓
Related bleeding events (Intensity Grade 2 or higher)[b]	Primary SOC and PT	✓	✓

Type of AE	MedDRA levels	Main period	LTE
Infection (Intensity Grade 2 or higher)[c]	Primary SOC and PT	✓	✓
Related infection (Intensity Grade 2 or higher)[c]	Primary SOC and PT	✓	✓
TEAE by age group (<65, >=65 years)	Primary SOC and PT	✓	
TEAE by gender	Primary SOC and PT	✓	
TEAE by concomitant ITP medications (No concomitant ITP medication, CS alone, TPO-RA alone, CS + TPO-RA)	Primary SOC and PT	✓	

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation
b Bleeding events is identified by narrow search of SMQ = Haemorrhages
c Infection identified by primary SOC = "Infections and infestations"

Analysis of deaths

Death will be listed.

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs, and electrocardiograms

The following laboratory variables, vital signs, and electrocardiogram (ECG) variables will be analyzed. They will be converted into International System of Units (SI) unless otherwise specified.

- Hematology:
  - Red blood cells (RBC) and platelets: RBC, Hemoglobin, Hematocrit, Mean Cell Volume (MCV)*, Mean Corpuscular Hemoglobin (MCH)*, Mean Corpuscular Hgb Concentration (MCHC)*, Mean Platelet Volume (MPV)*, Red cell distribution width (RDW)*, Reticulocyte
  - White blood cell (WBC) count with differential: WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
- Coagulation: prothrombin time/International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT)
- Serum chemistry:
  - Metabolism: Glucose, Creatinine phosphokinase (CPK)
  - Electrolytes: Sodium, Chloride, Calcium, Phosphorus, Potassium
  - Renal function: Creatinine, Blood Urea Nitrogen (BUN)
  - Liver function: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total bilirubin, Direct bilirubin, Indirect bilirubin, Alkaline phosphatase (ALP), Albumin, Total Protein

- Thrombopoietin (TPO) levels

- Urinalysis*: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase
- Vital signs: blood pressures (BP), pulse, temperature* and respiratory rate* and body weight, height*
- ECG variables: pulse rate*, QT interval*, PR interval, RR interval*, QRS duration, QTcF interval and overall ECG assessments (normal, abnormal – not clinically significant and abnormal – clinically significant)
- Immunoglobulins: Immunoglobulin G, Immunoglobulin M, Immunoglobulin E (IgE), Immunoglobulin G Subclass 1, Immunoglobulin G Subclass 4
- Hemolysis Panel: Direct Coombs (Anti-Human Globulin), Haptoglobin

* Only PCSA or PCSA similar tables will be provided.

For descriptive summary, data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

Quantitative analyses

For all laboratory variables, vital signs, and ECG variables above, descriptive statistics for results and change from baseline will be provided for each planned visit, including the last value during the on-treatment period. These analyses will be performed using central measurements (when available) for laboratory variables and using local measurements for ECG variables.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock (Section 5.4). For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable. For parameters defined as efficacy endpoints, PCSA or PCSA similar summaries will not be provided.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated). For laboratory variables, vital signs, and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

4.8 OTHER ANALYSES

4.8.1 PK analysis

Pharmacokinetic (PK) of rilzabrutinib (PRN1008) and its metabolites[redacted], if available, will be descriptively summarized by scheduled visit and nominal sampling timepoint in the PK population. Individual PK data will be listed. The mean concentration of all three metabolites will be plotted against sampling times. Samples outside of window may be excluded from the summary as determined by PK scientist.

For PRN1008 and [redacted], all concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics excepted for the geometric mean and associated coefficient of variation for which they will be considered as missing. Fo[redacted] all concentrations below LLOQ will be treated as LLOQ/2, given it is an endogenous compound.

Plasma rilzabrutinib concentration data might be used for population PK modeling if considered necessary and the results of population PK modeling will be reported separately from the study report.

Exploratory PK/PD analyses will be performed by PK group as deemed necessary to evaluate the expose-response relationships.

4.8.2 BTK occupancy analysis

Bruton tyrosine kinase (BTK) occupancy data will be descriptively summarized by scheduled visit and nominal sampling timepoint. Individual BTK occupancy data will be listed. Mean BTK occupancy will be plotted against sampling times.

4.8.3 Quality of life analyses

The ITP Bleeding Scale (IBLS), Immune Thrombocytopenic Purpura Patient Assessment Questionnaire (ITP-PAQ), EuroQoL-5 Dimension 5 Level (EQ-5D-5L) are administered in this study. For continuous variables, the overall score and its change from baseline will be analyzed descriptively for each time point.

IBLS

IBLS comprises of 11 sites for female and 10 sites for male, and each site is scored from 0 (none) to 2 (marked bleeding). A copy of the IBLS assessment form is provided in Section 5.5. The IBLS bleeding scales were assessed at each visit for each participant.

For each participant, an IBLS score at each visit will be calculated by taking the average across 11 items (10 for male and postmenopausal women) at 9 anatomical sites (8 for male and postmenopausal women). For each patient, a mean IBLS score will also be calculated by taking the average across all post-baseline visits during the 24-week main treatment period. Frequency and severity of bleeding according to IBLS will be summarized at each visit. The IBLS score as

defined above will be descriptively summarized at each visit. Mean IBLS score will also be descriptively summarized.

EQ-5D-5L

EQ-5D-5L is a standardized health-related quality of life questionnaire that provides a simple, generic measure of health for clinical and economic appraisal. EQ-5D consists of 2 parts – a 5-dimension descriptive system and the EQ visual analogue scale. A copy of the questionnaire is provided in Section 5.6.

The descriptive system contains 5 categories: mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The number and percentage of subjects in each response category will be tabulated. Percentages are based on the number of subjects for whom an assessment is provided at the respective visit.

The EQ visual analogue scale (VAS) is a visual scale from 0–100 to record a respondent's overall self-rated health state. The respondent is asked to mark an "X" on the scale then record the corresponding number; 0 refers to the worst possible health state, 100 refers to the best possible health state. The EQ visual analogue scale will be summarized for the observed response and change from baseline.

ITP-PAQ

ITP-PAQ is a 44-item ITP-specific Patient Assessment Questionnaire. A copy of the questionnaire is attached in Section 5.7. The content of ITP-PAQ can be described as follows:

- 44 questions, rated on a Likert-type scale containing 4–7 responses (recall period: past 4 weeks)
- 10 scales for females and 9 scales for males are covered: Symptoms (6 items, items 1 to 6), Fatigue (4 items, items 7 to 10), Bother-Physical Health (3 items, items 11 to 13), Activity (2 items, items 14 to 15), Psychological Health (5 items, items 16 to 20), Fear (5 items, items 21 to 25), Overall QoL (5 items, items 26 to 30), Social Activity (4 items, items 31 to 34), Women's Reproductive Health (6 items, items 35 to 40), Work (4 items, items 41 to 44)

The ITP-PAQ scores that are used for analysis for an individual participant is obtained as follows:

- Each item/questionnaire rated on a Likert-type scale containing 4–7 responses will be transformed from 0 to 100 continuum with higher score indicating better health status, below describes the transformed score for each response category:

  The transformed score for each response category equals to 100×(possible maximal item score - item score)/range, item score is recorded as PAQ_STD in the EDC database where higher score corresponds to higher frequency while lower score indicates low frequency.

  For example, for an item with 5 responses, the categories contained in the item, the item score (as recorded in EDC), and the transformed score are listed below:

Category	Item score (PAQ_STD in EDC)	Transformed score
All the time	5	0
Most of the time	4	25 (100×1/4)
Some of the time	3	50 (100×2/4)
Rarely	2	75 (100×3/4)
Never	1	100 (100×4/4)

Each item checked (i.e., non-missing) will generate a numerical score ranging from 0 to 100

- The scale score is obtained by taking the arithmetic mean of its associated items. For example, symptoms score will be obtained by averaging its associated 6 item scores, ranging from 0 to 100, with higher scores indicating better health status
- Each female and male participants will have 10 scale scores and 9 scale scores respectively per visit where ITP-PAQ is performed

In the computation of scale scores, missing data on a particular scale will be imputed if >= 50% of the items in that scale is non-missing. Such missing values will be imputed using the mean of the non-missing items. If there are more than 50% of missing data, the scale score is considered as missing.

ITP-PAQ will be summarized for the observed response and change from baseline by scale and by visit. Graphic presentation may be provided as needed.

4.9 INTERIM ANALYSES

No interim analysis is planned for this study.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ALP:	Alkaline phosphatase
ALT:	Alanine aminotransferase
aPTT:	activated partial thromboplastin time
AST:	Aspartate aminotransferase
ATC:	anatomic category
BTK:	Bruton tyrosine kinase
BUN:	Blood Urea Nitrogen
CPK:	Creatinine phosphokinase
CS:	corticosteroid
DBL:	data base lock
ECG:	electrocardiogram
EQ-5D-5L:	EuroQoL-5 Dimension 5 Level
HLGT:	high-level group term
HLT:	high-level term
IMP:	investigational medicinal product
INR:	International Normalized Ratio
ITP:	immune thrombocytopenia
ITP-BAT:	ITP Bleeding Assessment Tool
ITP-PAQ:	Idiopathic Thrombocytopenic Purpura Patient Assessment
ITT:	intent-to-treat
LLT:	lower-level term
LTE:	long-term extension
NCI-CTCAE:	National cancer institute common terminology for adverse events
NPV:	Negative predictive value, negative predictive value
PCSA:	potentially clinically significant abnormality
PK:	Pharmacokinetic
PPV:	positive predictive value
PT:	preferred term
SAP:	statistical analysis plan
SOC:	system organ class
TE:	treatment-emergent , treatment-emergent
TEAE:	treatment-emergent adverse event
TPO-RA:	thrombopoietin receptor agonist
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, ITP history, medical history

The following demographics and baseline characteristics, ITP history, medical history will be summarized using descriptive statistics in the enrolled population.

Demographic and baseline characteristics

- age in years as quantitative variable and in categories (<65, ≥65)
- gender (Male, Female)
- race (White, Black or African American, Asian, American Indian or Alaska native, native Hawaiian or other pacific islander, Other)
- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- weight (kg) at screening
- body mass index (BMI) (kg/m^2) at screening

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

ITP history

- type of ITP: primary vs secondary
- duration of ITP: persistent vs chronic, the definition of which is the same as Section 4.3.5
- duration of ITP (primary or secondary) (years), where:

  duration of ITP (years) = ((Date of first study drug dosing – Date participant was diagnosed with ITP+ 1)/30.4)/12
- average of two qualified screening platelet counts as collected in eCRF
- baseline platelet count, as defined in Section 4.1
- baseline platelet count: <15,000/µL vs. ≥15,000/µL
- splenectomy (Y/N)

Medical and surgical history will be coded to a PT and associated primary SOC using the MedDRA currently in effect at Sanofi at the time of database lock.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration of IMP or can be ongoing during treatment period.
- Concomitant medications are any interventions received by the participant concomitantly to the IMP during the on-treatment period (from the first administration of IMP to the last IMP intake + 1).
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior, concomitant, and post-treatment non-ITP medications will be summarized for the ITT population, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC). Therapeutic classes are sorted by decreasing frequency within each anatomic class. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Prior ITP, concomitant non-rescue ITP, and concomitant rescue ITP therapies/medications will be summarized separately by the ATC level 4 chemical class and medication name.

The following prior ITP therapies will be presented:

- number of prior unique ITP therapies identified using standardized medication name
  - counting splenectomy as an ITP therapy
  - not counting splenectomy as an ITP therapy
- number of prior unique ITP therapies identified using standardized medication name and counting different corticosteroids as one therapy
  - counting splenectomy as an ITP therapy
  - not counting splenectomy as an ITP therapy
- number of prior ITP therapies, identified by eCRF entry records
- number of participants with the following ITP medications, respectively:
  - Corticosteroids
  - TPO-RA
  - IVIG

- Anti-D immunoglobulin
- Rituximab
- Fostamatinib
- Immunosuppressants and other immunomodulatory agents (including Cyclophosphamide)
- Dapsone
- Danazol
- Investigational ITP medications

- number of participants responded to prior ITP therapy including splenectomy, (i.e., resulted in platelet count ≥50,000/μL per eCRF) including splenectomy
- number of participants responded to 1) prior corticosteroids, 2) prior TPO-RA, 3) prior Rituximab, 4) prior IVIG or Anti-D immunoglobulin respectively.

5.3 APPENDIX 3 DATA HANDLING CONVENTIONS

Platelet count assessments

For efficacy analyses using weekly platelet counts, the use of local platelet count will be prioritized, central platelet count will be used only when local is missing; the use of scheduled visit will be prioritized, and unscheduled visit will be used when scheduled is missing. If a weekly (starting from week 2) scheduled platelet count is missing, then an unscheduled platelet count will be allocated to the corresponding visit. See Table 6 for details.

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, and participant reported outcome variables.

Platelet counts conducted locally will be used for the efficacy analyses. Platelet counts conducted centrally at Clinic Visits will be used as a back-up for missed or non-analyzable local lab samples.

A scheduled measurement will be used if it is available. Otherwise, an unscheduled measurement (including early withdrawal visit) will be allocated to a scheduled visit if it is within the analysis window of the scheduled visit. After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 6 - Analyses window definition

Scheduled visit post baseline	Targeted study day (Analysis window) – Platelet count only	Targeted study day (Analysis window) – Other[a]
Week 1 to LTE Month 6		
Week n[b]	1+7*(n-1) (+/-3)	
Week 5	29 (+/-3)	29 (-13,+14)
Week 9	57 (+/-3)	57 (-13,+14)
Week 13	85 (+/-3)	85 (-13,+14)
Week 17	113 (+/-3)	113 (-13,+14)
Week 21	141 (+/-3)	141 (-13,+14)
Week 25/ C1D1_LTE	169 (+/-3)	169 (-13,+14)
C1D8_LTE	176 (+/-3)	
C1D15_LTE	183 (+/-3)	
C1D22_LTE	190 (+/-3)	
C2D1_LTE	197 (+/-3)	197 (-13,+14)
C2D8_LTE	204 (+/-3)	
C2D15_LTE	211 (+/-3)	
C2D22_LTE	218 (+/-3)	
C3D1_LTE	225 (+/-3)	225 (-13,+14)
C3D8_LTE	232 (+/-3)	
C3D15_LTE	239 (+/-3)	
C3D22_LTE	246 (+/-3)	
C4D1_LTE	253 (+/-3)	253 (-13,+14)
C4D8_LTE	260 (+/-3)	
C4D15_LTE	267 (+/-3)	
C4D22_LTE	274 (+/-3)	
C5D1_LTE	281 (+/-3)	281 (-13,+14)
C5D8_LTE	288 (+/-3)	
C5D15_LTE	295 (+/-3)	
C5D22_LTE	302 (+/-3)	
C6D1_LTE	309 (+/-3)	309 (-13,+14)
C6D8_LTE	316 (+/-3)	
C6D15_LTE	323 (+/-3)	
C6D22_LTE	330 (+/-3)	

Scheduled visit post baseline	Targeted study day (Analysis window) – Platelet count only	Targeted study day (Analysis window) – Other[a]
LTE Month 7 afterwards		
C7D1_LTE	337 (-3,+14)	337 (-13,+14)
C8D1_LTE	365 (-13,+14)	365 (-13,+14)
C9D1_LTE	393 (-13,+14)	393 (-13,+14)
C10D1_LTE	421 (-13,+14)	421 (-13,+14)
C11D1_LTE	449 (-13,+14)	449 (-13,+14)
C12D1_LTE	477 (-13,+14)	477 (-13,+14)
Q1_LTE	505 (-13,+42)	505 (-13,+42)
QX_LTE where X=2,3,….	505+28*3*(X-1) for X=2,3,…. (-41,+42)	505+28*3*(X-1) for X=2,3,…. (-41,+42)

Study days are calculated considering Day 1 as the day of first administration of intervention.

a Other includes all the other assessments excluding platelet counts unless otherwise specified.

b For platelet counts, on-site visits will occur once every four weeks, Week n represents the weekly clinical visits between the on-site visits, and n= 2,3,4, 6,7,8, 10,11,12, 14,15,16, 18,19,20, 22,23,24.

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and QOL data will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety whenever applicable. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.4 APPENDIX 4 CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzyme's activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
AST	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzyme's activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzyme's activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black); <1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male); ≤0.32 v/v (Female) ≥0.55 v/v (Male); ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	
	>90 bpm	Categories are cumulative
	>90 bpm and increase from baseline ≥20bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
PR	>200 ms	Categories are cumulative
	>200 ms and increase from baseline ≥25%	
	> 220 ms	
	>220 ms and increase from baseline ≥25%	
	> 240 ms	
	> 240 ms and increase from baseline ≥25%	
QRS	>110 ms	Categories are cumulative
	>110 msec and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	
QT	>500 ms	
QTc	Absolut values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patient's listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

5.5 APPENDIX 5 ITP BLEEDING SCALE

Assess how much bleeding the subject has at the following sites by physical examination and record the severity at each site below

Site	0	1	2
Skin (Physical Examination (PE))	☐ None ☐ Not Done	☐ 1–5 bruises and/or scattered petechiae	☐ >5 bruises with size >2 cm and/or diffuse petechiae
Oral (PE)	☐ None ☐ Not Done	☐ 1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	☐ Multiple blood blisters and/or gum bleeding

Ask the subject to assess how much bleeding they have experienced over the previous week at the following nine anatomical sites and check the box that represents each answer

Site	0	1	2
Skin (Hx)	☐ None ☐ Not Done	☐ 1–5 bruises and/or scattered petechiae	☐ >5 bruises with size >2 cm and/or diffuse petechiae
Oral (Hx)	☐ None ☐ Not Done	☐ 1 blood blister or >5 petechiae and/or gum bleeding <5 min	☐ Multiple blood blisters and/or gum bleeding >5 min
Epistaxis	☐ None ☐ Not Done	☐ Blood when blowing nose and/or epistaxis <5 min (per episode)	☐ Bleeding >5 min (per episode)
Gastrointestinal (GI)	☐ None ☐ Not Done	☐ Occult blood	☐ Gross blood
Urinary (U)	☐ None ☐ Not Done	☐ Microscopic (+ve dipstick)	☐ Macroscopic
Gynecological (GYN)	☐ None (normal period) ☐ Not Done	☐ Spotting not at time of normal period	☐ Bleeding >spotting not at time of period or very heavy period
Pulmonary	☐ None ☐ Not Done	☐ N/A	☐ Yes
Intracranial haemorrhage	☐ None ☐ Not Done	☐ N/A	☐ Yes
Subconjunctival haemorrhage	☐ None ☐ Not Done	☐ Yes	☐ N/A

5.6 APPENDIX 6 EUROQOL-5 DIMENSION 5 LEVEL (EQ-5D-5L)

EQ-5D-5L descriptive system

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discom ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

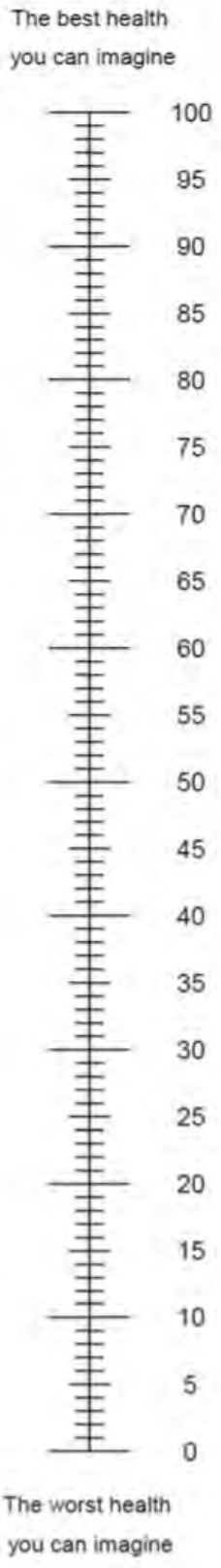
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

The EQ-VAS in EQ-5D-5L [31]

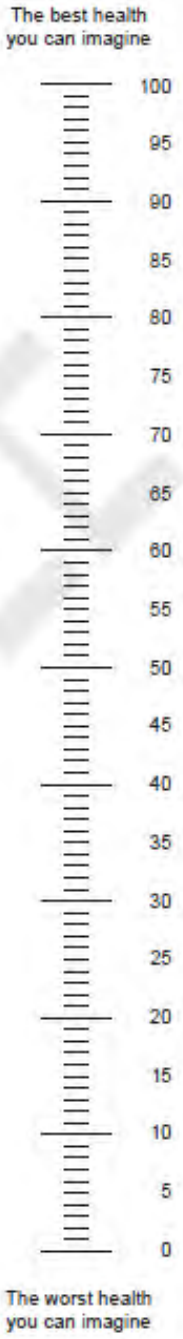
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



5.7 APPENDIX 7 IDIOPATHIC THROMBOCYTOPENIC PURPURA PATIENT ASSESSMENT QUESTIONNAIRE (ITP-PAQ)

ITP-PAQ

This survey asks for your views about the impact of ITP on your health. Please check one box for each of the following questions.

	all the time	most of the time	some of the time	rarely	never
1. In the past 4 weeks, how often did you have **either bruising or petechiae** (broken blood vessels)?	☐	☐	☐	☐	☐
2. In the past 4 weeks, how often did you have **wounds or scars** from blood tests, injections, or IV needles?	☐	☐	☐	☐	☐
3. In the past 4 weeks, how often did you have **blood blisters** in your mouth?	☐	☐	☐	☐	☐
4. In the past 4 weeks, how often did you have **bleeding episodes** (nose bleeds, gum bleeds, etc.)?	☐	☐	☐	☐	☐
5. In the past 4 weeks, how often did you have **muscle aches**?	☐	☐	☐	☐	☐
6. In the past 4 weeks, how often did you have **cramps in your legs**?	☐	☐	☐	☐	☐

	all the time	most of the time	some of the time	rarely	never
7. In the past 4 weeks, how often did ITP or its treatments cause you to have **difficulty falling asleep** at bedtime?	☐	☐	☐	☐	☐
8. In the past 4 weeks, how often did ITP or its treatments cause you to **awaken during the night**?	☐	☐	☐	☐	☐
9. In the past 4 weeks, how often did ITP or its treatments cause you to **feel sleepy during the daytime**?	☐	☐	☐	☐	☐
10. In the past 4 weeks, how often did ITP or its treatments cause you to **feel physically fatigued**?	☐	☐	☐	☐	☐

	all the time	most of the time	some of the time	rarely	never
11. In the past 4 weeks, how often did you feel **physically unattractive** due to bruising, scarring, wounds or the effects of ITP medications?	☐	☐	☐	☐	☐

12. Overall, in the past 4 weeks, to what extent have ITP and its treatment(s) affected your **physical health**?

extremely	very much	quite a bit	a good bit	somewhat	a little bit	not at all
☐	☐	☐	☐	☐	☐	☐

13. Overall, in the past 4 weeks, how bothered have you been by the effect of ITP and its treatment(s) on your **physical health**?

extremely	very much	quite a bit	a good bit	somewhat	a little bit	not at all
☐	☐	☐	☐	☐	☐	☐

	extremely	quite a bit	a good bit	a little bit	not at all
14. In the past 4 weeks, how much have your ITP symptoms or the effects of its treatments interfered with your **ability to exercise**?	☐	☐	☐	☐	☐
15. In the past 4 weeks, to what extent has having ITP limited the types of **physical or sporting activities** you participate in?	☐	☐	☐	☐	☐

	all the time	most of the time	some of the time	rarely	never
16. In the past 4 weeks, how often did you feel like you had **no control over your health** because of your ITP or its treatments?	☐	☐	☐	☐	☐
17. In the past 4 weeks, how often did you feel like you were **unable to manage stress** because of your ITP or its treatments?	☐	☐	☐	☐	☐
18. In the past 4 weeks, how often did you have feelings of **sadness or depression** because of your ITP or its treatments?	☐	☐	☐	☐	☐

	extremely	quite a bit	a good bit	a little bit	not at all
19. Overall, in the past 4 weeks, how much has ITP or its treatments affected you **psychologically** (mental state, emotions)?	☐	☐	☐	☐	☐
20. Overall, in the past 4 weeks, how bothered have you been by the effect that ITP or its treatments have had on you **psychologically** (mental state, emotions)?	☐	☐	☐	☐	☐

	extremely fearful	quite a bit fearful	a good bit fearful	a little bit fearful	not at all fearful
21. In the past 4 weeks, how fearful have you been of **having a bleeding episode** (nose bleeds, gum bleeds, etc.)?	☐	☐	☐	☐	☐
22. In the past 4 weeks, how fearful have you been of **death or dying**?	☐	☐	☐	☐	☐

	extremely fearful	quite a bit fearful	a good bit fearful	a little bit fearful	not at all fearful
23. In the past 4 weeks, how fearful have you been of **being too far away from your doctor** in case you needed medical help?	☐	☐	☐	☐	☐
24. In the past 4 weeks, how fearful have you been about **getting an infection**?	☐	☐	☐	☐	☐
25. In the past 4 weeks, how fearful have you been of needing to have an **emergency surgery** (due to concerns about bleeding during surgery)?	☐	☐	☐	☐	☐

26. Overall, in the past 4 weeks, to what extent have ITP and its treatment(s) affected your **quality of life**?

extremely	very much	quite a bit	a good bit	somewhat	a little bit	not at all
☐	☐	☐	☐	☐	☐	☐

27. Overall, in the past 4 weeks, how bothered have you been by the effect of ITP and its treatment(s) on your **quality of life**?

extremely	very much	quite a bit	a good bit	somewhat	a little bit	not at all
☐	☐	☐	☐	☐	☐	☐

	strongly agree	somewhat agree	somewhat disagree	strongly disagree
28. I have made significant changes to my lifestyle because I have ITP	☐	☐	☐	☐
29. My ITP prevents me from doing things in life that I want to do	☐	☐	☐	☐
30. My ITP prevents my spouse, partner or family members from doing things in life that they want to do	☐	☐	☐	☐

	all the time	most of the time	some of the time	rarely	never
31. In the past 4 weeks, how often has having ITP limited your ability to participate in **social activities**?	☐	☐	☐	☐	☐
32. In the past 4 weeks, how often have you avoided social activities to limit your **exposure to infection**?	☐	☐	☐	☐	☐

	extremely	quite a bit	a good bit	a little bit	not at all
33. In the past 4 weeks, how bothered were you by what people might think about your **bruising or scarring**?	☐	☐	☐	☐	☐
34. In the past 4 weeks, to what extent have you been unable to lead a **normal social life** because of your ITP?	☐	☐	☐	☐	☐

Women's Health Issues (Men, please skip to Q 41)

The next questions ask about your menstrual periods and reproductive history such as adoption and pregnancy.

Thinking about your last period, how bothered were you by:

	extremely	quite a bit	a good bit	a little bit	not at all
35. Heavier bleeding than before having ITP?	☐	☐	☐	☐	☐
36. Bleeding for more days than before having ITP?	☐	☐	☐	☐	☐
37. More pain than before having ITP?	☐	☐	☐	☐	☐

How much has having ITP made it less likely that you:

	extremely	quite a bit	a good bit	a little bit	not at all
38. Would get pregnant?	☐	☐	☐	☐	☐
39. Would give birth?	☐	☐	☐	☐	☐
40. Would adopt?	☐	☐	☐	☐	☐

	extremely	quite a bit	a good bit	a little bit	not at all	not applicable
41. Since you were diagnosed, to what degree has ITP negatively interfered with your **choice of career(s)**?	☐	☐	☐	☐	☐	☐
42. Since you were diagnosed, how much has ITP negatively interfered with your **ability to get a promotion at your job**?	☐	☐	☐	☐	☐	☐
43. Since you were diagnosed, how much has ITP negatively interfered with your **relationships with coworkers**?	☐	☐	☐	☐	☐	☐

	extremely fearful	quite a bit fearful	a good bit fearful	a little bit fearful	not at all fearful	not applicable
44. In the past 4 weeks, how fearful have you been of **losing your job because of your ITP**?	☐	☐	☐	☐	☐	☐

6 REFERENCES

Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15:708-15

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

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

Feng Y, Devlin N, Herdman M. Assessing the health of the general population in England: how do the three- and five-level versions of EQ-5D compare? Health Qual Life Outcomes. 2015 Oct 21;13:171.

Signature Page for VV-CLIN-0635741 v1.0
dfi17124-prn1008-010b-16-1-9-sap

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]