STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with an Open-Label Extension to Evaluate the Efficacy and Safety of Oral Rilzabrutinib (PRN1008) in Adults and Adolescents with Persistent or Chronic Immune Thrombocytopenia (ITP)**
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TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN **1**

TABLE OF CONTENTS **2**

LIST OF TABLES **5**

LIST OF FIGURES **5**

VERSION HISTORY **6**

1 INTRODUCTION **7**

1.1 STUDY DESIGN 7

1.2 OBJECTIVE AND ENDPOINTS 7

1.2.1 Objectives 7
1.2.1.1 Primary Efficacy Objective (Blinded Treatment Period) 7
1.2.1.2 Key Secondary Efficacy Objectives (Blinded Treatment Period) 7
1.2.1.3 Other Secondary Objective 8

1.2.2 Endpoints 9
1.2.2.1 Primary Efficacy Endpoint (Blinded Treatment Period) 9
1.2.2.2 Key Secondary Efficacy Endpoints (Blinded Treatment Period) 9
1.2.2.3 Other Secondary Endpoints 9
1.2.2.4 Exploratory Endpoints 10

1.2.3 Estimands 12

2 ANALYSIS POPULATIONS **17**

3 STATISTICAL ANALYSES **19**

3.1 GENERAL CONSIDERATIONS 19

3.2 PRIMARY ENDPOINT(S) ANALYSIS 21

3.2.1 Definition of endpoint(s) 21

3.2.2 Main analytical approach 22

3.2.3 Sensitivity analysis 23
3.2.3.1 Sensitivity Analysis - Primary estimand - Adults in ITT 26
3.2.3.2 Sensitivity Analyses - modified primary estimand - Adults in mITT, 24-week completer, participants not receiving Covid-19 vaccine (for Definition 1 and Definition 2, respectively) 28
3.2.3.3 Sensitivity Analyses - modified primary estimand - missing due to Covid-19 imputed with participant's median value (for Definition 1) 29

3.2.4 Subgroup analyses 29

3.3 SECONDARY ENDPOINT(S) ANALYSIS 30

3.3.1 Key/Confirmatory secondary endpoint(s) 30
3.3.1.1 Definition of endpoint(s) 30
3.3.1.2 Main analytical approach 31
3.3.1.3 Supplementary analysis I 35
3.3.1.4 Supplementary analysis II 36
3.3.2 Supportive secondary endpoint(s) 37
3.3.2.1 Other secondary endpoint - Stability of platelet response 37
3.3.2.2 Other secondary endpoint - QOL endpoints 38
3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS 38
3.4.1 Definition of endpoint(s) 38
3.4.2 Main analytical approach 39
3.5 MULTIPLICITY ISSUES 40
3.6 SAFETY ANALYSES 42
3.6.1 Extent of exposure 42
3.6.2 Adverse events 43
3.6.3 Additional safety assessments 50
3.6.3.1 Laboratory variables, vital signs, and electrocardiograms (ECGs) 50
3.6.3.2 SAR-CoV-2 testing 54
3.7 OTHER ANALYSES 54
3.7.1 PK analyses 54
3.7.2 Bruton's Tyrosine Kinase (BTK) Occupancy (at selected sites) 54
3.7.3 Clinical Outcome Assessment 55
3.7.3.1 ITP Bleeding Scale (IBLS) 55
3.7.3.2 ITP Patient Assessment Questionnaire™ (ITP-PAQ™) 55
3.7.3.3 KIDS' ITP-KIT 56
3.7.3.4 EQ-5D-5L 57
3.7.3.5 Patient Global Impression of [Fatigue] Severity (PGIS-Fatigue), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC) 57
3.8 INTERIM ANALYSES 57
3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES 60
4 SAMPLE SIZE DETERMINATION 62
5 SUPPORTING DOCUMENTATION 63
5.1 APPENDIX 1 LIST OF ABBREVIATIONS 63
5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS 65
5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS 66

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS 69
5.5 APPENDIX 5 PATIENT OR INVESTIGATOR REPORTED OUTCOMES 71
5.5.1 ITP Disease Activity - ITP Bleeding Scale (IBLS) 71
5.5.2 ITP Disease Activity - ITP-PAQ 72
5.5.3 ITP Disease Activity - ITP-PAQ scoring 82
5.5.4 ITP Disease Activity - ITP-KIT 83
5.5.5 General Quality of Life Evaluation: EQ-5D-5L 87
5.5.6 Patient Global Impression of [Fatigue] Severity (PGIS-Fatigue), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC) 90
5.6 APPENDIX 6 CRITERIA FOR POTENTIALLY SIGNIFICANT ABNORMALITIES 92
5.6.1 Criteria for Potentially Clinically Significant Abnormalities - for Phase 2/3 studies (oncology excepted) 92
5.6.2 Criteria for Potentially Clinically Significant Abnormalities for Studies in Children 97
5.7 APPENDIX 7 SAMPLE SAS® CODE 108
5.7.1 Primary endpoint: main analyses (CMH test) 108
5.7.2 Primary endpoint: sensitivity analysis (Missing data handled via multiple imputation) (Definition 2) 108
5.7.3 Primary endpoint: sensitivity analysis (Tipping point analysis) 110
5.7.4 Key secondary endpoints: main analytic approach 110
5.8 APPENDIX 8 LIST OF PT FOR SELECTED AE OF INTEREST (MEDDRA VERSION 25.1) 113
6 REFERENCES 114

LIST OF TABLES

Table 1 - Major changes in statistical analysis plan 6
Table 2 - Summary of primary estimand for main endpoints 13
Table 3 - Populations for analyses 17
Table 4 - Missing Data Handling for Primary Efficacy Endpoint.....24
Table 5 - Tipping Point Analysis: Durable Platelet Response Status 28
Table 6 - Sorting of AE tables 43
Table 7 - Analyses of adverse events 45
Table 8 - Selections for AESIs and other AEs of interest.....48
Table 9 - Analyses of laboratory variables, vital signs and electrocardiograms 53
Table 10 - Potential steps of analyses 59
Table 11 - Major statistical changes in protocol amendment(s).....60
Table 12 - Analysis window definition for unscheduled measurements.....69

LIST OF FIGURES

Figure 1 - Fixed-sequence testing procedure 41

VERSION HISTORY

This statistical analysis plan (SAP) for study EFC17093/PRN1008-018 is based on the amended protocol 03 dated 11 August 2022 (current protocol). This section summarizes the major changes to the statistical analysis features in the SAP including major changes from the current protocol.

The first participant was randomized on 16 April 2021. This SAP is approved before the early analysis is conducted when the last adult participant has concluded the blinded treatment period (see Section 3.8).

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	13-Mar-2023	Primary efficacy endpoint will be tested at a 2-sided significance level of 0.05 (instead of 0.01 specified in the protocol) (Section 3.2.2, Section 3.5, Section 4). The protocol will be amended to reflect this change before the early analysis (Section 3.8).	Following health authority's comments and common standard
2	18-Jan-2024	Clarification of geographic region as a covariate in Table 2, Section 3.3.1.2.4 and Section 3.3.1.3.2.	Clarification
		Multiple imputation on missing platelet counts is applicable only to participants who stayed on IMP beyond Week 13 in Section 3.2.3.1.2 to ensure the stability of imputations.	Clarification
		Worst value carried forward will be applied after the data is censored for rescue medication in Section 3.3.1.2.4.	Clarification and consistent handling of missing data
		Supplementary analysis is added for change from baseline in ITP-PAQ Item 10 at Week 25 in Section 3.3.1.4.2 to support the key secondary endpoint at Week 13.	To support the main analysis of key secondary endpoint
3	18-Mar-2024	Criterion of observed non-responder updated in Table 5	Correction
		Supplementary analysis of % rescued is added	To support the main analysis of key secondary endpoint

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension.

After screening (up to 4 weeks), participants who met the eligibility criteria will be centrally randomized via Interactive Response Technology (IRT) in a 2:1 allocation ratio to 1 of 2 intervention groups: rilzabrutinib 400 mg twice daily (bid/BID) or placebo. The randomization will be carried out separately for the two age groups. For the adult group, stratified permuted block randomization will be implemented; for the pediatric group, dynamic randomization algorithm (minimization) will be implemented. The randomization will be stratified by splenectomy status (yes/no) and by severity of thrombocytopenia (Inclusion Criteria 3 platelet counts <15,000/μL or ≥15,000/μL).

After randomization, participants will start a Double-Blinded (DB) Treatment period of up to 24 weeks followed by an Open-Label (OL) Period of 28 weeks during which all participants will receive rilzabrutinib, and then a 4-week safety follow-up period after the last dose. Participants who respond per the criteria specified in the protocol at the end of the OL Period will be able to enter Long-Term Extension (LTE) where they will continue to receive treatment until the time expected for the last participant who enters the LTE to complete 12 months.

Approximately 224 participants (194 adults and 30 pediatric participants) will be randomized from approximately 150 sites.

Study primary analyses will be conducted when the last adult participant has concluded the blinded treatment period (see details in Section 3.8).

1.2 OBJECTIVE AND ENDPOINTS

1.2.1 Objectives

1.2.1.1 Primary Efficacy Objective (Blinded Treatment Period)

- To demonstrate the efficacy of rilzabrutinib versus placebo in participants with refractory/relapsed ITP, based on the durability of platelet response (Section 1.2.2.1) during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy.

1.2.1.2 Key Secondary Efficacy Objectives (Blinded Treatment Period)

- To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline, over the 24-week blinded treatment period in the absence of rescue therapy.

- To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet counts ≥30,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.
- To evaluate the effect of rilzabrutinib versus placebo on the time to first platelet count of ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline.
- To evaluate the effect of rilzabrutinib versus placebo on the proportion of participants requiring rescue therapy.
- To evaluate the effect of rilzabrutinib versus placebo on the change from baseline on Item 10 of the ITP-Patient Assessment Questionnaire (ITP-PAQ) (ie, physical fatigue) in adult participants (≥18 years) at Week 13.
- To evaluate the change from baseline in Idiopathic Thrombocytopenic Purpura Bleeding Scale (IBLS) {applicable to countries within the European Union (EU) [European Economic Area (EEA) countries] and United Kingdom (UK)} only.

1.2.1.3 Other Secondary Objective

1.2.1.3.1 Efficacy Objectives

- To evaluate the stability of platelet response of rilzabrutinib.

1.2.1.3.2 Safety Objectives

- To evaluate the safety and tolerability of rilzabrutinib in pediatric participants (<18 years) and in adult participants (≥18 years) with refractory/relapsed ITP.

1.2.1.3.3 PK Objectives

- To characterize the PK of rilzabrutinib in pediatric participants (<18 years) and in adult participants (≥18 years) with refractory/relapsed ITP.

1.2.1.3.4 Quality of Life (QOL) Objectives

- To evaluate the effect of rilzabrutinib on the general and disease-specific QoL of adult participants (≥18 years) with refractory/relapsed ITP.
- To evaluate the effect of rilzabrutinib on disease-specific QoL in pediatric participants with refractory/relapsed ITP.

1.2.2 Endpoints

1.2.2.1 Primary Efficacy Endpoint (Blinded Treatment Period)

- The primary endpoint is the durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 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 blinded treatment period in the absence of rescue therapy, 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 blinded treatment period (Definition 1).

Country-specific definition [countries within the EU (EEA countries) and UK]

- The primary endpoint is the durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy (Definition 2).

1.2.2.2 Key Secondary Efficacy Endpoints (Blinded Treatment Period)

- Number of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.
- Number of weeks with platelet counts ≥30,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.
- Time to first platelet count of ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and doubled from baseline.
- Proportion of participants requiring rescue therapy during the 24-week blinded treatment period.
- Change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (≥18 years) at Week 13.
- Change from baseline in IBLS assessment at Week 25 (applicable to countries within the EU (EEA countries) and UK only).

1.2.2.3 Other Secondary Endpoints

1.2.2.3.1 Efficacy Endpoint

- Stability of response defined as the proportion of participants able to achieve stable platelet response, which is defined as no 2 scheduled visits, at least 4 weeks apart, with a platelet count less than 50,000/μL, without an intervening visit with a platelet count ≥50,000/μL, within a period of 24 weeks following initial achievement of the platelet response (initial platelet response defined as platelet count ≥50,000/μL within 12 weeks of initiation of treatment with rilzabrutinib during the study).

1.2.2.3.2 Safety Endpoints

- Frequency and severity of treatment-emergent adverse events (TEAEs).
- Frequency and severity of bleeding TEAEs.
- Change from baseline in physical examination, electrocardiogram (ECG), vital signs and clinical laboratory test results: serum chemistry and hematology (except for platelet counts included in the primary efficacy endpoint).

1.2.2.3.3 Pharmacokinetic Endpoints

- Plasma concentrations of rilzabrutinib.

1.2.2.3.4 Quality of Life (QOL) Endpoints

- Change from baseline on the Symptoms, Bother and Activity domains of the ITP-PAQ in adult participants (≥18 years).
- Change from baseline in disease-specific QOL as measured by the Kids' ITP Tools (ITP-KIT) score in pediatric participants.

1.2.2.4 Exploratory Endpoints

1.2.2.4.1 Blinded Treatment Period

- Proportion of participants able to achieve platelet counts ≥50,000/μL for 4 out of last 8 weeks of the 24-week treatment period.
- Percentage of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.
- Proportion of participants with complete response (defined as platelet count ≥100,000/μL on 2 consecutive visits at least 5 days apart and no bleeding or rescue ITP therapy use on and through these two visits.
- Proportion of participants with platelet count ≥50,000/μL on 2 consecutive visits at least 5 days apart and no rescue ITP therapy use on and through these two visits.
- Proportion of participants who have a platelet count that exceeds 250,000/μL or 450,000/μL (for participants on thrombopoietin receptor agonist (TPO-RA)).
- Change from baseline in IBLS assessment at Week 13 and Week 25.
- Change from baseline and change from Week 13 on the Fatigue (Item 10 of the IT-PAQ; physical fatigue), Psychological, Fear, Social Activity, Women's Reproductive Health and Work domains of the ITP-PAQ in adult participants (≥18 years) at Week 25.
- Change from baseline on the Psychological, Fear, Social Activity, Women's Reproductive Health and Work domains of the ITP-PAQ in adult participants (≥18 years) at Week 13.

- Change from baseline in QoL as measured by the Euroqol-5 Dimensions-5 Level (EQ-5D-5L) in adult participants (≥18 years).
- Change from baseline in disease-related symptom severity as measured by the Patient Global Impression of Severity (PGIS) scale.
- Change from baseline in disease-related fatigue severity as measured by the Patient Global Impression of [Fatigue] Severity (PGIS-Fatigue) scale.
- Patient perception of disease-related symptom improvement as measured by the Patient Global Impression of Change (PGIC) scale.
- Pharmacokinetic (PK) parameters as assessed by population pharmacokinetic analysis.
- Bruton's tyrosine kinase (BTK) occupancy (not applicable to the participants in China).
- Changes from baseline in Thrombopoietin (TPO) levels, T-lymphocytes/ B-lymphocytes/natural killers (T/B/NK) counts, immunoglobulin (IgG, IgG1, IgG4, IgM, IgE) levels (not applicable to the participants in China).
- (Optional) Vaccine-specific IgG response during treatment (not applicable to the participants in China).

1.2.2.4.2 Open Label Period and Long-Term Extension

The following exploratory endpoints will be assessed at the end of the open label period (Week 53) and after 12 months on the LTE period.

- Proportion of participants who received placebo during the blinded part and able to achieve durable platelet response during the open label part. Durable platelet response is defined as platelet counts at or above 50,000/μL for ≥ two-thirds of at least 10 non-missing weekly scheduled platelet measurements during the last 16 weeks of the 28 of the open label period in the absence of rescue therapy, provided that at least 3 non-missing weekly scheduled platelet measurements are at or above 50,000/μL during the last 8 weeks of the 28-week open label period
- Percentage of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline
- Proportion of participants with complete response (defined as platelet count ≥100,000/μL on 2 consecutive visits at least 5 days apart and no bleeding or rescue ITP therapy use on and through these two visits)
- Proportion of participants who have a platelet count that exceeds 250,000/μL or 450,000/μL (for participants on TPO-RAs)
- Proportion of participants requiring rescue therapy
- Change from baseline on the Fatigue (Item 10 of the ITP-PAQ; physical fatigue), Psychological, Fear, Social Activity, Women's Reproductive Health and Work domains of the ITP-PAQ in adult participants (≥18 years)
- Change from baseline in IBLS assessment

- Change from baseline in QOL as measured by the EuroQOL-Dimensions-5 Level in adult participants (≥18 years)
- Percent change from baseline on corticosteroids (CS) dose
- Percent change from baseline on TPO-RA dose
- Proportion of participants who switch to rilzabrutinib as a monotherapy during the first year of the LTE period
- Proportion of participants who decrease their CS dose >50% relative to baseline values during the first year of the LTE
- Proportion of participants who manage to reduce their dose or stop TPO-RA agonists during the first year of the LTE

1.2.3 Estimands

Primary estimand defined for main endpoints are summarized in Table 2 below. More details are provided in Section 3.

For all estimands, the comparison of interest will be the comparison of SAR444671 rilzabrutinib 400 mg BID vs. placebo.

The population of interest is the ITT population of adult participants aged ≥18 and pediatric participants aged 10 to <18 years (recruitment of pediatric participants aged 10 to <18 from EU [EEA] countries only) with persistent or chronic immune thrombocytopenia. The primary analysis will be based on adult participants (see details in Section 3.8).

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint [a]	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To demonstrate the efficacy of rilzabrutinib versus placebo in participants with refractory/relapsed ITP, based on the durability of platelet response during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy				
Primary endpoint (Composite estimand)	Durable platelet response is defined as the proportion of participants able to achieve platelet counts at or above 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 blinded treatment period in the absence of rescue therapy, 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 blinded treatment period (Definition 1) [b] Country-specific definition [c] : Durable platelet response is defined as the proportion of participants able to achieve platelet counts at or above 50,000/µL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy (Definition 2)	ITT	1) Rescue medication: participants will be considered as non-responders if taking rescue medication after 8 weeks of double-blind treatment and before Week 25 (or last IMP intake, whichever earlier) (composite strategy). 2) Discontinuation of study intervention before Week 25 due to lack of response or related adverse events per eCRF: participants will be considered as non-responders (composite strategy). 3) Discontinuation of study intervention before Week 25 due to reasons other than the aforementioned: data during the double-blind on-treatment period will be included in the analysis. Post-treatment data will be considered to have had no platelet response (composite strategy)	Adults: p-value from Cochran-Mantel-Haenszel (CMH) test adjusted by randomization stratification factors [d]. Mantel- Haenszel common risk difference and 95% CI based on Mantel-Haenszel stratum weights (1) and the Sato variance estimator (2). Pediatrics: Descriptive. For Definition 2, Missing data due to Covid-19 (per eCRF) are assumed missing at random and will be imputed using the participant's median value of available (a minimum of 3 available required) weekly platelet counts during the last 12 weeks of double-blind on-treatment period. Otherwise, missing data will be considered as no response.

Endpoint Category (estimand)	Estimands			
	Endpoint [a]	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Secondary objective: To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet response, the time to first platelet response, the proportion of participants requiring rescue therapy over the 24-week blinded treatment period, the change from baseline in physical fatigue (Item 10 of the ITP-PAQ) in adults at Week 13, and the change from baseline in IBLS assessment at Week 25				
Secondary endpoint (Hypothetical + composite estimand)	# weeks with platelet count ≥50,000/µL OR 30,000/µL to <50,000/µL and doubled from baseline in the absence of rescue therapy # weeks with platelet count ≥30,000/µL and doubled from baseline in the absence of rescue therapy	ITT	1) Rescue medication: platelet counts will be censored for 4 weeks after the use of rescue therapy. That is, the weeks from the date when the rescue medication is initiated up to 4 weeks after the use of rescue medication will be considered to have had no platelet response (hypothetical strategy). 2) Discontinuation of study intervention before Week 25: data during the double-blind on-treatment period will be included in the analysis. Post-treatment data will be considered to have had no platelet response (composite strategy).	Adults: p-value, least squares mean number of weeks of response and 95% CI from a mixed-effect model with repeated measures (MMRM) approach on the binary response data including treatment, randomization stratification factors [d], week, treatment-by-week interaction as categorical fixed effects. Pediatrics: Descriptive. Missing data will be considered as no response. If no platelet measurement is available at a specific weekly visit, that week will be considered to have had no platelet response.
Secondary endpoint (Hypothetical + composite estimand)	Time to first platelet count of ≥50,000/µL OR 30,000/µL to <50,000/µL and doubled from baseline in the absence of rescue therapy	ITT	1) Rescue medication: platelet counts will be censored for 4 weeks after the use of rescue therapy. That is, the weeks from the date when the rescue medication is initiated up to 4 weeks after the use of rescue medication will be considered to have had no platelet response (hypothetical strategy). 2) Discontinuation of study intervention before Week 25: data during the double-blind on-treatment period will be included in the analysis. Post-treatment data will be considered to have had no platelet response (composite strategy).	Adults: p-value from stratified log-rank test adjusted by randomization stratification factors [d]. Hazard ratio and 95% CI from Cox regression model with treatment group and randomization stratification factors [d] as covariates. Pediatrics: Descriptive. Missing data will be considered as no response. If no platelet measurement is available at the weekly visit, that week will be considered to have had no platelet response. Participants who never responded will be censored at 1 week after Week 25 if prematurely discontinued due to related AE or lack of efficacy; Otherwise censored at the last platelet count assessment during the double-blind on-treatment period.

Endpoint Category (estimand)	Estimands			
	Endpoint [a]	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Secondary endpoint (while on-treatment estimand)	% participants requiring rescue therapy	ITT	Rescue therapy after 1st double-blinded IMP administration and before Week 25 (or last double-blinded IMP administration, whichever earlier) will be included in the analysis (while on-treatment strategy).	Adults: p-value from stratified log-rank test adjusted by randomization stratification factors[d]. Hazard ratio and 95% CI from Cox regression model with treatment group and randomization stratification factors[d] as covariates. Estimated % participants rescued at Week 25 based on Kaplan-Meier method. Pediatrics: Descriptive. Participants who have not been rescued any time during the 24-week double-blind treatment period will be censored at Week 25 (Day 169) visit (or last double-blinded IMP administration, whichever earlier).
Secondary endpoint (Composite + hypothetical estimand)	Change from baseline in physical fatigue (Item 10 of the ITP-PAQ) in adults at Week 13 [b]	ITT	1) Rescue therapy (after 8 weeks of double-blind treatment): data after the initiation of rescue therapy will be imputed by the participant's worst post-baseline value on or before the use of rescue therapy, ie, worst observation carried forward, (for participants whose post-baseline values are all missing, the baseline value will be used to impute the missing Week 13 value) (composite strategy). 2) Discontinuation of study intervention before Week 13 due to lack of response or related adverse events: the same handling as 1) above (composite strategy). 3) Discontinuation of study intervention before Week 13 due to reasons other than the aforementioned: data during the double-blind on-treatment period up to Week 13 will be included in the analysis. Post-treatment data will be considered missing (hypothetical strategy).	Adults only: p-value, least squares mean difference and 95% CI from an analysis of covariance (ANCOVA) model with treatment group, randomization stratification factors [d] and geographic region as fixed effects, and baseline value as a covariate. Missing data handling: A multiple imputation approach assuming missing at random will be used to impute missing Week 13 value, using all data during the double-blind on-treatment period up to Week 13 from participants who did not take rescue medication (after 8 weeks of double-blind treatment), nor discontinued before Week 13 due to related AE or lack of response. Note: before imputation (worst observation carried forward or multiple imputation), data will be set to missing for 4 weeks after the use of rescue therapy.

Endpoint Category (estimand)	Estimands			
	Endpoint [a]	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Secondary endpoint (Composite + hypothetical estimand)	Change from baseline in IBLS assessment at Week 25 [c]	ITT	The same handling as for ITP-PAQ Item 10 above except that Week 25 will replace Week 13.	Adult population: p-value from ANCOVA with treatment group and randomization stratification factors [d] and geographic region as fixed effects and baseline value as a covariate. Pediatrics: Descriptive. The same handling of missing data as for ITP-PAQ Item 10 above except that Week 25 will replace Week 13.

a Additional secondary/exploratory endpoints that are not included in this table will be handled with a similar strategy by the endpoint type (ie continuous, proportion, time-to-event) during respective periods (double-blind, open-label, long-term extension).

b Not applicable to countries within the EU (EEA countries) and UK.

c Applicable to countries within the EU (EEA countries) and UK only.

d Randomization stratification factors are splenectomy status (yes, no) and severity of thrombocytopenia (platelet counts <15,000/µL, ≥15,000/µL).

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the informed consent form (ICF).
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received or not.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Modified ITT (mITT)	All participants from ITT population who are exposed. Participants will be analyzed according to the intervention allocated by randomization.
Population without trial impact (disruption) due to COVID-19	All randomized participants without any major deviation related to Covid-19.
Safety	All randomized participants who take at least 1 dose of study intervention, regardless of the amount of treatment administrated. Participants will be analyzed according to the intervention they actually received (ie, "as-treated" defined below).
Pharmacokinetic (PK)	All randomized and exposed participants (safety population) with at least one post-baseline PK sample. Participants will be analyzed according to the intervention they actually received.
Open-Label (OL)	All participants who are exposed to active intervention (ie, rilzabrutinib) during the open-label period (ie, between the first OL visit at the nominal protocol visit Week 25 and the first LTE visit at the nominal protocol visit Week 53).
Long-term-extension (LTE)	All participants who are exposed to active intervention (ie, rilzabrutinib) during the LTE period (ie, on or after the first LTE visit at the nominal protocol visit Week 53).
Rilzabrutinib safety	All randomized participants who take at least 1 dose of the active intervention (ie, rilzabrutinib) during the study (ie, exposed to rilzabrutinib in the safety population during double-blind, open-label or LTE period).

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the intervention group as randomized if the participant received at least one administration as-randomized. The participants in the as-treated “placebo” group will not be included in the Rilzabrutinib safety population (Table 3) if they are not exposed to rilzabrutinib during the open-label or long-term extension treatment period.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, (Q1 and Q3 as needed), 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 double-blind investigational medicinal product (IMP). For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

The baseline value of platelet count is defined as the average of a patient's three platelet counts before the first dose of double-blind IMP): the two qualifying platelet counts at screening collected in eCRF and the platelet count at Week 1 (Study day 1).

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

Unless otherwise specified,

- Analyses will be performed separately for adult and pediatric populations.
- Analyses will be performed by intervention group (and overall for baseline and demographics characteristics) during the double-blind period.
- Analyses will be performed in the participants who have been exposed to rilzabrutinib during each respective period for OL and LTE. Please refer to Section 2, Section 3.6, Section 3.6.2, Section 3.6.3.
- Cumulative safety analyses across periods will be based on rilzabrutinib safety population. Please refer to Section 2, Section 3.6, Section 3.6.2, Section 3.6.3.
- Limited analyses will be provided during the initial 12 weeks of double-blind treatment period before participants cross over to open-label period to have a full safety profile (see Table 7).

General considerations for efficacy analyses

The statistical tests will be two-sided tests at a nominal 5% significance level for primary efficacy endpoint and key secondary efficacy endpoints.

Primary and secondary efficacy analyses will be performed in the ITT population, unless otherwise specified. The analyses of primary and key secondary endpoints are to compare the rilzabrutinib treatment group and the placebo treatment group.

The study primary and key secondary efficacy analyses will be based on the adult population at the time when the last adult participant has completed the 24-week blinded treatment period. The results based on the adults at the early analysis will be considered as final and serve as the basis

for registration application submissions. A separate analysis for the pediatric population will be similarly performed after pediatric participants have completed the blinded treatment period which may be at the same or different time when the adults have completed the blinded treatment period. The efficacy analyses on the pediatric population will be descriptive. Final analysis will be performed at the completion of the study. Additional analyses (eg, OL and LTE parts) may be performed before the final analysis. Please refer to Section 3.8 for more details.

The randomization stratification factors will include splenectomy status (yes, no) and severity of thrombocytopenia (platelet counts <15,000/μL, ≥15,000/μL).

For platelet count, a scheduled measurement will be used if it is available. Otherwise, an unscheduled measurement will be allocated to a scheduled visit if it is within the analysis window of the scheduled visit (see details in Section 5.4).

Rescue medications are recorded in eCRF by the investigator. Per protocol, rescue medications include IVIg, high-dose CSs, platelet infusion, and anti-D immunoglobulin infusion intended to increase platelet counts or prevent bleeding when platelet counts are less than 20,000/μL, or for bleeding or wet purpura. Other rescue medications are not permitted.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first double-blind IMP administration.
- **Double-blinded (DB) period**
  - The DB on-treatment period is defined as the period from the first DB IMP administration to the last DB IMP administration + 1 day for participants who did not enter the OL period or to the first OL IMP (the first OL visit is the nominal protocol visit Week 25) for participants who entered the OL period.
  - The DB post-treatment period is defined as the period after the DB on-treatment period for participants who did not enter the OL period.
- **Open-Label (OL) period**
  - The OL on-treatment period is defined as the period from the end of the DB on-treatment period to the last OL IMP administration + 1 day for participants who did not enter the LTE period or to the first OL IMP during the LTE (the first LTE visit is the nominal protocol visit Week 53) for participants who entered the LTE period.
  - The OL post-treatment period is defined as the period after the OL on-treatment period for participants who did not enter the LTE period.
- **Long-term extension (LTE)**
  - The LTE on-treatment period is defined as the period from the end of OL on-treatment period to the last IMP administration + 1 day.

- The LTE post-treatment period is defined as the period after the LTE on-treatment period to the end of study.

Note: Per protocol, the end of study visit occurs 4 weeks post last dose of IMP during the DB, OL or LTE period, whichever later.

Events occurred after the first double-blind IMP administration are considered treatment emergent, including on- and post-treatment events, as defined above. That is, **double-blind treatment-emergent period** includes double-blind on- and post-treatment period. **Open label treatment-emergent period** and **LTE treatment-emergent period** are defined similarly. For rilzabrutinib safety population, the entire treatment-emergent period will start from the 1st administration of rilzabrutinib.

For safety analysis, the 12-week double-blind treatment emergent period is the double-blind treatment emergent period for those discontinued before Week 13 (Day 85) or the period from the first double-blinded IMP administration to the visit date of Week 13 otherwise.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The efficacy analyses will be based on each on-treatment period for DB, OL and LTE respectively, unless otherwise specified.

3.2.1 Definition of endpoint(s)

Please refer to Section 1.2.2.1 for primary efficacy endpoint.

To qualify for a durable responder (Definition 1, Section 1.2.2.1), a participant must have met ALL of the following criteria:

- At least 8 non-missing weekly platelet measurements during the last 12 weeks of the 24-week treatment period, and
- Platelet counts ≥50,000/μL for ≥two-thirds of the 8 non-missing weekly assessments above, 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 8 weeks of treatment and before Week 25 (or last IMP intake, whichever earlier). A participant who is rescued during this period will be considered as a non-responder, and
- Not discontinued before Week 25 due to related TEAE (per investigator's assessment) or lack of response. A participant who discontinues before Week 25 and the reason for discontinuation is treatment related adverse event (AE) or lack of response will be considered as a non-responder.

Country-specific definition [countries within the EU (EEA countries) and UK]

To qualify for a durable responder (Definition 2, Section 1.2.2.1), a participant 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 double-blind treatment period, and
- Not rescued after 8 weeks of treatment and before Week 25 (or last IMP intake, whichever earlier). A participant who is rescued during this period will be considered as a non-responder, and,
- Not discontinued before Week 25 due to related TEAE (per investigator's assessment) or lack of response. A participant who discontinues before Week 25 and the reason for discontinuation is treatment related AE or lack of response will be considered as a non-responder.

3.2.2 Main analytical approach

The main analysis of the primary endpoint is to compare the responder rate of the rilzabrutinib treatment group with the placebo treatment group via the primary estimand as defined in Table 2.

To reject the null hypothesis of no treatment difference, the two-sided p-value based on a Cochran-Mantel-Haenszel (CMH) test adjusted by randomization stratification factors (Section 3.1) must be <0.05 in the adult ITT population. The Mantel-Haenszel estimate of common risk difference in response rates and its associated 95% confidence interval based on Mantel-Haenszel stratum weights (1) and the Sato variance estimator (2) will be reported. The observed response rate for each treatment group will be presented along with its associated 95% asymptotic confidence interval (CI).

For pediatric participants, the observed response rate will be calculated along with its associated (90% and 95%, respectively) CI in each treatment group using the Clopper-Pearson exact method. The difference in response rate and its associated 95% exact CI will be presented.

For Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the consistency of efficacy in pediatric population will be assessed with Method 2: the difference in response rate in the pediatric population is in the same direction as that in the adult population (ie, the response rate in rilzabrutinib group is numerically higher than that in the placebo group in the pediatric population) given that the treatment effect in adults is significant (ie, p value<0.05).

Graphical presentations of the results will be provided as needed. SAS® sample code could be found in Section 5.7.

Intercurrent events will be handled with the primary estimand specified in Table 2. Specifically,

1. Rescue medication: participants will be considered as non-responders if taking rescue medication after 8 weeks of double-blind treatment and before Week 25 (or last IMP intake, whichever earlier) (composite strategy).

2. Discontinuation of study intervention before Week 25 due to lack of response or related AE (per investigator's assessment in eCRF): participants will be considered as non-responders (composite strategy).
3. Discontinuation of study intervention before Week 25 due to reasons other than the aforementioned: data during the double-blind on-treatment period will be included in the analysis. Post-treatment data will be considered to have had no platelet response (composite strategy).

   Note: per protocol, the end of study visit is performed at 4-week post-dose follow up where participants will have their final assessment (weekly post-dose platelet assessment not required starting from amended protocol 03).

Missing data will be handled as followed,

For durable platelet response Definition 2 (Section 1.2.2.1), missing data will be handled as follows,

- Missing data due to Covid-19 (per eCRF) are assumed missing at random and will be imputed using the participant's median value of available weekly platelet counts (a minimum of 3 available weekly platelet counts required) during the last 12 weeks of double-blind on-treatment period.
- Otherwise, missing data will be considered as no response. That is, if no platelet measurement is available at a specific weekly visit, that week will be considered to have had no platelet response.

Table 4 in Section 3.2.3 outlines assumption of missing data and its handling for each type of analyses - main analyses (Section 3.2.2) and sensitivity analyses (Section 3.2.3) of the primary efficacy endpoint.

The n (%) of participants with missing data during the last 12 weeks of the 24-week double-blind period will be summarized as follows,

- Any missing weekly platelet counts.
  - Due to any reasons,
  - Due to Covid-19,
- Number of missing weekly platelet counts: 1 to 2, 3 to 4, >4,
  - Due to any reasons,
  - Due to Covid-19.

3.2.3 Sensitivity analysis

Sensitivity analyses will be performed in adults to assess the impact of the missing data handling strategy as outlined in Table 4.

Table 4 - Missing Data Handling for Primary Efficacy Endpoint

Definition	Analysis Type	Estimand	Alternatives to main analysis	Missing data Handling	Missing data Assumption
Definition 1[a]	Main [c] (Section 3.2.2)	Primary estimand (Composite)		No imputation of missing data	Not applicable
	Sensitivity (Section 3.2.3.1.3)		Alternative handling of missing data	Tipping-point analysis: post-treatment data considered missing for Intercurrent Event #3	Missing not at random: Assuming various treatment difference for missing data
	Sensitivity (for completers) (Section 3.2.3.2)	Modified primary estimand	Alternative analysis population	No imputation of missing data	Missing completely at random: completers are representatives of non-completers
	Sensitivity (Section 3.2.3.3)		Alternative handling of missing data due to Covid-19	Missing data due to Covid-19 imputed with the median value of available platelet counts	Missing (due to Covid-19) at random: missing data not associated with outcome
Definition 2[b]	Main [c] (Section 3.2.2)	Primary estimand (Composite)		1) Missing data due to Covid-19 imputed with the median value of available platelet counts, 2) No response otherwise	1) Missing (due to Covid-19) at random: missing data not associated with outcome; 2) Missing (not due to Covid-19) not at random: Missing data indicates lack of response
	Sensitivity (Section 3.2.3.1.1)		Alternative handling of missing data	Missing data considered as no response	Missing not at random: Missing data indicates lack of response
	Sensitivity (Section 3.2.3.1.2)		Alternative handling of missing data	On-treatment missing data handled using multiple imputation	Missing at random: on-treatment missing data not associated with outcome
	Sensitivity (Section 3.2.3.1.3)		Alternative handling of missing data	Tipping-point analysis: post-treatment data considered missing for Intercurrent Event #3	Missing not at random: Assuming various treatment differences for missing data

Definition	Analysis Type	Estimand	Alternatives to main analysis	Missing data Handling	Missing data Assumption
	Sensitivity (for completers) (Section 3.2.3.2)	Modified primary estimand	Alternative analysis population	No imputation of missing data	Missing completely at random: completers are representatives of non-completers

All efficacy analyses based on ITT, unless otherwise specified.

a Definition 1. Durable platelet response defined as a proportion of participants able to achieve platelet counts at or above 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 blinded treatment period in the absence of rescue therapy, 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 blinded treatment period. Definition 1 not applicable to countries within the EU (EEA countries) and UK.

b Definition 2. Durable platelet response defined as a proportion of participants able to achieve platelet counts at or above 50,000/µL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy. Definition 2 applicable to countries within the EU (EEA countries) and UK only.

c Sensitivity analysis for mITT; sensitivity analysis for participants who did not receive Covid-19 vaccine during the last 16 weeks of double-blind treatment period. (Section 3.2.3.2).

3.2.3.1 Sensitivity Analysis – Primary estimand – Adults in ITT

Each sensitivity analysis for durable response will be carried out via the same primary estimand and the same analysis method as defined in the main analytical approach (Section 3.2.2), using different handlings of missing data as specified below.

3.2.3.1.1 Alternative assumption of missing data (missing data considered as no response) (for Definition 2)

For durable platelet response Definition 2 (Section 1.2.2.1), missing weekly platelet count regardless of due to Covid-19 or not will be considered as no response assuming missing not at random.

3.2.3.1.2 Alternative assumption of missing data (missing data handled via multiple imputation) (for Definition 2)

As indicated in the primary estimand (Section 3.2.2), weekly platelet counts may not be available (due to missing or discontinuation) during the double-blind on-treatment period in participants who were not rescued (after 8 weeks of double-blind treatment and before Week 25) nor discontinued before Week 25 due to related AE or lack of response. These participants could be categorized into two groups: (1) those who discontinue IMP on or before Week 13 for which their missing data will not be imputed due to a large portion (≥50%) of missing data points during the double-blind treatment period) at participant level, and (2) those who stay on IMP beyond Week 13 for which their missing data will be imputed as specified below.

The missing data will be imputed using multiple imputation assuming missing at random and assuming logarithm transformed platelet values to be multivariate normally distributed. Specifically,

- Post-baseline missing weekly platelet counts (from Week 2 up to Week 25 during the double-blind on-treatment period) will be imputed using a model estimated from the participants who were not rescued (after 8 weeks of double-blind treatment and before Week 25) nor discontinued before Week 25 due to related AE or lack of response) and who stay on IMP beyond Week 13 and have available data during the double-blind on-treatment period at the corresponding visits.

  Note: before multiple imputation, data will be set to missing for 4 weeks after the use of rescue therapy during the initial 8 weeks of double-blind treatment.

- The imputation model will include treatment group, randomization stratification factors, geographic region (Section 3.1) as classified variables and baseline value as a covariate.
- Binary durable platelet response will be derived from each of the imputed complete data and analyzed using the same analysis method as defined in the main analytical approach (Section 3.2.2). Statistical inference obtained from all imputed data will be combined using Rubin's rule (3).

The above sensitivity analysis via multiple imputation approach will be implemented under the following scenarios:

1. No missing data will need to be handled by multiple imputation in the placebo group (ie, missing data occurred in rilzabrutinib group only), OR
2. There are missing data that will need to be handled by multiple imputation in the placebo group and there are ≥3 participants in the placebo group who have completed the 24-week double-blind treatment without being rescued (after 8 weeks of double-blind treatment) and had post-baseline weekly platelet counts during the last 12 weeks of double-blind on-treatment period.

Please see sample SAS® code in Section 5.7.

3.2.3.1.3 Alternative assumption of missing data (tipping-point analysis) (for Definition 1 and Definition 2 respectively)

The tipping point analyses will be two-dimensional, i.e., assumptions about the missing outcomes in each treatment group would vary independently. The response rate among those participants with missing durable response status (identified in Table 5) is assumed to be p0 for the placebo group and p1 for the rilzabrutinib group, and the response rate p0 and p1 will systematically vary starting from 0% and ending at 100% by every 10% respectively. Given a set of (p0, p1), a participant with missing response will be randomly assigned as a responder or a non-responder using binomial distribution to generate multiple imputed datasets. The same analysis method as defined in the main analytical approach (Section 3.2.2) will be performed on each of the imputed datasets to obtain the results for each comparison of the rilzabrutinib group versus the placebo group. The results across multiple imputed datasets will be combined using Rubin's rule (3). If one pair of (p0, p1) is found to just reverse the study conclusion, in terms of p-value larger than 0.05, then the (p0, p1) is identified as the tipping point. The results for a grid of (p0, p1) combinations will be provided.

Please see sample SAS® code in Section 5.7.

Table 5 - Tipping Point Analysis: Durable Platelet Response Status

Definition	Criteria (during the last 12 weeks of DB on-treatment period)	Status
Definition 1 [a]	Rescued after 8 weeks of treatment and before Week 25	Non-responder
	Discontinued before Week 25 due to related TEAE or lack of response	Non-responder
	Observed non-responder: >=5 weekly platelet counts <50,000/µL	Non-responder
	Observed responder: 1. >=8 weekly platelet counts >=50,000/µL, OR 2. 6 or 7 weekly platelet counts >=50,000/µL in total out of >=8 non-missing weekly platelet counts among which >=2 weekly platelet counts >=50,000/µL out of last 6 weeks	Responder
	Undetermined: due to missing data, or discontinuation not due to related AE or lack of response	Missing
Definition 2 [b]	Rescued after 8 weeks of treatment and before Week 25	Non-responder
	Discontinued before Week 25 due to related TEAE or lack of response	Non-responder
	Observed non-responder: >=5 weekly platelet counts <50,000/µL	Non-responder
	Observed responder: >=8 weekly platelet counts ≥50,000/µL	Responder
	Undetermined: due to missing data, or discontinuation not due to related AE or lack of response	Missing

a Definition 1. Durable platelet response defined as a proportion of participants able to achieve platelet counts at or above 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 blinded treatment period in the absence of rescue therapy, 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 blinded treatment period. Definition 1 not appliable to countries within the EU (EEA countries) and UK.

b Definition 2. Durable platelet response defined as a proportion of participants able to achieve platelet counts at or above 50,000/µL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy. Definition 2 applicable to countries within the EU (EEA countries) and UK only.

TEAE = treatment emergent adverse event.

3.2.3.2 Sensitivity Analyses – modified primary estimand – Adults in mITT, 24-week completer, participants not receiving Covid-19 vaccine (for Definition 1 and Definition 2, respectively)

Sensitivity analyses in adults will be performed to assess respectively, the potential impact of,

- Non-IMP exposure by including participants who have been randomized and exposed (ie, mITT)
- The premature discontinuation by including participants who have completed the 24-week double-blind treatment period without rescue medication (ie, 24-week completer).
- The Covid-19 vaccine by including participants who did not receive Covid-19 vaccine during the last 16 weeks of the double-blind treatment period.

Each sensitivity analysis will be carried out via a modified primary estimand, which is the same as the primary estimand defined in the main analytic approach, except for the analysis population. The same analysis as specified in Section 3.2.2 will be performed (Table 4).

For the analysis in the 24-week completer, the treatment difference will likely be estimated via normal approximation without being adjusted by stratification factors due to the expected high dropout particularly in the placebo group. The analysis method and stratification factors will be specified in the footnote of the corresponding outputs.

3.2.3.3 Sensitivity Analyses – modified primary estimand – missing due to Covid-19 imputed with participant's median value (for Definition 1)

Sensitivity analysis on the durable response Definition 1 will be carried out via the same primary estimand and the same analysis method as defined in the main analytical approach (Section 3.2.2), after the handling of missing data due to Covid-19. That is, missing data due to Covid-19 (per eCRF) will be imputed using the participant's median value of available weekly platelet counts (a minimum of 3 available weekly platelet counts required) during the last 12 weeks of double-blind on-treatment period.

3.2.4 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary endpoint (Definition 1 and Definition 2 respectively) in the adult ITT population across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

- Race (White, Asian, Other)
- Age group (<65 years, ≥65 years)
- Sex (Male, Female)
- Duration of ITP since diagnosis (≤1 year, >1 year to ≤3 years, >3 years)
- Prior splenectomy status (yes, no)
- Baseline platelet counts (<15,000/μL, ≥15,000/μL)
- Prior CS (No prior CS, Prior CS and no concomitant CS, Prior and concomitant CS, Prior CS and concomitant CS and TPO-RA)
- Prior TPO-RA (No prior TPO-RA, Prior TPO-RA and no concomitant TPO-RA, Prior and concomitant TPO-RA, Prior TPO-RA and concomitant TOP-RA and CS)
- Prior intravenous immunoglobulin (IVIg) or anti-D immunoglobulin (Yes, No)
- Prior rituximab (Yes, No)
- Concomitant ITP medications (Yes, No)
- Concomitant ITP medications (CS, TPO-RA, both CS and TPO-RA, neither CS nor TPO-RA)
- US vs. Non-US
- Geographic region:
  - Asia/Pacific (Australia, China, Japan, Singapore, South Korea, Thailand),

- West Europe (Austria, France, Germany, Italy, Norway, Spain, United Kingdom, Netherlands),
- East Europe (Hungary, Israel, Poland, Russia, Turkey, Ukraine),
- North America (Canada, United States),
- South America (Argentina, Brazil, Chile, Mexico).

The observed response rate will be presented along with its associated 95% asymptotic CI in each treatment group and each subgroup. The treatment difference in response rates and its associated 95% CI will be summarized for the subgroups defined above. The treatment difference for each subgroup will likely be estimated via normal approximation without being adjusted by stratification factors due to the expected small cell size. The Mantel-Haenszel estimate of common treatment difference and associated 95% (Section 3.2.2) adjusted by stratification factors may be considered if appropriate. The analysis method and stratification factors will be specified in the footnote of the corresponding outputs. The consistency of the treatment difference among these sub-populations will be examined by the forest plot.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

3.3.1 Key/Confirmatory secondary endpoint(s)

3.3.1.1 Definition of endpoint(s)

Please see Section 1.2.2.2 for the definition of key secondary efficacy endpoints. Additional details are provided below for specific endpoints.

Number of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy

To qualify for having a platelet response at a given week, a participant must have met ALL the following criteria,

- Platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and doubled from baseline at a given week during the 24-week double-blind treatment period from Week 2 (Day 8) to Week 25 (Day 169) (Section 3.2),
- Not rescued within the 4 weeks prior to the elevated platelet count at the given week. If a participant receives rescue medication during the 24-week double-blind treatment, the participant's 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 to have had no platelet response.

Number of weeks with platelet count ≥30,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy

Similar derivation will be applied as the secondary endpoint above.

Time to first platelet count of ≥50,000/µL OR between ≥30,000/µL and <50,000/µL and doubled from baseline (platelet counts will be censored for 4 weeks after the use of rescue therapy, if any)

Time to first platelet count in days will be calculated as:

(Date of first occurrence of platelet response - Date of first IMP dosing) + 1,

where platelet response is defined as ≥50,000/µL OR between ≥30,000/µL and <50,000/µL and doubled from baseline. Please see the censoring rule, handling of intercurrent events and missing data in Section 3.3.1.2.2 and Section 3.3.1.3.1.

Proportion of participants requiring rescue therapy during the 24-week Blinded Treatment period

Participants requiring rescued therapy are those who are rescued after first double-blinded IMP administration and before Week 25 or last double-blinded IMP administration, whichever earlier. The Kaplan-Meier (K-M) method will be used to estimate the probabilities of first rescue therapy use. Please see handling of intercurrent events and the censoring rule in Section 3.3.1.2.3.

Change from baseline in Item 10 of ITP-PAQ at Week 25; Change from baseline in IBLS assessment at Week 13

Please refer to Section 3.7.3.

3.3.1.2 Main analytical approach

3.3.1.2.1 Number of weeks with platelet count ≥50,000/µL OR between ≥30,000/µL and <50,000/µL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy;

Number of weeks with platelet counts ≥30,000/µL and at least doubled from baseline over the 24-week Blinded Treatment period in the absence of rescue therapy

The analysis of this key secondary endpoint is to compare the number of weeks with platelet response between the rilzabrutinib treatment group and the placebo treatment group via the primary estimand as defined in Table 2.

Considering a participant's platelet response at each visit a binary response data, a mixed-effect model with repeated measures (MMRM) approach will be used to analyze the longitudinal binary platelet response data across visits (4) in the adult ITT population. The analysis model will include treatment, randomization stratification factors (Section 3.1), week (Weeks 2 to 25), treatment-by-week interaction as categorical fix effects. Generalized estimating equations will be used to obtain statistical inference. A variance component working covariance matrix which is merely a weight matrix will be used in the model to obtain unweighted proportions.

To prepare the data for MMRM analysis, each participant will have complete weekly response status across 24 weeks as a 24-dimensional vector after the handling of intercurrent events and missing data (specified below).

Least squares (LS) mean number of weeks (% weeks) with platelet response across 24 weeks in each treatment group, difference in LS mean number of weeks (% weeks) with platelet response between treatment groups and its corresponding 95% CIs will be provided along with the p-value.

For each of the adult and pediatric populations respectively, descriptive statistics (eg, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be provided by treatment group for the number of weeks with observed platelet response.

Intercurrent events will be handled with the primary estimand as specified in Table 2. Specifically,

1. Rescue medication: platelet counts will be censored for 4 weeks after the use of rescue therapy. That is, the weeks 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, thus will be considered to have had no platelet response (hypothetical strategy).
2. Discontinuation of study intervention before Week 25: data during the double-blind on-treatment period will be included in the analysis. Post-treatment data will be considered to have had no platelet response (composite strategy).

Missing data (ie, missing weekly platelet counts) will be considered as no response.

3.3.1.2.2 Time to first platelet count of ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and doubled from baseline during the 24-week Blinded Treatment period (platelet counts will be censored for 4 weeks after the use of rescue therapy, if any)

The analysis of this key secondary endpoint is to compare the time to first platelet response as defined between the rilzabrutinib treatment group and the placebo treatment group via the primary estimand as defined in Table 2.

To reject the null hypothesis of no treatment difference, the two-sided p-value based on a stratified log-rank test adjusted by randomization stratification factors (Section 3.1) must be <0.05 in the adult ITT population. The hazard ratio between rilzabrutinib and placebo along with its 95% confidence interval will be estimated based on a Cox regression model with treatment group and randomization stratification factors (Section 3.1) as covariates.

For each of adult and pediatric populations respectively, the K-M method will be used to estimate the probabilities of first platelet response in each group, along with 1st, 2nd (median) and 3rd quartile time to response. K-M plot will also be provided.

Intercurrent events will be handled with the primary estimand as specified in Table 2. Specifically,

1. Rescue medication: platelet counts will be censored for 4 weeks after the use of rescue therapy. That is, the weeks 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, thus will be considered to have had no platelet response (hypothetical strategy).

2. Discontinuation of study intervention before Week 25: data during the double-blind on-treatment period will be included in the analysis. Post-treatment data will be considered to have had no platelet response (composite strategy).

Missing data (ie, missing weekly platelet counts) will be considered as no response.

Participants who have never experienced platelet response (as defined in Section 3.3.1.1) any time during the 24-week double-blind treatment period will be censored,

- At 1 week after the protocol scheduled Week 25 (Day 169) visit for those who prematurely discontinued the 24-week treatment period due to related AE or lack of response, or,
- At the last assessment during the double-blind on-treatment period otherwise.

3.3.1.2.3 Proportion of participants requiring rescue therapy during the 24-week Blinded Treatment period

The analysis of this key secondary endpoint is to compare proportion of participants requiring rescue therapy (via the time to event analysis due to the expected high rate of treatment discontinuation) during the 24-week blinded treatment period between the rilzabrutinib treatment group and the placebo treatment group via the primary estimand as defined in Table 2.

To reject the null hypothesis of no treatment difference, the two-sided p-value based on a stratified log-rank test adjusted by randomization stratification factors (Section 3.1) must be <0.05 in the adult ITT population. The hazard ratio between rilzabrutinib and placebo along with its 95% confidence interval will be estimated based on a Cox regression model with treatment group and randomization stratification factors (Section 3.1) as covariates.

For each of adult and pediatric populations respectively, the K-M method will be used to estimate the probabilities of first rescue therapy use at specific timepoints (eg, Weeks 9, 25) in each group, along with 1st, 2nd (median) and 3rd quartile time to first rescue therapy use. K-M plot will also be provided.

Intercurrent events will be handled with while-on treatment strategy, that is, rescue therapy during the double-blind period, ie, after first double-blinded IMP administration and before Week 25 (or last double-blinded IMP administration, whichever earlier), will be included in the analysis.

Participants who have not been rescued any time during the 24-week double-blind treatment period will be censored at Week 25 (Day 169) visit (or last double-blinded IMP administration, whichever earlier).

3.3.1.2.4 Change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (≥18 years) at Week 13

The analysis of this key secondary endpoint is to compare the change from baseline at Week 13 on Item 10 score of ITP-PAQ (Section 3.7.3.2) between the rilzabrutinib treatment group and the placebo treatment group in the adult ITT population via the primary estimand as defined in Table 2.

Change from baseline in Item 10 score at Week 13 will be analyzed using an analysis of covariance (ANCOVA) model with the treatment group, randomization stratification factors and geographic region (Section 3.1) as fixed effects and baseline Item 10 score as a covariate. Missing score at Week 13 will be imputed via worst observation carried forward (WOCF) or multiple imputation as specified below which will result in multiple data sets of complete data. Each complete dataset will be analyzed by fitting an ANCOVA model. Statistical inference obtained from all imputed data will be combined using Rubin's rule (3). LS mean score changes in each treatment group, LS mean difference between treatment groups and their corresponding 95% CIs will be provided along with the p-value.

Observed Item 10 score at each visit and its change from baseline will be descriptively summarized. Cumulative distribution functions of Item 10 score in changes from baseline to Week 13 will be displayed by treatment groups. A shift summary from baseline to Week 13 and Week 25 will be provided for Item 10 raw score categorically.

Intercurrent events will be handled with a hybrid of composite and hypothetical strategy (Table 2). Specifically,

1. Rescue medication (after the initial 8 weeks of double-blind treatment): data after initiation of rescue therapy will be imputed by the participant's worst post-baseline value on or before the use of rescue therapy, ie, worst observation carried forward (for participants whose post-baseline values are all missing, the baseline value will be used to impute the missing Week 13 value) (composite strategy). For the purpose of worst observation carried forward, data will be set to missing for 4 weeks after the use of rescue therapy. In other words, only data more than 4 weeks after the use of rescue therapy will be carried forward.
2. Discontinuation of study intervention before Week 13 due to lack of response or related adverse events: the same handling as 1) above (composite strategy).
3. Discontinuation of study intervention before Week 13 due to reasons other than the aforementioned: data at Week 13 during the double-blind on-treatment period will be included in the analysis. Post-treatment data will be considered missing (hypothetical strategy).

   Note, per protocol the end of study visit is performed at 4-week post-dose follow up where participants will have their final assessment.

Missing data will be handled as followed,

- A multiple imputation approach will be used to impute missing Week 13 value, using all data during the double-blind on-treatment period up to Week 13 from participants who did not take rescue medication (after 8 weeks of double-blind treatment), nor discontinued before Week 13 due to related AE or lack of response, assuming missing at random and multivariate normal distribution. The imputation model will include treatment group, randomization stratification factors, geographic region (Section 3.1) as classified variables and baseline item score as a covariate. In case the baseline score is missing for a participant, the pooled mean of baseline score will be used.

Note: before multiple imputation, data will be set to missing for 4 weeks after the use of rescue therapy.

3.3.1.2.5 Change from baseline in Idiopathic Thrombocytopenic Purpura Bleeding Scale (IBLS) assessment at Week 25 (applicable to countries within the EU (EEA countries) and UK only)

The analysis of this key secondary endpoint is to compare the change from baseline at Week 25 on IBLS score (Section 3.7.3.1) between the rilzabrutinib treatment group and the placebo treatment group via the primary estimand as defined in Table 2.

Change from baseline in IBLS score at Week 25 will be analyzed in the adult ITT population using the same analysis method as specified in Section 3.3.1.2.4 for change from baseline in ITP-PAQ Item 10 except that Week 25 will replace Week 13.

For pediatric population, descriptive summary will be provided based on observed data.

Intercurrent events and missing data will be handled similarly as defined in Section 3.3.1.2.4, except that Week 25 will replace Week 13.

Graphical presentations of the results will be provided as needed for the above secondary endpoints. Sample SAS® code could be found in Section 5.7.

3.3.1.3 Supplementary analysis I

3.3.1.3.1 Number of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy;

Number of weeks with platelet counts ≥30,000/μL and at least doubled from baseline over the 24-week Blinded Treatment period in the absence of rescue therapy;

Time to first platelet count of ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and doubled from baseline during the 24-week Blinded Treatment period

Alternative estimand regarding handling of intercurrent events

A sensitivity analysis will be performed using the same analysis method as the main analytical approach specified in Section 3.3.1.2.1 or Section 3.3.1.2.2 except that the intercurrent events will be handled as follows,

1. Rescue medication:
   a) During the initial 8 weeks of double-blind treatment - *same handling as the primary estimand in Section 3.3.1.2.1 or Section 3.3.1.2.2.*
   b) After the initial 8 weeks of double-blind treatment: platelet counts after initiation of rescue therapy will be considered as no platelet response, ie, only the platelet counts up to the start date of rescue therapy will be included in analysis (composite strategy) - *more conservative handling than the primary estimand.*

2. Discontinuation of study intervention before Week 25.
   a) Due to related AE: platelet counts after the onset of AE will be considered as no platelet response, ie, only the platelet counts up to the onset of AE will be included in analysis (composite strategy) – *more conservative handling from the primary estimand*.
   b) Not due to related AE – *same handling as the primary estimand*.

3.3.1.3.2 Proportion of participants requiring rescue therapy during the 24-week Blinded Treatment period

Alternative estimand (analyzed via CMH)

Proportion of participants requiring rescue therapy during the 24-week Blinded Treatment period will be analyzed via CMH, the same analysis method as defined in the main analytical approach (Section 3.2.2) for the primary efficacy endpoint.

3.3.1.3.3 Change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (≥18 years) at Week 13

Alternative estimand (analyzed via MMRM)

Change in Item 10 of the ITP-PAQ from baseline to Week 13, will be analyzed using a MMRM under the missing at random framework. The MMRM model will include treatment, randomization stratification factors and geographic region (Section 3.1), visit (Weeks 5, 9, 13), treatment-by-visit interaction as fixed effects, and baseline score-by-visit interaction as a covariate. The LS mean change for each treatment group, as well as the between-group LS mean difference and their associated 95% CI will be provided.

The MMRM model will be implemented using SAS® MIXED procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degree of freedom will be estimated using the Kenward-Roger approximation by fitting values from post-baseline scheduled visits.

3.3.1.4 Supplementary analysis II

3.3.1.4.1 Change from baseline in Idiopathic Thrombocytopenic Purpura Bleeding Scale (IBLS) assessment at Week 13 (applicable to countries within the EU (EEA countries) and UK only)

The same analyses as specified in Section 3.3.1.2.5 will be performed similarly on change from baseline in IBLS score at Week 13.

3.3.1.4.2 Change from baseline in Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (≥18 years) at Week 25

The same analyses as specified in Section 3.3.1.2.4 will be performed similarly on change from baseline in Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants at Week 25.

3.3.2 Supportive secondary endpoint(s)

3.3.2.1 Other secondary endpoint – Stability of platelet response

To qualify for a stable platelet responder (see endpoint definition in Section 1.2.2.3.1), a participant must have met ALL of the following criteria:

- Achieving initial platelet response, ie, platelet count ≥50,000/μL within 12 weeks of initiation of rilzabrutinib [during double-blind period (protocol visit Week 2 to Week 13) for participants randomized to rilzabrutinib group, or during open-label period (protocol visit Week 26 to Week 37) for participants randomized to placebo group], and
- Following the initial platelet response, achieving platelet count ≥50,000/μL for a period of 24 weeks, where
- There would be no 2 scheduled visits, at least 4 weeks apart, with a platelet count less than 50,000/μL, without an intervening visit of platelet count ≥50,000/μL. In other words, a participant would not be qualified for a stable responder if the participant has consecutive platelet counts <50,000/μL for 4 weeks or longer (ie, from the first to the last occurrence of <50,000/μL without any intervening visit of platelet count ≥50,000/μL) during this 24 weeks period after the initial response has been achieved. The participant's platelet counts within 4 weeks of rescue regimen will be considered as no response.
- Missing platelet count will be considered as no response.

The proportion of stable response will be calculated along with its 95% confidence interval (via normal approximation) in the open-label population (Section 2) as well as by randomized treatment group at the beginning of double-blind treatment, respectively.

For participants who are identified as a stable platelet responder, the duration of response will be descriptively summarized in the rilzabrutinib safety population (Section 2) as well as by randomized treatment group at the beginning of double-blind treatment, respectively. The duration of stable platelet response defined above is from the start date of stable platelet response up to

- The date of the first occurrence of 2 or more consecutive platelet counts <50,000/μL for 4 weeks or longer (ie, when the stable response is lost), or
- 12 months after entering LTE,

whichever earlier.

3.3.2.2 Other secondary endpoint – QOL endpoints

ITP-PAQ transformed score by scale (domain) and its change from baseline will be descriptively described for adult participants (see details in Section 3.7.3.2).

ITP-KIT summary score and its change from baseline will be descriptively described for pediatric participants (see details in Section 3.7.3.3).

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

3.4.1 Definition of endpoint(s)

Please see Section 1.2.2.4.1 and Section 1.2.2.4.2.

Additional details are provided for specific exploratory efficacy endpoints below. Details of COA related endpoints could be found in Section 3.7.3.

Proportion of participants able to achieve platelet counts ≥50,000/μL for 4 out of last 8 weeks of the 24-week treatment period

Refer to Section 3.2.1.

Percentage of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy

Refer to Section 3.3.1.1. For each participant, percentage will be based on the available number of weeks with platelet counts including the weeks censored due to rescue therapy during the double-blind period.

Proportion of participants with complete response (defined as platelet count ≥100,000/μL on 2 consecutive visits at least 5 days apart and no bleeding or rescue ITP therapy use on and through these two visits.

To qualify for a complete responder, a participant must have met ALL of the following criteria:

- Platelet counts ≥ 100,000/μL on 2 consecutive visits at least 5 days apart, any time from Week 2 to Week 25 and
- No bleeding on and through these two visits (ie, bleeding events identified by SMQ = Haemorrhages via broad and narrow search in eCRF “Adverse Events”);
- Not rescued within the 4 weeks prior to the elevated platelet count and on and through these two visits.

Proportion of participants with platelet count ≥50,000/μL on 2 consecutive visits at least 5 days apart and no rescue ITP therapy use on and through these two visits.

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

- Platelet counts ≥ 50,000/μL on 2 consecutive visits at least 5 days apart, any time from Week 2 to Week 25 and

- Not rescued within the 4 weeks prior to the elevated platelet count (Section 3.3.1.1) and on and through these two visits.

Proportion of participants who have a platelet count that exceeds 250,000/µL or 450,000/µL (for participants on TPO-RA)

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

- Concomitantly on TPO-RA;
- Platelet counts >250,000/µL (or >450,000/µL respectively) any time from Week 2 to Week 25 and
- Not rescued within the 4 weeks prior to the elevated platelet count (Section 3.3.1.1).

Percent change from baseline on CS dose / TPO-RA dose

Percent of dose change will be calculated at Week 53 (ie, Study day 365 +/- 3 days) and after 12 months on the LTE period (ie, Study day 701 ie, Study day 365 +/- 14 days).

Proportion of participants who switch to rilzabrutinib as a monotherapy during the first year of the LTE period

To qualify for "switching to rilzabrutinib as a monotherapy", a participant must have stopped the concomitant ITP medication permanently during the first year of the LTE period (ie, from 1st dose during LTE up to Study day 701 +/- 7 days).

Proportion of participants who decrease their CS dose >50% relative to baseline values during the first year of the LTE

Qualified participants are those who have CS dose decrease by >50% from baseline during the first year of the LTE period (ie, from 1st dose during LTE up to Study day 701 +/- 7 days).

Proportion of participants who manage to reduce their dose or stop TPO-RA agonists during the first year of the LTE

Qualified participants are those who have TPO-RA agonist dose decreased or stopped during the first year of the LTE period (ie, from 1st dose during LTE up to Study day 701 +/- 7 days).

3.4.2 Main analytical approach

Exploratory efficacy endpoints will be analyzed using the same methodology as specified for primary (Section 3.2) and secondary endpoints (Section 3.3) for similar data (continuous, proportion, or time to event). Analyses of exploratory endpoints will be mainly descriptive, with no testing.

For binary and response endpoints, frequency and percentage will be presented.

For other categorical endpoints (eg, IBLS, EQ-5D-5L, PGIS, PGIS-Fatigue, PGIC), frequency and percentage will be presented.

For continuous endpoints (eg, IBLS, ITP-PAQ, EQ-5D), descriptive summary will be provided at scheduled visits.

Please refer to Section 3.7.3 for more details on COA related endpoints.

In addition, the following three predictive values of platelet count will be crossed tabulated in a performance metrics to predict the primary efficacy response (Section 3.2.1).

Predictive value of platelet count:

- ≥30,000/μL and ≥20,000/μL above baseline during the first 13 weeks of treatment in absence of rescue medication 4 weeks prior to the elevated platelet count
- ≥50,000/μL any time during the first 13 weeks of treatment in absence of rescue medication 4 weeks prior to the elevated platelet count

The performance metrics will be constructed as follows, for each predictor and each definition of primary efficacy endpoint:

	Primary efficacy response achieved	Primary efficacy endpoint not achieved	Total
Predictive Value$_i$ (Y)	a	b	a + b
Predictive Value$_i$ (N)	c	d	c + d

Positive Predictive Value (PPV) and Negative Predictive Value (NPV) will be calculated as:

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

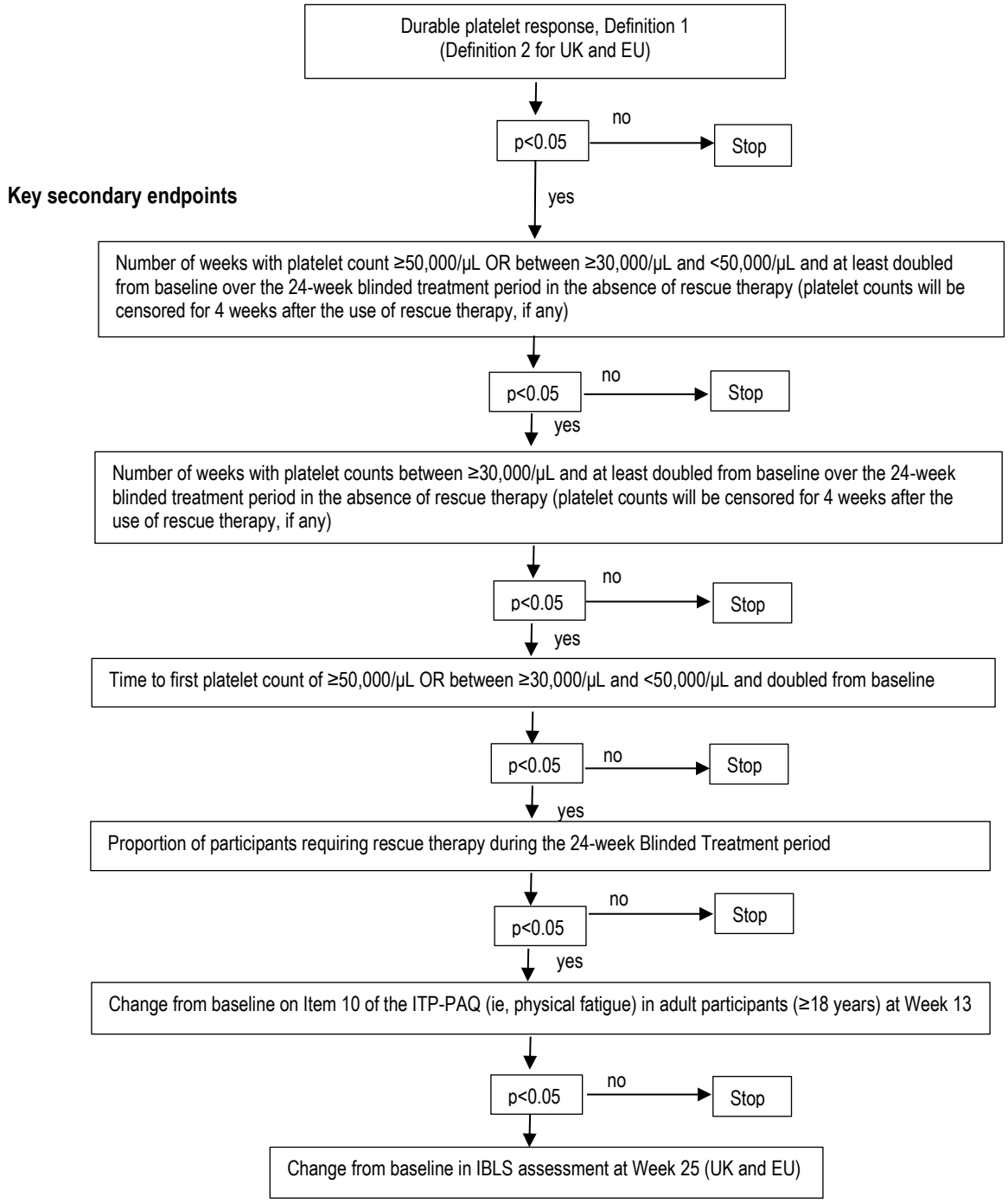
3.5 MULTIPLICITY ISSUES

All comparisons will be between rilzabrutinib and placebo in the adult ITT population.

To control the family-wise type I error, a fixed-sequence procedure will be applied to the primary endpoint and key secondary endpoints at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level (see Figure 1 below).

No multiplicity adjustment will be made on efficacy variables other than those mentioned above.

Figure 1 - Fixed-sequence testing procedure



3.6 SAFETY ANALYSES

All safety analyses during DB period will be performed on the safety population as defined in Section 2, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Adverse events in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided separately.
- Adverse events in participants who did not receive treatment as randomized will be provided separately.

In addition, safety analyses will be performed in the OL and LTE populations during the corresponding treatment periods, as well as on rilzabrutinib safety population across periods (see Section 2, Section 3.6.2, Section 3.6.3).

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure as well as compliance and summarized during each treatment period (safety population for double-blind, open-label population, and LTE population, rilzabrutinib safety population respectively).

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 1 day, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure in days will be summarized quantitatively and categorically during the double-blind period and open-label period respectively: 1 to 28, 29 to 56, 57 to 84, 85 to 112, 113 to 140, 141 to 168, >168 (double-blind period only), afterwards monthly (every 4 weeks) for open-label period and quarterly for LTE period.

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

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the administrated doses as required by the protocol.

Percentage of treatment compliance for a participant will be defined as the number of days that the participant was compliant divided by the total number of days that the participant was planned to take.

Treatment compliance will be summarized quantitatively and categorically: <60%, 60% to <80%, 80% to 100%, >100%.

3.6.2 Adverse events

General common rules for adverse events

All AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0) 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) version currently in effect at Sanofi at the time of 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.
- TEAEs: AEs that developed, worsened, or became serious during the treatment-emergent periods (Section 3.1)

The primary focus of AE reporting will be on TEAEs. Pre-treatment AEs will be described separately.

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 severity/grade is missing for 1 of the treatment-emergent occurrences of an AE, the severity/grade will be imputed (by treatment-emergent period) with the maximal severity/grade of the other occurrences. If the severity is missing for all the occurrences, the severity/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 an observation period, using the maximum (worst) grade (by treatment-emergent period). Summaries will be provided for all grades combined unless otherwise specified. Missing grades, if any, will be included in the "all grades" category.

The AE tables will be sorted as indicated in Table 6.

Table 6 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the SAR444671/rilzabrutinib intervention group.
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, 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 CTCAE Grade ≥3 TEAE
- Any treatment emergent serious adverse event (SAE)
- Any treatment emergent SAE related to IMP as per investigator's judgement
- TEAE leading to death
- Grade 5 TEAE
- Any TEAE leading to permanent discontinuation of study intervention
- Any TEAE related to IMP as per investigator's judgement
- Any treatment emergent AESI increase in alanine transaminase (ALT) >3 × ULN (Table 8)
- Any ≥Grade 2 treatment-emergent bleeding events (criteria in Table 8)
- Any ≥Grade 2 treatment-emergent bleeding events related to IMP as per investigator's judgement
- Any ≥Grade 2 treatment-emergent infections (criteria in Table 8)
- Any ≥Grade 2 treatment-emergent infections related to IMP as per investigator's judgement
- Any ≥Grade 2 treatment-emergent gastrointestinal events (criteria in Table 8)
- Any ≥Grade 2 treatment-emergent gastrointestinal events related to IMP as per investigator's judgement

The AE summaries in Table 7 will be generated with number (%) of participants experiencing at least one event. TEAE will be provided for each period respectively as specified.

The all TEAE summary by Primary SOC and PT (and other safety summaries (eg, SAEs, deaths), if deemed needed after TEAE evaluation) will be performed by trial impact (disruption) due to COVID-19.

Table 7 - Analyses of adverse events

	MedDRA levels	DB 12W		DB 24W		OL [d]	LTE [e]	DB+OL+LTE [f]
		Adults	Peds	Adults	Peds	Adults and Peds Separately		
All TEAE	Overview [a]	✓	✓	✓	✓	✓	✓	✓
	Primary SOC and PT	✓	✓	✓[g]	✓[g]	✓	✓	✓
	PT			✓				
Common TEAE (≥5% in rilzabrutinib group)	Primary SOC and PT			✓				
TEAE related to IMP as per Investigator's judgment	Primary SOC, and PT	✓	✓	✓	✓	✓	✓	✓
TEAE by maximal CTCAE grade	Primary SOC and PT			✓	✓			
Any ≥Grade 3 TEAE	Primary SOC and PT			✓	✓			
Any ≥Grade 3 TEAE related to IMP as per Investigator's judgment	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 study intervention	Primary SOC and PT			✓	✓	✓	✓	
TEAE leading to death	Primary SOC and PT			✓				✓
Any treatment emergent AESI	PT			✓	✓	✓	✓	

	MedDRA levels	DB 12W		DB 24W		OL [d]	LTE [e]	DB+OL+LTE [f]	
		Adults	Peds	Adults	Peds	Adults and Peds Separately			
Any ≥Grade 2 treatment-emergent bleeding event [b]	PT			✓	✓	✓	✓		
Any ≥Grade 2 treatment-emergent bleeding event [b] related to IMP as per Investigator's judgement	PT			✓	✓	✓	✓		
Any ≥Grade 2 TEAEs under SOC "Infections and Infestations"	PT			✓	✓	✓	✓		
Any ≥Grade 2 TEAEs under SOC "Infections and Infestations" related to IMP as per Investigator's judgement	PT			✓	✓	✓	✓		
Neutropenia [b]	PT			✓	✓	✓	✓		
Anemia [b]	PT			✓	✓	✓	✓		
Thromboembolic events [b]	PT			✓	✓	✓	✓		
GI events [b](analyses below within Section 3.6.2)	HLT and PT			✓	✓	✓	✓	✓	
Covid-19 related TEAEs [c]	Primary SOC and PT			✓					
Any TEAE by age group (<65, ≥65 years)	Primary SOC and PT			✓				✓	
Any TEAE by sex (male, female)	Primary SOC and PT			✓	✓			✓	
Any TEAE by concomitant ITP medications (CS, TPO-RA, Both CS and TPO-RA, Neither CS nor TOP-RA)	Primary SOC and PT			✓	✓			✓	

	MedDRA levels	DB 12W		DB 24W		OL [d]	LTE [e]	DB+OL+LTE [f]
		Adults	Peds	Adults	Peds	Adults and Peds Separately		
Pre-treatment AE	Overview [a]			✓				
	Primary SOC and PT			✓	✓			
Post-treatment AE	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 Selection criteria in Table 8.
c Covid-19 related AEs identified by narrow search of SMQ = COVID-19, #20000237.
d Cumulative data from 1st dose of rilzabrutinib during OL period. Adult and pediatric populations separately.
e Cumulative data from 1st dose of rilzabrutinib during LTE period. Adult and pediatric populations separately.
f Cumulative data from 1st dose of rilzabrutinib regardless of period. Adult and pediatric populations separately.
g Including number (percent) of participants with events, number of events and event rate per participant-years of exposure.

DB = double-blind period ; OL = open-label period ; LTE = long-term extension. 12W = 12-week double-blind period ; 24W = 24-week double-blind period;
AE = adverse event ; TEAE = treatment emergent adverse event ; SAE = serious adverse event ; AESI = adverse event of special interest ; GI = gastrointestinal.
SOC = system organ class ; HLT = high level term ; PT = preferred term. CTCAE = common terminology for adverse events.
CS = corticosteroids ; TPO-RA = Thrombopoietin receptor agonist ; CMQ = Customized MedDRA query; SMQ = Standardized MedDRA query.

Analysis of deaths

In addition to the analyses of deaths included in Table 6 the number (%) of participants in the following categories will be provided as appropriate:

- Deaths will be summarized by primary cause of death and treatment period.
  - Death on-study: deaths occurring during the on-study observation period (ie, up to the end of the study)
    a) Death on-treatment: deaths occurring during the on-treatment period (double-blind, open-label, long-term extension, respectively, Section 3.1)
    b) Death post-treatment: deaths occurring during the post-treatment period (Section 3.1)
  - Death post-study: deaths occurring after the end of the study

    Note: End of the study is the last scheduled visit for those who completed the study, the end-of-study visit date, or the "Completion/Early Withdrawal Date" of the latest period (DB, OL, LTE), whichever later. If death is the end-of-study reason, date of death will be used.
- Deaths in non-randomized participants or randomized but not treated participants

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 8. Number (%) of participants experiencing at least one treatment emergent event by PT will be provided for each event of interest during the treatment emergent period (Section 3.1, Table 7). Tables will be sorted as indicated in Table 6.

Table 8 - Selections for AESIs and other AEs of interest

AESIs and other AEs of interest	Selection
Pregnancy	e-CRF "Adverse Events", AE category=" Pregnancy", AESI checked yes
Symptomatic overdose (serious or nonserious) with IMP	e-CRF "Adverse Events", AE category="Overdose", AESI checked yes (complementary e-CRF "Overdose", "Overdose of Rilzabrutinib" checked yes, "Symptomatic Overdose" checked yes)
Increase in alanine transaminase (ALT) >3 × ULN	e-CRF "Adverse Events", AE category="ALT increase", AESI checked yes (Complementary e-CRFs "ALT Increase – Associated Signs and Symptoms" and "ALT Increase – Trigger Factors")
Infection: Grade 4 or 5 infection where the participant is hospitalized ≥24 h and/or requires emergency care and/or requires IV antibiotics.	e-CRF "Adverse Events", AE category="Infection", AESI checked yes (complementary e-CRF "Infection event form")
Infection	SOC "Infections and Infestations"

AESIs and other AEs of interest	Selection
Bleeding event	SMQ = Haemorrhages, #20000038, broad and narrow search
Neutropenia	CMQ10801 based on the list of PTs in Section 5.8 [a]
Anemia	SMQ = Haematopoietic erythropenia, #20000029, broad and narrow search
Thromboembolic events	SMQ = Embolic and thrombotic events, #20000081, broad and narrow search
Gastrointestinal events	HLT "Diarrhoea (excl infective)", "Nausea and vomiting symptoms"

a The list of terms may be adjusted according to MedDRA version changes.
eCRF = electronic case report form. SMQ = Standardized MedDRA queries. CMQ = customized MedDRA queries. HLT = high level term.

For treatment emergent infection (≥ Grade 2), bleeding (≥ Grade 2), and gastrointestinal events, the following analyses will be presented, in addition to those specified in Table 7.

- n (%) of participants with any TEAE, treatment emergent SAE, TEAE leading to death, TEAE leading to permanent study intervention discontinuation, TEAE related to IMP.

Analysis of gastrointestinal events for each PT (ie, nausea, vomiting and diarrhoea, respectively)

- Maximal CTCAE grade: Grades 1 to 5
- Worst outcome (from most to least severe): Fatal, Not Recovered/Not Resolved, Recovering/Resolving, Recovered/Resolved with sequelae, Recovered/Resolved, Unknown
- Time to first onset in days: mean (SD), median, min, max
- Incidence rate
  - Frequency of events (ie, incidence) by interval of onset: ≤1 week, >1 to 2 weeks, >2 to 4 weeks, >4 to 8 weeks, >8 to 12 weeks, >12 to 16 weeks, >16 to 20 weeks, >20 to 24 weeks, and >24 weeks. The numerator is the number of participants with an occurrence of the event in the given interval. The denominator is the number of participants exposed at the beginning of the interval. Multiple occurrences of the same event for a participants can be counted in several intervals, but only once in the same interval.
  - Kaplan-Meier estimate of cumulative incidence rate at the end of Weeks 1, 2, 4, 8, 12, 16, 20, 24.
- Average duration of TEAEs
  - Average duration of TEAEs in days (ie, average duration across all resolved occurrences): mean (SD), median, min, max
  - Average duration by interval: 0 to 2 days, >2 to 7 days, >7 days to 1 month, >1 month to 4 months, >4 months

- Cumulative duration of TEAEs
  - Cumulative duration of TEAEs in days (total duration of events over time): mean (SD), median, min, max
  - Cumulative duration by interval: 0 to 2 days, >2 to 7 days, >7 days to 1 month, >1 month to 4 months, >4 months

Kalan-Meier curves will be provided for the time to each GI event (ie, nausea, vomiting and diarrhoea, respectively), as well as for the time to IMP discontinuation due to any GI events. Participants without any event will be censored at the end of the treatment-emergent period.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs, and electrocardiograms (ECGs)

The following laboratory variables, vital signs, and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units and conventional units (as appropriate).

- Hematology
  - Red blood cells (RBC), platelets: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC Morphology, Reticulocyte, Mean platelet volume (MPV), platelet count (efficacy endpoint),
  - Coagulation: prothrombin time, International Normalized Ratio (INR), thrombin time, activated partial thromboplastin time (aPTT), fibrinogen,
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes. basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase (screening only),
  - Electrolytes: sodium, potassium, chloride, calcium, phosphorus,
  - Renal function: creatinine, urea (blood urea nitrogen), creatinine clearance (Cockcroft and Gault method) (screening only, for adult participants), estimated glomerular filtration rate (eGFR) (Schwartz method) (screening only, for pediatric participants)
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, direct bilirubin and indirect bilirubin
- Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes
- Immunoglobulin Levels: immunoglobulin G (IgG), immunoglobulin G Subclass 1 (IgG1), immunoglobulin G Subclass 4 (IgG4), immunoglobulin M (IgM), immunoglobulin E (IgE)
- Hemolysis panel: direct Coombs (anti-human globulin), haptoglobin

- Thrombopoietin (TPO)
- T-lymphocytes/ B-lymphocytes/natural killers (T/B/NK) counts:
  - CD3+ T Lymphocytes (Absolute), %CD3+ among lymphocytes
  - CD3+CD4+ T Lymphocytes (Absolute), %CD3+CD4+ among lymphocytes
  - CD3+CD8+ T Lymphocytes (Absolute), %CD3+CD8+ among lymphocytes,
  - CD4+/CD8+ T Lymphocyte ratio
  - CD3-CD16/56+ NK Lymphocytes (Absolute), %CD3-CD16/56+ among lymphocytes,
  - CD3-CD19+ B Lymphocytes (Absolute), %CD3-CD19+ among lymphocytes
- Anti-SARS-CoV-2 S protein RBD (Covid-19 vaccine antibody)
- Vital signs: pulse rate, systolic and diastolic blood pressure, respiratory rate, body temperature, weight.
- 12-lead single ECG (supine position): heart rate, PR interval, QRS duration, QT interval, corrected QTc (Fridericia's formula, QTcF), and RR interval. ECG assessments will be interpreted by the investigator as "Normal", "Abnormal - Not Clinically significant", "Abnormal - Clinically significant", "not evaluable", or "Not done".

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 upper limit of quantitation/detection limit (ULOQ) value.

Quantitative analyses

For all laboratory variables, vital signs, and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each scheduled visit (including the last value on-treatment) during the on-treatment period (Section 3.1). These analyses will be performed using central measurements only for laboratory variables.

For selected laboratory parameters, mean change (or percent change) from baseline maybe be plotted over time.

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 5.6). 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 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

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/Not evaluable/Not done
- Abnormal - Not Clinically significant
- Abnormal - Clinically significant

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury:

- Time to onset of the initial ALT or AST elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) (time to first observation of ALT or AST elevation or total bilirubin elevation, whichever comes first) during the treatment-emergent period will be analyzed using Kaplan-Meier method.
- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories (for each treatment period or cumulatively as appropriate): Returned to baseline PCSA status (or returned to value ≤ ULN in case of missing baseline) before last IMP dose, Returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status (or not yet returned to baseline PCSA status at the data cutoff if applicable), No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

Table 9 - Analyses of laboratory variables, vital signs and electrocardiograms

		DB 24W		OL[a]	LTE [b]	DB+OL+LTE [c]
		Adults	Pediatrics	Adults and Peds Separately		
Laboratory, vital signs, ECG	Descriptive summary [d]	✓	✓	✓	✓	
	Overtime (by-visit) plot [d]	✓	✓	✓	✓	
	PCSA (or PCSA-like) shift summary	✓	✓	✓	✓[d]	✓[d]
DILI	Time to first onset	✓	✓	✓		
	Plot of peak values of ALT versus peak values of total bilirubin	✓	✓	✓		✓
	Return to baseline PCSA status summary	✓	✓	✓		✓

a Cumulative data from 1st dose of rilzabrutinib during OL period. Adult and pediatric populations separately.
b Cumulative data from 1st dose of rilzabrutinib during LTE period. Adult and pediatric populations separately.
c Cumulative data from 1st dose of rilzabrutinib regardless of period. Adult and pediatric populations separately.
d For selected laboratory tests only.
DB = double-blind period; OL = open-label period; LTE = long-term extension; 24W = 24-week double-blind period;
DILI = drug-induced liver injury; ECG = electrocardiograms; PCSA = Potentially Clinically Significant Abnormalities; ALT = alanine aminotransferase.

3.6.3.2 SAR-CoV-2 testing

Number (%) of participants who had SARS-CoV-2 testing performed and test result will be summarized during each on-treatment period as well as during last 16 weeks (Week 9 to Week 25) of double-blind on-treatment period.

3.7 OTHER ANALYSES

3.7.1 PK analyses

Plasma concentrations of rilzabrutinib and its metabolites (eg, PRN834 & PRN4400 if applicable) will be summarized by scheduled visit and nominal sampling time in the PK population (Adult and pediatric population separately) in the rilzabrutinib group, using descriptive statistics such as mean, standard deviation, geometric mean, coefficient of variation, median, minimum and maximum. The mean concentration of rilzabrutinib and its metabolites will be plotted against sampling times. The same analyses will be provided which will include the samples collected within the windows specified in the protocol based on the PK sampling time and the dosing time recorded.

Nominal sampling time is as follows

- Pre-dose at Weeks 1, Week 13, and Week 25 visits.
- Post dose at Week 1 and Week 25 visits,
  - For adults: 2-hour post-dose.
  - For pediatric participants: 0.5-hour, 2-hour, 4-hour and 6-hour post-dose.
- Arbitrary timepoint at Week 53 and early termination visits.

Population PK modeling and other analyses might be pursued for exploratory purpose by the PK group in Sanofi which is not in the scope of this SAP and would be reported separately.

For PRN1008 and PRN834, all concentration values below 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. For PRN4400, all concentrations below LLOQ will be treated as LLOQ/2, given it is an endogenous compound.

3.7.2 Bruton's Tyrosine Kinase (BTK) Occupancy (at selected sites)

BTK occupancy (%) will be summarized by scheduled visit and nominal sampling time (the same time points as specified in Section 3.7.1) in the safety population at selected sites in the rilzabrutinib group, using descriptive statistics such as mean, standard deviation, geometric mean, coefficient of variation, median, minimum and maximum. Mean BTK occupancy will be plotted against sampling times.

BTK occupancy (%) below 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.

3.7.3 Clinical Outcome Assessment

The IBLS, ITP-PAQ, ITP-KIT, EQ-5D-5L, PGIS, PGIS-Fatigue and PGIC are utilized in this study. For continuous variables, the domain score (overall score when applicable) and its change from baseline will be analyzed descriptively for each time point.

When applicable, missing items will be handled based on the specific clinical outcome assessment tool instrument. Subjects missing baseline evaluations would not be included in the analyses.

3.7.3.1 ITP Bleeding Scale (IBLS)

The ITP IBLS (5) is a bleeding assessment system comprising 11 (10 for male) site-specific grades from 0 (none) to 2 (marked bleeding) assessed at nine anatomical sites by history over the previous period (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. Refer to Section 5.5 for an example of the copyrighted scale.

The IBLS were assessed at each visit with a 1-week recall period for Hx. For each participant, an IBLS score at each visit will be calculated by taking the average across 11 items (10 for male and postmenopausal female) at 9 sites (8 for male and postmenopausal female). Specifically,

- IBLS score will be calculated only if it is assessed for ≥ 1 anatomic sites at a visit. "Not done" is handled the same as "None" with grade 0 (Section 5.5.1).
- IBLS score will not be calculated if it is not assessed at any anatomic sites at a visit.

For each patient, a mean IBLS score will also be calculated by taking the average across post-baseline visits during the double-blind on-treatment period.

Frequency and severity of bleeding according to IBLS will be summarized at each visit including IBLS score defined above. Mean IBLS score will also be descriptively summarized. In addition, change from baseline in IBLS score will be compared between rilzabrutinib and placebo in the adult participants at Week 25 (Section 3.3.1.2.5) and Week 13 (Section 3.3.1.4.1).

3.7.3.2 ITP Patient Assessment Questionnaire™ (ITP-PAQ™)

The ITP-PAQ (6, 7) is a disease-specific instrument designed to measure the QoL of adult participants with ITP. The instrument comprises 38 items completed by male respondents and 44 items completed by female respondents. Refer to Section 5.5 for an example of the copyrighted scale.

The ITP-PAQ includes 10 scales,

- Symptoms (6 items, Items 1 to 6),
- Fatigue/Sleep (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), and
- Work (4 items, Items 41 to 44)

The items employ a 4-week recall with responses recorded on 4- to 7-point Likert scales containing 4-7 responses. For example, five response options in a 5-point scale: 1 (never), 2 (rarely), 3 (some of the time), 4 (most of the time), 5 (all the time). The full list of 4- to 7-point scale scores could be found in Section 5.5.3. All item scores are transformed to a 0 to 100 continuum where higher scores represent better QoL and are weighted equally to derive the scale scores.

- Each item score is transformed using the formula, transformed item score = 100 * [(possible maximal item score - item score) / range].
- The Women's Reproductive Health Scale will not be calculated for postmenopausal women.
- "Not applicable" will be treated as missing in Items 41 to 44.
- A scale score will be calculated by taking the average of transformed item scores within that scale if at least 50% of items for that scale are answered.

Each individual scale score and its change from baseline will be descriptively summarized at each visit. In addition, the change from baseline in the transformed score of Item 10 of the ITP-PAQ (i.e. physical fatigue) at Week 13 will be compared between the rilzabrutinib group and the placebo group (Section 3.3.1.2.4).

3.7.3.3 KIDS' ITP-KIT

The ITP-KIT (8), a disease-specific instrument, used in this study is a child self-report form designed to be completed by children ≥7 years. It has a total of 27 items among which 26 items are structured as Likert scales with five response options 1 (never), 2 (rarely), 3 (sometimes), 4 (often), 5 (always). An additional "Not applicable" option is available for Items 18 to 26, which is scored as 1, the same as "never". Item 27 is a descriptive question answered "yes" or "no" which is not included in the calculation of the summary score. Respondents record their disease experience based on a 1-week recall. Refer to Section 5.5 for an example of the copyrighted scale.

The instrument yields a summary KIT score which is the summation of the items converted to a 0 to 100 score with higher scores indicating better disease-specific QoL as follows,

- Summary KIT score = 100*{1-[(Sum of all valid responses – number of valid responses)/(number of valid responses*4)]};

- A minimum data rule of 75% will be applied, meaning that at least 20 items must be completed, or no more than 6 missing values may be present for a respondent's data to be considered useable.

The KIT score and its change from baseline will be descriptively summarized at each visit.

3.7.3.4 EQ-5D-5L

EQ-5D-5L (9, 10) 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 (VAS). Refer to Section 5.5 for an example of the copyrighted scale.

EQ-5D-5L

The descriptive system contains 5 domains: 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.

EQ VAS

The EQ 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 by visit for the observed response and change from baseline.

3.7.3.5 Patient Global Impression of [Fatigue] Severity (PGIS-Fatigue), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC)

Each questionnaire (Section 5.5) will be summarized as an ordinal variable by visit. PGIS and PGIS-Fatigue at Week 13 and Week 25 will be summarized according to their baseline value respectively.

3.8 INTERIM ANALYSES

No formal interim analysis is planned for the double-blind part of the study.

The enrollment of adult population is expected to be completed earlier than that of the pediatric population. Thus, an early analysis may be performed with the cutoff when the last adult participant has completed the blinded treatment period. As the primary analysis for the study is based on the adult population, the results at the early analysis will be considered as final and served as basis for registration application submissions. In case of similar enrollment, the analyses on both adult and pediatric populations will be performed at the same time when they have

completed the blinded treatment period and the primary analysis on efficacy will be based on the adult population.

Final analysis will be performed at the completion of the study. Additional analyses (eg, OL and LTE parts) may be performed at the Sponsor's discretion for purposes of regulatory filings, publications, or future planning after the early analysis without α adjustment.

Table 10 outlines the potential steps of analyses during each period (DB, OL, LTE) in each population (adult, pediatric). The timing, common data cutoff, scope of analyses and unblinding are specified for each step. A combination of steps may be possible as indicated in the last column of the table, due to the uncertainty of enrollment at the time of SAP finalization. Data will be cleaned for each step (or each combination of steps) of analyses.

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply at each step of analyses before the final analysis,

- Participants will be considered as ongoing and exposed up to the cut-off date if the date of last dose is not available at the time of the cut-off date for each period (DB, OL, LTE). Therefore,
  - Participants who did not complete treatment period nor prematurely discontinued the study intervention at cut-off date will be analyzed as "ongoing" in the disposition summary during corresponding period.
  - Their TE period, treatment period and concomitant medication period will end at the cut-off date.
  - Their treatment duration will be derived by considering date of cut-off as last IMP date.
- Analyses of compliance will be performed up to the last IMP administration reported in the e-CRF up to the cut-off date.
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an AE starting prior to the cut-off date will be taken into account. Medications, intervention discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.

An independent Data Monitoring Committee (DMC) is used to monitor and assess the safety of participants from this trial through periodic review of the accumulated safety data provided by an independent statistical group. Related details are provided in separate documents (DMC charter).

Table 10 - Potential steps of analyses

Step	Period	Timing	Common Cutoff	Scope of Analyse	Analysis Population	Unblinding	Additional Considerations
1	DB	Adults concluded DB	Last adult last Week 25 visit (or last adult EOS visit if not entering OL, whichever later)	Full analyses including safety by period (DB, OL, LTE) and cumulatively [a], and efficacy for DB only.	Adults only	Adults unblinded; Pediatrics remain blinded	**This early analyses** of primary and key secondary efficacy endpoints in adults **are considered final** and served as basis for registration application submissions**. No α adjustment for future analyses.**
2	DB	Pediatric population concluded DB	Last pediatric participant last Week 25 visit (or last pediatric participant EOS visit if not entering OL, whichever later)	Analyses including safety by period (DB, OL, LTE) and cumulatively [a], and efficacy for DB only.	Pediatrics only	Pediatrics unblinded	Step 2 may be combined with Step 1, or with Step 3 as 1 single step depending on the enrollment status and regulatory strategy
3	OL	Adults concluded OL	Last adult last Week 53 visit (or last adult EOS visit if not entering LTE, whichever later)	Analyses including safety by period (OL, LTE) and cumulatively [a], and efficacy for OL only.	Adults and Pediatrics	NA	Steps 3 and 4 may be combined as 1 single step depending on the enrollment status and regulatory strategy
4	OL	Pediatric population concluded OL	Last pediatric participant last Week 53 visit (or last pediatric participant EOS visit if not entering LTE, whichever later)	Analyses including safety by period (OL, LTE) and cumulatively [a], and efficacy for OL only.	Adults and Pediatrics	NA	
5	LTE	All concluded LTE	Last participant last visit	Analyses including safety for LTE and cumulatively [a], and efficacy for LTE only.	Adults and Pediatrics	NA	Additional analyses may be performed at the Sponsor's discretion for purposes of regulatory filings, publications etc.

DB = double-blind ; OL = open-label ; LTE = long-term extension ; NA = not applicable.

a Cumulatively means cumulative safety analyses across periods (DB, OL, LTE) in rilzabrutinib safety population.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Table 11 - Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
1	19 Feb 2021	Revised text to specify that randomization will be carried out separately for the two age groups {ie, stratified permuted block randomization for adult group and dynamic randomization algorithm (minimization) for pediatric group}	To achieve balance across stratification factors simultaneously in a small sample size of 30 pediatric participants.
		The analysis population for efficacy revised to ITT population (instead of mITT population).	Health authority request; ITT includes all randomized participants and preserves the rigor of randomization
2	21 Jul 2021	Randomization stratification by age removed	Correction
		Sample size increased to 194 adults (129 in the rilzabrutinib group and 65 in placebo group) from 129 adults.	Assumptions revised based on Phase 2 DFI17124 results
3	11 Aug 2022	Primary endpoint revised to durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 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 blinded treatment period in the absence of rescue therapy 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 blinded treatment period {Not applicable to EU (EEA countries) and UK}.	To better define the primary objective (durable platelet response) and the criteria for meeting the primary efficacy objective/endpoint
		Key secondary endpoint revised to “Number of weeks with platelet counts ≥30,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.” from “Number of weeks with platelet counts between ≥30,000/μL and <50,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy”.	Correction

Amendment Number	Approval Date	Changes	Rationale
		Platelet count testing conducted in local laboratories	Hematology samples at the central laboratory subjected to clotting due to logistic reasons
		Fatigue assessment using Item 10 of the ITP-PAQ introduced as a Key Secondary endpoint	IBLS considered not validated; Fatigue in general is of major concern to patients with ITP
		Idiopathic Thrombocytopenic Purpura Bleeding Scale (IBLS) assessment moved from the Secondary to the Exploratory endpoints {Not applicable to EU (EEA countries) and UK}	Replaced by ITP-PAQ Item 10
		Efficacy objectives and endpoints added to the open label and long-term extension periods	Clarification
		End of long-term extension lengthened to “the last participant who enters the LTE to complete 12 months”	To allow participants who respond to the study medication to continue treatment, and to evaluate the long-term safety and efficacy of treatment with rilzabrutinib.
		After the end of treatment (EOT) visit, weekly platelet count assessment is not required.	Clarification
		Section 10.4 Interim analysis added to further clarify the early analysis at the end of double-blind period for adults and the final analysis at the end of study for all participants.	Clarification
4	24 Jul 2023	Updated the 2-sided significance level from 0.01 to 0.05 for the hypothesis testing of the primary efficacy endpoint.	To align with health authority common standard, in response to the feedback received from health authority.

4 SAMPLE SIZE DETERMINATION

A sample size of approximately 194 (129 versus 65 adult participants in the rilzabrutinib versus placebo arms, respectively) will provide 95% power to detect a 20% difference in response rates as defined in the primary endpoint (Section 1.2.2.1) between the 2 arms (25% vs 5%, in the rilzabrutinib versus placebo arms, respectively), using the Fisher's Exact test with a 0.05 two-sided significance level.

The assumption of a 25% response rate in the rilzabrutinib group is based on the Phase 2 study PRN1008-010 Part A (DFI17124 Part A) (durable response [8 out of the last 12 weeks with platelet count at or above 50,000/μL in the absence of rescue medication]) and the 5% response rate is estimated based on the observed placebo response in previous randomized controlled trials of ITP medications (11). The participants who are not evaluable for primary efficacy due to dropout or missing data will be considered as non-responders.

The pediatric sample size of 30 participants (20 participants on rilzabrutinib and 10 on placebo) was determined based on clinical practice and is adequate to descriptively describe the safety and efficacy in pediatric participants. With a sample size of 20 pediatric participants on rilzabrutinib the maximum width of an exact 90% CI on response rate would be 40%.

Calculations were made based on 2-sample Exact test using SAS® 9.4.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
aPTT:	activated partial thromboplastin time
AST:	aspartate aminotransferase
bid/BID:	twice daily
BTK:	Bruton's tyrosine kinase
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CS:	Corticosteroids
DB:	Double-Blinded
DMC:	Data Monitoring Committee
ECG:	electrocardiogram, electrocardiogram
EEA:	European Economic Area
eGFR:	estimated glomerular filtration rate
EQ-5D-5L:	EuroQOL-5 Dimension-5 Level
EU:	European Union
GEE:	Generalized estimating equations
HLGT:	high-level group term
HLT:	high-level term
IBLS:	Idiopathic Thrombocytopenic Purpura Bleeding Scale
ICF:	Informed consent form
IMP:	investigational medicinal product
INR:	International Normalized Ratio
IRT:	Interactive Response Technology
ITP:	Immune Thrombocytopenia
ITP-KIT:	Kids' ITP Tools
ITP-PAQ:	ITP-Patient Assessment Questionnaire
ITT:	intent-to-treat
IVIg:	Intravenous immunoglobulin
K-M:	Kaplan-Meier
LLOQ:	lower limit of quantitation/detection limit
LLT:	lower-level term
LS:	Least squares
LTE:	Long-Term Extension
MCH:	mean corpuscular hemoglobin
MCHC:	mean corpuscular hemoglobin concentration
MCV:	mean corpuscular volume
MedDRA:	Medical Dictionary for Regulatory Activities

mITT:	Modified ITT
MMRM:	mixed-effect model with repeated measures
MPV:	Mean platelet volume
NCI-CTCAE:	National cancer institute common terminology for adverse events
OL:	Open-Label
PCSA:	Potentially clinically significant abnormality
PGIC:	Patient Global Impression of Change
PGIS:	Patient Global Impression of Severity
PK:	pharmacokinetic
PMDA:	Pharmaceuticals and Medical Devices Agency
PT:	preferred term
QOL:	Quality of life
RBC:	Red blood cells
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
T/B/NK:	T-lymphocytes/ B-lymphocytes/natural killers
TEAE:	treatment-emergent adverse event
TPO:	Thrombopoietin
TPO-RA:	thrombopoietin receptor agonist
UK:	United Kingdom
ULOQ:	upper limit of quantitation/detection limit
VAS:	visual analogue scale
WHO-DD:	World Health Organization-drug dictionary
WOCF:	worst observation carried forward

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. 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:

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the 12-week double-blind treatment period
- Participants who completed the 24-week double-blind treatment period
- Participants who did not complete the 24-week double-blind period and main reason for discontinuation.
- Participants who entered the open-label period
  - Participants who completed the 28-week open-label period
  - Participants who did not complete the 28-week open-label period and main reason for discontinuation
  - Participants who were ongoing
- Participants who entered the LTE
  - Participants who completed the 12-month LTE
  - Participants who did not complete the LTE and main reason for discontinuation
  - Participants who were ongoing
- Status at the last contact (alive, dead).

The number (%) of exposed and not randomized participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, randomized, discontinued during double-blind period, during open-label period, during LTE will be provided by country and site.

Protocol deviations

Major protocol deviations will be summarized in the randomized population, as well as major deviations related to COVID-19.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical history

The following demographics and baseline characteristics, medical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (<65, 65 to <75, ≥75)
- Sex (Male, Female); Post-menopausal status if female.
- Race (White, Black or African American, Asian (Chinese, Japanese, Other Asian), American Indian or Alaska native, native Hawaiian or Other pacific islander, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Geographic region: Asia/Pacific, East Europe, West Europe, North America, South America (see country list in Section 3.2.4).

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

Medical history will be recorded at screening and include a history of all underlying medical conditions (other than ITP) within the last 10 years. Medical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

ITP disease history

- Time since ITP diagnosis in years as quantitative variable and in categories (≤1 year, >1-3 years, >3 years)
- Average of the 2 qualifying platelet counts (x10E9/L, equally x10E3/µL) at screening collected in eCRF
- Baseline platelet count: defined as the average of a patient's three platelet counts, ie, the two qualifying platelet counts at screening and the platelet count at Week 1 (study day 1).
- Baseline platelet count in categories (<15,000/µL, ≥15,000/µL)
- Randomization strata of severity of thrombocytopenia [platelet counts <15,000/µL, ≥15,000/µL per Inclusion 3 - an average of 2 platelet counts at least 5 days apart of <30,000/µL (and no single platelet count >35,000/µL) within 14 days prior to the first dose of study drug]
- Randomization strata of splenectomy (yes, no)

- Splenectomy (yes, no) collected in eCRF

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 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 days.
- 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 and concomitant and post-treatment medications will be summarized for the randomized and exposed population, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence in experimental intervention group. 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.

The prior and concomitant and post-treatment ITP medications as well as concomitant rescue ITP medication will be presented separately by chemical class and standardized medication name.

The following information of ITP medication/therapy will also be presented,

- Prior ITP medication by category
  - Corticosteroids
  - TPO-RA
  - IVIg
  - Anti-D immunoglobulin
  - Anti-CD20 monoclonal antibody / Rituximab
  - Fostamatinib
  - Immunosuppressants and other immunomodulatory agents (including Cyclophosphamide)
  - Dapsone
  - Danazol

- Investigational ITP medications

- Prior corticosteroids and/or TPO-RAs: corticosteroids, TPO-RAs, both corticosteroids and TPO-RAs, neither corticosteroids nor TPO-RAs
- Never responded to prior ITP medication: corticosteroids, TPO-RAs, rituximab, fostamatinib, IVIg/anti-D immunoglobulin
- Number of prior ITP therapy by category specified above): as quantitative variable (1-2, 3-4, ≥5)

  Note: different corticosteroids as one therapy; immunoglobulin, immunoglobulin G human and immunoglobulin human normal as one therapy; and different TPO-RAs (eg, eltrombopag and eltrombopag olamine) as one therapy; prior splenectomy as 1 therapy
- Number of prior unique ITP therapy (by WHO-DD standardized medication name): as quantitative variable and by category (1-2, 3-4, ≥5)

  Note: different corticosteroids as one therapy; prior splenectomy as 1 therapy
- Number of prior ITP therapy (by record identifier): as quantitative variable and by category (1-2, 3-4, ≥5)

  Note: prior splenectomy as 1 therapy

Medical procedure

Medical procedures on or after the 1st administration of IMP will be summarized by primary SOC and PT.

Vaccine history

Vaccine history will be summarized by type: Influenza vaccine, Covid-19 vaccine, Tetanus Vaccine, Measles Vaccine, Shingles Vaccine (Varicella Zoster Virus), Other.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

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, vital sign, ECG, IBLS, QOL variables.

Platelet counts conducted locally will be used for efficacy analyses. Platelet counts conducted centrally 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 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 12 - Analysis window definition for unscheduled measurements

Scheduled Visit	Targeted study day (Analysis window) for Platelet Count [a]	Targeted study day (Analysis window) for Others [b]
Week n [c]	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	169 (+/-3)	169 (-13, +14)
Week 29	197 (+/-3)	197 (-13, +14)
Week 33	225 (+/-3)	225 (-13, +14)
Week 37	253 (+/-3)	253 (-13, +14)
Week 41	281 (+/-3)	281 (-13, +14)
Week 45	309 (+/-3)	309 (-13, +14)
Week 49	337 (+/-3)	337 (-13, +14)
Week 53	365 (-3, +14)	365 (-13, +14)
Month 1 LTE	393 (-13, +14)	393 (-13, +14)
Month 2 LTE	421 (-13, +14)	421 (-13, +14)
Month 3 LTE	449 (-13, +14)	449 (-13, +14)

Scheduled Visit	Targeted study day (Analysis window) for Platelet Count [a]	Targeted study day (Analysis window) for Others [b]
Month 4 LTE	477 (-13, +14)	477 (-13, +14)
Month 5 LTE	505 (-13, +14)	505 (-13, +14)
Month 6 LTE	533 (-13, +14)	533 (-13, +14)
Month 7 LTE	561 (-13, +14)	561 (-13, +14)
Month 8 LTE	589 (-13, +14)	589 (-13, +14)
Month 9 LTE	617 (-13, +14)	617 (-13, +14)
Month 10 LTE	645 (-13, +14)	645 (-13, +14)
Month 11 LTE	673 (-13, +14)	673 (-13, +14)
Month 12 LTE	701 (-13, +42)	701 (-13, +42)
QX_LTE where X=1,2,3,....	701+28*3*X for X=1,2,3,.... (-41, +42)	

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

a Applicable to hematology, differential, reticulocytes. Hematology are measured weekly up to protocol Week 53, then every 4 weeks for 1 year, then quarterly afterwards.

b Applicable to parameters other than hematology, differential, reticulocytes.

c n = 2-4, 6-8, 10-12, 14-16, 18-20, 22-24, 26-28, 30-32, 34-36, 38-40, 42-44, 46-48, 50-52.

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG, IBLS 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 when applicable. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

For the safety analyses, local results (scheduled or unscheduled) will only be used in the PCSA (or PCSA-like) summary if accompanied by corresponding normal ranges.

5.5 APPENDIX 5 PATIENT OR INVESTIGATOR REPORTED OUTCOMES

5.5.1 ITP Disease Activity - ITP Bleeding Scale (IBLS)

ITP BLEEDING SCALE (IBLS)

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

5.5.2 ITP Disease Activity - 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.

	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?**	☐	☐	☐	☐

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

	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**?	☐	☐	☐	☐	☐

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

	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				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
☐	☐	☐	☐	☐	☐	☐

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

	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?	☐	☐	☐	☐	☐

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

	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**?	☐	☐	☐	☐	☐

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

	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
☐	☐	☐	☐	☐	☐	☐

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

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	☐	☐	☐	☐

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

	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?	☐	☐	☐	☐	☐

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

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.

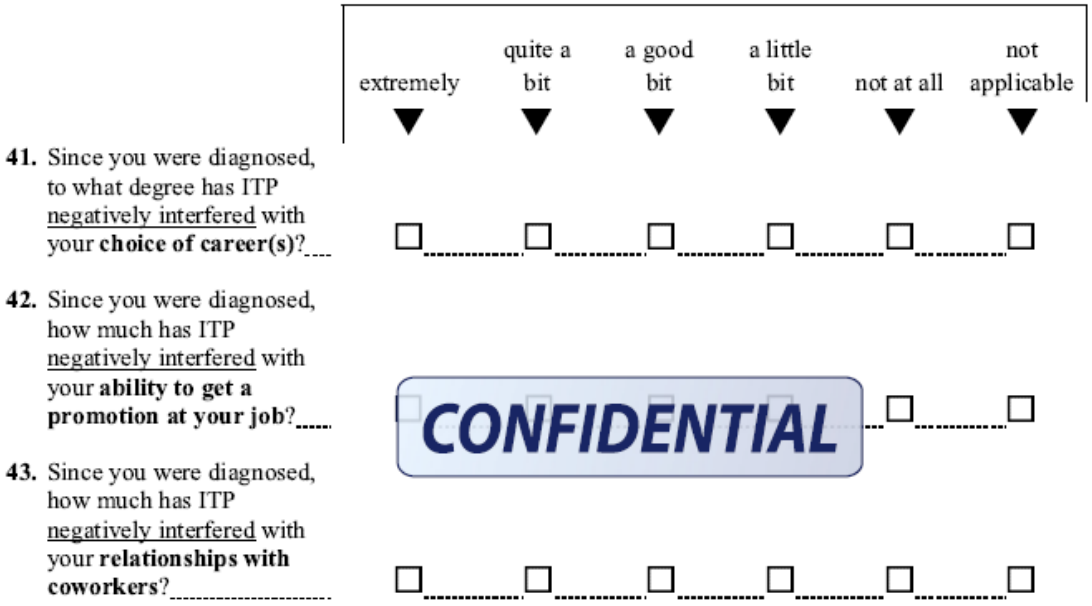
Thinking about your last period, how bothered were you by:

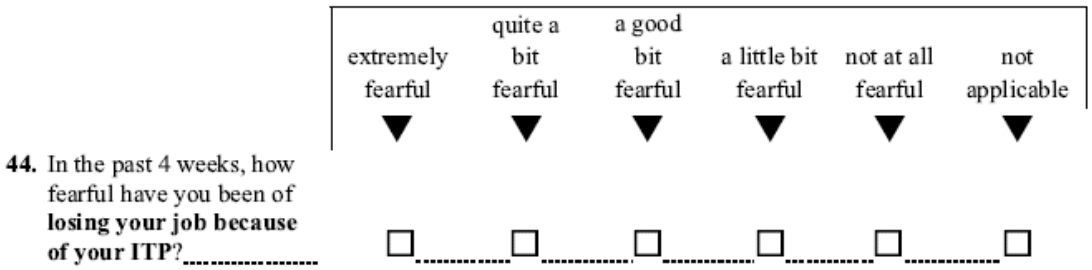
	extremely	quite a bit	a good bit	a little bit	not at all
35. Heavier bleeding than before having ITP?	☐	☐	☐	☐	☐
36. Bleeding for more days than before having ITP?	☐	☐	☐	☐	☐
37. More pain than before having ITP?	☐	☐	☐	☐	☐

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?	☐	☐	☐	☐	☐

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





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

5.5.3 ITP Disease Activity - ITP-PAQ scoring

	Answer	Raw score
4-point Likert scale	Strongly agree	4
	Somewhat agree	3
	Somewhat disagree	2
	Strongly disagree	1
5-point Likert scale	All the time	5
	Most of the time	4
	Some of the time	3
	Rarely	2
	Never	1
	Extremely	5
	Quite a bit	4
	A good bit	3
	A little bit	2
	Not at all	1
	Extremely fearful	5
	Quite a bit fearful	4
	A good bit fearful	3
	A little bit fearful	2
	Not at all fearful	1
7-point Likert scale	Extremely	7
	Very much	6
	Quite a bit	5
	A good bit	4
	Somewhat	3
	A little bit	2
	Not at all	1

5.5.4 ITP Disease Activity - ITP-KIT

Your initials: _____	**Your DOB:**_____
Study ID: _____	**Date:** _____

Time points for completion:

- **within the first 2 weeks of diagnosis**
- **at 6 weeks**
- **at 6 months**
- **yearly (if ITP persisting)**

KIDS' ITP TOOLS

(UK – English)
Child Self-Report of Quality of Life

INSTRUCTIONS

On the next two pages, there are questions that ask you **about this past week.** We know that ITP has mattered to you from when you first came to hospital, but **for this study, we really need you to focus on what you thought about and did over the past week.** You may have done things at home, at the hospital, at school and with your friends. Record your answer by putting a tick (✔) in the box of the most correct choice.

It is important that you answer all questions about this past week.

What do the answers mean?

Answers		Meaning
Never	=	none of the time
Rarely	=	almost none of the time
Sometimes	=	once in a while
Often	=	almost all of the time
Always	=	all of the time

In general, over the past week ...	Never	Rarely	Sometimes	Often	Always
1. I felt poorly...	☐	☐	☐	☐	☐
2. I had a headache...	☐	☐	☐	☐	☐
3. I felt tired...	☐	☐	☐	☐	☐
4. I felt upset (sad or angry)...	☐	☐	☐	☐	☐
5. I felt cranky (bad tempered or moody)...	☐	☐	☐	☐	☐
6. I felt anxious (worried or nervous or afraid)...	☐	☐	☐	☐	☐
7. I was more hungry than usual...	☐	☐	☐	☐	☐

In general, over the past week ...	Never	Rarely	Sometimes	Often	Always
8. I was bothered that I could not do things with my friends...	☐	☐	☐	☐	☐
9. I was bothered because I could not do the activities I like...	☐	☐	☐	☐	☐
10. I was more frustrated with my parents than usual...	☐	☐	☐	☐	☐
11. I was bothered by how much my parents watched me...	☐	☐	☐	☐	☐
12. I was bothered because I did not know enough about ITP...	☐	☐	☐	☐	☐
13. I was bothered that I didn't know how long my ITP would last...	☐	☐	☐	☐	☐
14. I was bothered that I could not do anything to get better...	☐	☐	☐	☐	☐

Over the past week ...	Never	Rarely	Sometimes	Often	Always
15. I worried about my platelet count...	☐	☐	☐	☐	☐
16. I worried about my ITP getting worse...	☐	☐	☐	☐	☐
17. I worried about having a more serious disease...	☐	☐	☐	☐	☐

Please Note: the next set of questions have an **additional** answer.

Over the past week ...	Never	Rarely	Sometimes	Often	Always
18. I was bothered by my bruises...	☐	☐	☐	☐	☐
or ☐ I did not have any bruises in the past week.					
19. I was bothered by changes in how I looked...	☐	☐	☐	☐	☐
or ☐ I did not have any changes in how I looked in the past week.					
20. Having blood taken bothered me...	☐	☐	☐	☐	☐
or ☐ I did not have blood taken in the past week.					
21. Staying overnight in the hospital bothered me...	☐	☐	☐	☐	☐
or ☐ I did not stay overnight in hospital in the past week.					
22. Going to clinic bothered me...	☐	☐	☐	☐	☐
or ☐ I did not go to clinic in the past week.					
23. Having my treatment through a drip bothered me...	☐	☐	☐	☐	☐
or ☐ I did not have treatment through a drip in the past week.					
24. Taking medicine by mouth bothered me...	☐	☐	☐	☐	☐
or ☐ I did not take medicine by mouth in the past week.					
25. I was bothered by missing school...	☐	☐	☐	☐	☐
or ☐ I did not miss school in the past week.					
26. I worried that I might need to have a bone marrow test...	☐	☐	☐	☐	☐
27. Have you ever had a bone marrow test?	☐ yes	☐ no			

Was there anything else that bothered you?

Thank you!

If you have any questions about these forms, please talk to the person who gave them to you. If you have any questions about your ITP, please talk to your doctor or nurse.

Please return this form to:

Stephanie Farrell
UK Paediatric ITP Registry Data Manager
Immunology, CSB3, Offices 10 & 11
3rd floor Manchester Royal Infirmary
Oxford Road, Manchester
M13 9WL, UK

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

Health Questionnaire

English version for the USA

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

MOBILITY

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

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 discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

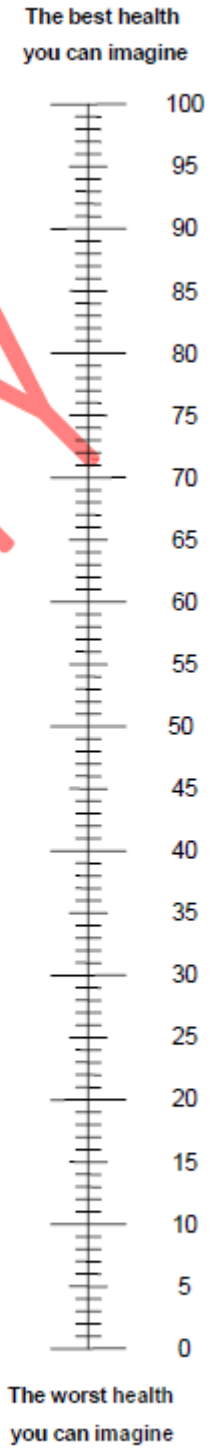
ANXIETY / DEPRESSION

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 ❑

2

- 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 = ☐



3

5.5.6 Patient Global Impression of [Fatigue] Severity (PGIS-Fatigue), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC)

PGIS-Fatigue

Please choose the response below that best describes the severity of your disease-related fatigue over the past week. (Check one response)

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

PGIS

Please choose the response below that best describes the severity of your disease-related symptoms over the past week. (Check one response)

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

PGIC

Thinking about the past week, please choose the response below that best describes the overall change in your disease-related symptoms since you started taking the study medication. (Check one response)

- ☐ Very much better
- ☐ Moderately better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Very much worse

5.6 APPENDIX 6 CRITERIA FOR POTENTIALLY SIGNIFICANT ABNORMALITIES

5.6.1 Criteria for Potentially Clinically Significant Abnormalities – for Phase 2/3 studies (oncology excepted)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes 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.
AST	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes 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	Enzymes 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.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
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
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	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	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.
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.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
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	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

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

5.6.2 Criteria for Potentially Clinically Significant Abnormalities for Studies in Children

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
ECG parameters			Ref. : Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
HR	Birth/0 to 27 days old (Neonates)	≤90 bpm and decrease from baseline ≥20 bpm ≥190 bpm and increase from baseline ≥20 bpm	
	28 days/1 month to 23 months old (Infants)	≤80 bpm and decrease from baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm	
	24 months/2 years to <6 years old (Children)	≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	
	6 to <12 years old (Children)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
	12 to 16/18 years old (Adolescents)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	Birth/0 to 27 days old (Neonates)	≥120 ms	
	28 days/1 month to 23 months old (Infants)	≥140 ms	
	24 months/2 years to <6 years old (Children)	≥160 ms	
	6 to <12 years old (Children)	≥170 ms	
	12 to 16/18 years old (Adolescents)	≥180 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
QRS	Birth/0 to 27 days old (Neonates)	≥85 ms	
	28 days/1 month to 23 months old (Infants)	≥85 ms	
	2 to <6 years old (Children)	≥95 ms	
	6 to <12 years old (Children)	≥100 ms	
	12 to 16/18 years old (Adolescents)	≥110 ms	
QTc	Birth/0 to <12 years old (Neonates, Infants, Children)	Absolute values (ms) Borderline: 431-450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	**To be applied to QTcF** *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.
	12 to 16/18 years old (Adolescents)	Borderline: 431-450 ms (Boys); 451-470 ms (Girls) Prolonged*: >450 ms (Boys); >470 ms (Girls) Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Vital Signs			Ref. : Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/
SBP	Birth/0 to 27 days old (Neonates)	≤60 mmHg and decrease from baseline ≥20 mmHg ≥85mHg and increase from baseline ≥20 mmHg	Based on definition of Hypertension as average SBP or DBP ≥ 95th percentile for gender, age, and height on ≥ 3 occasions
	28 days/1 month to 23 months old (Infants)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg	
	24 months/2 years to <6 years old (Children)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥101mHg and increase from baseline ≥20 mmHg	
	6 to <12 years old (Children)	≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg	
	12 to 16/18 years old (Adolescents)	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119mmHg and increase from baseline ≥20 mmHg	
DBP	Birth/0 to 27 days old (Neonates)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥50mHg and increase from baseline ≥10 mmHg	
	28 days/1 month to 23 months old (Infants)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥54mHg and increase from baseline ≥10 mmHg	
	24 months/2 years to <6 years old (Children)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥59mHg and increase from baseline ≥10 mmHg	
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72mHg and increase from baseline ≥10 mmHg	
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78mHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP : St — Su ≤ - 20 mmHg DBP : St — Su ≤ - 10 mmHg	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Temperature	All age ranges	Rectal, ear or temporal artery: ≥100.4 °F/38.0 °C Oral or pacifier: ≥99.5 °F/37.5 °C Axillary or skin infrared: ≥99 °F/37.2 °C	Ear temperature not accurate below 6 months of age
Respiratory rate	Birth/0 to 27 days old (Neonates)	< 30 per minutes > 60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	< 24 per minutes > 40 per minutes	
	24 months/2 years to <6 years old (Children)	< 22 per minutes > 34 per minutes	
	6 to <12 years old (Children)	< 18 per minutes > 30 per minutes	
	12 to 16/18 years old (Adolescents)	< 12 per minutes > 20 per minutes	
Sa02	All age ranges	≤95 %	
Weight	All ranges	≥5 % weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007
Clinical Chemistry			Ref Molleston JP et al. JPGN 2011; Moritz et al., Pediatrics 1999; Moritz et al., Pediatr Nephrol 2005 ; Sedlacek et al., Seminars in Dialysis 2006) Gong G et al. Clinical Biochemistry 2009; Masilamani et al. Arch Dis Children 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
ALT/SGPT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 6 to 50 U/L (0-5 days), 5 to 45 U/L (1-19 years)
AST/SGOT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 35 to 140 U/L (0-5 days), 15 to 55 U/L (1-9 years), 5 to 45 U/L (10-19 years)
Alkaline Phosphatase	All age ranges	≥1.5 ULN	Based on normal ranges: 145 to 420 U/L (1-9 years), 130 to 560 U/L (10-11 years), 200 to 495 U/L (Boys 12-13 years), 105 to 420 U/L (Girls 12-13 years), 130 to 525 U/L (Boys 14-15 years), 70 to 130 U/L (Girls 14-15 years), 65 to 260 U/L (Boys 16-19 years), 50 to 130 U/L (Girls 16-19 years)
Total Bilirubin	All age ranges	≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Conjugated Bilirubin	All age ranges	>35% Total Bilirubin and TBILI≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal range: 0 to 0.4 mg/dL
ALT and Total Bilirubin	All age ranges	ALT ≥ 3 ULN and Total Bilirubin ≥ 2 ULN	
CPK	All age ranges	≥3 ULN	
Creatinine	Birth/0 to <6 years old (Neonates, Infants, Children)	>53 µmol/L or 0.6 mg/dL	CF = mg x 8.8 = µmol Based on normal ranges: ≤0.6 mg/dL (0-1 year), 0.5 to 1.5 mg/dL (1 to 16/18 years)
	6 years to <12 years old (Children)	≥90 µmol/L or 1.1mg/dL	
	12 years to 16/18 years old (Adolescents)	≥132µmol/L or 1.5mg/dL	
Creatinine Clearance	All age ranges	50 % of normal <60 ml/min/1.73m2 (After 1 year old)	Based on GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)
Uric Acid	All age ranges	≤2.0 mg/dL or 119 µmol/L ≥8.0 mg/dL or 476 µmol/L	CF = mg x 5.95 = µmol Based on normal ranges: 2.4 to 6.4 mg/dL
Blood Urea Nitrogen (BUN)	Birth/0 to 27 days old (Neonates)	≥4.3 mmol/L or 12 mg/dl	CF = g x 16.66 = mmol Based on normal ranges: 3 to 12 mg/dL (NN; 5 to 18 mg/dL (other classes of age)
	28 days/1 month to 16/18 years old (Infants, Children, Adolescents)	≥6.4 mmol/L or 18 mg/dl	
Chloride	All age ranges	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L	CF = 1 Based on normal range: 98 to 106

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Sodium	All age ranges	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	CF = 1 Based on normal range : 134 to 146
Potassium	Birth/0 to 27 days old (Neonates)	≤3.0 mmol/L or 3.0 mEq/L ≥7.0 mmol/L or 7.0 mEq/L	CF = 1 Based on normal ranges: 3.0 to 7.0 (NN); 3.5 to 6.0 (Infants); 3.5 to 5.0 (>Infants)
	28 days/1 month to 23 months old (Infants)	≤3.5 mmol/L or 3.5 mEq/L ≥6.0 mmol/L or 6.0 mEq/L	
	24 months/2 years to 16/18 years old (Children, Adolescents)	≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L	
Bicarbonate	All age ranges	≤16 mmol/L or 16 mEq/L ≥30 mmol/L or 30 mEq/L	CF = 1 Based on normal range: 18 to 26
Calcium total	All age ranges	≤2.0 mmol/L or 8.0 mg/dL ≥2.9 mmol/L or 11.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 8.4 to 10.9 mg/dL
Calcium ionized	All age ranges	≤1.0 mmol/L or 4.0 mg/dL ≥1.4 mmol/L or 5.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 4.0 to 5.1 mg/dL
Total Cholesterol	All age ranges	≥6.20 mmol/L or 240 mg/dL	CF = g x 2.58 = mmol Based on normal ranges: 45 to 182 mg/dL (1-3 years), 109 to 189 mg/dL (4-6 years), 126 to 191 mg/dL (Boys 6-9 years), 122 to 209 mg/dL (Girls 6-9 years), 130 to 204 mg/dL (Boys 10-14 years), 124-217 mg/dL (Girls 10-14 years), 114 to 198 mg/dL (Boys 15-19 years), 125 to 212 mg/dL (Girls 14-19 years)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Triglycerides	All age ranges	≥4.0 mmol/L or 350 mg/dL	After >12 hours of fast) CF = g x 1.14 = mmol Based on normal ranges: 30 to 86 mg/dL (Boys 0-5 years), 32 to 99 mg/dL (Girls 0-5 years), 31-108 mg/dL (Boys 6-11 years), 35 to 114 mg/dL (Girls 6-11 years), 36 to 138 mg/dL (Boys 12-15 years), 43 to 138 mg/dL (Girls 12-15 years), 40 to 163 mg/dL (Boys 16-19 years), 40-128 mg/dL (Girls 16-19 years)
Lipasemia	All age ranges	≥2 ULN	Based on normal ranges: 3 to32 U/L (1-18 years)
Amylasemia	All age ranges	≥2 ULN	Based on normal ranges: 10 to 30 U/L (NN), 10 to 45 U/L (1-18 years)
Glucose	All age ranges	Hypoglycaemia <2.7 mmol/L or 50 mg/dL Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); ≥10.0 mmol/L or 180 mg/dL (unfasted)	CF = g x 5.55 = mmol Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child)
CRP	All age ranges	>2 ULN or >10 mg/L (if ULN not provided)	Based on normal ranges: <6 mg/L
Hematology			Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006 ; Division of Microbiology and Infections Diseases Pediatric Toxicity Tables, 2007 ; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
WBC	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4,000 /mm3 >25.0 GIGA/L or 25,000 /mm3	To be used if no differential count available Based on normal ranges: 9,000 to 30,000 /mm3 (birth), 9,400 to 38,000 /mm3 (0-1 day), 5,000 to 21,000 /mm3 (1 day-1 month), 6,000 to 17,500 /mm3 (1 month-2 years), 5,000 to 17,000 /mm3 (2-6 years), 4,500 to 15,500 /mm3 (6-11 years), 4,500 to 13,500 /mm3 (11-18 years)
	28 days/1 month to 23 months old (Infants)	<4.0 GIGA/L or 4,000 /mm3 >20.0 GIGA/L or 20,000 /mm3	
	24 months/2 years to <6 years old (Children)	<3.0 GIGA/L or 3,000 /mm3 >16.0 GIGA/L or 16,000 /mm3	
	6 to <12 years old (Children)	<5.0 GIGA/L or 5,000 /mm3 >17.0 GIGA/L or 17,000 /mm3	
	12 to 16/18 years old (Adolescents)	<4,5 GIGA/L or 5,000 /mm3 >13.5 GIGA/L or 17,000 /mm3	
Lymphocytes (ALC)	Birth/0 to 27 days old (Neonates)	<1.2 GIGA/L or 1,200 /mm3 >17.0 GIGA/L or 17,000 /mm3	Based on normal ranges: 2,000 to 11,500 /mm3 (0-1 days), 2,000 to 17,000 /mm3 (2 days-1 month), 3,000 to 13,500 /mm3 (1 month-2 years), 1,500 to 9,500 /mm3 (2-6 years), 1,500 to 8,000 /mm3 (6-10 years), 1,200 to 5,200 /mm3 (10-18 years)
	28 days/1 month to 23 months old (Infants)	<2.0 GIGA/L or 2,000 /mm3 >13.5 GIGA/L or 13,500 /mm3	
	24 months/2 years to <6 years old (Children)	<1.0 GIGA/L or 1,000 /mm3 >9.5 GIGA/L or 9,500 /mm3	
	6 to <12 years old (Children)	<1.0 GIGA/L or 1,000 /mm3 >8.0 GIGA/L or 8,000 /mm3	
	12 to 16/18 years old (Adolescents)	<0.6 GIGA/L or 600 /mm3 >6.0 GIGA/L or 6,000 /mm3	
Absolute Neutrophil Count (ANC)	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4,000 /mm3 (1 day old) <1.5 GIGA/L or 1,500 /mm3 (2-7 days old) <1.25 GIGA/L or 1,250 /mm3 (>7 day-1 month old) > 1 ULN	Based on normal ranges: 5,000 to 28,000 /mm3 (0-1 day), 1,000 to 10,000 (1 day-1 month), 1,000 to 8,500 (1-12 months), 1,500 to 8,500 (1 to 6 years), 1,500 to 8,000 (6 to 10 years), 1;800 to 8,000 (10 to 18 years)
	28 days/1 month to 23 months old (Infants)	<1.0 GIGA/L or 1,000/mm3 (1-3 months) <1.2 GIGA/L or 1,200 /mm3 (3-24 months) > 1 ULN	
	24 months/2 years to <6 years old (Children)	<1.2 GIGA/L or 1,200 /mm3 > 1 ULN	
	6 to <12 years old (Children)	<1.2 GIGA/L or 1,200 /mm3 > 1 ULN	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
	12 to 16/18 years old (Adolescents)	<1.2 GIGA/L or 1,200 /mm3 > 1 ULN	
Eosinophils	All age ranges	>0.5 GIGA/L or 500 /mm3 Or >ULN if ULN >0.5 GIGA/L or 500 /mm3	Based on normal ranges: 0 to 500 /mm3 (0-1 month), 0 to 300 /mm3 (1 month-18 years)
Hemoglobin	Birth/0 to 27 days old (Neonates)	< 86 mmol/L or 12.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL	CF = g x 1.55 = mmol Based on normal ranges: 15 to 20 g/dL (0-3 days), 12.5 to 18.5 g/dL (1-2 weeks), 10.0 to 13.0 g/dL (1-6 months), 10.5 to 13.0 g/dL (7 months-2 years), 11.5 to 13.0 g/dL (2-5 years), 11.5 to 14.5 (5-8 years), 12.0 to 15.2 g/dL (13-18 years)
	28 days/1 month to 23 months old (Infants)	< 1.40 mmol/L or 9.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL	
	24 months/2 years to <16/18 years old (Children, Adolescents)	< 1.55 mmol/L or10.0 g/dL or any decrease > 0.31 mmol/L or 2 g/dL	
Hematocrit	Birth/0 to 27 days old (Neonates)	< 0.39 l/l or 40 % > 0.61 l/l or 47 %	CF = % x 0.01 = l/l Based on normal ranges: 45 to 61 % (0-3 days), 39 to 57 % (1-2 weeks), 29 to 42 % (1-6 months), 33 to 38 % (7 months-2 years), 34 to 39 % (2-5 years), 35 to 42 % (5-8 years); 36 to 47 % (13-18 years)
	28 days/1 month to 23 months old (Infants)	< 0.29 l/l or 29 % > 0.42 l/l or 42 %	
	24 months/2 years to <16/18 years old (Adolescents)	< 0.32 l/l or 32 % > 0.47 l/l or 47 %	
Platelets	All age ranges	<100 GIGA/L or 100,000 /mm3 > 700 GIGA/L or 700,000 /mm3	Based on normal ranges: 250,000 to 450,000 /mm3 (NN); 300,000 to 700,000 /mm3 (1-6 months), 250,000 to 600,00 /mm3 (7 months-2 years), 250,000 to 550,000 /mm3 (2-12 years), 150,000 to 450,000 /mm3 (13-18 years)
Urinalysis			Patel HP, Pediatr Clin N Am, 2006
Ketonuria	All age ranges	Presence	Semi-quantitative methods
Glycosuria	All age ranges	Presence	Semi-quantitative methods

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Hematuria	All age ranges	≥ 1+	Semi-quantitative methods
Proteinuria	All age ranges	≥ 1+	Semi-quantitative methods

5.7 APPENDIX 7 SAMPLE SAS® CODE

5.7.1 Primary endpoint: main analyses (CMH test)

```
PROC FREQ DATA=dataset;
   TABLE strata1*strata2*treatment*response /
            CMH (MF) COMMONRISKDIFF (TEST=MH CL=MH) ALPHA=0.05;
   ODS OUTPUT COMMONPDIFF=mhdiff
            CMH=cmh  (where=(AltHypothesis="General  Association"));
RUN;
```

5.7.2 Primary endpoint: sensitivity analysis (Missing data handled via multiple imputation) (Definition 2)

Step 1. Impute missing weekly platelet counts using the available platelet counts at Week 2 through Week 25 in the participants who satisfy conditions as specified in Section 3.2.3.1.2 using fully conditional specification predictive mean matching.

```
PROC SORT DATA=dataset;
        BY  treatment  strata1  strata2  region;
RUN;

PROC MI DATA=dataset (where=(MULIMPFL="Y")) OUT= mi SEED=17093
NIMPUTE=500;
        CLASS treatment strata1 strata2 region;
        VAR  treatment  region  strata1  strata02  baseline  value02-value25;
        TRANFORM log(value02- value25 /c=1);
        FCS  regpmm  (value02-  value25  /  k=6);
RUN;
```

Step 2. Each of the multiple imputed datasets (including participants who did not take rescue therapy after the initial 8 weeks of double-blind treatment and did not discontinue due to related AE or lack of efficacy before Week 25) will be combined with the one dataset without imputation (including participants who took rescue therapy, or discontinued due to related AE or lack of efficacy before Week 25, or discontinued due to any reasons before Week 13) to generate multiple complete datasets (including all participants).

```
%macro w1;
        %do i=1 % to nimpute;
                data nomi&i.;
                   set nomi;
                   _imputation_=&i.;
                run;
        %end;
        data nomi _all;
```

```
        set %do j=1 % to &nimpute; nomi &j. %end;;
    run;
%mend   w1;
%w1;

data combine;
  set  mi  nomi_all;
run;
```

Step 3. Derive durable response during double-blind on-treatment period per Definition 2 in each of the multiple imputed datasets.

Step 4. Perform CMH test on each of the multiple complete datasets (see Section 5.7.1).

Step 5. Combine results (12) using Rubin's rule (3) across imputed datasets.

```
* Apply Wilson-Hilferty transformation (13) to the CMH statistic and
standardize the resulting normal variable;
DATA cmh_wh;
   SET cmh (WHERE=(AltHypothesis="General Association"));
   cmh_value_wh=((VALUE/DF)**(1/3)  -  (1-2/(9*DF)))/SQRT(2/(9*DF));
   cmh_sterr_wh = 1.0;
RUN;

* Combine results;
PROC MIANALYZE DATA=cmh_wh;
MODELEFFECTS cmh_value_wh;
STDERR cmh_sterr_wh;
   ODS  OUTPUT  PARAMETERESTIMATES=mian_cmh_wh;
RUN;

* Compute one-sided p-value;
DATA mian_cmh_wh_p; SET
mian_cmh_wh;
   IF tValue > 0 THEN Probt_upper = Probt/2;
   ELSE Probt_upper = 1-Probt/2;
RUN;

* Combine Mantel-Haenszel estimate and CI;
PROC MIANALYZE DATA=mhdiff;
WHERE method="Mantel-Haenszel";
MODELEFFECTS RiskDifference;
STDERR StdErr;
   ODS  OUTPUT  parameterestimates=mhriskdiff;
RUN;
```

5.7.3 Primary endpoint: sensitivity analysis (Tipping point analysis)

Step 1. Generate independent samples from Bernoulli (p0) and Bernoulli (p1) for participants with missing response status for placebo and Rilzabrutinib group respectively. For each combination of (p0, p1), generate multiple complete imputed datasets (including all participants). Note: the number of imputation will be set at 100 initially which may be increased as appropriate.

```
%let seed= %sysevalf(&seed+1);
DATA tipping;
   SET dataset;
   IF response= . THEN DO;
      (note: response has values 1=responder, 0=nonresponder, .=missing)
      IF treatment = 0 THEN response= RANBIN(&seed., 1, &p0.);
   IF treatment = 1 THEN response= RANBIN(&seed., 1, &p1.);
   END;
RUN;
```

Step 2: For each combination of (p0, p1), perform CMH test on each of the imputed datasets (see Section 5.7.1).

Step 3. For each combination of (p0, p1), combine results across imputed datasets (see Section 5.7.2).

5.7.4 Key secondary endpoints: main analytic approach

Number of weeks with platelet response

```
PROC SORT DATA = dataset;
        (Note: each participant must have response status at all 24-week visits.
              Missing data must be imputed as non-responder at a visit)
   BY treatment strata1 strata2 subjid week;
RUN;

PROC GLIMMIX DATA = dataset EMPIRICAL;
CLASS treatment strata1 strata2 subjid week;
   MODEL resp = treatment strata1 strata2 week treatment*week;
   RANDOM _resid_ / SUBJECT = subjid TYPE = VC;
   LSMEANS treatment / PDIFF CL;
   LSMESTIMATE treatment*week 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 / CL;
   LSMESTIMATE treatment*week 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
                              1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 / CL;
   LSMESTIMATE treatment*week -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1
-1 -1 -1 -1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 / CL;
   ODS OUTPUT LSMEstimates=lsmean;
RUN;
```

Time to platelet response

```
PROC  LIFETEST  DATA=dataset;
TIME aval*cnsr(1);
        (Note: 1 indicates censoring)
   STRATA strata1 strata2 / TEST=logrank GROUP=treatment;
   ODS OUTPUT HOMTESTS = logrank;
RUN;

PROC PHREG DATA=dataset;
   CLASS treatment (REF=first) strata1 strata2;
   MODEL aval*cnsr(1) = treatment strata1 strata2 / RL TIES=EFRON;
ODS OUTPUT PARAMETERESTIMATES = estimates;
RUN;
```

Change from baseline in Item 10 of ITP-PAQ

Step 1. Impute missing post-baseline data up to Week 13 using the available data at Week 5, Week 9, and Week 13 in participants who satisfy conditions as specified in Section 3.3.1.2.4 using fully conditional specification regression.

```
PROC MI DATA=dataset OUT= out_mi, SEED=17093 NIMPUTE=500;
        CLASS treatment strata1 strata2 region;
        FCS reg;
        VAR treatment strata1 strata2 region baseline Value05 Value09 Value13;
RUN;
```

Step 2. Each of the multiple imputed datasets (including participants who did not take rescue therapy and did not discontinue due to related AE or lack of efficacy before Week 13) will be combined with the one dataset imputed by WOCF approach (including participants who took rescue therapy after 8 weeks of double-blind treatment or discontinued due to related AE or lack of efficacy before Week 13) to generate multiple complete datasets (including all participants).

```
%macro w1;
        %do i=1% to &nimpute;
                data wocf&i.;
                   set wocf;
                   _imputation_=&i.;
                run;
        %end;
        data wocf_all;
           set %do j=1 % to &nimpute; wocf&j. %end;;
        run;
%mend   w1;
%w1;

data combine;
```

```
   set  out_mi  wocf_all;
run;
```

Step 3. Perform ANCOVA on each of the multiple imputed datasets.

```
PROC MIXED DATA = dataset;
   BY _IMPUTATION_;
   CLASS treatment strata1 strata2 region;
   MODEL change = treatment strata1 strata2 region score0;
   LSMEANS treatment / DIFF CL;
   LSMESTIMATE treatment "A1 Placebo" 1 0 /CL;
   LSMESTIMATE treatment "A2 Rilza" 0 1/CL;
   LSMESTIMATE treatment "B1 Rilza vs Placebo" -1 1/CL;
   ODS OUTPUT DIFFS=diffs LSMESTIMATES=lsmestimates;
RUN;
```

Step 4. Combine results using Rubin's rule (3).

```
PROC SORT DATA = lsmestimates;
BY label _IMPUTATION_;
RUN;

PROC MIANALYZE DATA= lsmestimates;
BY label;
   MODELEFFECTS   estimate;
   STDERR stedrr;
RUN;

PROC MIANALYZE DATA= diffs;
BY label;
   MODELEFFECTS   estimate;
   STDERR stedrr;
RUN;
```

5.8 APPENDIX 8 LIST OF PT FOR SELECTED AE OF INTEREST (MEDDRA VERSION 25.1)

AE Group	Preferred term code *	Preferred term *
Neutropenia	10001507	Agranulocytosis
	10014877	Enteritis leukopenic
	10016288	Febrile neutropenia
	10018681	Granulocyte count decreased
	10018687	Granulocytopenia
	10018688	Granulocytopenia neonatal
	10024384	Leukopenia
	10028560	Myeloid maturation arrest
	10029354	Neutropenia
	10029358	Neutropenia neonatal
	10029366	Neutrophil count decreased
	10047942	White blood cell count decreased
	10049151	Neutropenic sepsis
	10050443	Granulocytes maturation arrest
	10050504	Leukopenia neonatal
	10051645	Idiopathic neutropenia
	10052223	Neutrophil percentage decreased
	10053176	Cyclic neutropenia
	10053213	Febrile bone marrow aplasia
	10055128	Autoimmune neutropenia
	10057950	Band neutrophil count decreased
	10059130	Band neutrophil percentage decreased
	10059482	Neutropenic infection
	10061313	Neutrophil count abnormal
	10062959	Neutropenic colitis
	10065553	Bone marrow failure
	10067354	Radiation leukopenia
	10068043	Pure white cell aplasia
	10074832	Benign ethnic neutropenia
	10075173	Bone marrow infiltration
	10075528	Toxic leukoencephalopathy
	10075813	Basophilopenia
	10081503	Transfusion-related alloimmune neutropenia
	10085996	Granulocyte percentage decreased
	10087412	Radiation neutropenia

* The list of preferred terms is subject to MedDRA version update.

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