PRINCIPIA BIOPHARMA
A SANOFI COMPANY

AMENDED CLINICAL TRIAL PROTOCOL 05

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)**
Protocol number:	**PRN1008-018 (EFC17093)**
Amendment number:	**05**
Compound number (INN/Trademark):	**PRN1008/SAR444671 (Rilzabrutinib/Not Applicable)**
Brief title:	**LUNA 3**
Study Phase:	**3**
Sponsor name:	**Principia Biopharma Inc.**
Legal registered address:	**55 Corporate Drive Bridgewater, NJ 08807 USA**
Monitoring team's representative name and contact information:	

Regulatory agency identifier number(s):

IND:	132668
EU trial number:	2023-509401-71
NCT:	NCT04562766
WHO:	Not applicable
EUDAMED:	Not applicable
Other	Not applicable

Date: 15-May-2024 Total number of pages: 199

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, electronic version
Amended Clinical Trial Protocol 05	All	15 May 2024, version 1 (electronic 9.0)
Amended Clinical Trial Protocol 04	All	24 Jul 2023, version 1 (electronic 8.0)
Amended Clinical Trial Protocol 03	All	11 Aug 2022, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 02[c]	All	21 Jul 2021, version 1 (electronic 4.0)
Clinical Study Protocol PRN1008-018 Version 2.0[b]	All	19 Feb 2021, electronic version 2.0
Clinical Study Protocol PRN1008-018 Version 1.2 Ukraine	Ukraine only	21 Jan 2021
Clinical Study Protocol PRN1008-018 Version 1.2 Turkey	Turkey only	06 Jan 2021
Clinical Study Protocol PRN1008-018 Version 1.3 France	France only	02 Jan 2021
Clinical Study Protocol PRN1008-018 Version 1.2 Norway	Norway only	15 Dec 2020
Clinical Study Protocol PRN1008-018 Version 1.2 France	France only	04 Dec 2020
Clinical Study Protocol PRN1008-018 Version 1.2 Austria	Austria only	03 Dec 2020
Clinical Study Protocol PRN1008-018 Version 1.2 United Kingdom	United Kingdom only	09 Nov 2020
Clinical Study Protocol PRN1008-018 Version 1.3 Canada	Canada only	06 Nov 2020
Clinical Study Protocol PRN1008-018 Version 1.2 Canada	Canada only	03 Nov 2020
Clinical Study Protocol PRN1008-018 Version 1.2 Germany	Germany only	28 Oct 2020
Clinical Study Protocol PRN1008-018 Version 1.1[a]	All	06 Aug 2020
Clinical Study Protocol PRN1008-018 Version 1.0	All	10 Jul 2020

a First version distributed to sites; original protocol.
b First protocol amendment.
c Sponsor naming convention adopted.

Amended Clinical Trial Protocol 05 (15 May 2024)

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation No 536/2014 of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment are to incorporate language to comply with new European Union (EU) clinical trial regulations and to update the overall benefit-risk assessment.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Replaced EudraCT number with EU trial number	To comply with EU CTR requirements
Section 1.0 Synopsis Section 5.1 Inclusion Criteria	Inclusion #4: For estimated glomerular filtration rate (GFR), language modified from "Cockcroft and Gault method" to "Cockcroft and Gault method for adult and Bedside Schwartz Equation for Pediatric participants".	To Adopt "Bedside Schwartz Equation" to improve the calculation accuracy of eGFR in pediatric participants.
	Inclusion #6 removal of the text "with low user dependency" regarding the contraceptive method for a WOCBP	To correct an error in the protocol text. Both Low and high user dependent highly effective contraception methods should be permitted.
Section 1.0 Synopsis	In Table 1 - Schedule of Assessments - Blinded Treatment Period footnote K, added "eGFR will be calculated using the Bedside Schwartz Equation in pediatric participants (10 to <18 years old) and using the Cockcroft and Gault method in adult participants."	To Adopt "Bedside Schwartz Equation" to improve the calculation accuracy of eGFR in pediatric participants.
Section 2.4.1 Safety	Removed general outdated safety information from the safety profile and referenced publications detailing safety and efficacy findings.	To align with the investigator brochure (IB) and take new data into consideration.
	Added "Please refer to the most recent version of the IB for updated safety information." and "For summary of overall benefit/risk assessment, refer to Section 2.7."	
Section 2.7.1 Risk Assessment	Updated Risk Assessment subsection and introduced uveitis as a new "important potential risk" of rilzabrutinib.	To update details of liver enzyme increase and serious infection, which are known "important potential risks" of rilzabrutinib, as well as to introduce uveitis as a new "important potential risk" based on recent findings of ongoing rilzabrutinib clinical trials.
Section 2.7.1.1 "Potential risks reported with other BTK inhibitors"	Added "Class Effect" to describe specific AEs in subsection 2.7.1.1 "Potential risks reported with other BTK inhibitors"	
Section 2.7.3 "Overall benefit: risk conclusion"	Updated subsection 2.7.3. "Overall benefit: risk conclusion" to summarize updated safety information.	
Section 3.1.2.2 Safety Objectives	Modified description of pediatric participants from "(<18 years)" to "(≥10 years – <18 years)"	To provide additional clarity on the age range of pediatric participants

Section # and Name	Description of Change	Brief Rationale
Section 4 Study Design Figure #1	Modified Figure #1 "Decision tree for assessing response at Week 13" to remove the "continue in the blinded part" option.	To correct the figure and to be consistent with text that non-responders cannot continue in the blinded portion of the study.
Section 6.4.2 Destruction of Investigational Medicinal Product	Added "No destruction of unused (not dispensed) IMP takes place without Sponsor's written authorization. Storage conditions must be kept until approval from the Sponsor to remove the product from its storage location (eg, refrigerator). Products must be kept in a dedicated quarantine area until destruction, with a clear sign of "quarantined" until the Sponsor's Site Monitor authorizes the destruction."	To be consistent with recently updated Pharmacist's Manual v6.0
	Added "If a site does not have a destruction SOP, study drug can be returned to the depot."	
Section 6.5 Treatment of Overdose	Modified Section 6.5 to include clear definitions and guidelines for treating overdose with the IMP	To align treatment of overdose text with the latest protocol template language
Section 6.6.2 Particular Permissible Medications	Modified "per day" to "or equivalent per day" regarding permitted prednisone dosing.	To account for the fact that steroid medications other than prednisone could be used.
Section 7.9.15 Use of biological samples and data for future research	Updated language pertaining to "Use of biological samples and data for future research"	To align with new EU CTR guidelines.
Section 7.9.16 Medication errors or misuses of medicinal product	Modified title "Overdose, medication errors, misuses or abuses of medicinal product" to "Medication errors or misuses of medicinal product"	Template language updated to align with new EU CTR guidelines and as per the latest protocol template language.
	Definition of overdose moved to Section 6.5.	
	Language added clarifying medication errors and misuse of medicinal product.	
Section 9.3.9.4 Regulatory reporting requirements for SAEs	Added reference to safety reporting for the EU with direction to Appendix 10.7	To align with new EU CTR guidelines.
Section 9.3.9.6 "Adverse events of special interest"	Added uveitis including Vogt-Koyanagi-Harada disease as an adverse event of special interest.	To introduce uveitis as a new "adverse event of special interest" based on recent findings of ongoing rilzabrutinib clinical trials.
	Removed sub-bullet defining overdose	Definition of overdose is now under Section 6.7
Section 13.5 Data Protection	Added subsection 13.5 "Data Protection" with language pertaining to the protection of participant personal data and personal data of professionals involved in the study.	To align with new EU CTR guidelines.
Section 13.6. Financial Disclosure	Added subsection 13.6 "Financial Disclosure" that details investigator responsibilities.	To provide additional details on responsibility of the investigators and sub-investigators.

Section # and Name	Description of Change	Brief Rationale
Section 14.1 Regulatory and ethical considerations	Modified title with removal of "Local Regulations/Declaration of Helsinki"	Template language updated to align with new EU CTR guidelines and as per the latest protocol template language.
	Revised language to clarifying that the study will be conducted in accordance with EU CTR regulation and updated ethical considerations.	
Section 16, Appendix 10.6 Italy country-specific requirements	Removed "For pediatric participants (10 to <18 years old) enrolled in Italy, eGFR will be calculated using the Bedside Schwartz Equation."	To clarify that the Bedside Schwartz Equation will no longer be specific to Italy and is adopted in the inclusion criteria #4 and in the schedule of assessment footnotes for all pediatric participants.
Section 16, Appendix 10.7 EU (EEA countries) and UK-specific requirements	Added safety reporting to the agency language in the subsection "EU (EEA countries) only"	To align with new EU CTR guidelines.
Section 16, Appendix 13.2 Contraception guidance	Added highly effective contraception methods that are user dependent.	To correct an error in the contraception guidance text and to align with the ICF
Section 16, Appendix 15 Liver AND OTHER Safety: Suggested Actions and Follow-up Assessments	Updated subsection heading to include "AND OTHER"	To provide updated algorithm for accessing neutropenia and increase in ALT per the latest protocol template.
	Added figure for neutropenia assessment.	
	Updated "Increase in ALT" figure with latest template version.	
Section 16, Appendix 16 Collection, storage and future use of data and human biological samples	Added Appendix 16 to include statement "This appendix is provided separately" related to the "Collection, storage and future use of data and human biological samples"	To align with new EU CTR guidelines.
In addition, other minor editorial changes were implemented throughout the protocol.		

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{last}	Area under the plasma concentration curve
BID	Twice daily
BTK	Bruton's tyrosine kinase
CA	Competent authority
CLL	Chronic lymphocytic leukemia
CFR	Codes of Federal Regulations
CPK	Creatinine phosphokinase
CRA	Clinical research associate
CRO	Contract research organization
CS	Corticosteroids
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQOL-5 Dimension 5 Level
EU	European Union
FDA	United States Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
H2	Histamine 2
HBcAb	Hepatitis B core antigen antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IBLS	ITP Bleeding Scale

ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International normalized ratio
IR	Immediate release
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVIg	Intravenous immunoglobulin
ITP	Immune thrombocytopenia
ITP-KIT	Kids' ITP Tools
ITP-PAQ	ITP-Patient Assessment Questionnaire
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LAR	Legally authorized representative
LTE	Long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed adverse effect level
PD	Pharmacodynamics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGIS-Fatigue	Patient Global Impression of [Fatigue] Severity
PK	Pharmacokinetics
PRN1008	Rilzabrutinib
PRO	Patient response outcome
PT	Prothrombin time
PV	pemphigus vulgaris
QOL	Quality of life
QTcF	QT corrected for heart rate using Fredericia correction
QTF Plus	QuantiFERON®-TB Gold Plus
RBC	Red blood cell
Rh	Rhesus factor
RNA	Ribonucleic acid
rSDV	Remote source data verification
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Study day
SoA	Schedule of assessments
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
T/B/NK	T-lymphocytes/ B-lymphocytes/natural killers
TEAE	Treatment-emergent adverse event
Tmax	Time of observed maximum plasma concentration
TPO	Thrombopoietin
TPO-RA	Thrombopoietin receptor agonist

UK	United Kingdom
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WC	World Courier
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

1. SYNOPSIS

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)
PROTOCOL NUMBER PRN1008-018 (EFC17093)
SPONSOR Principia Biopharma Inc.
STUDY MEDICATION The investigational drug product is rilzabrutinib (PRN1008/SAR444671).
PHASE This is a Phase 3 pivotal study.
STUDY POPULATION Participants with refractory or relapsed ITP of >3 months duration (age 18 years and above) or with >6 months duration (age ≥12 to <18 years; see Appendix 10.2, Appendix 10.3, and Appendix 10.7 for country-specific criteria).
DURATION OF STUDY PARTICIPATION For each participant, the study will last up to 60 weeks from the start of the screening period to the End of Study (EOS) visit. This includes screening (up to 4 weeks) through a 12 to 24-week blinded treatment period followed by a 28-week open label period. Followed by a 4-week post-dose follow-up. For adult participants, the maximum duration of the long-term extension (LTE) period will be 12 months from the date of the last adult participant to enter the LTE. For pediatric participants, the maximum duration of the LTE period will be 12 months from the date of the last pediatric participant to enter the LTE.
NUMBER OF STUDY SITES Approximately 150 sites worldwide.
OBJECTIVES **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 during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy. **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

See Appendix 10.7 for EU (EEA countries) and UK-specific requirements.

Other Secondary Objectives
Efficacy Objectives

- To evaluate the stability of platelet response of rilzabrutinib

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

Pharmacokinetic (PK) Objectives

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

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

Refer to Appendix 10.7 for EU (EEA countries) specific age ranges.

INVESTIGATIONAL PLAN
Study Design

This is a global, randomized, parallel-group, double-blind, multicenter clinical study in participants with primary ITP who had a response to either intravenous immunoglobulin (IVIg) or corticosteroid (CS) that was not sustained.

After providing informed consent, participants will enter a 28-day screening period. Upon completion of the screening period, participants who satisfy all the inclusion criteria and none of the exclusion criteria of this protocol will be randomized in a 2:1 allocation ratio to one of two study arms: rilzabrutinib or placebo.

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 factors used for stratification (for adult participants), or balance (for pediatric participants) are 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 blinded treatment period of up to 25 weeks followed by an open-label period of 28 weeks during which all participants will receive rilzabrutinib, and then a 4-week safety follow-up period or long-term extension.

At the end of 12 weeks of treatment, participants will be assessed for achieving a platelet response defined as:

a) platelet count of ≥50,000/µL OR a platelet count between ≥30,000/µL and <50,000/µL and at least doubled from baseline at any time during the first 12 weeks and

b) absence of rescue medication in the 4 weeks prior to the elevated platelet count that meets platelet response criteria.

Figure 1 depicts the decision process for assessing response. The baseline value of platelet count is defined as the average of all the participant's Predose platelet counts (Screening and Study Day 1).

- Participants who respond will continue the blinded treatment period for a total of 24 weeks before entering the open label period.
- Participants who do not respond (including participants who receive rescue medication after 8 weeks of treatment) may discontinue from the study or enter the 28-week open label period at the end of Week 12, receiving treatment with 400 mg twice daily (BID) of rilzabrutinib. The initial study medication assignment will remain blinded.

Concomitant ITP medications (an oral CS and/or a thrombopoietin receptor agonist [TPO-RA]) will be permitted in both treatment arms and must be maintained at stable doses from 14 days before Study Day 1 until the last dose of study medication. Reductions in the doses of concomitant ITP medications will be permitted for associated safety concerns only.

The use of rescue medications (one of IVIg, high-dose CSs, platelet infusion, or 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, will be allowed.

After completing the open label period, participants who demonstrate a platelet response defined as platelet counts ≥50,000/μL or ≥30,000/μL and at least doubled from baseline at ≥50% of the visits without receiving rescue therapy while on treatment during the last 8 weeks of the open label period, will be allowed to enter the LTE.

Participant(s) may continue in the LTE until:

a) The participant is no longer responding (platelet counts <30,000/μL or less than 20,000/μL above baseline on two consecutive visits)

b) The drug is no longer being developed by the Sponsor for ITP

c) The program is stopped for safety reasons or

d) The drug becomes commercially available in the participant's country.

Safety Measures Due to Coronavirus (COVID-19) Pandemic

Due to the COVID-19 pandemic, safety measures have been implemented to ensure continued supply of study medication and safety monitoring for participants. These measures are described in the "Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19." When the COVID-19 pandemic resolves, the measures will be repealed back to the previous state as government rules and benefit/risk assessment allow.

STUDY DRUG AND DOSING REGIMEN

Participants will receive one 400 mg tablet of rilzabrutinib, or placebo BID in the double-blind portion of the study. Participants will receive one 400 mg tablet of rilzabrutinib BID in the open label portion of the study and the LTE.

Tablets should be taken with (~8oz/250mL) of water and may be taken with or without food.

PLANNED NUMBER OF PARTICIPANTS:

- Up to 30 pediatric participants aged 12 to <18 years; pediatric participants 10 to <12 years will be enrolled only in EEA countries; see Appendix 10.2, Appendix 10.3, and Appendix 10.7 for country-specific age ranges).
- Approximately 194 participants aged 18 years or older.

INDIVIDUAL PARTICIPANT STOPPING RULES

- Life-threatening or Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 rilzabrutinib-related treatment-emergent adverse event (TEAE) except for adverse events (AEs) related to the disease under study or other underlying medical conditions
- Serious allergic reaction to rilzabrutinib or placebo, including anaphylactic reaction
- Pregnancy
- Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the participant to risk if the participant continues with rilzabrutinib or placebo or that prevents the participant's adherence to the protocol
- Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), viral hepatitis (B and C) infection occurring during the study
- Violation of protocol inclusion or exclusion criteria, that in the opinion of the Sponsor, would significantly compromise data interpretation
- Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Appendix 15 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

STUDY STOPPING RULES

Study stopping rules will include, however not be limited to:

- More than one rilzabrutinib-related death
- Two or more life-threatening or CTCAE Grade 4 rilzabrutinib-related TEAEs except for AEs related to the disease under study (lack of efficacy)
- The Sponsor elects to stop the study.

INCLUSION CRITERIA

Participants may be included in the study if ALL of the following criteria are met:

1. Participants will be male and female with primary ITP with duration of >6 months in pediatric participants aged 12 to <18 years (pediatric participants aged 10 to <12 years will be enrolled in the EU [EEA countries] only; refer to Appendix 10.2, Appendix 10.3, and Appendix 10.7 for country-specific requirements) and duration of >3 months in adults aged ≥18 years

2. Participants who had a response (achievement of platelet count ≥50,000/µL) to IVIg/anti-D or CSs that was not sustained and who have documented intolerance, insufficient response, or any contraindication to any appropriate courses of standard of care ITP therapy
3. An average of 2 platelet counts at least 5 days apart of <30,000/µL during the screening period, and no single platelet count >35,000/µL, within 14 days prior to the first dose of study drug
   - Pediatric participants must additionally be determined to need treatment for ITP as per clinical assessment by the Investigator (see Appendix 10.7 for EU [EEA countries] specific requirements).
4. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 × 10^9/L, aspartate aminotransferase/alanine aminotransferase ≤1.5 × upper limit of normal [ULN], albumin ≥3 g/dL, total bilirubin ≤1.5 × ULN [unless the participant has documented Gilbert syndrome], glomerular filtration rate >50 [Cockcroft and Gault method for adult and Bedside Schwartz Equation for Pediatric participants]).
5. Hemoglobin >9 g/dL within 1 week prior to Study Day 1
6. All contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

   A) Male participants

   Male participants are eligible to participate if they agree to the following during the intervention period and for at least 13 weeks after the last administration of study intervention:

   - Refrain from donating or cryopreserving sperm

   Plus, either:

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

     OR

   - Must agree to use contraception/barrier as detailed below
     - A male condom; the participant should also be advised of the benefit for a female partner to use a highly effective method of contraception (as described in Appendix 13 Contraceptive and barrier guidance of the protocol) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

   B) Female participants

   A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

   - Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 13 of the protocol.

OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Appendix 13 of the protocol, during the study intervention period (to be effective before starting the intervention) and for at least 4 weeks after the last administration of study intervention AND agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- A WOCBP must have a negative highly sensitive pregnancy test (serum) as required by local regulations) within 3 days before the first administration of study intervention
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

7. Participants must be able to provide written informed consent or informed assent with corresponding informed consent obtained from the participant's guardian and agree to the schedule of assessments (SoA).

EXCLUSION CRITERIA

Participants will be excluded from the study if any of the following criteria are met:

1. Participants with secondary ITP
2. Pregnant or lactating women
3. Electrocardiogram (ECG) findings for participants:
   - Aged ≥10 and <16 years: QTcF >449 msec (males) or >457 msec (females)
   - Aged ≥16 and <18 years: QTcF >450 msec (males) or >460 msec (females)
   - Aged ≥18 years, of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic participants or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities
4. History (within 5 years of Study Day 1) or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the study, with the exception of non-melanoma skin cancer
5. Transfusion with blood, blood products, plasmapheresis, or use of any other rescue medications with intent to increase platelet count within 14 days before Study Day 1
6. Change in CS and/or TPO-RA dose within 14 days prior to Study Day 1 (more than 10% variation from current doses)
7. Immunosuppressant drugs other than CSs within 5 times the elimination half-life of the drug or 14 days of Study Day 1, whichever is longer
8. Treatment with rituximab or splenectomy within the 3 months prior to Study Day 1
   - Participants treated with rituximab will have normal B-cell counts prior to enrollment
9. Ongoing need for the use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change participant to histamine 2 receptor blocking drugs prior to Study Day 1)

10. Use of known strong-to-moderate inducers or inhibitors of cytochrome P450 (CYP) 3A within 14 days or 5 half-lives (whichever is longer) of Study Day 1 and until the end of the active treatment period
11. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin (except for low dose aspirin up to 100 mg per day), nonsteroidal anti-inflammatory drugs, and/or thienopyridines within 14 days of Study Day 1 and until the end of the active treatment period
12. Has received any investigational drug within the 30 days before receiving the first dose of study medication, or at least 5 times elimination half-life of the drug (whichever is longer); participant should not be using an investigational device at the time of dosing
    - Participants who previously received treatment with Bruton's Tyrosine Kinase (BTK) inhibitors (except rilzabrutinib) within 30 days before the first dose of study drug are not eligible
    - Participants who previously received rilzabrutinib at any time are not eligible
13. Current drug or alcohol abuse
14. Refractory nausea and vomiting, malabsorption, external biliary shunt, significant bowel resection, or any other condition that would preclude adequate study drug absorption
15. History of solid organ transplant
16. Positive at Screening for HIV, hepatitis B virus (HBV) (surface and core antibodies unrelated to vaccination), or hepatitis C virus (anti-HCV antibody confirmed with Hep C RNA)
    - Participants who are hepatitis B virus surface antigen (HBsAg) positive will not be eligible.
    - Participants who are HBsAg negative and hepatitis B core antigen antibody (HBcAb) positive will be tested for HBV surface antibody (HBsAb) and HBV DNA. If HBV DNA is negative and HBsAb titer is ≥100 IU/L, participants may be enrolled. Monthly HBV DNA monitoring will be required while on treatment and for 6 months after the last dose of the study drug. Positive HBV DNA results will be managed appropriately as per local standard of care.
    - Participants who are HBcAb positive and HBsAg negative with HBsAb titer <100 IU/L or negative, are not eligible.
17. Positive QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus) at Screening unless all of the following 3 conditions are true (see Appendix 10 country-specific requirements):
    a) Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease
    b) There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease
    c) Documented receipt of one of the following prophylactic treatment regimens:
        i. Oral daily Isoniazid for 6 months or
        ii. Oral daily Rifampin for 4 months or
        iii. Isoniazid and Rifapentine weekly for 3 months (3HP)

On a case-by-case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to 1 of the above tests may be used for eligibility. For example, if a QuantiFERON®-TB Gold, or QuantiFERON-TB Gold Plus (QFT Plus) is indeterminate for any reason and a local blood test or T-Spot® TB test is negative, the participant may be enrolled using the local result upon approval of the Sponsor.

18. History of recurring (2 or more) serious infections requiring intravenous antibiotic, antivirals, or antifungals therapy within the last 3 months before Study Day 1 or active serious or moderate infection ongoing on the day of randomization
19. Myelodysplastic syndrome
20. Live vaccine within 28 days prior to Study Day 1 or plan to receive one during the study
21. Planned surgery in the time frame of the dosing period
22. Any other clinically significant disease, condition, known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent (please see Section 6.1.1 for information on excipients), or medical history that, in the opinion of the Investigator or Sponsor's medical monitor, would interfere with participant safety, study evaluations, and/or study procedures
23. Positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) molecular test (if COVID-19 testing required per local guidelines to be determined for each site)
24. The COVID-19 vaccine within 14 days prior to Study Day 1 or planned during the last 12 weeks of the blinded treatment period

RANDOMIZATION PROCEDURE

Participants will be randomized in a 2:1 ratio to either active rilzabrutinib or placebo. The study is designed so that 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 factors used for stratification or balance are splenectomy status (yes/no), and by severity of thrombocytopenia (Inclusion Criteria 3 platelet counts <15,000/μL or ≥15,000/μL).

STUDY ASSESSMENTS

Clinical assessments will include:

- Physical examination; assessment of vital signs, height, and weight; 12-lead ECG, collection of medical history, collection of concomitant medication information, assessment of bleeding with ITP Bleeding Scale (IBLS) and/or other bleeding scales, QOL questionnaires, collection of AEs.

Laboratory assessments will include:

- Hepatitis B and C, HIV, pregnancy test, follicle-stimulating hormone (FSH), urinalysis, ABO and Rh, hemolysis panel (Coombs and haptoglobin), mean platelet volume, serum chemistry, hematology, platelet counts, prothrombin time (PT)/international normalized ratio (INR), thrombopoietin (TPO) level, PK sampling, T-lymphocytes/ B-lymphocytes/natural killers (T/B/NK) count, Immunoglobulin levels, activated partial thromboplastin time (aPTT), fibrinogen, and BTK occupancy (at select sites).

SAFETY AND TOLERABILITY ASSESSMENTS

Safety and tolerability will be assessed by collection of frequency, severity, and causal relationship of TEAEs.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board will review unblinded participant safety data.

ENDPOINTS

Primary Efficacy Endpoint (Blinded Treatment Period)

- 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; see Appendix 10.7 for country-specific definition of durable platelet response (EU [EEA countries] and UK).

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

See Appendix 10.7 for EU (EEA countries) and UK-specific requirements.

Other Secondary Endpoints

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)

Safety Endpoints

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

Pharmacokinetic Endpoints

- Plasma concentrations of rilzabrutinib

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

Exploratory Endpoints (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 TPO-RAs)
- 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-Dimensions-5 Level 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
- PK parameters as assessed by population PK analysis
- BTK occupancy
- Changes from baseline in TPO levels, T/B/NK counts, immunoglobulin (IgG, IgG1, IgG4, IgM, IgE) levels
- (Optional) Vaccine-specific IgG response during treatment

See Appendix 10 (Appendix 10.5) for China-specific requirements.

Exploratory Endpoints (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 on the Psychological, Fear, Social Activity, Women's Reproductive Health and Work domains of the ITP-PAQ in adult participants (≥18 years)
- Change from baseline in QOL as measured by the EuroQOL-Dimensions-5 Level in adult participants (≥18 years)
- Percent change from baseline on 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

See Appendix 10.7 for EU (EEA countries) and UK-specific requirements.

SAFETY ASSESSMENTS

Safety will be assessed by the incidence, severity, and causal relationship of TEAEs, including clinically significant changes in physical examination, vital signs, ECG, laboratory parameters.

PHARMACOKINETICS

Blood samples for the determination of plasma rilzabrutinib (and metabolites, if applicable) concentrations will be collected at specified timepoints. Concentrations will be summarized by timepoint. PK data may also be analyzed using a nonlinear mixed effects (population PK) model in isolation and/or pooled with PK data from other studies. Exploratory analyses will be conducted to evaluate potential relationships between PK and PD, safety, and efficacy endpoints. The results of these analyses may be reported outside of the main clinical study report.

SAMPLE SIZE

The adult sample size chosen for this study was selected to achieve enrollment of 129 adult participants (≥18 years) on rilzabrutinib and 65 adult participants on placebo. The pediatric sample size of up to 30 participants (20 participants on rilzabrutinib and 10 participants 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%.

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 3.2.1) 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.

PRIMARY EFFICACY ANALYSIS

The primary analysis will compare the proportion of participants in the adult intent-to-treat (ITT) population who achieve durable platelet response defined as 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 medication (with at least 2 platelet counts at or above 50,000/μL during the last 6 weeks of the 24-week blinded treatment period) between rilzabrutinib and placebo with a Cochran-Mantel-Haenszel test using the two stratification factors at a 2-sided alpha level of 0.05 (See Appendix 10.7 for country-specific definition of durable platelet response (EU [EEA countries] and UK). Participants who do not respond in the first 12 weeks and enter the open label period will be treated as non-responders in the primary analysis.

The primary endpoint will be analyzed for adult and pediatric participants separately.

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

KEY SECONDARY EFFICACY ANALYSES

The following five comparisons will be conducted between rilzabrutinib and placebo in the adult ITT population using sequential (hierarchical) testing with a fixed sequence, which controls the family-wise error for multiple comparisons at alpha level of 0.05 (two-sided):

- Compare the number of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least double from baseline over the 24-week blinded treatment period (platelet counts will be censored for 4 weeks after the use of rescue therapy, if any)
- Compare the number of weeks with platelet counts ≥30,000/μL and at least double from baseline over the 24-week blinded treatment period
- Compare the time to first platelet count of ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least double from baseline

- Compare the proportion of participants requiring rescue therapy during the 24-week blinded treatment period
- Compare the change from baseline on Item 10 of the ITP-PAQ (physical fatigue) in adult participants at Week 13

See Appendix 10.7 for EU (EEA countries) and UK-specific requirements.

OTHER EFFICACY ANALYSES

- Estimate the predictive value of platelet count for each of the three predictors separately or in combination:
  - ≥30,000/µL on Study Day 8
  - ≥20,000/µL above baseline on Study Day 8
  - ≥50,000/µL at any time over first 8 weeks of the treatment period to achieve the primary endpoint

OTHER STATISTICAL CONSIDERATIONS

The primary endpoint will be analyzed for adult and pediatric participants separately. The primary analysis will be based on the adult population. 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 regulatory submissions.

The pediatric participants will not be tested, and descriptive statistics will be done on these participants. Additional statistical analyses on these pediatric participants may be provided for specific regulatory requests.

The primary efficacy analysis will be conducted when all adult participants aged ≥18 years have completed the Blinded Study Week 25 visit, ie, completed the blinded treatment period.

A formal Statistical Analysis Plan (SAP) will be developed prior to database lock and unblinding. The SAP will contain a more detailed and/or comprehensive presentation of statistical methods or procedures, attention to any changes of substance to planned analysis procedures relative to those indicated in the protocol and will be the final authority for all statistical analyses.

Descriptive summaries of variables by treatment will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be tabulated by treatment and where appropriate by study day and study timepoint.

Summaries will also be presented for the change from baseline, when appropriate. For categorical variables, the counts and proportions of each value will be tabulated by treatment and where appropriate by study day and study timepoint. For time to event variables, point estimates (25th, 50th, and 75th percentiles) along with 95% confidence intervals will be tabulated by treatment. Survival estimates will also be shown graphically for each treatment.

All statistical tests will be two-sided unless otherwise noted.

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

Table 1 - Schedule of Assessments - Blinded Treatment Period

	Screening	Blinded Treatment Period[w]							
	(D-28 to Study Day -1 Predose)[a]	WK 1 SD1	WK5 SD29	WK9 SD57	WK13 SD85	WK17 SD113	WK21 SD141	Weekly Lab Visits Between Clinic Visits	Early Termination[x]/ Unscheduled visit
Visit Window		±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	
Informed Consent	X[t]								
Inclusion/Exclusion Criteria	X	X							
AEs	X	X	X	X	X	X	X		X
Review of Platelet Counts for Response[b]					X				
Concomitant Medications	X	X	X	X	X	X	X		X
Height (cm)[c]	X				X				
Weight (kg)	X	X	X	X	X	X	X		X
Physical exam/medical history[d]	X	X	X	X	X	X	X		X
ECG (12-lead, single)	X	X[e]							X
Vital Signs	X	X	X	X	X	X	X		X
Urinalysis[f]	X	X	X	X	X	X	X		X
Hep B & C, HIV[g]	X								
QuantiFERON-TB Test	X								
Pregnancy Test[h]	X	X	X	X	X	X	X		X
FSH[i]	X								
ABO and Rh Blood Type[j]	X								
Serum Chemistry[k]	X	X	X	X	X	X	X		X
Hematology, differential, reticulocytes[l]	X	X	X	X	X	X	X	X[u]	X
T/B/NK counts[r]		X	X		X				
PT/INR, aPTT[m]	X	X	X	X	X	X	X		
TPO levels[r]		X	X	X	X	X	X		
Hemolysis panel[n, r]		X	X	X	X	X	X		
Immunoglobulin Levels[r]		X	X		X				
PK sample[o]		X			X				X
BTK Occupancy (at select sites)[p, r]		X			X				
(Optional) sample for vaccine-specific IgG[r, s]		←==========						==========→	X
QOL Questionnaires[q]	X	X	X	X	X	X	X		X
IBLS	X	X	X	X	X	X	X		X
Rilzabrutinib or Placebo dispensed		X	X	X	X	X	X		
Patient Medication Diary		X	X	X	X	X	X		
SARS-CoV-2 test	X[a,v]	X[r]							

AE = adverse event; aPTT = activated partial thromboplastin time; BTK = Bruton's tyrosine kinase; D = day; ECG = electrocardiogram; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; Hep = hepatitis; HIV = human immunodeficiency virus; IBLS = ITP Bleeding Scale; IgG = immunoglobulin G; INR = international normalized level; IMP = investigational medicinal product; ITP = immune thrombocytopenia; ITP-PAQ = ITP- Patient Assessment Questionnaire; ITP- KIT = Kids' ITP Tools; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PGIS-Fatigue = Patient Global Impression of [Fatigue] Severity; PK = pharmacokinetics; PT = Prothrombin time; QOL = Quality of Life; Rh = rhesus factor; SARS-CoV-2 = severe acute respiratory syndrome–related coronavirus-2; SD = study day; TB = tuberculosis; T/B/NK = T-lymphocytes/B-lymphocytes/natural killers; TPO = Thrombopoietin; WK = Week.

a Participants may be re-screened once. The screening period can be up to -31 days of Study Day 1.

b At the Week 13 visit review previous platelet counts for response during the first 12 weeks. If the participant met the criteria for response continue with the Week 13 visit assessments, the participant should continue in the blinded part. If the participant did not meet the criteria for response, complete the Week 25 visit assessments and the participant may start the open label period or discontinue from the study. Platelet response is defined as a) a platelet count of ≥50,000/µL OR a platelet count of between ≥30,000/µL and <50,000/µL and at least doubled from baseline at any time during the first 12 weeks and b) absence of rescue medication in the 4 weeks prior to the latest elevated platelet count that meets platelet response criteria.) Participants who receive rescue medication during the last 12 weeks also may join the open-label part or discontinue from the study. See Figure 1 for decision tree for assessing response at Week 13 and for calculation of baseline platelet count.

c For pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) height is recorded at Screening, Week 13, Week 25, Week 37, and Week 53. For participants aged 18 years and older height is recorded at Screening only.

d Full physical examination at Screening, 4-week follow-up and early termination; abbreviated physical examination at all other visits. Medical history should include vaccine history. See Appendix 10.6 for Italy-specific requirements.

e ECG for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) will be performed predose and 2 hours postdose (±15 mins) at the Week 1 and Week 25 visits.

f Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes.

g Participants enrolled with positive HBV core antibody test result and HBsAb titer ≥100 IU/L will have HBV DNA monitored monthly while on treatment and for 6 months after treatment has ended.

h For women of childbearing potential only. Serum pregnancy test must be performed at Screening; a urine pregnancy test must be performed at all other study timepoints.

i To confirm postmenopausal status for women who are not surgically sterile and of reproductive potential.

j Historical lab results may be used for ABO and Rh Blood Type.

k Serum chemistry will include the following: aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin levels; alkaline phosphatase (ALP); albumin; creatinine; urea; total protein; sodium; chloride; calcium; phosphate; potassium; and glucose (random). Creatine phosphokinase (CPK) and estimated glomerular filtration rate (eGFR) is to be performed at Screening only. eGFR will be calculated using the Bedside Schwartz Equation in pediatric participants (10 to <18 years old) and using the Cockcroft and Gault method in adult participants.

l Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), mean platelet volume, leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Local laboratories will be used for platelet analysis required at ALL visits (ie, Clinic Visits and Weekly Lab Visits in between Clinic Visits).
The central laboratory will be used for the analyses required at Clinic Visits including hematology, differential, and reticulocytes. The results of hematology, differential and reticulocytes obtained at local laboratories will be used only if the central lab results of Clinic Visits are missing due to any reason. Central platelet counts assessed at Clinic Visits will be used if local platelet results are missing for any reason.

m Coagulation will include: PT/INR, thrombin time, activated partial thromboplastin time (aPTT), and fibrinogen level.

n Hemolysis panel: consisting of Coombs test, haptoglobin levels.

o PK samples for participants aged 18 years or older will be collected predose (within 1.5 hours predose) and 2 hours postdose (±15 minutes) at the Week 1 visit. PK samples for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (±5 mins), 2 hours (±5 mins) and 4 hours (±15 mins), 6 hours (±15 mins) at the Week 1 visit. At the Week 13 visit a sample will be taken Predose only. At these visits, participants will wait to take their morning dose until they complete the blood draw of pre-dose sample.

p BTK Occupancy samples for participants aged 18 years or older will be collected Predose (within 1.5 hours predose) and 2 hours postdose (±15 mins) at the Week 1 visit. BTK Occupancy samples for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (±5 mins), 2 hours (±5 mins) and 4 hours (±15 mins), 6 hours (±15 mins) at the Week 1 visit. At the Week 13 visit a sample will be taken Predose only. At these visits, participants will wait to take their morning dose until they complete the blood draw of pre-dose sample.

q QOL Questionnaires include EQ-5D-5L, ITP-Patient Assessment Questionnaire (ITP-PAQ) or Kids' ITP Tools (ITP-KIT), and PGIS-Fatigue/PGIS/PGIC. ITP-PAQ, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC (in that order) will be administered for adults 18 years or older. ITP-KIT and EQ-5D-5L (in that order) will be administered for pediatric participants (see Appendix 10.7 for EU (EEA countries) age ranges). **Questionnaires should be completed prior to all other study procedures and interactions with site staff.** Note: The PGIC will be collected starting after Day 1.

r See Appendix 10 for country-specific requirements.

s Optional collection of 2 blood samples for vaccine-specific IgG in serum (See Section 7.9.9 for a list of routine vaccines). The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine- specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded.

t Participants enrolled into the pediatric portion of the trial will still be considered as part of the pediatric group with all the planned assessments when they turn 18 years old, unless specified, and they should be re-consented with an adult consent. See Appendix 10.7 for EU (EEA countries) age ranges.

u This visit is for platelet count assessment and can be conducted on-site or remotely. After the end of treatment (EOT) visit, weekly platelet count assessment is not required; however, it is up to the Investigator to decide whether to conduct weekly platelet assessments using unscheduled visits, if deemed necessary for participant safety.

v SARS-CoV-2 molecular test (if COVID-19 testing is required per local guidelines to be determined for each site).

w During the blinded treatment period (Week 13 to Week 24): Participants who discontinue from the blinded treatment period due to safety (or other) reasons and choose to join the open label period will attend the Week 25 assessments at their next scheduled visit.

x **All participants who discontinue treatment during the blinded or open-label period need to have an Early Termination visit as specified in Table 1 and an End of Study visit (4 weeks after last IMP intake) as specified in the End of Study visit in Table 2 (See End of Study Table 2).**

Table 2 - Schedule of Assessments - Open Label Period

	Open Label Period								End of Study 4 weeks post-last dose SD393	Weekly Lab Visits Between Clinic Visits[r]	Early Termination/ Unscheduled visit
	First Day of WK25[o, p] SD169	WK 29 SD197	WK33 SD225	WK37 SD253	WK41 SD281	WK45 SD309	WK49 SD337	First Day of WK53[q] SD365			
Visit Window	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	
AEs	X	X	X	X	X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X		X
Height (cm)[a]	X			X				X			
Weight (kg)	X	X	X	X	X	X	X	X	X		X
Physical exam[b]	X	X	X	X	X	X	X	X	X		X
ECG (12-lead, single)	X[c]							X	X		X
Vital Signs	X	X	X	X	X	X	X	X	X		X
Urinalysis[d]	X	X	X	X	X	X	X	X	X		X
Pregnancy test[e]	X	X	X	X	X	X	X	X	X		X
Serum Chemistry[f]	X	X	X	X	X	X	X	X	X		X
Hematology, differential, reticulocytes[g]	X	X	X	X	X	X	X	X	X	X[r]	X
T/B/NK counts[m]	X	X	X		X			X	X		
PT/INR, aPTT[h]	X	X	X	X	X	X	X	X	X		
TPO levels[m]	X	X	X	X	X	X	X	X	X		
Hemolysis panel[i, m]	X	X	X	X	X	X	X	X	X		
Immunoglobulin Levels[m]	X	X	X		X			X	X		
PK sample[j]	X							X			X
BTK Occupancy (at select sites)[k, m]	X							X			
(Optional) sample for vaccine-specific IgG[m, n]	←==========									==========→	X
QOL Questionnaires[l]	X	X	X	X	X	X	X	X	X		X
IBLS	X	X	X	X	X	X	X	X	X		X
Rilzabrutinib dispensed	X	X	X	X	X	X	X	X			
Patient Medication Diary	X	X	X	X	X	X	X	X			
SARS-CoV-2 test (see Appendix 10 for country-specific requirements)	X										

AE = adverse event; aPTT = activated partial thromboplastin time; BTK = Bruton's tyrosine kinase; ECG = electrocardiogram; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; IBLS = ITP Bleeding Scale; IgG = immunoglobulin G; INR = international normalized level; ITP = immune thrombocytopenia; ITP-PAQ = ITP-Patient Assessment Questionnaire; ITP- KIT = Kids' ITP Tools; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PGIS-Fatigue = Patient Global Impression of [Fatigue] Severity; PK = pharmacokinetics; PT = Prothrombin time; QOL = Quality of Life; SARS-CoV-2 = severe acute respiratory syndrome–related coronavirus-2; SD = study day; T/B/NK = T-lymphocytes/ B-lymphocytes/natural killers; TPO = Thrombopoietin; WK = Week.

a For pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) height is recorded at Screening, Week 13, Week 25, Week 37, and Week 53. For participants aged 18 and older height is recorded at Screening only.

b Full physical examination at Screening, 4-week follow-up and early termination; abbreviated physical examination at all other visits. See Appendix 10.6 for Italy-specific requirements.

c ECG for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) will be performed predose and 2 hours postdose (±15 minutes) at the Week 25 visit. Adult participants are also required to complete ECG at Week 25.

d Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes.

e For women of childbearing potential only. A urine pregnancy test must be performed at all study timepoints.

f Serum chemistry will include the following: aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin levels; alkaline phosphatase (ALP); albumin; creatinine; urea; total protein; sodium; chloride; calcium; phosphate; potassium; and glucose (random).

g Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), mean platelet volume, leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Local laboratories will be used for platelet analysis required at ALL visits (ie, Clinic Visits and Weekly Lab Visits in between Clinic Visits).
The central laboratory will to be used for the analyses required at Clinic Visits including hematology, differential, and reticulocytes. The results of hematology, differential and reticulocytes obtained at local laboratories will be used only if the central lab results of Clinic Visits are missing due to any reason. Central platelet counts assessed at Clinic Visits will be used if local platelet results are missing for any reason.

h Coagulation will include: PT/INR, thrombin time, activated partial thromboplastin time (aPTT), and fibrinogen level.

i Hemolysis panel: consisting of Coombs test, haptoglobin levels.

j At Week 25 visit, PK samples for participants aged 18 years or older will be collected Predose (within 1.5 hours predose) and 2 hours postdose (±15 minutes). At the Week 25 visit, PK samples for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (±5 minutes), 2 hours (±5 minutes) and 4 hours (±15 minutes), 6 hours (±15 minutes). At these visits, participants will wait to take their morning dose until they complete the blood draw of pre- dose sample. At Week 53 and early termination visits, a random timepoint PK samples will be collected and the time of sample and time of the last dose of rilzabrutinib will be captured.

k At Week 25 visit, BTK occupancy samples for participants aged 18 years or older will be collected Predose (within 1.5 hours predose) and 2 hours postdose (±15 minutes). At Week 25 visit, BTK Occupancy samples for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (±5 minutes), 2 hours (±5 minutes) and 4 hours (±15 minutes), 6◦hours (±15 minutes). At these visits, participants will wait to take their morning dose until they complete the blood draw of pre-dose sample. At Week 53, a random timepoint BTK occupancy sample will be collected and the time of sample and time of the last dose of rilzabrutinib will be captured.

l QOL Questionnaires include EQ-5D-5L, ITP-PAQ or ITP-KIT, and PGIS-Fatigue/PGIS/PGIC. ITP-PAQ, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC (in that order) will be administered for adults 18 years or older. ITP-KIT and EQ-5D-5L (in that order) will be administered for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges). **Questionnaires should be completed prior to all other study procedures and interactions with site staff.**

m See Appendix 10 for country-specific requirements.

n Optional collection of 2 blood samples for vaccine-specific IgG in serum (see Section 7.9.9 for a list of routine vaccines). The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine- specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded.

o Week 25/SD169 visit is the last visit of the blinded treatment period and may also serve as the start of the open label period.

p For participants who will enter the open label period directly after 12 weeks of blinded treatment, they will attend the Week 13/SD85 visit which corresponds to the Week 25/SD169 visit (Table 2), this would be their last visit of the blinded treatment period and also the start of the open label period. They will follow the open label period schedule of assessments from Week 29 (Table 2) starting at their next scheduled visit for a total of 28 weeks.

q For participants who will enter the open label period directly after 12 weeks of blinded treatment, they will follow the open label period schedule of assessments (**Week 25 to Week 53**) which means that they will be treated on the open-label part for a total of 28 weeks. After Week 53, the participants will follow the schedule of assessments according to their eligibility for the LTE period.

r This visit is for platelet count assessment and can be conducted on-site or remotely. Lab visits will occur weekly from Week 25 to Week 53. The Investigator can request that the participant visits the clinic for additional platelet monitoring during unscheduled visits if needed. After the end of treatment (EOT) visit, weekly platelet count assessment is not required; however, it is up to the Investigator to decide whether to conduct weekly platelet assessments using unscheduled visits, if deemed necessary for participant safety.

Table 3 - Schedule of Assessments - Long-Term Extension

	On-treatment clinic visits				Early Termination/ Unscheduled Visit
	Week 53/Rollover to LTE[n]	Clinic Visits Every 28 Days for the first year of LTE then every 3 months thereafter	Last Day of Active Rilzabrutinib Treatment	End of Study (4 weeks post-last dose)	
Visit Windows	±7 days	±7 days	±7 days	±7 days	
AEs	X	X	X	X	X
Concomitant Medications[a]	X	X	X	X	X
Weight (kg)	X	X	X	X	X
Physical Exam[b]	X	X	X	X	X[m]
ECG (12-lead, single)	X			X	X[m]
Vital Signs	X	X	X	X	X
Urinalysis[c]	X	X	X	X	X
Pregnancy test[d]	X	X	X	X	X
Serum Chemistry[e]	X	X	X	X	X
Hematology, differential, reticulocytes[f]	X	X	X	X	X
T/B/NK counts[g, k]	X	X		X	
PT/INR aPTT[h]	X	X	X	X	
TPO levels[k]	X	X	X	X	
Hemolysis panel[i, k]				X	
Immunoglobulin Levels[k]				X	
(Optional) sample for vaccine-specific IgG[k, l]	←==========→				X
QOL Questionnaires[j]	X	X	X	X	X
IBLS	X	X	X	X	X
Rilzabrutinib dispensed	X	X			
Patient Medication Diary	X	X			X[m]
SARS-CoV-2 test (see Appendix 10 for country-specific requirements)	X				X[m]

AE = adverse event; aPTT = activated partial thromboplastin time; CS = corticosteroids; ECG = electrocardiogram; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; IBLS = ITP Bleeding Scale; IgG = immunoglobulin G; INR = international normalized level; ITP = Immune thrombocytopenia; ITP-PAQ = ITP-Patient Assessment Questionnaire; ITP-KIT = Kids' ITP Tools; PGIS = Patient Global Impression of Severity PGIS-Fatigue = Patient Global Impression of [Fatigue] Severity; QOL = Quality of Life; SD = study day; T/B/NK = T-lymphocytes/B-lymphocytes/natural killers; PGIC = Patient Global Impression of Change; PT = prothrombin time; TPO = Thrombopoietin; TPO- RA = thrombopoietin receptor agonist

a Reductions in the doses or withdrawal of concomitant ITP medications will be permitted if the participant achieves platelet count of ≥50,000/μL in three scheduled visits (over 12 weeks). Retreatment with the same medication(s) and doses of ITP concomitant medication(s) used at baseline (an oral CS and/or a TPO-RA), changing the dose or initiation of new ITP medications (an oral CS and/or a TPO-RA) will also be allowed. Tapering of concomitant CS and/or TPO-RA should be performed in accordance with the schedule in Section 6.6.2.

b Full physical exam at End of Study, abbreviated physical exam at all other visits. See Appendix 10.6 for Italy-specific requirements.

c Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes.

d Urine pregnancy test for women of childbearing potential only.

e Serum chemistry will include the following: aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin levels; alkaline phosphatase (ALP); albumin; creatinine; urea; total protein; sodium; chloride; calcium; phosphate; potassium; and glucose (random).

f Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), mean platelet volume, leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Local laboratories will be used for platelet analysis required at ALL visits (ie, Clinic Visits and Unscheduled Lab Visits in between Clinic Visits). The central laboratory will to be used for the analyses required at Clinic Visits including hematology, differential, and reticulocytes. The results of hematology, differential and reticulocytes obtained at local laboratories will be used only if the central lab results of Clinic Visits are missing due to any reason. Central platelet counts assessed at Clinic Visits will be used if local platelet results are missing for any reason. After the end of treatment (EOT) visit, weekly platelet count assessment is not required; however, it is up to the Investigator to decide whether to conduct weekly platelet assessments using unscheduled visits, if deemed necessary for participant safety.

g T-lymphocytes/ B-lymphocytes/natural killers (T/B/NK) counts at Week 53, every 6 months during the long-term extension period and at End of Study.

h PT/INR, aPTT: only if needed to follow-up on bleeding adverse events.

i Hemolysis panel: consisting of Coombs test, haptoglobin levels.

j QOL Questionnaires include EQ-5D-5L, ITP-PAQ or ITP-KIT, and PGIS-Fatigue/PGIS/PGIC to be completed every 3 months. ITP-PAQ, EQ-5D-5L and PGIS-Fatigue/ PGIS/PGIC (in that order) will be administered for adults 18 years or older. ITP-KIT and EQ-5D-5L (in that order) will be administered for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges). Questionnaires should be completed prior to all other study procedures and interactions with site staff.

k See Appendix 10 for country-specific requirements.

l Optional collection of 2 blood samples for vaccine-specific IgG in serum (see Section 7.9.9 for a list of routine vaccines). The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine- specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded.

m Early Termination Visit only.

n Assessments performed at the open label period Week 53 Visit will be used at the starting visit (Week 53) of the LTE.

2. BACKGROUND

2.1. Overview of Immune Thrombocytopenia (ITP)

Immune Thrombocytopenia (ITP) is characterized by autoantibody-mediated destruction of platelets and impaired platelet production, which result in thrombocytopenia and a predisposition to bleeding associated with morbidity and mortality.

In general, pharmacotherapy (corticosteroids [CSs], intravenous immunoglobulin [IVIg] or anti-D) is used for symptomatic participants with low platelet counts for reducing platelet destruction. While a majority of participants respond initially to CSs, the rate of continued remission is low. Second line therapies include rituximab and splenectomy and are associated with risk of sepsis and immune suppression. Thrombopoietin (TPO) mimetics (Bussel 2007) are approved for the treatment of participants with chronic ITP who have not had sufficient responses to CSs, IVIg, or splenectomy. Second-line treatment with TPO-RAs have a clinical response rate of 80%, however approximately one-third of participants discontinue TPO-RAs due to lack of response (Ghanima 2019). Novel, safe, and effective oral treatments to maintain platelet counts in this setting would be a significant therapeutic advantage. Thus, there remains a high unmet medical need for novel, safe, and effective oral therapies for ITP.

2.2. BTK Inhibitor Rilzabrutinib

Bruton's Tyrosine Kinase (BTK) is expressed in cells of the B-cell lineage, including marrow-derived hematopoietic stem cells, common lymphoid progenitor cells and developing B and myeloid lineages. BTK is also expressed in other cells of hematopoietic lineage with the exception of T cells, natural killer cells and plasma cells (Sideras 1995, Rip 2018).

A BTK inhibitor such as rilzabrutinib has the potential to target multiple pathways and cell types involved in inflammation and autoimmunity. These include B-cell receptor-mediated B-cell pathways, FcγR-induced cytokine release from monocytes and macrophages, FcεR-induced mast cell degranulation and granulocyte migration and mediator release.

There is preliminary evidence to support the role of BTK inhibition in participants with autoimmune cytopenias (Rogers 2016, Montillo 2017), where sequential episodes of severe autoimmune hemolytic anemia and ITP ceased after initiation of treatment with ibrutinib, a BTK/epidermal growth factor receptor /interleukin-2-inducible T-cell kinase inhibitor, in participants with chronic lymphatic leukemia (CLL).

Rilzabrutinib is a high-affinity inhibitor of BTK. Pertinent to the treatment of ITP, rilzabrutinib treatment in vitro profoundly inhibited human B-cell activation and blocked antibody (IgG, IgE) mediated activation of immune cells via Fc receptor signaling.

2.3. Nonclinical Experience

The nonclinical safety profile of rilzabrutinib has been well-characterized in safety pharmacology studies and repeat-dose oral toxicity studies in multiple animal species. Orally administered rilzabrutinib did not affect the gross behavioral, physiological, or neurological state of rats at dose levels up to 500 mg/kg/day and the no-observed-adverse-effect level (NOAEL) of the cardiovascular and respiratory systems in dogs considered to be 500 mg/kg/day.

Rilzabrutinib was well-tolerated in rats and dog studies of up to 6- and 9-month duration, respectively. In 6-month oral rat study, the NOAEL for female rats was 50 mg/kg/day (area under the plasma concentration curve [AUClast] 5480 hr.ng/mL) and 150 mg/kg/day in males (AUClast 5327 hr.ng/mL), based on lethality, decreased body weight gain, macroscopic and microscopic changes in the gastrointestinal (GI) tract, and neutrophilic inflammation in the brain. In a 9-month oral dog study, the NOAEL was 30 mg/kg/day (AUClast 963 hr.ng/mL), based on body weight loss and the euthanasia of 1 male dog at 50 mg/kg/day. The estimated human exposure of 400 mg twice daily (BID) at steady state is 890 hr.mg/mL. Rilzabrutinib was not genotoxic and did not demonstrate toxicities in fertility and early embryo-fetal development reproductive studies. Overall, the nonclinical safety profile of rilzabrutinib supports continuation of clinical studies. Additional nonclinical information on rilzabrutinib is provided in the current version of the rilzabrutinib (PRN1008) Investigator's Brochure (IB).

Please refer to the IB for more details.

2.4. Clinical Experience

As of the data cut-off date of 22 April 2021, Rilzabrutinib was administered to 289 healthy volunteers and was well-tolerated.

Details of clinical experience with rilzabrutinib in the PRN1008-005 (NCT02704429) study in participants with pemphigus and PRN1008-010 study in participants with ITP can be found in the IB. Preliminary efficacy results of PRN1008-010 Part A of the study were presented at European Hematology Association 2020 (Kuter 2020).

2.4.1. Safety

As of the data cut-off date of 22 April 2021, in 8 completed Phase 1 studies and 4 ongoing Phase 1 studies (more than 280 healthy volunteers), the completed Phase 2 study in participants with pemphigus (41 participants, PRN1008-005), and ongoing Phase 1/2 studies in ITP (61 participants, PRN1008-010), and IgG4 (4 participants, PRN1008-017), rilzabrutinib demonstrated a safety profile characterized by predominantly mild-to-moderate adverse events (AEs) such as GI disturbance and headache, no rilzabrutinib-related deaths, and no evidence of increased risk of infections. There have been no related thrombotic or major bleeding events in the clinical experience with rilzabrutinib to date. In addition, there are no patterns or clinically significant findings from physical examinations, laboratory parameters, electrocardiograms (ECG), or vital signs in healthy-volunteers and in participants from studies conducted to date.

The most common treatment-related AEs as of 22 April 2021 were GI in nature, including nausea, vomiting, and diarrhea. The majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity. There was 1 serious adverse event (SAE) in Study PRN1008-005 that was assessed by the Sponsor as related to the study drug (cellulitis). Safety and efficacy findings of Study PRN1008-010 (main treatment periods) and LTE-Part A interim analysis were published (Kuter et al 2022, Cooper et al 2023, Kuter et al 2024). Please refer to the most recent version of the IB for updated safety information.

The marketed BTK inhibitor, ibrutinib, has been studied in combination with rituximab in the treatment of chronic lymphocytic leukemia without published evidence of increased drug-related

AEs (Burger 2019). There is no a priori drug interaction potential between anti-CD20 biologic drugs and the small molecule rilzabrutinib.

PRN1008-010 (Part A and Part B) study results demonstrated a rapid and sustained platelet response in patients with primary ITP who failed multiple prior therapies and showed a favorable safety profile (Kuter et al 2022, Cooper et al 2023). For summary of overall benefit/risk assessment, refer to Section 2.7.

2.4.2. Cardiodynamic Evaluation

A cardiodynamic evaluation of rilzabrutinib was conducted in healthy volunteer subjects in which 400 mg rilzabrutinib, 400 mg rilzabrutinib plus ritonavir, placebo, and moxifloxacin (positive control) were given in separate, randomized periods to healthy volunteer subjects in a 4-way crossover design. Serial ECGs were extracted from continuous Holter monitors at baseline (predose) and for 24 hours post-dose on Day 1 in each period (Cardiac Safety Report PRN1008-014). Rilzabrutinib at the studied doses did not have a clinically relevant effect on cardiac conduction (ie, the PR and QRS intervals).

In summary, rilzabrutinib at the studied doses did not have a clinically relevant effect on the studied ECG parameters.

2.4.3. Pharmacokinetics and Pharmacodynamics

Rilzabrutinib is rapidly cleared from the plasma, with a terminal half-life of approximately 4 hours, maximum concentration time of approximately 2 hours after ingestion, and a volume of distribution of 149 L after intravenous administration. No significant accumulation was observed after multiple dosing. Approximately 3% of rilzabrutinib is excreted unchanged in the urine.

Rilzabrutinib is available in a tablet formulation for investigation in-patient populations in clinical studies. Food delays the time of observed maximum plasma concentration (Tmax) by 1.5 hours and decreases AUC and Cmax of rilzabrutinib by 20% and 30%, respectively, which is not considered to be clinically relevant. Rilzabrutinib showed approximately linear increases in exposure between doses of 150 mg and 600 mg.

Rilzabrutinib demonstrated sustained, dose-dependent occupancy of BTK in peripheral blood mononuclear cells in healthy volunteers. Twice daily dosing with 400 mg tablet is expected to result in BTK occupancy that is within the therapeutic range.

Additional details of the clinical pharmacokinetics (PK) and safety information of rilzabrutinib are provided in the current version of the IB.

2.4.4. Drug-Drug Interaction Potential

Rilzabrutinib is a substrate of the cytochrome P450 (CYP) 3A isoenzyme. In a clinical drug-drug interaction study, the CYP3A inhibitor ritonavir increased plasma rilzabrutinib concentrations (PRN1008-014) and the CYP3A inducer rifampin decreased plasma rilzabrutinib concentration (PRN1008-024); therefore, concomitant use of strong and moderate CYP3A inhibitors or inducers should be avoided. Rilzabrutinib is also a substrate of P-gp from in-vitro studies. However, the P-gp inhibitor quinidine didn't change plasma concentrations of rilzabrutinib (PRN1008-024); thus, rilzabrutinib could be administered with P-gp inhibitors clinically.

In healthy volunteers, 400 mg of rilzabrutinib given simultaneously or two hours prior to the CYP3A substrate midazolam increased the AUC of midazolam by approximately 2-fold, classifying rilzabrutinib as a "weak CYP3A inhibitor" (PRN1008-011). Appropriate caution should be used when co-administering CYP3A "sensitive" substrates with rilzabrutinib, including an assessment of medical risk-benefit for each medication. Consideration should also be given to avoidance of high doses, dose reduction, or replacement of "sensitive" CYP3A substrate drugs. Rilzabrutinib is not an inhibitor of other CYP enzymes. Concomitant administration of rilzabrutinib immediate release (IR) tablet with a proton pump inhibitor, esomeprazole, decreased its exposure by approximately 50%. Concomitant administration of rilzabrutinib IR tablet with famotidine, a histamine 2 (H2) receptor antagonist, modestly reduced (by ~36%) its exposure. When rilzabrutinib IR tablet was dosed at least 2 hours prior to famotidine, no significant exposure change of rilzabrutinib was observed; hence, H2 receptor antagonists should be administered at least 2 hours after rilzabrutinib.

Additional details are provided in the current version of the rilzabrutinib (PRN1008) IB.

2.5. Study Design Rationale

Study PRN1008-018 is a randomized, double-blind, parallel-group, multicenter, placebo-controlled study with a blinded treatment period of up to 24 weeks followed by an open label period of 28 weeks, and a safety follow-up period of 4 weeks, which is intended to evaluate the efficacy and safety of oral rilzabrutinib in participants with refractory or relapsed ITP of >3 months duration in participants aged 18 years and above, and of >6 months duration in pediatric participants aged 12 to <18 years (see Appendix 10.7 for EU [EEA countries], where an age range of 10 to <18 years is applicable). Participants who are eligible at the end of the open label period can be considered for a long-term extension (LTE).

Placebo has been selected as the comparator to rilzabrutinib, as there are no globally approved medicinal products, other than CS (approved in EU but not United States [US]) that could serve as a suitably rapid-acting and active comparator. Use of placebo is ethical in this context, as participants who are on concomitant ITP medications (an oral CS and/or a thrombopoietin receptor agonist [TPO-RA]) will be eligible for the study. Participants have to have an inadequate response to these medications as evidenced by the average of two platelet counts below 30,000/µL (with no platelet count greater than 35,000/µL) and will have to maintained stable doses of these medications from 14 days before Study Day 1 and until the last dose of study medication. In addition, the use of rescue medications (limited to IVIg, anti-D, CS, and platelet infusion only) will be permitted to increase platelet counts or prevent bleeding when platelet counts are less than 20,000/µL, or for bleeding or wet purpura.

The marketed BTK inhibitor, ibrutinib, has been studied in combination with rituximab in the treatment of chronic lymphocytic leukemia without evidence of increased drug-related AEs (Burger 2017). There is no prior drug interaction potential between anti-CD20 biologic drugs and the small molecule rilzabrutinib.

The primary purpose of the 28-week, open label period is to allow access to study drug for participants who were on placebo medication as well as to evaluate durability of clinical response and accrue additional long-term data on the safety of rilzabrutinib.

The LTE is designed to further evaluate durability of clinical response and accrue additional long-term data on the safety of rilzabrutinib.

During the COVID-19 pandemic, measures to ensure continued drug supply and safety monitoring for participants are described in the "Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID- 19" (Appendix 8). These measures include remote study visits, enrollment procedures, direct to participant delivery of study medication and urine pregnancy tests, as well as handling of protocol deviations, and remote site monitoring (where allowed by local regulations).

Enrollment of pediatric participants

Inclusion of participants aged 10 to <18 years in the study is possible based on clinical and pathophysiological similarities between persistent/chronic ITP with adult participants. These similarities include presenting platelet counts (mean, 18.1×10^9/L in children and 25.4×10^9/L in adults), incidence and type of bleeding when platelet counts are $<20 \times 10^9$/L, family history of thrombocytopenia (2% in children and 3% in adults), rates of treatment (80% of children and 71% of adults at presentation and 58% of children and adults at 6 months, with similarly decreasing rates within both groups at 12 and 24 months) (Kühne 2001, Schifferli 2018) and similar late remission rates among children and adults with persistent and chronic ITP at 12 and 24 months (Schifferli 2018). Lowe and Buchanan confirmed that pediatric patients with ITP (age 10 to 18 years) had chronic disease with a chronicity rate up to 57%, which is higher than the rate of chronic ITP in younger children (<10 years of age) (Lowe 2002). Moreover, it has been reported that children diagnosed with ITP between 10 and18 years of age showed only a 32% recovery rate (Lowe 2002, Kühne 2003). The pathological mechanism of ITP (antibody-mediated platelet destruction) as well, is not different between children and adults. It can be expected that rilzabrutinib acts in the same way in adults and children with persistent/chronic ITP. It is well known that that the immune system matures and significantly changes throughout childhood (Blanco 2018, Comans-Bitter 1997, Simon 2015). The most significant changes were observed in the first 10 years of life (Duchamp 2014, Ghraichy 2020, Piatosa 2010). B-cells percentage declined between the ages of 6 months and 8 years, after which it remained stable at about 70-80%. Memory B-cells are already present at birth and their numbers increase throughout childhood, stabilizing between the ages of 12 and 18 years (Duchamp 2014). Literature reports indicate that total B-cell counts increase 2-fold immediately after birth, remain high until the age of 2 years, and then gradually decrease approximately 6.5-fold until adulthood (Blanco 2018). The percentage of naive B-cells among total B-cells decrease steadily from birth to the age of 12 years and the memory B-cell numbers stabilize between the ages of 12 to 18 years (Duchamp 2014). Total serum IgG levels gradually increase at early ages, and IgG3 and IgG1 levels reach adult like concentrations at 5 to 10 years of age (Blanco 2018). In addition, renal function and drug metabolizing enzymes are fully developed by age 12 (Fernandez 2011). Thus, the developmental immunological and physiological characteristics justify the inclusion of children ages 10 to <18 years in the current study.

2.6. Dose Rationale

A dosing regimen of 400 mg rilzabrutinib BID has been selected for evaluation in participants with ITP based on the observed safety and efficacy profile in Study PRN1008-005. In addition, Phase 1 dose-ranging data indicate that the plasma concentrations associated with this dose level are sufficient to maintain near-maximal BTK occupancy over the entire dosing interval, thereby robustly testing the efficacy of BTK inhibition.

Dose-response analyses conducted on preliminary data from Study PRN1008-010 indicate that the 400 mg rilzabrutinib BID dosing regimen was associated with a faster and more pronounced increase in platelet count compared to lower doses. After 28 days of rilzabrutinib treatment, increases in mean platelet count ranged from 7.59 × 10^9/L at the low dose of 200 mg once daily to 22.5 × 10^9/L at the high dose of 400 mg BID. In addition, patients treated with lower daily doses were less likely to achieve the primary endpoint (Kuter 2019). Patient responses were improved in patients who started the study at the 400 mg BID dose with 43.8% achieving the primary endpoint of 2 or more consecutive platelet counts, separated by at least 5 days of ≥50 × 10^9/L AND an increase of platelet count of ≥20 × 10^9/L from baseline (Kuter 2020). This evidence of treatment effect supports the evaluation of 400 mg BID in the Phase 3 PRN1008-018 study under this protocol.

The same dosing regimen (400 mg rilzabrutinib BID) has been selected for evaluation in pediatric participants (10 to <18 years of age) as the PK of rilzabrutinib are expected to be similar in pediatric participants (10 to <18 years old) and adults. Rilzabrutinib is metabolized by the CYP3A isoenzyme; the clearance of CYP3A substrates has been observed to be similar in adolescents and adults (Ginsberg 2002), suggesting that the clearance of rilzabrutinib will also be similar in adolescents (12 to <18 years old) and adults, and the adult and adolescent doses were found to be equivalent in the majority of approved drugs in a recent US Food and Drug Administration (FDA) survey (Momper 2013). A body weight ≥30 kg is added as inclusion criteria, to ensure the body weight of pediatric participants (10 to <12 years old) is within the 95% percentile body weight of pediatric participants at 12 years old, so that the PK exposure for participants 10 to <12 years is not anticipated to be higher than that for participants at 12 years old, and the same dose (400 mg BID tablet) could be used in the entire pediatric population (10 to <18 years old) (See Appendix 10.7). This dosing regimen is therefore expected to be associated with a comparable benefit-risk profile in adolescent participants with ITP relative to adult participants, and evaluation in this study may expedite the availability of an efficacious treatment to the adolescent population.

Please refer to the IB for more details.

2.7. Overall Risk-Benefit Assessment

2.7.1. Risk assessment

Based on the review of the cumulative data, as of 02 January 2024, with an estimated exposure of 1137 participants who received at least one dose of rilzabrutinib or placebo across multiple disease conditions (826 participants on rilzabrutinib with approximately 545 patient-years, estimated based on randomization ratio), there are no important identified risks for rilzabrutinib. The following are considered as important potential risks for rilzabrutinib:

- Serious infections
- Liver enzyme elevation
- Uveitis

Details of important potential risks together with a summary of the cumulative clinical safety data are provided below.

Table 4 - Risk assessment

Important Potential risk	Summary of data/rationale for risk	Mitigation Strategy
Serious infection	Rilzabrutinib may increase the risk of serious infection due to inhibition of human B-cell activation and antibody mediated activation of immune cells via FC receptor signaling. Refer to the latest IB for additional detail on the pharmacology of rilzabrutinib. As of 02-Jan-2024, the overall exposure was 1137 participants in Phase 2/3 studies (rilzabrutinib/ placebo) in whom 2 SUSARs of serious infections have been reported in studies of pemphigus (n=1) and ITP (n=1). Most patients have recovered while on treatment with either rilzabrutinib or blinded IMP and cases are confounded by underlying disease and/or treatment with high dose corticosteroids. No imbalance observed between rilzabrutinib arm and the placebo arm for participants treated for Pemphigus (10-May-2022) and CSU (19-Jul-2023). No serious infections were observed in the atopic dermatitis randomized controlled clinical trial (20-Jul-2023). A causal association between IMP and these conditions has not been established.	• Participants with evidence suggestive of active tuberculosis or non-tuberculous mycobacterial infections are excluded. • Participants with a history of serious infection requiring IV therapy within 4 weeks of randomization or with active moderate-to-severe infections at screening are excluded. • Risk management includes screening, regular monitoring, and identification of early signs of infections (HBV, HCV, HIV, or active COVID-19) or with active moderate-to-severe infection. • Routine collection of AEs • Designation of severe or serious infection as an AESI
Liver enzyme elevation	As of 02-Jan-2024, the overall exposure was 1137 participants in Phase 2/3 (rilzabrutinib/ placebo) studies in whom 26 events of elevations of liver enzymes have been observed in studies with pemphigus, ITP, Asthma, CSU, AD, and IgG4-RD participants. The majority were of mild/moderate severity; few events resulted in interruption of IMP. Most patients had alternative etiologies or confounding factors for the elevations observed. As of 02-Jan-2024, there is insufficient evidence for a causal relationship between liver enzyme elevations and rilzabrutinib. There were no Hy's Law or hepatic failure cases reported.	• Participants with AST/ALT > 1.5 × ULN or total bilirubin >1.5 × ULN are excluded. • Participants with acute or chronic liver disease (other than the disease under investigation) are excluded. • Routine collection of AEs • Routine monitoring of AST, ALT, and total bilirubin • Designation of ALT > 3 × ULN as an AESI and suggested actions and follow up assessments.

Important Potential risk	Summary of data/rationale for risk	Mitigation Strategy
Uveitis	As of 02-Jan-2024, the overall exposure was 1137 participants in Phase 2/3 (rilzabrutinib/ placebo) studies in which cases of uveitis (n=5) occurred, including 2 Vogt-Koyanagi-Harada disease (VKHD) cases. The events of uveitis were observed in different indications across the rilzabrutinib program in studies of pemphigus (n=2), ITP (n=1), and CSU (n=2). All events resolved; 4 of the 5 events resolved with treatment, while continuing rilzabrutinib. A definitive causal association between rilzabrutinib and these ocular conditions has not been established.	• Participants are advised to report new onset or worsening eye symptoms to the site study doctor in ICF. • Inclusion of eye-assessment in all physical examinations • Designation of uveitis as an AESI • Examination by an ophthalmologist should be considered for patients who develop ocular symptoms, eg, eye erythema, pain, or blurred vision suggestive of uveitis, as appropriate.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; ALT=alanine aminotransferase; BID=twice daily; BTK=Bruton's tyrosine kinase; CMV=Cytomegalovirus; COVID-19=Coronavirus disease 2019; CSU=chronic spontaneous urticaria; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; ITP=immune thrombocytopenic purpura; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; SUSAR=suspected unexpected serious adverse reaction; ULN=upper limit normal.

2.7.1.1. Potential risks reported with other BTK inhibitors

There are AEs that have been reported during the administration of other drugs from the same therapeutic class (BTK inhibitors) as rilzabrutinib, however primarily for oncologic indications, including B-cell malignancies (Lipsky 2020).

These Class Effect AEs include:

- Cytopenia
- Bleeding
- Atrial fibrillation

Rilzabrutinib has characteristics that may solve many of the selectivity- and reversibility-related concerns accompanying currently available BTK inhibitors. Rilzabrutinib binds in a covalent manner, increasing selectivity by forming a chemical bond to a specific cysteine residue present in BTK. This durable covalent engagement allows for maximal efficacy. However, rilzabrutinib's unique binding mechanism provides the opportunity for a tailored residence time while reducing safety concerns associated with irreversible inhibitors such as ibrutinib and acalabrutinib (Langrish 2021).

There are important differences between the background safety risk profiles of chronic autoimmune and/or inflammatory disease populations versus the oncologic population (where these events have been observed). Taken together, it is postulated that there is a low probability of occurrence of the above-mentioned "BTK inhibitor class" AEs during the administration of rilzabrutinib.

2.7.2. Benefit assessment

ITP is associated with an increased risk of mortality due to bleeding, thrombosis, and reduced quality of life (QOL) (Trotter and Hill 2018). The disease burden is more significant in patients with severe and chronic thrombocytopenia and those who are unresponsive to current therapy. Patients with such severe thrombocytopenia have a high risk of hemorrhage which increases with age. Intracranial hemorrhage is the major cause of death which is reported to occur in 1.5% of adult patients (Neunert et al 2015). Besides the high risk of bleeding, patients with chronic ITP experience significant fatigue, cognitive impairment, fear of bleeding and a negative impact on social and work activities (Frith et al 2012; Trotter and Hill 2018). Treatment with rilzabrutinib may induce durable platelet response in participants not responsive to prior therapies.

2.7.3. Overall benefit: risk conclusion

The safety of rilzabrutinib to date (02-Jan-2024), and the resulting benefit risk balance profile, supports the continued investigation in participants with ITP. There is no important identified risk associated with the use of rilzabrutinib. The important potential risks of "increased risk for serious infections", "liver enzyme elevation", and "uveitis" have been characterized and appropriate risk mitigation procedures have been defined. The AEs seen with other BTK inhibitors (cytopenia, bleeding, atrial fibrillation) will continuously closely monitored and their risk-evaluation will continuously be reassessed, and if needed mitigations will be adjusted as the safety profile matures. Overall, benefit/risk balance is in favor of continuing evaluation of rilzabrutinib in patients with persistent or chronic ITP.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Efficacy Objectives

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 during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy

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

See Appendix 10.7 for EU (EEA countries) and UK-specific requirements.

3.1.2. Other Secondary Objectives

See Appendix 10.7 for EU (EEA countries) specific requirements.

3.1.2.1. Efficacy Objectives

- To evaluate the stability of platelet response of rilzabrutinib

3.1.2.2. Safety Objectives

- To evaluate the safety and tolerability of rilzabrutinib in pediatric participants (≥10 years – <18 years) and in adult participants (≥18 years) with refractory/relapsed ITP

3.1.2.3. Pharmacokinetic Objectives

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

3.1.2.4. 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

3.2. Endpoints

3.2.1. Primary Efficacy Endpoint (Blinded Treatment Period)

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 (See Appendix 10.7 country-specific definition of durable platelet response (EU [EEA countries] and UK).

3.2.2. 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

See Appendix 10.7 for EU (EEA countries) and UK-specific requirements.

3.2.3. Other Secondary Endpoints

3.2.3.1. 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).

3.2.3.2. Safety Endpoints

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

3.2.3.3. Pharmacokinetic Endpoints

- Plasma concentrations of rilzabrutinib

3.2.3.4. 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

3.2.4. Exploratory Endpoints

3.2.4.1. 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 TPO-RAs)
- Change from baseline in ITP Bleeding Scale (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 (EuroQOL-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
- PK parameters as assessed by population pharmacokinetic analysis
- BTK occupancy
- Changes from baseline in TPO levels, T-lymphocytes/ B-lymphocytes/natural killers (T/B/NK) counts, immunoglobulin (IgG, IgG1, IgG4, IgM, IgE) levels
- (Optional) Vaccine-specific IgG response during treatment

See Appendix 10 (Appendix 10.5) for China-specific requirements.

3.2.4.2. 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 of 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 on the Psychological, Fear, Social Activity, Women's Reproductive Health and Work domains of the ITP-PAQ in adult participants (≥18 years)
- Change from baseline in QOL as measured by the EuroQOL-Dimensions-5 Level in adult participants (≥18 years)

- Percent change from baseline on 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

See Appendix 10 for country-specific requirements of endpoints.

4. STUDY DESIGN

This is a global, randomized, parallel-group, double-blind, multicenter clinical study in patients with primary ITP who had a response to either IVIg or CS that was not sustained.

After providing informed consent, participants will enter a 28-day screening period. Upon completion of the screening period, participants who satisfy all the inclusion criteria and none of the exclusion criteria of this protocol will be randomized in a 2:1 allocation ratio to one of two study arms: rilzabrutinib or placebo. 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 factors used for stratification (for adult participants), or balance (for pediatric participants) are splenectomy status (yes/no), and by severity of thrombocytopenia (Inclusion Criteria #3 platelet counts <15,000/μL or ≥15,000/μL).

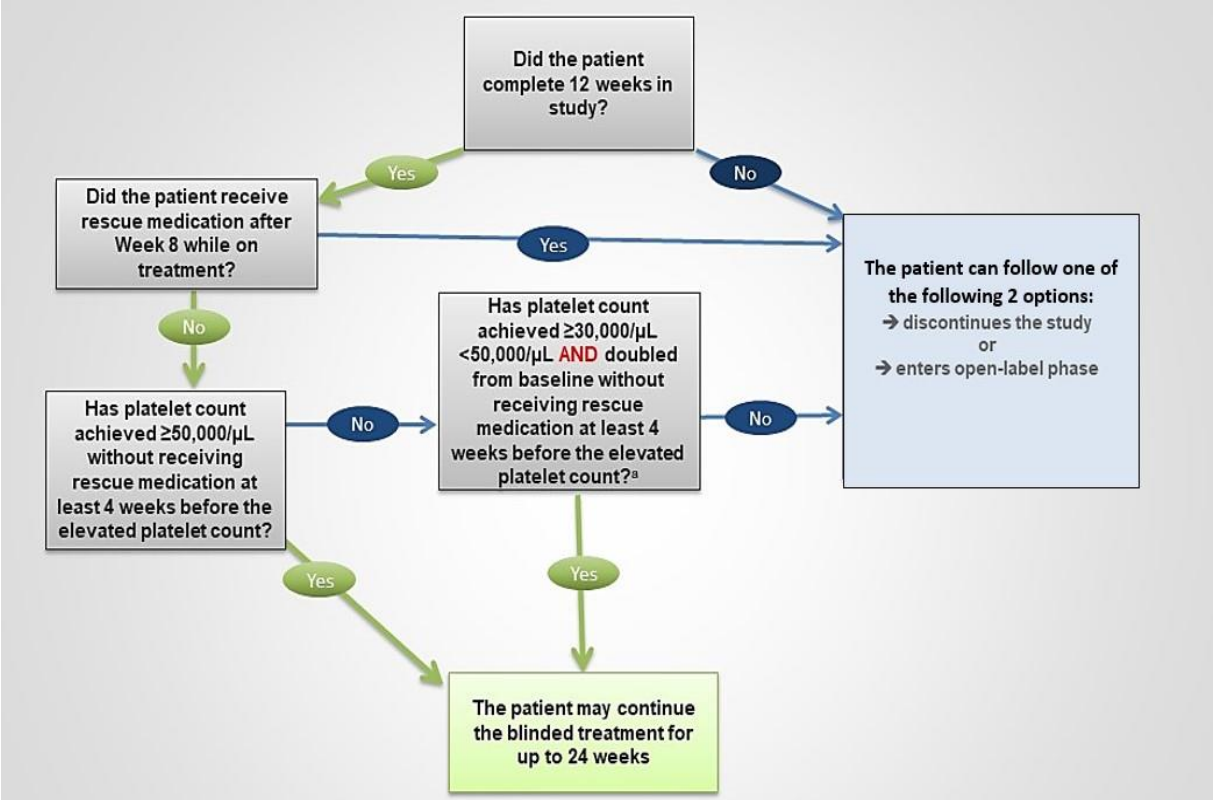
After randomization, participants will start a blinded treatment period of up to 24 weeks followed by an open label period of 28 weeks during which all participants will receive rilzabrutinib, and then a 4-week safety follow-up period or LTE.

At the end of 12 weeks of treatment, participants will be assessed for achieving a platelet response defined as a) platelet count of ≥50,000/μL OR a platelet count of between ≥30,000/μL and <50,000/μL and at least doubled from baseline at any time during the first 12 weeks and b) absence of rescue medication in the 4 weeks prior to the elevated platelet count that meets platelet response criteria.

Figure 1 depicts the decision process for assessing response. The baseline value of platelet count is defined as the average of all the participant's Predose platelet counts (Screening and Study Day 1).

- Participants who respond will continue the blinded treatment period for a total of 24 weeks before entering the open label period.
- Participants who do not respond (including participants who receive rescue medication after 8 weeks of treatment) may discontinue from the study or enter the 28-week open label period at the end of Week 12, receiving treatment with 400 mg BID of rilzabrutinib. The Initial study medication assignment will remain blinded.

Figure 1 - Decision tree for assessing response at Week 13



During the blinded treatment period (Week 13 to Week 24):

- Participants who discontinue from the blinded treatment period due to safety or other reasons and choose to join the open label period will undergo the Week 25 assessments at their next scheduled visit.

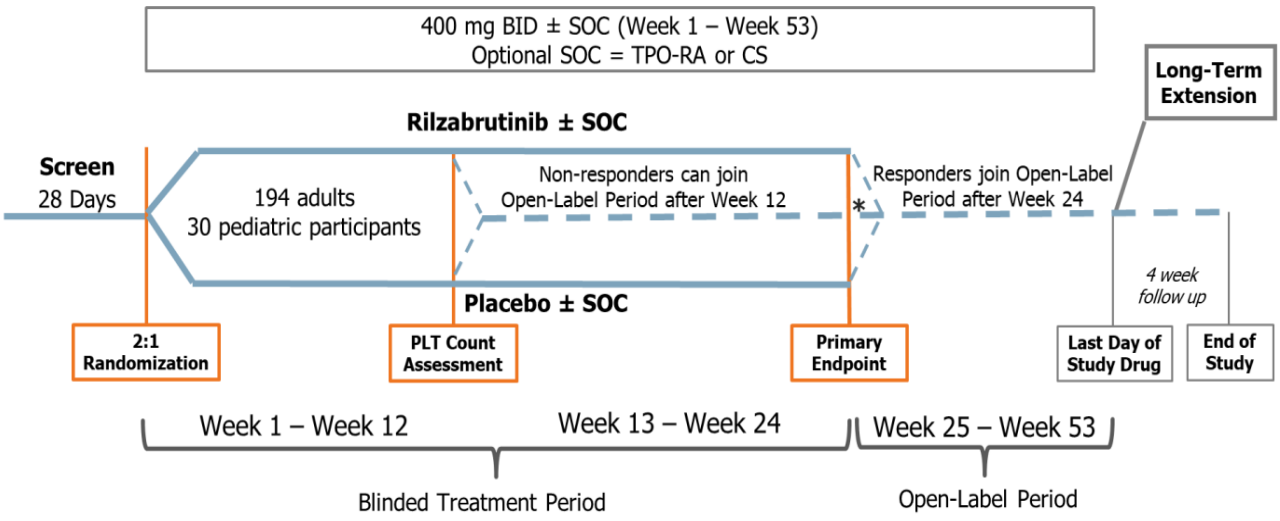
Participants who discontinue the blinded treatment period and choose not to join the open label period, should attend an Early Termination (ET) visit as shown in the Schedule of Assessments (SoA) (Table 1) for collection of data at the time of study discontinuation and complete the follow-up (EOS visit) and any further evaluations in need of completion.

Concomitant ITP medications (an oral CS and/or a TPO-RA) will be permitted in both treatment arms and must be maintained at stable doses from 14 days before Study Day 1 and until the last dose of study medication. Reductions in the doses of concomitant ITP medications will be permitted for associated safety concerns only. In the LTE portion of the trial, reductions in dose or withdrawal of concomitant ITP medications (an oral CS and/or a TPO-RA) will also be permitted if the participant achieves platelet count of ≥50,000/µL in three scheduled visits (over 12 weeks). Retreatment with the same medication(s) and doses of ITP concomitant medication(s) used at baseline (an oral CS and/or a TPO-RA), changing the dose or initiation of new ITP

medications (an oral CS and/or a TPO-RA) will also be allowed. Tapering of concomitant CS should be performed in accordance with the schedule in Section 6.6.2.

The use of rescue medications (one of IVIg, high-dose CSs, platelet infusion, or 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, will be allowed.

Figure 2 - Study Design Flow Chart



* Week 25 visit is the last visit of the blinded treatment period and also serve as the start of the open-label period.

Note: Responders will join start open-label period at Week 25.
Non-responders in blinded treatment period can join open-label period directly after Week 12.

BID = twice daily; CS = corticosteroid; PLT = platelet; SOC = standard of care; TPO-RA = thrombopoietin receptor agonist.

After completing the open label period, participants who demonstrate a platelet response defined as platelet counts ≥50,000/µL or ≥30,000/µL and at least doubled from baseline at ≥50% of the visits without receiving rescue therapy while on treatment during the last 8 weeks of the open label period, will be allowed to enter the LTE.

Participant(s) may continue in the LTE until:

a) The participant is no longer responding (platelet counts <30,000/µL or less than 20,000/µL above baseline on two consecutive visits)
b) The drug is no longer being developed by the Sponsor for ITP
c) The program is stopped for safety reasons or
d) The drug becomes commercially available in the participant's country

Safety Measures Due to coronavirus (COVID-19) Pandemic

Due to the COVID-19 pandemic, safety measures have been implemented to ensure continued supply of study medication and safety monitoring for participants. These measures are described in the "Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19." When the COVID-19 pandemic resolves, the measures will be repealed back to the previous state as government rules and benefit/risk assessment allow.

4.1. Duration of Study Participation

For each participant, the study will last up to 60 weeks from the start of the screening period to the End of Study (EOS) visit. This includes screening (up to 4 weeks) through a 12 to 24-week blinded treatment period followed by a 28-week open label period. There is a 4-week postdose follow-up.

For adult participants, the maximum duration of the LTE period will be 12 months from the date of the last adult participant to enter the LTE.

For pediatric participants, the maximum duration of the LTE period will be 12 months from the date of the last pediatric participant to enter the LTE.

4.1.1. Screening (Day -28 to Study Day-1 Predose)

- Informed consent
- Verify participant meets Inclusion/Exclusion criteria (use screening lab results for eligibility determination, with the exception of hemoglobin, which is to be rechecked prior to dosing on Day 1)
- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient QOL questionnaires
- Record concomitant medications
- Record height (cm)
- Record weight (kg)
- Conduct full physical examination and medical history
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect 12-lead single ECG
- Collect urine sample for urinalysis
- Collect hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) blood samples
- Collect QuantiFERON-Tuberculosis (TB) blood sample
- Collect serum blood sample pregnancy test (women of childbearing potential)
- Collect follicle-stimulating hormone (FSH) blood sample (postmenopausal woman only)

- Collect ABO and Rh Blood Type blood sample (historical results may be used)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, red blood cells [RBCs], platelets, mean platelet volume, white blood cells [WBCs] with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total, direct, and indirect bilirubin levels, alkaline phosphatase [ALP], albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random]); creatinine phosphokinase (CPK) and estimated glomerular filtration rate (eGFR) (See Appendix 10 for country-specific requirements) to be performed at screening only
  - Coagulation (prothrombin time [PT]/international normalized ratio [INR], thrombin time, activated partial thromboplastin time [aPTT], fibrinogen level)
- Record AEs
- Perform SARS-CoV-2 molecular test (if COVID-19 testing is required per local guidelines to be determined for each site).
- For country-specific requirements please refer to Appendix 10.

4.1.2. Blinded Treatment Period (Weeks 1 to 25)

Day 1 Week 1:

- Verify participant still meets Inclusion/Exclusion criteria (use screening lab results for eligibility determination) and randomize eligible participants to treatment
- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L, and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination; See Appendix 10.6 for Italy-specific requirements
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect 12-lead single ECG
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])

  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect PK blood samples
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts
  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - BTK occupancy (at select sites)
  - (Optional) vaccine-specific IgG response
- Dispense rilzabrutinib or placebo
- For country-specific requirements please refer to Appendix 10.

Week 5:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts

  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib or placebo
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Week 9:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - TPO levels
  - Hemolysis panel
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib or placebo
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Week 13:

- Assess participant response to determine continuation in blinded treatment period or move to the open label period, if participant is moved to open label period, please proceed to Section 4.1.3.
- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record height (cm) - pediatric participants
- Record weight (kg)
- Conduct abbreviated physical examination
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials, [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect PK blood sample - Predose only
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts
  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - BTK occupancy (at select sites) - Predose only
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib or placebo
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Week 17 and Week 21:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - TPO levels
  - Hemolysis panel
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib or placebo
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

4.1.3. Open Label Period (Weeks 25 to 53)

Week 25 (First Day of Open Label Period):

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record height (cm) - pediatric participants
- Record weight (kg)

- Conduct abbreviated physical examination; See Appendix 10.6 for Italy-specific requirements
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect 12-lead single ECG
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect PK blood sample
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts
  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - BTK occupancy (at select sites)
  - (Optional) vaccine-specific IgG response
- Collect and reconcile all study medications
- Dispense open label rilzabrutinib
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Week 29:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination

- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts
  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Week 33:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaire
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)

- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts
  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Week 37:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record height (cm) - pediatric participants
- Record weight (kg)
- Conduct abbreviated physical examination
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials, [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)

- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - TPO levels
  - Hemolysis panel
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Week 41:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts
  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib

- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Weeks 45 and 49:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - TPO levels
  - Hemolysis panel
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

Week 53 (Last Day of Open Label Period):

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaires
- Record concomitant medications
- Record AEs
- Record height (cm) - pediatric participants

- Record weight (kg)
- Conduct abbreviated physical examination; See Appendix 10.6 for Italy-specific requirements
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect 12-lead single ECG
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect PK blood sample
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts
  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - BTK occupancy (at select sites)
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib if entering Long-Term Extension
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

4.1.4. End of Study visit (Four Weeks Post Last Dose of Study Drug)

The following assessments will be performed four weeks post last dose of study drug in the double blind, open label period, or LTE:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaire
- Record concomitant medications
- Record AEs

- Record weight (kg)
- Conduct full physical examination; See Appendix 10.6 for Italy-specific requirements
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect 12-lead single ECG
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level)
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts
  - TPO levels
  - Hemolysis panel
  - Immunoglobulin levels
  - (Optional) vaccine-specific IgG response
- For country-specific requirements please refer to Appendix 10.

4.1.5. Long-Term Extension (LTE)

The following assessments will be performed at each visit during the LTE:

- Complete ITP-PAQ or ITP-KIT, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC patient questionnaire (every 3 months only)
- Record concomitant medications
- Record AEs
- Record weight (kg)
- Conduct abbreviated physical examination; See Appendix 10.6 for Italy-specific requirements
- Complete IBLS
- Capture vital signs (body temperature, respiratory rate, blood pressure, and pulse rate)
- Collect urine sample for urinalysis

- Conduct urine pregnancy test (women of childbearing potential)
- Collect clinical laboratory blood samples:
  - Hematology (hemoglobin, hematocrit, RBCs, platelets, mean platelet volume, WBCs with differentials [neutrophils, eosinophils, basophils, lymphocytes, and monocytes])
  - Serum chemistry (AST, ALT, bilirubin, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, and glucose [random])
  - Coagulation (PT/INR, thrombin time, aPTT, fibrinogen level) - only if needed to follow-up on bleeding related AEs
- Collect exploratory laboratory blood samples (see Appendix 10 for country-specific requirements):
  - T/B/NK counts (every 6 months only)
  - TPO levels
  - (Optional) vaccine-specific IgG response
- Reconcile all study medications and dispense rilzabrutinib
- Collect Patient Medication Diary
- For country-specific requirements please refer to Appendix 10.

See Section 4.1.4 for the End of Study visit assessments in LTE period.

Completion for the overall clinical study is defined as the point at which the last participant has completed the last visit of the study.

4.2. Study Population

Participants with refractory or relapsed ITP of >3 months duration (age 18 years and above) or with >6 months duration (age 12 to <18 years; see Appendix 10.2, Appendix 10.3, and Appendix 10.7 for country-specific age ranges).

4.3. Study Assessments Overview

See Figure 2 for a diagram of the study design and the Schedules of Assessments (Table 1, Table 2, and Table 3) and for description of the assessments.

5. ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

Participants may be included in the study if ALL of the following criteria are met:

1. Participants will be male and female with primary ITP with duration of >6 months in pediatric participants aged 12 to <18 years (pediatric participants aged 10 to <12 years will be enrolled in the EU [EEA countries] only; refer to Appendix 10.2, Appendix 10.3, and Appendix 10.7 for country-specific requirements) and duration of >3 months in adults aged ≥18 years
2. Participants who had a response (achievement of platelet count ≥50,000/μL) to IVIg/anti-D or CSs that was not sustained and who have documented intolerance, insufficient response, or any contraindication to any appropriate courses of standard of care ITP therapy
3. An average of 2 platelet counts at least 5 days apart of <30,000/μL during the screening period and no single platelet count >35,000/μL, within 14 days prior to the first dose of study drug
   - Pediatric participants must additionally be determined to need treatment for ITP as per clinical assessment by the Investigator (see Appendix 10.7 for EU [EEA countries] specific criteria)
4. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 × 10^9/L, AST/ALT ≤1.5 × upper limit of normal (ULN), albumin ≥3 g/dL, total bilirubin ≤1.5 × ULN [unless the participant has documented Gilbert syndrome], estimated glomerular filtration rate (GFR) >50 [Cockcroft and Gault method for adult and Bedside Schwartz Equation for Pediatric participants])
5. Hemoglobin >9 g/dL within 1 week prior to Study Day 1
6. All contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   A) Male participants

   Male participants are eligible to participate if they agree to the following during the intervention period and for at least 13 weeks after the last administration of study intervention:

   - Refrain from donating or cryopreserving sperm

   Plus, either:

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

     OR

   - Must agree to use contraception/barrier as detailed below
     - A male condom; the participant should also be advised of the benefit for a female partner to use a highly effective method of contraception (as described in Appendix 13 Contraceptive and barrier guidance) of the protocol as a

condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

B) Female participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 13 of the protocol.

OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Appendix 13 of the protocol, during the study intervention period (to be effective before starting the intervention) and for at least 4 weeks after the last administration of study intervention AND agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- A WOCBP must have a negative highly sensitive pregnancy test (serum) as required by local regulations) within 3 days before the first administration of study intervention
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

7. Participants must be able to provide written informed consent or informed assent with corresponding informed consent obtained from the participants' guardian and agree to the SoA.

5.2. Exclusion Criteria

Participants will be excluded from the study if any of the following criteria are met:

1. Participants with secondary ITP
2. Pregnant or lactating women
3. Electrocardiogram (ECG) findings for participants:
   - Aged ≥10 and <16 years: QTcF >449 msec (males) or >457 msec (females)
   - Aged ≥16 and <18 years: QTcF >450 msec (males) or >460 msec (females)
   - Aged ≥18 years, of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic participants or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities
4. History (within 5 years of Study Day 1) or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the study, with the exception of non-melanoma skin cancer
5. Transfusion with blood, blood products, plasmapheresis, or use of any other rescue medications with intent to increase platelet count within 14 days before Study Day 1

6. Change in CS and/or TPO-RA dose within 14 days prior to Study Day 1 (more than 10% variation from current doses)
7. Immunosuppressant drugs other than CSs within 5 times the elimination half-life of the drug or 14 days of Study Day 1, whichever is longer
8. Treatment with rituximab or splenectomy within the 3 months prior to Study Day 1
    - Participants treated with rituximab will have normal B-cell counts prior to enrollment
9. Ongoing need for the use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change participant to H2 receptor blocking drugs prior to Study Day 1)
10. Use of known strong-to-moderate inducers or inhibitors of CYP3A within 14 days or 5 half-lives (whichever is longer) of Study Day 1 and until the end of the active treatment period
11. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin (except for low dose aspirin up to 100 mg per day), nonsteroidal anti-inflammatory drugs, and/or thienopyridines within 14 days of Study Day 1 and until the end of the active treatment period
12. Has received any investigational drug within the 30 days before receiving the first dose of study medication, or at least 5 times elimination half-life of the drug (whichever is longer); participant should not be using an investigational device at the time of dosing
    - Participants who previously received treatment with BTK inhibitors (except rilzabrutinib) within 30 days before the first dose of study drug are not eligible
    - Participants who previously received rilzabrutinib at any time are not eligible
13. Current drug or alcohol abuse
14. Refractory nausea and vomiting, malabsorption, external biliary shunt, significant bowel resection, or any other condition that would preclude adequate study drug absorption
15. History of solid organ transplant
16. Positive at Screening for HIV, HBV (surface and core antibodies unrelated to vaccination), or HCV (anti-HCV antibody confirmed with Hep C RNA)
    - Participants who are HBV surface antigen (HBsAg) positive will not be eligible
    - Participants who are HBsAg negative and HBV core antigen antibody (HBcAb) positive will be tested for HBV surface antibody (HBsAb) and HBV DNA. If HBV DNA is negative and HBsAb titer is ≥100 IU/L, participants may be enrolled. Monthly HBV DNA monitoring will be required while on treatment and for 6 months after the last dose of the study drug. Positive HBV DNA results will be managed appropriately as per local standard of care
    - Participants who are HBcAb positive, HBsAg negative with HBsAb titer <100 IU/L or negative, are not eligible
17. Positive QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus) at Screening unless all of the following 3 conditions are true (see Appendix 10 country-specific requirements):

a) Chest X-ray does not show evidence suggestive of active TB disease

b) There are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease

c) Documented receipt of one of the following prophylactic treatment regimens:

i. Oral daily Isoniazid for 6 months or

ii. Oral daily Rifampin for 4 months or

iii. Isoniazid and Rifapentine weekly for 3 months (3HP)

On a case-by-case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to 1 of the above tests may be used for eligibility. For example, if a QuantiFERON-TB Gold, or QuantiFERON-TB Gold Plus (QFT Plus) is indeterminate for any reason and a local blood test or T-Spot® TB test is negative, the participant may be enrolled using the local result upon approval of the Sponsor.

18. History of recurring (2 or more) serious infections requiring intravenous antibiotic, antivirals, or antifungals therapy within the last 3 months before Study Day 1 or active serious or moderate infection ongoing on the day of randomization
19. Myelodysplastic syndrome
20. Live vaccine within 28 days prior to Study Day 1 or plan to receive one during the study
21. Planned surgery in the time frame of the dosing period
22. Any other clinically significant disease, condition, known allergy to any of the study medication, their analogues, or excipients in the various formulations of any agent (please see Section 6.1.1 for information on excipients), or medical history that, in the opinion of the Investigator or Sponsor's medical monitor, would interfere with participant safety, study evaluations, and/or study procedures
23. Positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) molecular test (if COVID-19 testing required per local guidelines to be determined for each site)
24. The COVID-19 vaccine within 14 days prior to Study Day 1 or planned during the last 12 weeks of blinded treatment period

6. TREATMENTS

6.1. Treatments Administered

6.1.1. Rilzabrutinib/Placebo

Each rilzabrutinib tablet contains 400 mg of rilzabrutinib and is orange in color. In addition, the tablet contains Microcrystalline Cellulose (filler), Crospovidone (disintegrant), Sodium Stearyl Fumarate (lubricant) and a non-functional film coating. Each tablet is coated with a light orange film coat (Opadry II 85F130006) containing polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and FD&C yellow #6.

The placebo treatment is a tablet that is identical in appearance and contains the same inactive ingredients as that of the rilzabrutinib study medication but does not contain rilzabrutinib. In addition, the inactive ingredient mannitol has been added as a filler to replace rilzabrutinib.

6.1.1.1. Packaging

Rilzabrutinib drug product or placebo will be supplied to the clinical sites in bottles. Each bottle will contain 70 tablets or a 5-week supply of rilzabrutinib or placebo.

6.2. Preparation and Administration

6.2.1. Rilzabrutinib/Placebo

No preparation of the rilzabrutinib or placebo study medication will be needed. Participants will use the study medication directly from the dispensed bottles.

Study medication will be taken BID by mouth starting on Day 1. Rilzabrutinib or placebo may be taken with or without food. The frequency and/or severity of GI AEs may be improved if rilzabrutinib/placebo is taken with food. Consecutive rilzabrutinib/placebo doses should not be taken within 8 hours of each other. Tablets should not be broken or crushed. Further details for dispensation and administration of blinded treatment are provided in the Pharmacy Manual.

6.3. Storage

6.3.1. Rilzabrutinib/Placebo

Rilzabrutinib or placebo tablets are supplied in 100cc bottles. The recommended storage condition is 2 to 25°C (IB).

6.4. Drug Management

Drug management will be the responsibility of the Investigator of the medical institution. The Investigator, the pharmacist of the medical institution, or another designated person must complete, in real time, all the documents concerning treatment management. Treatment management will be verified on a regular basis by the study monitor.

The study medication should be used only by healthcare professionals who are qualified by training and experience in the safe use and handling of investigational drugs.

During the COVID-19 pandemic, drug supply can be sent to participants when the participant is not able to travel to the site or the site cannot host a participant visit. Site instructions for shipment of supplies directly to participants and procedures for conducting remote site visits inclusive of ensuring drug supply maintenance are described in "Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" (Appendix 8).

6.4.1. Drug Accountability

The Investigator or his/her designated representatives will dispense study medication per the SoA (Table 1, Table 2, and Table 3).

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (eg, Drug Receipt Record) and disposition (eg, Investigational Drug Dispensing Log) of the study medication must be maintained. The Investigational Drug Dispensing Log must be kept current and should contain the following information:

- The identification (ID) of the participant to whom the study medication was dispensed (that is, participant ID number, and year of birth)
- The date(s), quantity, and lot number(s) of the study medication dispensed to the participant
- The ID of the person who dispensed the study medication

All used and unused drug supplies must be returned by the participant at every visit.

All records and used and unused drug supplies must be available for inspection by the study monitor at every monitoring visit. Reconciliation of all drug supplies (rilzabrutinib or placebo) will be performed by the study monitor.

6.4.2. Destruction of Investigational Medicinal Product

When the study is completed, any used and unused study medication (eg, empty, partially used, and unused containers) will be destroyed on-site or returned to the depot of destruction as requested. Copies of the completed Drug Dispensing Log and Drug Return Record(s) will be returned to the Sponsor. The Investigator's copy of the Drug Return Record(s) must accurately document the return of all drug supplies to the Sponsor.

Local or institutional regulations may require immediate destruction of used investigational medicinal product (IMP) for safety reasons. In these cases, it may be acceptable for investigational study center staff to destroy dispensed IMP before a monitoring inspection, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed, and provided that adequate storage and integrity of drug has been confirmed. Written authorization must be obtained from the Sponsor or Sponsor designee after final accountability prior to destruction.

Unused study medication from the site that has not been stored properly should not be destroyed until the monitor and/or Sponsor approve the destruction.

No destruction of unused (not dispensed) IMP takes place without Sponsor's written authorization. Storage conditions must be kept until approval from the Sponsor to remove the product from its storage location (eg, refrigerator). Products must be kept in a dedicated quarantine area until destruction, with a clear sign of "quarantined" until the Sponsor's Site Monitor authorizes the destruction.

Written documentation of destruction must contain the following:

- Identity of IMP(s) destroyed
- Quantity of IMP(s) destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed the IMP

If a site does not have a destruction SOP, study drug can be returned to the depot.

6.4.3. Treatment Compliance

Accountability and participant compliance will be assessed by maintaining adequate study medication dispensing records and medication counts. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. See Section 6.4.1 for instructions on Drug Accountability procedures.

6.4.4. Treatment Blinding/Unblinding

Allocation of participants to treatment groups will proceed through the use of an interactive web response system (IRT/IWRS) that is accessible 24 hours a day, 365 days a year.

- The randomized intervention kit number list is generated centrally by the IRT/IWRS.
- The randomization and intervention allocation are performed centrally by the IRT/IWRS. The IRT/IWRS generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.
- A randomized participant is a participant from the screened population who has been allocated to a randomized intervention by the IRT/IWRS regardless of whether the intervention was received or not.

The pharmacist or designee will be required to enter or select information that will include, but not be limited to; the user ID, and password, participant number, participant year of birth, as well as other information (as allowed locally). The pharmacist or designee will then be provided with a participant randomization number and treatment assignment. Once participant numbers and randomization numbers have been assigned, they cannot be reassigned. The randomization system will also send confirmation of the randomization, by email or fax, to the user. Specific instructions will be provided in the IWRS study reference guide. Access to the randomization code will be limited; all Sponsor personnel (and representatives), and site personnel who are directly involved in the conduct of the study will be blinded to randomization codes.

The treatment each participant receives will not be disclosed to the Investigator, study center personnel, participants, or the Sponsor or representatives on the clinical study team. Further details for blinding and dispensing of blinded treatment are provided in the Pharmacy Manual.

If deemed by the Investigator to be medically necessary, the Investigator can unblind a participant via the IWRS after consultation with Sponsor medical monitor (See Appendix 10 for UK country-specific requirements).

Sponsor PV operations/responsible third party may unblind the intervention assignment for any participant with a suspected unexpected serious adverse reaction (SUSAR). If the SUSAR requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

At the facilities where the systemic drug concentration measurements and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team. One programmer may be unblinded to prepare the dataset for population PK analysis, and there will be strict procedures to maintain blind beyond the programmer.

6.5. Treatment of Overdose

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as a single ingestion of a dose equal to or greater than 1200 mg (≥3 times the indicated single dose of 400 mg) provided that it has been taken at once or over a 2-hour period. No specific information is available on the treatment of overdose of rilzabrutinib.

In the event of an overdose, the Investigator/treating physician should:

1. Evaluate the participant to determine, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until rilzabrutinib can no longer be detected systemically (at least 20 hours).
3. Obtain a plasma sample for PK analysis within 20 hours from the date of the last dose of study intervention if possible.
4. Document appropriately in the eCRF

6.6. Concomitant Medications

6.6.1. Prohibited Medications

The following medications are prohibited for use during the study:

- Concomitant use of any ***immunosuppressant medication***, other than CS, as described in this protocol. Participants who need other immunosuppressant therapy during the study must be withdrawn. See Exclusion # 7, Section 5.2 for washout periods
- Concomitant use of known ***strong-to-moderate inducers or inhibitors of cytochrome P450 (CYP) 3A***. See Exclusion # 10, Section 5.2 for washout periods

- ***Proton pump inhibitors*** are not permitted. Esomeprazole was shown to reduce the exposure of rilzabrutinib by approximately 50%, presumably due to the effects of a lack of an acidic environment on tablet dissolution. Participants who are on proton pump inhibitors should be changed to H2 receptor blocking drugs if possible or not enroll in the study. Details of H2 receptor blocker administration is provided in Section 6.6.2. See Exclusion # 9, Section 5.2.
- ***Rescue medications*** other than one of IVIg, high-dose CSs, platelet infusion, or anti-D immunoglobulin infusion intended to increase platelet counts or prevent bleeding when platelet counts are less than 20×10^9/L, or for bleeding or wet purpura, are not permitted
- ***COVID-19 vaccine*** is prohibited during the last 12 weeks of the blinded treatment period.
- **Live vaccines** are not permitted during the study.

6.6.2. Particular Permissible Medications

The following medications are permitted for use during the study:

- ITP medications, an oral CS and/or a TPO-RA (authorized for the treatment of ITP)

  Note:

  - These medications must be maintained at stable doses from 14 days before Study Day 1 and until the last dose of study medication. Adjustments in the doses of concomitant ITP medications will be permitted for associated safety concerns only.
  - Administration of corticosteroids and TPO-RAs should follow corresponding updated package inserts/SmPCs of the marketing authorization.
  - Tapering is allowed during LTE period only due to achieving durable platelet response, and would follow the following guidelines with 2 weekly platelet counts between tapers:
    - 10 mg/day every one to two weeks from an initial dose >40 mg of prednisone or equivalent per day
    - 5 mg/day every one to two weeks at prednisone doses ≤40 to >20 mg or equivalent per day
    - 2.5 mg/day every one to two weeks at prednisone doses ≤20 to >10 mg or equivalent per day
    - 1 mg/day every one to two weeks at prednisone doses ≤10 to >5 mg or equivalent per day
    - 0.5 mg/day every one to two weeks at prednisone doses ≤5 mg or equivalent per day down to zero. This can be achieved by alternating daily doses (eg, 5 mg on day one and 4 mg on day two)
    - Dose of corticosteroid can be up titrated if platelet counts fall below 50,000/µL on two consecutive measurements
- IVIg or high- dose CS, platelet infusion, or anti-D immunoglobulin infusion as rescue medications

- Clinically relevant drugs that are substrates of CYP3A, including those considered to be sensitive CYP3A substrates. Appropriate caution should be used when co-administering sensitive CYP3A substrates with rilzabrutinib, including an assessment of medical risk-benefit for each medication. Consideration should also be given to avoidance of high doses, dose reduction, or replacement of sensitive CYP3A substrate drugs
- H_2 receptor blocking drugs (ranitidine or famotidine) and antacids are permitted provided they can be given 2 hours or more after administration of rilzabrutinib or placebo

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Study Recruitment Procedures

Participants will be identified for potential recruitment by the Investigator using a recruitment plan agreed upon with the Sponsor, possibly including, but not limited to, a listing from a study center, volunteer database, newspaper/radio/internet advertisement, or mailing list.

7.2. Study Enrollment Procedures

Participants eligible for screening cannot commence enrollment study procedures until the informed consent process and form has been properly administered and signed. Screening tests are then administered, including blood tests sent for laboratory testing. Where the clinical significance of an abnormal screening test result (lab or any other tests) is considered uncertain, the test may be repeated once at least 7 days apart.

The Investigator or designee will enter data for each enrolled participant in the study electronic case report form (eCRF) and enter the corresponding participant ID number in the appropriate place on each participant's eCRF. A participant enrollment and Identification Code List must be maintained by the investigator or pharmacist, or designee.

Under no circumstances will participants who enroll in this study and complete treatment as specified be permitted to re-enroll in the study.

During the COVID-19 pandemic, the Sponsor will need to assess the feasibility of implementing a plan for participant access to study drug and any additional measures required to monitor participant safety on an ongoing basis. Please notify the Sponsor and your contract research organization (CRO) study monitor if your site suspends participant enrollment.

7.3. Temporary Discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF. The Investigator should make the best effort to resume the IMP as early as clinically and practically possible. All efforts should be made to follow the study procedures as per the SoAs during temporary disruption of study medication.

Temporary discontinuation decided by the Investigator corresponds to a period of >2 missed consecutive doses of IMP.

7.4. Rechallenge

Reinitiation of the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical IMP judgment that the benefit/risk balance is in favor of resuming the IMP and if the selection criteria for the study are still met.

7.5. Participant Exit from the Study

7.5.1. Individual Participant Stopping Rules

- Life-threatening or Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 rilzabrutinib-related TEAE except for AEs related to the disease under study or other underlying medical conditions
- Serious allergic reaction to rilzabrutinib or placebo including anaphylactic reaction
- Pregnancy
- Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the participant to risk if the participant continues with rilzabrutinib or placebo or that prevents the participant's adherence to the protocol
- Human immunodeficiency virus/acquired immune deficiency syndrome (AIDS), viral hepatitis (B and C) infection occurring during the study
- Violation of protocol inclusion or exclusion criteria, that in the opinion of the Sponsor, would significantly compromise data interpretation
- Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Appendix 15 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

No follow-up or additional procedures will be performed on participants who discontinue before receiving rilzabrutinib or placebo. For participants who discontinue after receiving any amount of rilzabrutinib or placebo, the reason for a participant's discontinuation from the study must be clearly documented in the participant's medical records and on the appropriate page of the eCRF, and participants will be asked to complete the ET assessments (see Table 1, Table 2 and Table 3).

7.5.1.1. Individual Long-term Extension Participant Stopping Rules

Participants may be withdrawn from the study if the participant is no longer responding according to the table below:

Time in the Long-Term Extension (LTE)	"No response" platelet counts defined as <30,000/µL or <20,000/µL above baseline based on:
During the first 12 months in the LTE	2 consecutive monthly visits
After the first 12 months in the LTE	1 quarterly visit In this case a second platelet count has to be obtained in one month to confirm lack of response. If the platelet count met the no response criteria, the participant may be terminated.

7.5.2. Participant Withdrawal

All participants have the right to withdrawal of consent and discontinue participation without prejudice at any time during the study. Every effort should be made to comply with the protocol; however, participants will be withdrawn from the study entirely with no further study visits if any of the following situation arise:

- Withdrawal of participant's consent or participant's request to discontinue from the study for any reason
- The participant is unwilling or unable to comply with the protocol

Participants who are withdrawn from the study will not be replaced. The reason for the participant's withdrawal from the study should be recorded on the eCRF.

7.5.3. Participant Lost to Follow-up

At the start of the study, the Investigator should try to obtain all relevant contact details for the participant to facilitate contacting the participant, if necessary. In addition, each participant should be encouraged to attend all study visits for which the participant is scheduled.

If a participant discontinues the study without notifying the Investigator, the Investigator must make every effort to contact the participant to identify the reason for the participant's discontinuation and to encourage the participant to complete the applicable ET visit assessments (see Table 1, Table 2 and Table 3). If documented attempts to contact the participant fail, and a reason for the participant's discontinuation is undiscoverable, the Investigator can declare the participant as "lost to follow-up" at the end of the study. The Investigator should document in the corresponding medical record all efforts to contact the participant.

7.6. Study Stopping Rules

Study stopping rules will include but not be limited to:

- More than one rilzabrutinib-related death
- Two or more life-threatening or CTCAE Grade 4 rilzabrutinib-related TEAEs except for AEs related to the disease under study (lack of efficacy)
- The Sponsor elects to stop the study.

7.7. Sponsor Study Termination

The Sponsor has the right to terminate this study at any time for any reason. Reasons for terminating the study may include but are not necessarily limited to the following:

- The incidence or severity of AEs indicates a potential health hazard to participants
- Participant enrollment is unsatisfactory, and the Sponsor wishes to stop the study
- New scientific knowledge or other conditions place study participants at undue risk by continuing in the study
- If the Data Safety Monitoring Board (DSMB) recommends study termination due to safety reasons.

After having informed the Investigators and the coordinators, the Sponsor may terminate the study before its scheduled term. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and regulatory authorities will be informed according to local regulations.

7.8. Visit Overview

During the study, participants will return at specified times on an outpatient basis for assessment of vital signs, physical examination, assessment of AEs and concomitant medication use, assessment of clinical benefit and for provision of blood samples for clinical safety, and PK assessment.

Study procedures and activities will occur at each visit as specified in Table 1, Table 2 and Table 3.

During the COVID-19 pandemic, remote (eg, telephone call, video call) study visits may be performed when a participant is not able to travel to the site or the site cannot host a participant visit. Procedures to be performed during remote site visits are described in "Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" (Appendix 8).

7.8.1. Screening (Day -28 to Study Day -1 Predose)

Informed consent will be obtained at Screening before performing any study procedures.

Participants will undergo screening assessments, including, but not limited to blood sampling, ECG, clinical assessment and various QOL assessments. Please refer to Table 1.

Medical history and demographic data, including sex, age, race, body weight (kg), and height (cm), will be recorded.

7.8.2. Baseline Study Day 1

Participants will undergo baseline assessments shown in Table 1. The first dose of rilzabrutinib or placebo will be administered after all predose procedures on Day 1 have been completed. Participants aged 18 and older will remain in the clinic for 2 hours post-dose for a 2-hour blood collection. Pediatric participants will remain in the clinic for 6 hours post-dose for a 6-hour blood collection.

7.8.3. Blinded Treatment Period (Weeks 1 to 25)

Please refer to Table 1 for specific assessments at each visit.

7.8.4. Open Label Period (Weeks 25 to 53)

Please refer to Table 2 for specific assessments at each visit.

7.8.5. 4 Week Post-Dose Follow-up Period (Weeks 53 to 56 or any 4-week period following the End of Treatment visit)

Please refer to Table 2 for specific assessments for the EOS Visit.

7.8.6. Early Termination Visit

Please refer to Table 1 (if terminating during double-blind treatment) and Table 2 (Open-Label Period) for specific ET assessments. An attempt should be made to have the participant return for the ET visit as soon as possible after the last dose of rilzabrutinib or placebo.

7.8.7. Long-Term Extension (LTE)

Please refer to Table 3 for specific LTE assessments.

7.9. Study Assessments

All study assessments will be collected as outlined at the visits noted in Table 1, Table 2 and Table 3.

7.9.1. Body Height and Weight

Body weight should be measured after checking for accurate zero calibration. Weight is recorded in kg to one decimal place.

Height is assessed at Screening only for participants aged 18 and older. Height is assessed at Screening, Week 13, 25, 37 and 53 (last day of study drug treatment) for pediatric participants. Height is recorded in cm.

7.9.2. Physical Examination

A full physical examination includes, at a minimum, assessment of the following: skin, eyes, ears, nose, throat, heart, chest/breast, abdomen, neurological system (briefly), lymph nodes, spine, and extremities (skeletal).

An abbreviated physical examination is inclusive of general appearance, cardiac, GI, and pulmonary assessments.

A licensed physician or nurse practitioner (or equivalent) will examine each participant.

Physical examination may be performed at various unscheduled time points if deemed necessary by the Investigator.

See Appendix 10.6 for Italy-specific requirements.

7.9.3. Medical History

Medical history will be recorded at Screening and include a history of all underlying medical conditions within the last 10 years as well as a detailed ITP history (separate disease history Case Report Form).

7.9.4. Vital Signs

Vital signs include body temperature, respiratory rate, blood pressure, and pulse rate.

Vital signs may be measured at unscheduled time points, if deemed necessary by the Investigator.

7.9.5. Electrocardiogram (ECG) Monitoring

Single 12-lead ECGs will be performed at Screening, Study Day 1, Week 25, Week 29, first day of Week 53, and at 4-weeks post-last dose. Electrocardiogram will be performed with the participant in a supine position. ECGs will not be performed at weekly lab visits between clinic visits (see Table 1 and Table 2).

Unscheduled ECGs may be performed as deemed necessary by the Investigator.

7.9.6. Clinical Laboratory Tests

See Table 1, Table 2 and Table 3 for laboratory test panels for chemistry, hematology, urinalysis and pregnancy testing. Laboratory safety tests may be performed at unscheduled time points, if deemed necessary by the Investigator. Screening laboratory safety tests may be repeated upon discussion with the Sponsor/Medical Monitor.

The Laboratory Manual will supply complete written instructions for collection, handling, processing, storage, and shipping of samples.

7.9.7. Pharmacokinetic Assessments

Plasma samples will be obtained for PK characterization of rilzabrutinib as outlined in the SoA (see Table 1 and Table 2). If applicable, residual plasma samples could be utilized to assess PK of relevant metabolites of rilzabrutinib (eg, PRN834 & PRN4400). Concentrations at each time point will be reported.

Pharmacokinetic samples could be used for testing analytical method performance such as comparability.

Details regarding the collection, handling, processing, storage, and shipping of samples are provided in the Laboratory Manual.

7.9.8. Bruton's Tyrosine Kinase (BTK) Occupancy

Blood samples will be collected at timepoints for rilzabrutinib concentration levels (BTK occupancy) per the SoA in Table 1 and Table 2. See Appendix 10 for country-specific requirements.

Details regarding the collection, handling, processing, storage, and shipping of samples are provided in the Laboratory Manual.

7.9.9. Vaccine IgG (optional)

To explore possible effects on vaccine response, Investigators will be encouraged to request injectable vaccination plans in line with age-appropriate local medical practice or guidelines from participants who have entered the study and completed at least 6 weeks of rilzabrutinib or placebo at the time of scheduled vaccination. Participants may receive vaccines for influenza, COVID-19, and tetanus (alone or in combination). Live attenuated vaccines are excluded.

Participants scheduled to receive any of the aforementioned vaccines, especially a COVID-19 vaccine, during the study periods may volunteer, after documenting informed consent, to provide

2 blood samples for vaccine-specific IgG in serum. The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine-specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. The collection of samples for the optional IgG assessment is applicable to both the blinded and open-label periods (See the SoA). Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded in the eCRF. Additional details are provided in the Laboratory Manual. See Appendix 10 for country-specific requirements.

7.9.10. Immune Thrombocytopenia (ITP) Assessment Tools (IBLS, ITP-PAQ, ITP-KIT)

Immune Thrombocytopenia Bleeding Scale (IBLS)

The IBLS is a bleeding assessment system comprising 11 site-specific grades from 0 (none) to 2 (marked bleeding) assessed at nine anatomical sites by history over the previous period (Hx) (Page LK 2007). In addition, two of these sites, skin and oral, were also assessed by physical examination. The 'worst ever' bleeding experienced at each site was graded using the same system. Refer to Appendix 1 for further details.

Immune Thrombocytopenia Patient Assessment Questionnaire (ITP-PAQ)

The ITP Patient Assessment Questionnaire™ (ITP-PAQ™) is a disease-specific instrument that was designed to measure the QOL of adult participants with immune thrombocytopenia. It is licensed for use in clinical studies through the Platelet Disorder Support Association. The instrument comprises 38 items completed by male respondents and 44 items completed by female respondents (Mathias 2007). The greater number of items for female respondents is due to additional questions dealing with the impact of ITP on the domains of women's reproductive health, menstrual symptoms, and fertility. The shared domains are Activity, Bother, Fatigue, Fear, QOL, Psychological, Social activity, Symptoms and Work. The items employ a 4-week recall with responses recorded on 4-, 5- or 7-point Likert scales. 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. Refer to Appendix 2 for an example of the copyrighted scale.

Treatment of ITP is intended to increase platelet counts to a hemostatic range, to decrease the risk of bleeding; it also seeks to ameliorate the associated reductions in health-related quality of life (HRQOL) (Provan 2019). A recent survey (I-WISh) of 1507 participants from 13 countries showed that fatigue was one of the most frequent patient-reported symptoms at diagnosis (58%) and especially at survey completion (50%) (Cooper 2021). These results complete the findings issued from 3 focus groups (Mathias 2008) and confirmed the importance of fatigue in ITP. The I-WISh study recruited non-hospitalized adult ITP participants. As the participants in Study PRN1008-018 should be intolerant or show insufficient response to any appropriate courses of standard of care ITP therapy and should have low platelet counts (<30,000/µL), the Sponsor anticipates a high burden of fatigue in its study population.

KIDS' ITP-KIT

The ITP-KIT include a battery of three disease-specific instruments, a child self-report form designed to be completed by children ≥7 years, a parent proxy report form for children <7 and a parent impact form (Mathias 2016). The child self-report form is being used in this clinical study. It has a total of 26 items which are structured as Likert scales with five response options (never, seldom, sometimes, often, always). Respondents record their disease experience based on a 1-week recall. The instrument yields a total score which is the summation of the items converted to a 0 to 100 score with higher scores indicating better disease specific QOL. Refer to Appendix 3 for an example of the copyrighted scale.

7.9.11. EuroQOL (EQ-5D-5L)

The EuroQOL-5 Dimension 5 Level (EQ-5D-5L) is a copyrighted, patient-based instrument for a standardized measure of health status developed by the EuroQOL Group in order to provide a simple and generic measure of health for clinical and economic appraisal (Feng 2015, EuroQOL Group 1990). The health status measured with EQ-5D-5L is used for estimating preference weight for that health status, then by combining the weight with time, quality-adjusted life-year can be computed. Quality-adjusted life-years gained is used as an outcome in cost-utility analysis which is a type of economic evaluation of healthcare programs and intervention. Refer to Appendix 4 for an example of the copyrighted scale.

7.9.12. Patient Global Impression of [Fatigue] Severity (PGIS-Fatigue) Scale

The PGIS-Fatigue is a single item generic patient response outcome (PRO) measure that asks the respondent to rate the severity of their disease-related fatigue over the past week. The item is constructed as a Likert scale on which respondents are asked to select the best response option describing the severity of their symptoms from None, Mild, Moderate, Severe and Very severe (Appendix 5).

7.9.13. Patient Global Impression of Severity (PGIS) Scale

The PGIS is a single item generic PRO measure that asks the respondent to rate the severity of their disease-related symptoms over the past week. The item is constructed as a Likert scale on which respondents are asked to select the best response option describing the severity of their symptoms from None, Mild, Moderate, Severe and Very severe (Appendix 5).

7.9.14. Patient Global Impression of Change (PGIC) Scal

The PGIC is a single item generic PRO measure on which the respondent assesses the degree to which their symptoms during the past week compared to what they experienced before initiating the study medication. PGIC is a commonly used method of assessing clinically important change. The Likert response options for this question allow for reports ranging from significant symptom improvement or significant symptom worsening (ie, Very much better, Moderately better, A little better, No change, A little worse, Moderately worse, Very much worse), Appendix 5.

7.9.15. Use of biological samples and data for future research

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) collected as part of the study will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded study data may be shared.

Coded study data and biological samples will be stored and used for future research only when consented to by participants (see Section 12.2) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of data/sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

Data protection – Processing of coded study data

The study participant will be provided with all mandatory details of the data processing in the ICF.
The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 13.5).

Use of leftover samples and additional samples for future research

Remaining leftover samples of adults and pediatric populations will be used only after the end of the blinded treatment period of each group, ie, end of the blinded period as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in the ICF.

Study participant data will be stored for up to 25 years for regulatory purposes. Biological samples for future use will be stored for up to 25 years after the end of the study unless local regulations require a different retention period. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.
See Appendix 10 (Appendix 10.5) for China-specific requirements.

7.9.16. Medication errors or misuses of medicinal product

All reports of medication error or misuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor's representative following standard processes.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant. This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

8. ASSESSMENT OF EFFICACY

8.1. Specification of the Efficacy Parameters

Clinical assessments will include physical examination; assessment of vital signs, height, and weight; 12-lead ECG, collection of medical history, collection of concomitant medication information, assessment of bleeding with IBLS and/or other bleeding scales, QOL questionnaires, collection of AEs

Laboratory assessments will include hepatitis B and C, pregnancy test, FSH, urinalysis, ABO and Rh, hemolysis panel (Coombs and haptoglobin), mean platelet volume, serum chemistry, hematology, platelet counts, PT/INR, TPO level, PK sampling, T/B/NK count, Immunoglobulin levels, BTK occupancy (at select sites), and optional vaccine IgG levels.

A summary of efficacy parameters is provided in Section 3.2. A review of study assessments is provided in Section 7.9. See Appendix 10 for country-specific requirements.

8.2. Methods and Timing for Assessing, Recording, and Analyses of Efficacy Parameters

Methods and timing for assessing, recording, and analyzing of efficacy parameters are provided in Table 1, Table 2, Table 3 and Section 7.9.

9. ASSESSMENT OF SAFETY

9.1. Overview

After a comprehensive baseline evaluation, the safety of the participants will be monitored by assessment of vital signs, laboratory tests (hematology, urinalysis, and chemistry), disease assessments, and abbreviated physical examinations. Concomitant medications and TEAEs will be monitored and tracked.

The Investigator should take appropriate and prompt remedial measures for AEs, including clinically significant laboratory result abnormalities, while trying to elucidate the etiology of the condition. The participant should then be followed-up until the condition resolves or becomes chronic or stable.

Study stopping criteria are discussed in Section 7.6 and individual stopping criteria in Section 7.5.

9.2. Data Safety Monitoring Board (DSMB)

An independent DSMB will regularly review and evaluate unblinded participant safety data including reported SAEs, tabulations of all AEs, and safety laboratory results. The DSMB will agree on the DSMB charter and an initial frequency of meetings. Subsequently, meeting frequency will be determined as appropriate by the DSMB.

Documentation of the participant data reviewed at each meeting, including the individual DSMB member's confirmation of data review and the findings and actions of the DSMB, will be included in the Study Master File. DSMB findings that impact the safety of participants in this study will be immediately reported to the local competent authority (CA) and IEC. Details of unblinding procedures, DSMB composition and responsibilities, and other DSMB information will be provided in a separate DSMB charter.

Detailed methodology for summary and evaluation of data to be reviewed by the DSMB will be documented in the DSMB charter.

9.3. Adverse Events (AEs)

9.3.1. Adverse Event Collection Period

The AE Collection Period begins at the signing of the ICF and ends at the end of the study for each participant.

During the COVID-19 pandemic, if a participant is not able to travel to the site or the site cannot host a participant visit AEs will be collected during phone or video calls and recorded in the electronic data capture (EDC) system as described in the "Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19" (Appendix 8).

9.3.2. Adverse Events

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the product. All AEs encountered during the clinical study will be reported in detail in the source documents and documented in the eCRF, from the date of participant consent throughout the follow-up visit. Pre-existing conditions that worsen during a study are to be reported as AEs, with the exception of expected variation in ITP disease activity itself.

Unexpected progression, signs, or symptoms of the disease under study (ITP) are not AEs and are not to be recorded on the AE page of the eCRF unless the event meets the definition of an SAE or is not consistent with the typical clinical course of the participant's disease as established by the participant's medical history. Worsening of the disease under study or other disease-related symptoms should be recorded as an AE only if the event meets the definition of an SAE or is not consistent with the typical clinical course of the disease.

Definitions:

The below guidelines should be followed when recording AEs:

- Medical terms: Whenever possible, use recognized medical terms when recording AEs on the AE eCRF. Do not use colloquialisms or abbreviations.
- Diagnosis: If known or suspected, record the diagnosis (except for eg, hypoglycemia) rather than component signs and symptoms on the AE eCRF and SAE form (eg, record congestive heart failure rather than dyspnea, rales, and cyanosis.) However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the AE eCRF and SAE form.
- Death: Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the AE eCRF and SAE form (except for sudden, unexplained death).
- Surgical or diagnostic procedures: For medical or surgical procedures (eg, colonoscopy, biopsy), the medical condition that led to the procedure is an AE. Elective procedures(eg, vasectomy) planned hospitalizations, and procedures for treatment of conditions noted in the participant's medical history that have not worsened (eg, hernia repair) are not considered AEs.
- Chronic disease: In the case of disease (excluding disease under study) that is progressing by episodes (chronic disease), if the disease is known when the participant enters the study, only worsening (increased frequency or intensity of the episodes or attacks) will be documented as an AE. If the disease is detected during the study, and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped together in the eCRF, and the diagnosis will be clearly described.

- Underlying disease conditions: Unchanged (stable), chronic conditions, or those related to the underlying disease that are consistent with the disease's natural progression are not AEs and are not to be recorded on the AE page of the eCRF. These conditions are considered part of the participant's medical history and must be adequately documented on the appropriate page of the eCRF. Day-to-day fluctuations of pre-existing disease should not be recorded as an AE on the AE eCRF.
- Disease under study (ITP): Unexpected progression, signs, or symptoms of the disease under study are not AEs and are not to be recorded on the AE page of the eCRF unless the event meets the definition of an SAE or is not consistent with the typical clinical course of the participant's disease as established by the participant's medical history. Worsening of the disease under study or other disease-related symptoms should be recorded as an AE only if the event meets the definition of an SAE or is not consistent with the typical clinical course of the disease.
- Laboratory abnormalities: An isolated, out-of-range laboratory result in the absence of any associated, clinical finding may or may not be considered an AE; the Investigator's evaluation should be based on a consideration of the overall clinical context.
- An out-of-range laboratory result will be considered clinically significant and recorded as an AE ***when it is part of a clinical abnormality requiring specific medical intervention or follow-up***. The test will be repeated (within 72 hours for ALT increased), and the participant will be followed-up until the test value has returned to the normal range or baseline, or the Investigator has determined that the abnormality is chronic or stable. The Investigator will exercise medical judgment in deciding whether out-of-range values are clinically significant and document the assessment in the source records

9.3.3. Adverse Event Intensity Grading

All clinical AEs encountered during the clinical study will be reported on the AE page of the eCRF. Intensity of AEs will be graded based on a modified CTCAE, Version 5.0 and reported in detail as indicated on the eCRF. For any AEs not found in the CTCAE, a description of intensity grading can be found in Appendix 12 and below:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences; urgent intervention indicated: by definition also a SAE.

Death will not be recorded as a Grade 5 severity - rather the underlying condition will be recorded, and its severity graded, with death regarded as an outcome.

9.3.4. Adverse Event Relationship to Study Medication

Investigators should use their knowledge of the study participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to any study drug (eg, rilzabrutinib or placebo), indicating "yes" or "no" accordingly.

The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of rilzabrutinib or placebo
- Course of the event, considering especially the effects of dose reduction, discontinuation of study medication, or reintroduction of rilzabrutinib or placebo (if applicable)
- Known association of the event with rilzabrutinib or placebo or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the study participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

9.3.5. Adverse Event Relationship to Standard of Care Medication

Investigators should use their knowledge of the study participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to their standard of care medication (eg, CSs or TPO-RA), indicating "yes" or "no" accordingly. For this study standard of care medications may only be reduced due to a safety concern (eg, a corresponding AE).

9.3.6. Treatment Unblinding to Determine Clinical Course

If deemed by the Investigator to be medically necessary in the event that a SUSAR occurs, to determine appropriate clinical treatment, the Investigator can unblind an individual participant via the IWRS after consultation with Sponsor medical monitor. See Appendix 10 for UK country-specific requirements.

Instructions for Investigators to unblind are located in the Investigator Site File.

9.3.7. Treatment and Follow-Up of Adverse Events (AEs)

Adverse events, especially those for which the relationship to rilzabrutinib or placebo is “related”, should be followed-up until they have returned to baseline status or stabilized.

If after follow-up, return to baseline status or stabilization cannot be established an explanation should be recorded on the eCRF.

9.3.8. Laboratory and Electrocardiogram (ECG) Abnormalities

Laboratory test results will appear on electronically produced laboratory reports or be recorded on the laboratory results pages of the eCRF if applicable.

Any treatment-emergent abnormal laboratory or ECG result which is clinically significant, ie, meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in rilzabrutinib or placebo (eg, dose interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (eg, addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

Note: Any laboratory or ECG result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

9.3.8.1. Follow-Up of Abnormal Laboratory Test Values

In the event of unexplained clinically significant abnormal laboratory test values, the tests should be repeated as soon as possible, no later than 72 hours after reporting of the results and should be followed-up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF.

9.3.9. Adverse events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 12. The definition of adverse event of special interest (AESI) is provided in Section 9.3.9.6.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up AEs, particularly those that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7.5).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 12.

9.3.9.1. Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Table 1, Table 2, and Table 3).

All AEs will be collected from the signing of the ICF at the time points specified in the SoA (Table 1, Table 2, and Table 3).

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 12. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

9.3.9.2. Method of detecting AEs and SAEs

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

9.3.9.3. Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and other AEs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.5.3). Further information on follow-up procedures is provided in Appendix 12.

9.3.9.4. Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information in the Investigator's Brochure.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.
- For the European Union, safety reporting to the agency is described in Appendix 10.7.

9.3.9.5. Pregnancy

- Details of all pregnancies will be collected after the start of study intervention and until 28 days after the last dose of study intervention.
- If a pregnancy is reported after the first dose of the IMP, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Appendix 12. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study must discontinue study intervention or be withdrawn from the study.

9.3.9.6. Adverse events of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification (within 24 hours) by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified. or removed during a study by protocol amendment; they include:

- Pregnancy of a female participant entered in a study and received at least one dose of the IMP as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 12).
  - In the event of pregnancy in a female participant, IMP must be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 13).
- Symptomatic overdose (serious or nonserious) with IMP

- Increase in ALT >3 × ULN (See Appendix 15 for follow-up instructions). If such laboratory values have been determined, follow-up within 72 hours of the same value and total bilirubin levels is required and if value is repeated (eg, ALT >3 × ULN), such value shall be reported as well together with the repeated total bilirubin values and any other laboratory values to determine the cause of the initially determined ALT increase.
- Any Grade 4 or 5 infection where the participant is hospitalized ≥24 hours and/or requires emergency care and/or requires intravenous antibiotics.
- Any occurrence of uveitis (including Vogt-Koyanagi-Harada disease [VKHD])

9.3.9.7. Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

10. STATISTICAL METHODS

A detailed Statistical Analysis Plan (SAP) will be developed and finalized before the study database is locked which will supersede the statistical analysis methods described in the protocol; however, any major modification of the outcome measures and/or its analysis will also be reflected in the clinical study report (CSR).

Descriptive summaries of variables by treatment will be provided where appropriate. Generally, continuous variables will be summarized using the following descriptive statistics: mean, standard deviation, number of observations, median, minimum, and maximum. Summaries will also be presented for the change from baseline, when appropriate. For categorical variables, the counts and proportions of each value will be tabulated by treatment. For time to event variables, point estimates (25th, 50th, and 75th percentiles) along with 95% confidence intervals will be tabulated by treatment using Kaplan-Meier methods. Survival estimates will also be shown graphically for each treatment.

All statistical tests will be two-sided unless otherwise noted.

The pediatric participants will not be tested, and descriptive statistics will be done on these participants. Additional statistical analyses on these pediatric participants may be provided for specific regulatory requests.

10.1. Determination of Sample Size

The adult sample size chosen for this study was selected to achieve enrollment of 129 adult participants (≥18 years) on rilzabrutinib and 65 adult participants on placebo. The pediatric sample size of up to 30 participants (20 participants on rilzabrutinib and 10 participants 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%.

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 3.2.1) 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 1/2 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 (Bussel 2018). The participants who are not evaluable for primary efficacy due to dropout or missing data will be considered as non-responders.

10.2. Objectives and Endpoints

Please refer to Section 3.

10.3. Analysis Populations

10.3.1. Safety Population

All participants who are randomized and receive at least one dose of study medication will be included in the Safety Population. The Safety Population is the primary analysis population for safety. Participants will be analyzed according to the treatment they actually received, not necessarily the treatment they were allocated to at randomization. Results for the blinded treatment period will be presented "as treated." Further details will be provided in the SAP on how data collected during the open-label period will be analyzed.

10.3.2. Intent-to-Treat (ITT) Population

All participants who are randomized will be included in the intent-to-treat (ITT) Population. The ITT Population will be used for efficacy analysis. Participants will be analyzed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented "as randomized."

10.3.3. Modified ITT (mITT) Population

All participants who are randomized and receive at least one dose of study medication will be included in the mITT Population. The mITT Population may be used for sensitivity analysis. Participants will be analyzed according to the treatment they were allocated to at randomization; not necessarily the treatment they actually received. Results will be presented "as randomized."

10.3.4. Pharmacokinetic (PK) Population

All participants who receive at least one dose of study medication in the safety population and have sufficient data for PK analysis will be included in the PK population.

10.3.5. Disposition of the Study Participants

The disposition of participants will be described with summaries of the number of participants treated and discontinued from the study, including the primary reason for premature discontinuation.

10.3.6. Demographic and Baseline Characteristics

Summaries of participant disposition, demographics, and baseline characteristics will be provided by treatment group.

Demographic and baseline characteristics (age, sex, race, ethnicity, weight, height, and body mass index) will be summarized using descriptive statistics. No formal statistical analyses will be performed, and no inferential statistics reported.

10.3.7. Exposure to Study Treatment

The number of received doses will be summarized by treatment group. Treatment duration and compliance for all participants will be described.

10.3.8. Safety and Tolerability Analysis

Safety will be assessed by the incidence, severity, and relationship of TEAEs, including clinically significant changes in physical examination, laboratory tests, ECG, clinical laboratory test results, and vital signs. AEs will be categorized as treatment-emergent after the first dose of rilzabrutinib has been administered.

The nature, frequency, and severity of AEs, including AESIs, SAEs, and AEs leading to discontinuation will be summarized descriptively by treatment group. AEs possibly related to protocol allowed ITP concomitant medications, TPO- RAs and CS, will be grouped and analyzed separately in addition to the above.

A by-participant TEAE data listing, including verbatim term, preferred term, and system organ class (SOC), treatment, relationship to the study drug and intensity (severity) will be provided.

The number of participants experiencing AEs and number of AEs will be summarized by treatment group using frequency counts.

A change from baseline table will be provided for vital signs and clinical laboratory results by treatment group.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results, as appropriate.

AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at the time of entry and the version will not change through completion of study data available at the Sponsor or designee.

Concomitant medications will be coded using the most current World Health Organization (WHO) drug dictionary and the version will not change through completion of study data available at the Sponsor or designee.

10.3.9. Primary Efficacy Analysis

The primary analysis will compare the proportion of participants in the adult ITT population who achieve durable platelet response defined as 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 medication (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) between rilzabrutinib and placebo with a Cochran-Mantel-Haenszel test using the two stratification factors at a 2-sided alpha level of 0.05 (see Appendix 10.7 for a description of the primary efficacy analysis in the EU [EEA countries] and UK). Participants who do not respond in the first 12 weeks and enter the open label period will be treated as non-responders in the primary analysis. Participants who discontinue the study due to a rilzabrutinib-related AE lack of efficacy or receive rescue medication (including an increase in allowed concomitant ITP medications dose) will be considered as non-responders. Sensitivity analyses will be conducted on the primary analysis.

The primary endpoint will be analyzed for adult and pediatric participants separately.

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

10.3.10. Key Secondary Efficacy Analysis

Multiplicity of the secondary analysis will be adjusted to control the overall type I error. Key secondary efficacy endpoints will be tested sequentially. The following five comparisons will be conducted between rilzabrutinib and placebo using sequential (hierarchical) testing with a fixed sequence as listed below, which controls the family-wise error for multiple comparisons at alpha level of 0.05 (two-sided):

- Compare the number of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least double from baseline over the 24-week blinded treatment period (platelet counts will be censored for 4 weeks after the use of rescue therapy, if any)
- Compare the number of weeks with platelet counts ≥30,000/μL and at least double from baseline over the 24-week blinded treatment period in the absence of rescue therapy
- Compare time to the first platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least double from baseline
- Compare the proportion of participants requiring rescue therapy during the 24-week blinded treatment period
- Compare the change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants at Week 13

See Appendix 10.7 for EU (EEA countries) and UK-specific requirements.

10.3.11. Other Efficacy Analysis

All other analyses will be performed at the 0.05 level and will not be corrected for multiple comparisons, as they will be viewed and handled in the perspective of not testing a formal hypothesis. Other analyses include the following:

- Estimate the predictive value of platelet count for each of the three predictors separately or in combination:
  - ≥30,000/μL on Study Day 8
  - ≥20,000/μL above baseline on Study Day 8
  - ≥50,000/μL at any time over first 8 weeks of the treatment period to achieve the primary endpoint

10.3.12. Pharmacokinetic (PK) Analysis

Plasma concentrations of rilzabrutinib (and metabolites, if applicable) in participants will be evaluated in each participant based on sampling at varied timepoints. Individual and group PK data will be summarized by descriptive statistics for each visit where measured.

Exploratory analyses will employ the use of nonlinear mixed effects (population PK) modeling to evaluate these data in combination with the data from other studies of rilzabrutinib. Exploratory analyses will also be conducted to evaluate potential relationships between PK and PD, safety, and efficacy endpoints. The results of these analyses may be reported outside of the main CSR.

10.3.13. Exploratory Analysis

Other subgroup and exploratory analyses not specified in the protocol may be performed. Health economic utility data related to the costs of AEs and hospitalizations may be explored. Full details will be provided in the SAP.

10.3.14. Missing Data

Details on the handling of missing data will be described in the SAP.

10.4. Interim Analysis

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 regulatory 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, Open Label 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.

11. INVESTIGATOR RESPONSIBILITIES

By signing the separate Protocol and amended protocol agreement form, the Investigator agrees to do the following:

1. Conduct the study in accordance with the relevant current protocol and make changes only after notifying the Sponsor, except when immediate changes are necessary to protect the safety, rights, or welfare of the participants
2. Comply with the E6 International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) Codes of Federal Regulations (CFRs)
3. Personally conduct or supervise the described investigation
4. Inform any participants, or any persons used as controls, that the drugs are being used for investigational purposes
5. Ensure that the requirements relating to obtaining informed consent and Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval have been met
6. Report to the Sponsor adverse experiences that occur in the course of the investigation as specified in 21 CFR 312.64 and the E6 ICH Tripartite Guideline on GCP and any local regulations
7. Have read and understood the Investigator's Brochure, including potential risks and side effects of the drug
8. Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments
9. Maintain adequate and accurate records and make these available for inspection by the Sponsor, its designee, the FDA, the IRB/IEC, and other applicable national or local health authorities or agency authorized by law, as defined in 21 CFR 312.68 and E6 ICH Tripartite Guideline on GCP
10. Ensure that an IRB/IEC that complies with the requirements of 21 CFR Part 56 and applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical investigation
11. Promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to human participants or others
12. Not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human participants
13. Comply with all other requirements regarding the obligations of Investigators and all other pertinent requirements

12. DATA QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data, including data collection and management, will be described in the Data Management Plan.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against the Investigator's records by the study monitor (source document verification), and the maintenance of Drug Accountability (see Section 6.4.1) by the Investigator.

Data for this study will be recorded in the study EDC eCRFs. The data will be entered by the study center from the source documents into the eCRF or will be loaded from other files (eg, safety lab data). In no case is the eCRF to be considered as source data for this study.

A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the Investigator. All discrepant data will be resolved in the EDC database and data entered in the database will be independently compared with the original Investigator's records.

For classification purposes, preferred terms will be assigned to the original terms recorded on the eCRF, using MedDRA for AEs, diseases and surgical and medical procedures, and the WHO drug dictionary for drug and herbal treatments.

12.1. Protocol Amendments and Study Completion

Protocol amendments must be made only with the prior approval of the Sponsor or its designees. The IRB/IEC must be informed of all amendments and give approval for all amendments. For studies conducted outside of the US, approval of substantial amendments must be obtained from the relevant Competent Regulatory Authority before implementation. The Investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor and/or the Sponsor's designee.

Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study participants, or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor(s), change of telephone number(s)).

The Sponsor reserves the right to terminate the study, according to the Clinical Study Agreement.

Study completion is defined as the date when all participants have completed the final study visit, and the study database has been locked.

12.2. Informed Consent

The Investigator and Sponsor must agree upon the format and content of the ICF before it is submitted to the IRB/IEC for approval. A copy of the IRB/IEC approved copy of the ICF will be forwarded to the Sponsor. Written IRB/IEC approved informed consent or assent and Health Insurance Portability and Accountability Act (HIPAA) release (or other privacy protection release, as governed by local regulations) must be obtained from each participant and/or Legally Authorized Representative (LAR) before any study-related activities are conducted. The Investigator must retain all original signed and dated ICFs or assents (together with any

subsequent IRB/IEC -approved amended versions) in the participant's file. A copy of the signed and dated ICF or assents (and any amendments) must be given to the participant and/or LAR.

The ICF and assent documents the study-specific information the Investigator provides to the participant and/or LAR for the participant's agreement to participate. Among other things, the Investigator or his/her designee will fully explain in layman's terms the nature of the study, along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. The ICF or assent must be appropriately signed and dated before the participant enters the study.

Participants and/or LARs will be informed of findings from earlier or concurrent clinical studies (including AEs), if it is considered that such information could potentially affect participant's willingness to participate or continue in the study. Depending on the nature, severity, and seriousness of these AEs, the ICF or assent may be amended as deemed appropriate. The original and any amended signed and dated ICF(s) or assent(s) must be retained in the participant's file at the study site; and a copy must be given to the participant and/or LAR.

Participants enrolled into the pediatric portion of the trial will still be considered as part of the pediatric group with all the planned assessments when they turn 18 years old. They should be reconsented with an adult consent when they become an adult per country-specific requirements.

For male participants, in case of pregnancy of your partner, your partner will be asked to provide consent for collection of the pregnancy data.

13. DATA HANDLING AND RECORD KEEPING

13.1. Participant Confidentiality and Disclosure of Data

The Investigator must ensure that each participant's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor and/or its designee, participants must only be identified by study, Participant Identification Number, and demographics, and pertinent restrictions of local regulations. No other personal identifiers will be used, and data will be de-identified in a manner compliant with Privacy Laws and, for US participants, the HIPAA regulations. Documents that are not for submission to the Sponsor and/or its designee (eg, signed ICFs and Patient Information Sheets) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICH and GCP Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor and/or its designee, by representatives of the FDA, national and local health authorities, and the IRB/IEC direct access to review the participant's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator is obligated to inform the participant in the ICF that his/her study-related records will be reviewed, by the above-named representatives.

Participants or LARs will be informed that data will be held on file, by the Sponsor, and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Participants or LARs will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, participants will be identified in such reports only by Participant Identification Number and demographics, pertinent to restrictions of local regulations. All participant data will be held in strict confidence, as allowed by law.

Upon the participant's (or LAR's) permission, medical information may be given to the participant's personal physician or other appropriate medical personnel responsible for the participant's welfare.

13.2. Electronic Case Report Forms (eCRF)

The data collected in the source documents for this study will be entered into the study EDC eCRF. An audit trail will maintain a record of initial entries and changes made; time and date of entry; and name of person making entry or change. For each participant enrolled, an eCRF must be completed and signed by the Principal Investigator or authorized delegate from the study staff. If a participant withdraws from the study, the reason must be noted in the eCRF. If a participant is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

13.3. Retention and Availability of Records

The Investigator is required to retain the study records and reports until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP If no marketing application is to be filed, or an application is not approved for the drug, the Investigator will retain the study records for 2 years after shipment and delivery of the drug for investigational use is discontinued and the Sponsor has so notified the FDA, per 21 CFR 312.57. Study records should, however, be retained longer if required by the applicable national and/or local regulatory requirements or by agreement with the Sponsor.

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor, and regulatory agency inspectors upon request. A file for each participant must be maintained that includes the signed ICF and the Investigator's copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was transcribed.

13.4. Audits and Inspections

In accordance with ICH, GCP and the Sponsor and/or its designee audit plans, this study may be selected for audit. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH, GCP, and applicable regulatory requirements. The Investigator/ institution should make available for direct access all requested study-related records (ICH GCP 4.9.7) to appropriately qualified personnel from the Sponsor or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents (ie, completed CRFs, Investigator site files, and any source documents should be stored in a protected secure location [ICH GCP 4.9.4]).

If for any reason the study records are moved to another location, the Investigator should notify the Sponsor of the new location.

13.5. Data Protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sponsor's databases, including trial participants, Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they might modify the drug response. They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification, the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow the Sponsor to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sponsor or to the Sponsor's service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sponsor's Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of the Sponsor, it will be impossible to involve the professionals in any Sponsor study. In case the professionals have already been involved in a Sponsor study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within the Sponsor or partners or service providers involved in the study
  - Judicial, administrative, and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by the Sponsor in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with the Sponsor's leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by the Sponsor for up to 25 years unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, the Sponsor participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry). Therefore, personal data will be securely shared by the Sponsor with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their

data up to date at once across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.

- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the the Sponsor's Data Protection Officer: Sanofi DPO, 46 avenue de la Grande Armée, 75017 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

13.6. Financial Disclosure

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

14. ETHICAL ASPECTS

This section provides information for the Investigator on the ethics requirements for the study, including participant informed consent, IRB/IEC review of the study and study materials, and conditions for modifying or terminating the study. Requirements for financial disclosure for the Investigator are also described.

14.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws
  - Any other applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's brochure, IDFU, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.
  - Determining whether an incidental finding (as per the Sponsor's policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding

is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:

- The return of such information to the study participant (and/or his/her designated healthcare professional, if so, designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has concerned reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

As applicable, according to requirements of the Regulation No536/2014 of the European Parliament and the Council of the European Union, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, the Sponsor needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48h after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

14.2. Institutional Review Board Review

This protocol and any accompanying material provided to the participant (such as participant information sheets or descriptions of the study used to obtain informed consent), as well as any advertising or compensation given to the participant, will be submitted by the principal Investigator, or coordinating Investigator to the relevant institutional IRB/IEC responsible for the investigational study.

An approval letter or certificate (specifying the protocol number and title) from the IRB/IEC must be obtained before starting the study (initiation). The approval letter to the Investigator should specify the date on which the committee met and granted the approval. The Local Sponsor must also obtain relevant CA approvals before starting the study.

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16. APPENDICES

Appendix 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

Appendix 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?	☐	☐	☐	☐	☐

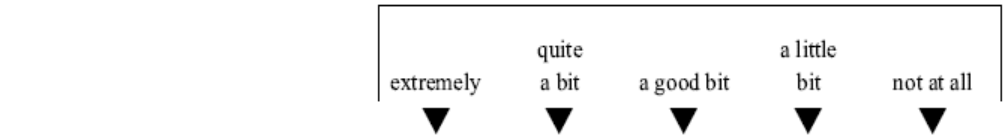
12. Overall, in the past 4 weeks, to what extent have ITP and its treatment(s) affected your **physical health**?

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**?

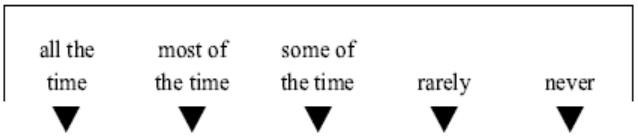
extremely	very much	quite a bit	a good bit	somewhat	a little bit	not at all
☐	☐	☐	☐	☐	☐	☐

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



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? .....



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)

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

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

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

Appendix 3 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

Appendix 4 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

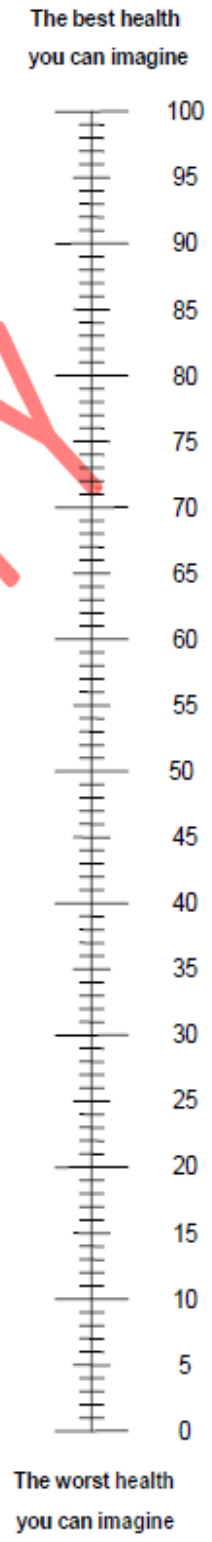
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

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 ☐

- 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

Appendix 5 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

Appendix 6 Strong-to-Moderate CYP3A Inhibitors and Inducers and Sensitive CYP3A Substrates

	Strong	**Moderate**
CYP3A Inducers	Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, phenobarbital, primidone
CYP3A Inhibitors	Boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit, starfruit, and products containing these fruits (such as juice and marmalades), idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir and ombitasvir and/or dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole	Aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, U.S. Food and Drug Administration. This list is not intended to be exhaustive and may be out of date. For updated information, please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers or product labeling.

Sensitive CYP3A Substrates
Alfentanil, aprepitant, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tolvaptan, tipranavir, triazolam, vardenafil

Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, U.S. Food and Drug Administration. This list is not intended to be exhaustive and may be out of date. For updated information, please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers or product labeling.

Appendix 7 Publication

Ownership of the Results-Publication Policy

Sponsor assumes full responsibility relating to this function and retains exclusive property rights over the results of the study, which Sponsor may use as it deems fit.

If the study has multiple centers, the first publication must include complete results from data analyzed by Sponsor from multiple centers. The Investigator commits himself not to publish or communicate data collected in only one center or part of a center before the publication of the complete results of the study unless prior written agreement from the other Investigators and Sponsor has been obtained.

A copy of any intended publication or communication related to the study or related to the results obtained during or after the study shall be submitted to Sponsor at least 90 days before the forecasted date of distribution or submission for publication. The authoring Investigator shall take Sponsor's comments into due consideration and hereby agrees to incorporate any changes in any such publication or communication that Sponsor may reasonably require to protect Sponsor's proprietary rights and interests. Should the authoring Investigator decide to not incorporate changes reasonably required by Sponsor, the authoring Investigator shall provide the reasons in writing to Sponsor.

In the case where Sponsor is in the process of filing a patent application on the results of the study, Sponsor may delay its authorization for publication or communication of the results of the study until the date of international registration of the patent.

Appendix 8 Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19

Sponsor understands that many study institutions have implemented restrictions to minimize in-person activities due to the rapidly evolving concerns and risks related to the COVID-19 outbreak. Refer to Appendix 10.7 for EU [EEA countries] specific guidance.

The safety data to date and the unique mechanism of action of rilzabrutinib continues to support a favorable risk-benefit profile for immune thrombocytopenia participants experiencing active disease manifestations.

Sponsor intends to continue to enroll participants, provide IMP to randomized participants, and to perform protocol assessments as possible during the pandemic while following the recent guidance issued from US FDA and European Medicines Agency (EMA) in March 2020. For FDA, the Guidance is dated 18 March 2020 entitled “FDA Guidance on the Conduct of Clinical Trials of Medical Products During COVID-19 Pandemic” and for EMA is dated 20 March 2020 entitled “Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic” for the management of studies and participant safety under these circumstances. In addition, with the advent of the COVID-19 pandemic, and in consideration of the recently issued guidance by the EMA referenced above, Sponsor is committed to provide measures that assure continued drug supply and safety monitoring for participants. We are working in collaboration with sites and their respective Independent Ethics Committees (IECs) to implement novel ways that support social distancing and stay at home measures while maintaining access to study drug and safety oversight.

Precautions regarding COVID-19 and management of participants should be followed as there is no data regarding the impact of rilzabrutinib on COVID-19. Please refer to the current version of the Investigator’s Brochure for further information on the potential risks and benefits of treatment with rilzabrutinib.

Since rilzabrutinib is an oral medication, maintaining drug supply for participants during these restrictive times is feasible, especially as the drug can be administered at home and we at Principia Biopharma Inc. are committed to making drug supply to participants a top priority. This is important because participants with immune thrombocytopenia (ITP) require uninterrupted treatment to maintain platelet response. Recommendations from the Centers for Disease Control and Prevention and WHO for minimizing the risk of exposure to COVID-19 should be followed at all times, and the investigator should make an assessment of the participant’s benefit/risk profile for inclusion and continuation in the study on a case-by-case basis.

We are committed to keeping you informed in writing if there are any new significant safety findings that emerge affecting a participant’s willingness to participate or pose additional risk. For sites affected by restrictions due to COVID-19, Sponsor will implement the following changes in research plans in order to eliminate apparent immediate hazards to research participants in study PRN1008-018 (EFC17093):

Remote study visits for active participants

It is expected that if your site is not affected and the participant may travel to the site for a regular scheduled protocol visit, that the visit occurs per schedule. It is important to discuss all upcoming visits in the next month with all participants in order to provide sufficient time to plan for the visit.

In the circumstance that the participant may not travel to the site, or the site is quarantined and cannot host a participant visit - please follow the guidelines below for allowing continued supply of rilzabrutinib (study drug).

In-clinic study visits as outlined in the protocol SoA, may be changed to a remote visit (eg, telephone call, video call) for visits as needed to address the COVID-19 restrictions. We are mindful that your site resources may be restrictive during this time, so please inform your site monitor of any concerns so we can address any specific needs at your site as well as understand your internet and source documentation access. Refer to - Remote Study Visits for Active Patients on how to perform and document these remote visits.

Enrollment

Please notify Sponsor and your CRO study monitor of your Institution policy during the pandemic and any temporary suspension prior to enrolling new participants. We need to ensure participant safety can be adequately monitored, access to study drug is feasible and a plan is in place for that participant to address how this will be implemented.

Local nurse service, home-health visits

Sponsor provides the option for participants to use a home-health care nurse. A nurse will be able to visit your home to collect necessary vital signs and blood draws. This will only be for sites that are permitted to use this service.

Quality of Life (QOL) Questionnaires:

Sponsor and the CRO are making all QOL Questionnaires available electronically for this study. The ITP-PAQ, Kids' ITP Tools (ITP-KIT), and EuroQOL-5 Dimension 5 Level (EQ-5D-5L) will all be available through our authorized vendor via the web or an application on the participant's own device. These will be submitted for approval with the original submission to the Institutional Review Board (IRC)/IEC.

Urine Pregnancy Testing (UPT) for Women of Childbearing Potential

It is important to confirm pregnancy status for women of childbearing potential. Please send 3 urine pregnancy tests to the subject with each shipment of IMP. If the UPT has a package insert with instructions on collection, include this in the shipment. During the follow up phone call with the participant, have the participant collect the urine sample and conduct the pregnancy test. During the follow-up call, confirm pregnancy status (negative or positive) and document the result in the source notes. The participant may confirm the result by showing the test over the video with site staff documenting the status was visualized (positive or negative) or provide a photo of the test to site staff. A positive test result will need to be reconfirmed with a second test.

Investigational Medicinal Product (IMP) shipments direct to research participants

Where participants are self-isolating or in quarantine, arrangements for a nominated person to collect and deliver product may be implemented with the participant's documented verbal consent. Sites are requested to obtain and document a participant's verbal consent to provide contact details for IP shipping and transport purposes. See Appendix 10.2 for Germany specific details concerning direct to participant shipment of IMP.

Options for IP transport:

- No change from current practice in protocol: Participant can pick up dispensed study medication when attending a site visit, using the normal practice for bringing study medication home.
- By direct from site/hospital to participant using PCI's World Courier Account or authorized vendor, insulated shipper and temperature monitor, study medication may be delivered from the site to the participant's home. Detailed instructions on this process are in the study Pharmacy Manual.

If you are not able to use PCI's World Courier Account or authorized vendor for shipping supplies and delivery to send study medication to the participant, you will need to provide the information to Sponsor regarding which local courier will be used, what kind of insulated shipper you will use and brand and model number of the temperature monitoring device. Sponsor will need to approve the material and courier prior to shipment to the participant. Upon approval by Sponsor in writing, the site may arrange the shipment with the local courier.

Protocol deviations:

Where the change to remote visits is being implemented due to COVID-19 to protect the safety and well-being of participants, failing to obtain assessments will need to be documented (eg, identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specific assessments). Please continue to document in your source documents all protocol deviations and inform your local site clinical research associate (CRA) monitor. Notify your IRB/IEC as required locally.

Remote site monitoring visits, if applicable (where allowed by local regulations):

As you know, the Sponsor is required to monitor the safety and risk-benefit for continued conduct of the study. In accordance with the FDA and EMA Guidance, the change in process required for monitoring due to COVID-19 must be documented. To meet our Sponsor oversight obligations while CRA monitors are not allowed on-site, we ask that you provide source documents with all personal information REDACTED for your site CRA monitor to perform remote source document verification. A separate manual will be sent to you for how this will be performed.

Please share this information with your study site staff and inform your local IRB/IEC.

Appendix 9 Remote Study Visits for Active Participants

1. Remote visit procedures to be performed:

a. Inform the participant that the study clinic visit will be changed to a remote visit.

b. Remind the participants of their online options to complete the QOL questionnaires.

   i. In the event the participant is unable to complete them online, email or mail the QOL Questionnaires to the participant. The participant should keep them and provide the completed questionnaires when they return to the clinic, or the site can send a pre-printed and labeled Airway Bill to return via courier.

c. Schedule a home-health care nurse to visit the participant and collect the required lab samples.

   i. Schedule a local lab visit to collect at a minimum the platelet count. Obtain the lab name and information when scheduling the test. If the platelet count cannot be obtained because a lab is not available, please notify your local contract research associate as this is both an efficacy and safety assessment.

d. Collect the following critical study data via the phone call or video call. Document the conversation of the 5 items below.

   i. New or changes in AEs/SAEs

   ii. New or changes in concomitant medications

   iii. New or changes in immune thrombocytopenia concomitant medications

   iv. Confirm IMP compliance

   v. Platelet count (done, yes/no, result and units)

2. Documentation:

a. Source documents: Continue to observe good documentation practice and record all details of the remote study visit, including:

   i. Participant Study Identification

   ii. Date and method of remote visit

   iii. Site staff who performed remote visit

   iv. All remote data collected

b. Electronic Case Report Forms: Enter all data collected within 5 days of the remote visit. Any data not collected should be entered as ‘Not done’ in the applicable eCRF.

c. If the participant is not able to complete the QOL electronically, after the participant completes the paper questionnaire, the participant can read their answers to the coordinator over the phone with the coordinator recording the verbal conversation in a telephone report noting the test name, question number and the participant verbal answer. This telephone report will reside with the source data and entered into the electronic data capture system. The data will then later be verified against the original supplied by the participant. This deviation in the process will be noted by the Study Coordinator and documented.

Appendix 10 Country-Specific Requirements

Appendix 10.1 UK country-specific requirements

- Synopsis and Section 5.2, Exclusion criteria, criterion 17: For participants in the UK, a positive QuantiFERON®-TB Gold Plus at Screening will result in exclusion. The 3 conditions to allow inclusion with a positive test do not apply to participants in the UK.
- Section 6.4.4, Treatment blinding/unblinding: For participants in the UK, the Investigator can unblind a participant via the IWRS if deemed medically necessary without previous consultation with the Sponsor medical monitor, but the Sponsor medical monitor should be notified.

Appendix 10.2 Germany country-specific requirements

- Inclusion criterion #1: Participants to be enrolled in Germany will be men and women with primary ITP with duration of >3 months who are ≥18 years of age.
- Table 1, Schedule of Assessments, Blinded Treatment Period; Table 2, Schedule of Assessments, Open Label period; Table 3, Schedule of assessments, Long-term Extension: Participants in Germany must be tested for SARS-CoV-2 infection within 1 week prior to or up to 2 days after each monthly in clinic visit. Every effort should be made to comply with local or institutional testing procedures. If the time required for obtaining results exceeds this testing window, an extension may be granted by the medical monitor. The test may no longer be required (with approval from the ethics committee) if the local regulations change with control of the SARS-CoV-2 pandemic.
- Direct to participant shipment is only allowed until 31 December 2023, as long as the ordinance "Ordinance to ensure the supply of medically necessary products to the population in the event of an epidemic caused by the SARS-CoV-2 Coronavirus (Ordinance to Ensure the Supply of Medicines)" is in place in Germany.

Appendix 10.3 Austria, Turkey, and Ukraine country-specific requirements

- Inclusion criterion #1: Participants to be enrolled in Austria, Turkey, and Ukraine will be men and women with primary ITP with duration of >3 months who are ≥18 years of age.

Appendix 10.4 Canada country-specific requirements

- Synopsis and Section 5.2, Exclusion criteria, criterion 17: For participants in Canada, a positive QuantiFERON®-TB Gold Plus at Screening will result in exclusion. The 3 conditions to allow inclusion with a positive test do not apply to participants in Canada.

Appendix 10.5 China country-specific requirements

- Synopsis and Section 3.2.4 Exploratory Endpoints: the following exploratory endpoints are not applicable to participants in China
  - BTK occupancy
  - Changes from baseline in TPO levels, T-lymphocytes/ B-lymphocytes/natural killers (T/B/NK) counts, immunoglobulin (IgG, IgG1, IgG4, IgM, IgE) levels

- (Optional) Vaccine-specific IgG response during treatment

- Synopsis Schedule of Assessments, Section 4.1.2 Blinded Treatment Period (Weeks 1 to 25), Section 4.1.3 Open Label Period (Weeks 25 to 53), Section 4.1.4 End of Study visit (Four Weeks post last dose of study drug), Section 4.1.5 Long-Term Extension, Section 7.9.8 Bruton's Tyrosine Kinase (BTK) Occupancy, and Section 8.1 Specification of the Efficacy Parameters: Exploratory biomarker samples (including BTK occupancy, TPO levels, T/B/NK counts, immunoglobulin levels, hemolysis panel, and optional vaccine-specific IgG response) will not be collected for participants in China. Therefore, exploratory biomarker sampling and assessment are not applicable to participants in China.
- Future use of biological samples is not applicable for participants in China. All residual mandatory samples collected from participants in China have to be destroyed upon CSR completion at the latest.

Appendix 10.6 Italy country-specific requirements

- For the pediatric population, Tanner staging should be performed at W1, W25, W53, EOS/ET, and every 1 year during the LTE period until the end of the trial or until the participant reaches Tanner stage V (whichever comes first). Self-reported Tanner staging or records from pediatric assessments in standard of care settings are considered acceptable.
- Details regarding risk mitigation measures for exceeding blood sample volumes are provided in the Laboratory Manual.

Appendix 10.7 EU (EEA countries) and UK-specific requirements

Synopsis, Section 3.1 Objectives, Section 3.1.1 Efficacy Objectives, Section 3.2 Endpoints, Section 10.3.9 Primary Efficacy Analysis; In the UK and countries within the EU (EEA countries):

- The primary endpoint in the blinded treatment period is 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.
- The primary efficacy analysis is as follows: The primary analysis will compare the proportion of participants in the adult ITT population who achieve durable platelet response defined as platelet counts at or above 50,000/μL for ≥8 out of the 12 scheduled observations in the last 12 weeks of the 24-week blinded treatment period in the absence of rescue medication between rilzabrutinib and placebo with a Cochran-Mantel-Haenszel test using the two stratification factors at a 2-sided alpha level of 0.05. Participants who do not respond in the first 12 weeks and enter the open label period will be treated as non-responders in the primary analysis. Participants who discontinue the study due to a rilzabrutinib-related AE, lack of efficacy or receive rescue medication (including an increase in allowed concomitant ITP medications dose) will be considered as non-responders. Sensitivity analyses will be conducted on the primary analysis.
- In the blinded treatment period, the following is a key secondary objective: To evaluate the change from baseline in IBLS.

- In the blinded treatment period, the following is a key secondary efficacy endpoint (the last endpoint in the multiplicity control): Change from baseline in IBLS assessment at Week 25
- Key secondary efficacy analysis: Compare the change from baseline in IBLS assessment at Week 25

EU (EEA countries) only
Throughout the protocol, the allowed age range for pediatric participants is ≥10 to <18 years, where permitted by local regulation.

Synopsis and Section 5.1, Inclusion criterion 1:

Participants will be male and female with primary ITP with duration of >6 months in pediatric participants aged ≥10 to <18 years (where allowed by local regulation) and duration of >3 months in adults ≥18 years.

Synopsis and Section 5.1, Inclusion criterion 3:

An average of 2 platelet counts at least 5 days apart of <30,000/µL during the screening period and no single platelet count >35,000/µL, within 14 days prior to the first dose of study drug.

- Pediatric participants who are 10 to < 12 years must have body weight ≥30 kg and must additionally be determined to need treatment for ITP as per clinical assessment by the Investigator.

Safety reporting to the agency

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.

Contingency measures for the COVID-19 pandemic:

For European countries contingency measures are currently only applicable for the COVID- 19 pandemic, not in other unspecified pandemics or emergencies.

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained).

Study intervention

The following contingencies may be implemented to make clinical supplies available to the participant for the duration of the emergency.

- The DTP supply of rilzabrutinib from the PI/site/Sponsor where allowed by local regulations and agreed upon by the participant. See Appendix 10.2 for Germany-specific requirements.

If a participant has to stop rilzabrutinib due the COVID-19 pandemic, reinitiation of the study intervention can only occur once the Investigator has determined, according to his/her best judgement, that 1) rilzabrutinib did not contribute to the occurrence of the concerned AE and 2) the selection criteria for the study are still met (refer to Section 5). Reinitiation of the study

intervention will be done under close and appropriate clinical/and or laboratory monitoring and following the instructions provided in Section 7.4.

Study assessments and procedures

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed and screening and/or enrollment may be temporarily delayed. Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If on-site visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data including 1) collection of samples for screening and clinical safety analyses, 2) ECG and vital signs assessments, and 3) AEs. See Table 1, Table 2, and Table 3 for examples of laboratory samples that may be collected at home.
- The Sponsor will continue safety reporting. Investigators will continue to collect AE information from participants through alternative means such as via phone calls or telemedicine if the participant is unable to visit the site. If on-site visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed when central labs cannot be performed due to a government declared national emergency. If the central lab assessment is related to a study endpoint and the sample cannot be shipped to the central laboratory, then analysis should be performed locally. Sponsor must have access to the normal ranges and certification information of any additional laboratory assessments used to support the evaluation of results.
- Contingencies implemented due to an emergency will be documented.
- Monitoring and quality assurance activities may need to be temporarily adjusted with the rights and safety of the participants in mind and according to local requirements. Once the situation is normalized, increased on-site monitoring may be necessary for a period of time to ensure any impact from adjusted monitoring is rectified.
- Remote source data verification (rSDV) should only be used if suitable data protection, including data security and the protection of personal data – is ensured with consideration given to pseudonymization of data. One of the following three methods for rSDV may be used as appropriate and in compliance with local regulations:
  - Sharing pseudonymized copies of trial related source documents with the monitor; this may be done electronically where manageable by the site staff;
  - Direct, suitably controlled remote access to trial participants' electronic medical records;

  - Video review of medical records with clinical site team support, without sending any copy to the monitor and without the monitor recording images during the review.

- Participant source data collected remotely are likely to require re-monitoring, in particular if it was based on pseudonymized documents, which cannot be considered as source documents, and considering that remote monitoring is expected to only have focused on the most critical information. Source documents/source data to be made available under the rSDV include but not limited to documents/data related to primary endpoints, SAEs, important medical events, or the reasons for exclusion of a subject from the trial.
- To share pseudonymized trial related source documents via secure platform, site staff should create copies of the requested trial participant's records, redact (ie, pseudonymize and mask any unnecessary personal information unrelated to the trial) the copies, and identify them with the trial participant identification code in the trial.

Statistical analyses

Analyses and methods required to evaluate the impact on efficacy (eg, missing data) and safety will be detailed in the SAP.

Informed consent

Contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs). If re-consent is necessary for the implementation of new urgent changes in trial conduct, alternative ways of obtaining reconsent should be considered such as contacting the trial participants by phone or video call and obtaining oral consent. If available per local regulation, a validated electronic system may be used per usual practice.

Trial participants should be informed in a timely manner by the Investigator of any changes to the trial conduct, eg, cancelled visits, change in laboratory testing or delivery of IMP. Any change in study conduct initiated by the Investigator due to an emergency situation should be reported to the Sponsor. The Sponsor will report these changes to the competent authorities and ethics committees.

Appendix 11 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Appendix 11.1 Clinical trial protocol version 1.1 (06 August 2020)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended to provide correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 5.1, Inclusion Criteria	Removed inclusion criterion #6, adolescent weight requirement.	Correction.

Appendix 11.2 Clinical study protocol version 1.2 Germany (28 October 2020)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.1 to incorporate Germany specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Inclusion criteria (Criterion 1); Section 5.1, Inclusion criteria (Criterion 1)	Added a bullet statement under this criterion stating the following: "The following countries will only enroll patients ≥18 years of age: Germany	Country-specific requirement.
Table 1, Schedule of assessments - blinded treatment period Table 2, Schedule of assessments - open label period Table 3, Schedule of assessments - Long-Term Extension	Footnote added to each table (footnote "r" for Table 1, footnote "l" for Table 2, and footnote "f" for Table 3 specifying that patients in Germany must be tested for SARS-CoV-2 infection within 1 week prior to or up to 2 days after each monthly in clinic visit.	Addition of country-specific requirements for Germany.
Section 2.5, Study design rationale; Appendix 8, Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19	Text added that remote monitoring is not available in Germany.	Addition of country-specific requirements for Germany.

Appendix 11.3 Clinical study protocol version 1.2 Canada (03 November 2020)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.1 to incorporate Canada specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Individual patient stopping rules	Added the information regarding serious allergic reaction to rilzabrutinib or placebo to list of individual patient stopping rules	Correction to match protocol Section 7.3.1.
Synopsis, Individual patient stopping rules; Section 7.3.1, Individual patient stopping rules	Added the information regarding HIV/AIDs, viral hepatitis (B and C) infection.	Added to align across rilzabrutinib immune thrombocytopenia (ITP) clinical studies.
Appendices, Appendix 8, Guidelines to sites for delayed patient visits or missed visits due to travel restrictions or any foreseeable impacts of COVID-19.	Added section regarding urine pregnancy testing for women of childbearing potential.	To clarify how to collect pregnancy test results if remote visits are needed for COVID-19.

Appendix 11.4 Clinical study protocol version 1.3 Canada (06 November 2020)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.2 Canada to incorporate Canada specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Table 2, Schedule of assessments - open label period	Removed row for Hep B& C, and HIV assessment.	Correction; not applicable to this open-label period.

Appendix 11.5 Clinical study protocol version 1.2 United Kingdom (09 November 2020)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.1 to incorporate United Kingdom specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Exclusion Criteria (Criterion 17); Section 5.2, Exclusion criteria (Criterion 17)	Exclusion criterion #17: added the information that for patients in the UK with a positive QuantiFERON®-TB Gold Plus (QFT Plus) at Screening is exclusionary	Addition of country-specific requirements for UK.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.4, End of study visit (four weeks post last dose of study drug)	Updated section title; updated first sentence in section for consistency with section title.	Clarification.
Section 4.1.5, Long-term Extension (LTE)	Moved text defining completion for the overall clinical study to this section.	Clarification.
Section 6.4.4, Treatment blinding/unblinding	Revised the text regarding the unblinding deemed by the Investigator to be medically necessary with notification to the Sponsor	Addition of country-specific requirements for UK.

Appendix 11.6 Clinical study protocol version 1.2 Austria (03 December 2020)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.1 to incorporate Austria specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Inclusion criteria (Criterion 1); Section 5.1, Inclusion criteria (Criterion 1)	Added a bullet statement under this criterion stating the following: "The following countries will only enroll patients ≥18 years of age: Austria"	Country-specific requirement.

Appendix 11.7 Clinical study protocol version 1.2 France (04 December 2020)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.1 to incorporate France specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 6.2.1, Rilzabrutinib/placebo	Added sentence to state that frequency and/or severity of GI AEs may be improved if rilzabrutinib/placebo is taken with food.	Clarification to align with Investigator's Brochure.
Section 6.5.2 Particular Permissible Medications	Parenthetical statement added to first bullet as follows: a TPO-RA (authorized for the treatment of ITP).	Clarification.
	Second sub-bullet added to first bullet as follows: Administration of corticosteroids and TPO-RAs should follow corresponding updated package inserts/SmPCs of the marketing authorization.	Clarification of guidance for investigators.

Appendix 11.8 Clinical study protocol version 1.2 Norway (15 December 2020)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.1 to incorporate Norway specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Inclusion criteria (Criterion 6); Section 5.1, Inclusion criteria (Criterion 6)	Added clarification of reproductive potential as follows: fertile, following menarche and until becoming post-menopausal unless permanently sterile.	Clarification.

Appendix 11.9 Clinical study protocol version 1.3 France (02 January 2021)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.2 France to incorporate France specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Inclusion criteria (Criterion 2); Section 5.1, Inclusion criteria (Criterion 2)	Added “or any contra-indication” to any appropriate courses of standard of care ITP therapy.	Clarification.

Appendix 11.10 Clinical study protocol version 1.2 Turkey (06 January 2021)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.1 to incorporate Turkey specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Inclusion criteria (Criterion 1); Section 5.1, Inclusion criteria (Criterion 1)	Added a bullet statement under this criterion stating the following: “The following countries will only enroll patients ≥18 years of age: Turkey”	Country-specific requirement.

Appendix 11.11 Clinical study protocol version 1.2 Ukraine (21 January 2021)

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended from protocol version 1.1 to incorporate Ukraine specific requirements.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Inclusion criteria (Criterion 1); Section 5.1, Inclusion criteria (Criterion 1)	Added a bullet statement under this criterion stating the following: "The following countries will only enroll patients ≥18 years of age: Ukraine"	Country-specific requirement.

Appendix 11.12 Clinical study protocol version 2.0 (19 February 2021)

This amended clinical trial protocol (version 2.0) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This protocol is being amended to incorporate feedback from health authorities as well as other clarifications deemed necessary by the Sponsor.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated protocol version and date; added company logo.	Administrative.
Approval of the protocol	Removed signature page.	For consistency with current Sanofi protocol template and processes. Protocol approval is conducted via electronic signature.
Investigator's agreement	Removed signature page.	For consistency with current Sanofi protocol template and processes. A separate signature page will be available.
Protocol amendment summary of changes	Inserted table to include the history related to the initial Clinical Study Protocol and the Amended Clinical Study Protocol. Inserted for the current Amended Clinical Study Protocol text related to the overall rationale and protocol amendment summary of changes table.	New section per Sanofi protocol template and process.
Synopsis, Objectives, Endpoints; Section 3.1, Objectives; Section 3.2, Endpoints	Added "Other Secondary Objectives" heading to clarify that safety objectives, pharmacokinetic objectives, and quality of life objectives are secondary objectives; and to distinguish them from the key secondary endpoints.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Individual patient stopping rules	In the list of stopping rules added as a second bullet the information regarding serious allergic reaction to rilzabrutinib or placebo.	Correction to match protocol Section 7.3.1.
Synopsis, Individual patient stopping rules; Section 7.3.1, Individual patient stopping rules	Added as a fifth bullet the information regarding HIV/AIDs, viral hepatitis (B and C) infection.	Added to align across rilzabrutinib immune thrombocytopenia (ITP) clinical studies.
Synopsis, Inclusion criteria (Criterion 1); Section 5.1, Inclusion criteria (Criterion 1)	Added a bullet statement under this criterion stating the following: "The following countries will only enroll patients ≥18 years of age: Austria, Germany, Turkey, Ukraine," with reference to Appendix 10.	Country-specific requirement.
Synopsis, Inclusion criteria (Criterion 2); Section 5.1, Inclusion criteria (Criterion 2)	Added "or any contra-indication" to any appropriate courses of standard of care ITP therapy.	Clarification.
Synopsis, Inclusion criteria (Criterion 6); Section 5.1, Inclusion criteria (Criterion 6)	Added clarification of reproductive potential as follows: fertile, following menarche and until becoming post-menopausal unless permanently sterile.	Clarification.
Synopsis, Exclusion criteria (Criterion 7); Section 5.2, Exclusion criteria (Criterion 7)	Revised text as follows: "Immunosuppressant drugs other than CSs within **5 times the elimination half-life of the drug or** 14 days of Study Day 1**, whichever is longer."**	Updated per Food and Drug administration feedback to ensure appropriate duration of wash-out period.
Synopsis, Exclusion criteria (Criterion 16); Table 1 Schedule of assessments - blinded treatment period (footnote "g"); Section 5.2, Exclusion criteria (Criterion 16)	Exclusion criterion #16, second bullet revised as follows: "If **HBV DNA is negative and** HBsAB titer is ≥100 IU/L, patients may be enrolled." New footnote "g" added to Table 1. The units were also corrected from 100 IU/mL to IU/L.	Added to emphasize that hepatitis B virus DNA has to be negative.
Synopsis, Exclusion Criteria (Criterion 17); Section 5.2, Exclusion criteria (Criterion 17)	Exclusion criterion #17: added the information that for patients in the UK with a positive QuantiFERON®-TB Gold Plus (QFT Plus) at Screening is exclusionary; reference to Appendix 10 for country-specific requirements added.	Addition of country-specific requirements for UK.
Synopsis, Randomization procedure	Revised text to specify that randomization will be carried out separately for the two age groups and added details.	Different randomization procedures are now used for the two age groups; therefore, randomization is done separately for each group.
Synopsis, Primary efficacy analysis, Key secondary efficacy analysis; Section 10.3.2, Intent-to-treat (ITT) population	Revised text to specify that efficacy analyses will be performed using the ITT population.	Health authority request; ITT includes all randomized patients and preserves the rigor of randomization.
Table 1, Schedule of assessments - blinded treatment period	Removed previous footnote "b" regarding AEs after Screening and before baseline, and renumbered footnotes.	Correction; The footnote is not applicable.
	Replaced "PRN1008" with "rilzabrutinib or placebo" in footnotes "o" and "p."	Correction.

Section # and Name	Description of Change	Brief Rationale
Table 1, Schedule of assessments - blinded treatment period; Section 4.1.1, Screening (Day -28 to Study Day -1 Predose)	Added "estimated glomerular filtration rate (eGFR)" to serum chemistry performed at screening in footnote "k" in Table 1; added creatinine phosphokinase (CPK) and estimated glomerular filtration rate (eGFR) to the bullet for serum chemistry in Section 4.1.1.	Correction; previously missing.
Table 2, Schedule of assessments - open label period	Removed row for Hep B& C, and HIV assessment.	Correction; not applicable to this open-label period.
	Added PK sample to ET/unscheduled visit.	Correction; previously missing.
	Added a new footnote "a" regarding measurement of height, and renumbered footnotes.	Clarification and consistency with Table 1.
	Revised footnote "e" to remove text regarding serum pregnancy test at screening.	Correction; not applicable to this open-label period.
	Revised footnote "f" to remove text regarding creatinine phosphokinase (CPK) at screening.	Correction; not applicable to this open-label period.
Table 1, Schedule of assessments - blinded treatment period Table 2, Schedule of assessments - open label period Table 3, Schedule of assessments - long-term extension	Footnote added to each table (footnote "r" for Table 1, footnote "m" for Table 2, and footnote "f" for Table 3 specifying that patients in Germany must be tested for SARS-CoV-2 infection within 1 week prior to or up to 2 days after each monthly in clinic visit along; further details provided in Appendix 10.	Addition of country-specific requirements for Germany.
Section 2.1, Overview of immune thrombocytopenia (ITP); Section 15, References	Second paragraph: Added sentence regarding clinical response rate of second line treatment with TPO-RAs, and added reference (Ghanima 2019).	Additional information provided.
Section 2.5, Study design rationale	Updated second paragraph with additional details regarding platelet counts.	Additional information provided.
Section 2.5, Study design rationale; Appendix 8, Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19; Appendix 9, Remote study visits for active patients (where allowed by local regulations)	Text added that remote monitoring is not available in Germany with reference to Appendix 10.	Addition of country-specific requirements for Germany.
Section 4.1.1, Screening (Day -28 to Study Day -1 predose) (Second bullet); Section 4.1.2, Blinded Treatment Period (Weeks 1 to 24) (First bullet)	Added text clarifying that screening lab results will be verified for eligibility determination, with the exception of hemoglobin, which is to be rechecked prior to dosing.	Clarification.
Section 4.1.3, Open label period (Weeks 25 to 53)	Removed height assessment from Week 29.	Correction, to match the procedures as listed in Table 2.
	Added "and dispense rilzabrutinib if entering Long Term Extension" to last bullet for Week 53.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.4, End of study visit (four weeks post last dose of study drug)	Updated section title; updated first sentence in section for consistency with section title.	Clarification.
Section 4.1.5, Long-term extension (LTE)	Moved text defining completion for the overall clinical study to this section.	Clarification.
Section 6.2.1, Rilzabrutinib/placebo	Added sentence to state that frequency and/or severity of GI AEs may be improved if rilzabrutinib/placebo is taken with food.	Clarification to align with Investigator's Brochure.
Section 6.4.4, Treatment blinding/unblinding	To the text regarding the unblinding deemed by the Investigator to be medically necessary, added a reference to Appendix 10 for UK country-specific requirements.	Addition of country-specific requirements for UK.
Section 6.5.1, Prohibited medications	Added text specifying that patients in Germany who need other immunosuppressant therapy during the study must be withdrawn, with a reference to Appendix 10.	Addition of country-specific requirements for Germany.
Section 6.5.2, Particular permissible medications	Parenthetical statement added to first bullet as follows: a TPO-RA (authorized for the treatment of ITP).	Clarification.
	Second sub-bullet added to first bullet as follows: Administration of corticosteroids and TPO-RAs should follow corresponding updated package inserts/SmPCs of the marketing authorization.	Clarification of guidance for investigators.
	Second bullet: Revised text to state "IVIg or **high-dose** CS, **platelet infusion, or anti-D immunoglobulin infusion** as rescue medication."	Correction to align across the protocol sections.
Section 7.6.6, Early Termination visit	Added a statement regarding having patients return for the ET visit as soon as possible after the last dose of rilzabrutinib or placebo.	Clarification.
Section 7.7.3, Medical history	Added text specifying that medical history will include a history of all underlying medical conditions **within the last 10 years** as well as detailed ITP history.	Clarification.
Section 9.4, Pregnancy	Added information regarding reporting pregnancy AEs/SAEs, including complication or elective termination, abnormal pregnancy outcomes. and post-study pregnancy related SAEs.	Clarification.
Section 10, Statistical methods	Updated text regarding SAP in first paragraph.	Clarification.
Section 10.3.3, Modified ITT (mITT) Population	The mITT population will not be used for primary efficacy analyses. Thus, the second sentence in this section was revised to state the following: "The mITT population may be used for sensitivity analyses."	Health authority request; the ITT population will be used for primary efficacy analyses.
Section 11, Investigator Responsibilities	Updated to specify that investigators will sign the separate protocol and amended protocol agreement form.	Template update.
Section 14.1, Local regulations/Declaration of Helsinki	Updated section with new template language.	Template update.

Section # and Name	Description of Change	Brief Rationale
Section 16, Appendices, Appendix 8, Guidelines to sites for delayed patient visits or missed visits due to travel restrictions or any foreseeable impacts of COVID-19.	Added section regarding urine pregnancy testing for women of childbearing potential.	To clarify how to collect pregnancy test results if remote visits are needed for COVID-19.
Appendix 10, Country-specific requirements	Appendix 10 added per Sanofi template to include country-specific requirements for UK, Germany, Austria, Turkey, and Ukraine.	Template update; incorporation of country-specific requirements into appendix.
Appendix 11, Protocol Amendment History	Appendix 11 added per Sanofi template.	Template update.
Throughout document	Replaced "PRN1008" with "rilzabrutinib" as applicable. Sanofi protocol number (EFC17093) add to protocol as applicable.	Administrative update.

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections) were implemented throughout the protocol.

Appendix 11.13 Amended Clinical Trial Protocol 02 (21 July 2021)

This amended clinical trial protocol 02 (Amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment to Protocol PRN1008-018 are：

- To incorporate feedback from health authorities as well as other clarifications deemed necessary by the Sponsor.
- To implement new clinical safety results and measures based on updated Investigator's Brochure (IB).
- To add the exploratory endpoint in order to evaluate the impact of the IMP on vaccine responses.
- To add other exploratory efficacy endpoints to enable comparison between studies and projects.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page and throughout the protocol	Document formatting revisions were made. The header and footnote were updated. Compound number, Sponsor name and regulatory information were updated on the title page.	Administrative changes to comply with Sanofi standard.
Synopsis: Investigational Plan, Section 4 Study Design	Stratification by age during randomization was removed.	Correction as age is not a stratification factor for this study.

Section # and Name	Description of Change	Brief Rationale
Synopsis: Investigational Plan, Table 1: Schedule of Assessments - Blinded Treatment Period, footnote b, Section 4 Study Design	The definitions of responder and non-responder were revised to: "At the end of 12 weeks of treatment**,** patients will be assessed for achieving a platelet response defined as platelet count of ≥50,000/μL OR a platelet count between ≥30,000/μL and <50,000/μL and at least doubled from baseline **at any time during the first 12 weeks and in the absence of rescue medication in the 4 weeks prior to the latest elevated platelet count that meets platelet response criteria**. Baseline is defined as the average of all the patient's Predose platelet counts (Screening and Study Day 1). • Participants who respond will continue the blinded treatment period for a total of 24 weeks before entering the open label Period. • Participants who do not respond (including patients who receive rescue medication **after Week 8**) will be allowed to discontinue from the study or may enter the 28-week open label period at the end of Week 12, receiving treatment with 400 mg BID of rilzabrutinib. Initial study medication assignment will remain blinded. … After completing the Open Label Period, patients who demonstrate a platelet response defined as platelet counts ≥50,000/μL or ≥30,000/μL and at least doubled from baseline at ≥50% of the visits **without receiving rescue therapy** during the last 8weeks of the open label period, will be allowed to enter the LTE."	Clarification
Synopsis: Planned number of participants, Sample size, and Section 10.1 Determination of Sample Size	The planned number of adult participants was updated to "approximately **194**". The Sample Size in Synopsis and Section 10.1 were revised to: "The adult sample size chosen for this study was selected to achieve enrollment of **129** adult patients (≥18 years) on rilzabrutinib and **65** adult patients on placebo."… "The primary efficacy endpoint…A sample size of **194** (**129** versus **65** adult patients in the rilzabrutinib versus placebo arms, respectively) will provide **86%** power to detect a **20%** difference in response rates between the 2 arms (**25% vs 5%**, in the rilzabrutinib	Sample size recalculated based on increasing the study power from 80% to 8 6% to detect a 20% difference in response rates between the 2 study arms.

Section # and Name	Description of Change	Brief Rationale
	versus placebo arms, respectively), using the Fisher's Exact test with a 0.01 two-sided significance level."	
Synopsis: Inclusion criteria #1, and Section 5.1 Inclusion criteria #1	Revised to: Participants will be **male and female** with primary ITP with duration of >6 months in ages 12 to <18 years (**If not permitted per the country-specific requirements, see Appendix 10 country-specific requirements)** and duration of >3 months in ages 18 years and above.	Grammar and stylistic change
Synopsis: Inclusion criteria #3, and Section 5.1 Inclusion criteria #3	"Participants from 12 to <18 years of age must additionally be determined to need treatment for ITP as per clinical assessment by the Investigator" was added as a note to clarify this criterion for pediatric patients.	Changes made according to the opinion of the EMA Pediatric Committee to ensure a thorough individualized assessment of each potential adolescent patient's need for treatment under the proposed protocol.
Synopsis: Inclusion criteria #4, and Section 5.1 Inclusion criteria #4	This criterion was updated to: "Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 X 10^9/L, AST/ALT ≤1.5 x upper limit of normal (ULN), albumin ≥3 g/dL, total bilirubin ≤1.5 x ULN, **[unless the patient has documented Gilbert syndrome]**, estimated glomerular filtration rate (GFR) >50 (Cockcroft and Gault method)"	Clarification
Synopsis: Inclusion criteria #5, Section 4.1.2 Blinded Treatment Period (Weeks 1 to 24), and Section 5.1 Inclusion criteria #5	This criterion was updated as: "Hemoglobin >9 g/dL **within 1 week** prior to Study Day 1". Therefore, the following was removed from Section 4.1.2 for Day 1 Week 1: "with the exception of hemoglobin which is to be rechecked prior to dosing".	Allow flexibility to get hemoglobin test results within 1 week prior to Study Day 1.
Synopsis: Inclusion criteria #6, Section 5.1 Inclusion criteria #6, and Appendix 13 Contraceptive and Barrier Guidance	Inclusion criterion regarding contraceptive use by men and women was revised. Male contraception requirements were added. Appendix 13 was added as part of standard appendices in Sanofi protocol template.	Updated contraceptive language and appendix as per Sanofi standard.
Synopsis: Exclusion criteria #10, Section 5.2 Exclusion criteria #10	Revised to: "Use of known strong-to-moderate inducers or inhibitors of CYP3A within **14** days or 5 half-lives (whichever is longer) of Study Day 1 and until the end of the active treatment period"	Correction to ensure no pharmacokinetic impact on rilzabrutinib by time-dependent CYP3A inhibitors and CYP3A inducers.

Section # and Name	Description of Change	Brief Rationale
Synopsis: Exclusion criteria #17, Section 5.2 Exclusion criteria #17, and Appendix 10 Country-specific requirements	Revised to: Positive QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus) at Screening unless all of the following 3 conditions are true (**see Appendix 10 country specific requirements**). Appendix 10.4 Canada country-specific requirements added with the following text: "**• Synopsis and Section 5.2, Exclusion criteria, criterion 17: For patients in Canada, a positive QuantiFERON®-TB Gold Plus at Screening will result in exclusion. The 3 conditions to allow inclusion with a positive test do not apply to patients in Canada.**"	Stylistic change and addition of country-specific requirements for Canada.
Synopsis: Exclusion criteria #18, Section 5.2 Exclusion criteria #18	Revised to: "History of recurring (2 or more) serious infections requiring intravenous antibiotic**, antivirals or antifungals** therapy within the last 3 months before Study Day 1 or active serious or moderate infection ongoing on the day of randomization"	To exclude patients with history of recurring (2 or more) serious viral and fungal infections requiring intravenous antivirals or antifungals therapy within the last 3 months before Study Day 1.
Synopsis: Exclusion criteria #23, #24, Section 5.2 Exclusion criteria #23, #24	Added the following exclusion criteria: **23. Positive COVID-19 molecular test (if COVID-19 testing required per local guidelines to be determined for each site)** **24. COVID-19 vaccine within 14 days prior to Study Day 1 or planned during the last 12 weeks of blinded treatment period**	COVID-19 testing, and COVID-19 vaccination requirement added to ensure patients safety during the study and as per local health authority recommendations. In addition, recent reports suggest exacerbation of immune thrombocytopenia following COVID-19 vaccination among patients with ITP (Kuter 2021). Administration of COVID-19 vaccination during the last 12 weeks of the blinded treatment period is prohibited because it may confound the primary endpoint results.
Table 1: Schedule of Assessments - Blinded Treatment Period	Added "SARS-CoV-2 test" at Screening in Table 1 and corresponding footnote v. **"v. COVID-19 molecular test (if COVID-19 testing is required per local guidelines to be determined for each site)."**	
Section 6.6.1 Prohibited Medications	Added: **"*COVID-19 vaccine* is prohibited during the last 12 weeks of the blinded treatment period"**	
Synopsis: Exploratory Endpoints, and Section 3.2.4 Exploratory Endpoints	Added the following 3 exploratory endpoints: • **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**	Added exploratory efficacy to enable comparison between studies and projects.

Section # and Name	Description of Change	Brief Rationale
	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.**	
Synopsis: Exploratory Endpoints, and Section 3.2.4 Exploratory Endpoints	The following exploratory endpoint: "(Optional) Vaccine-specific IgG response during treatment" was added.	Changes made to address the purpose of adding the exploratory endpoint in order to evaluate the impact of the IMP on vaccine responses, and for consistency with this added exploratory endpoint, changes were made through the protocol.
Synopsis: Table 1: Schedule of Assessments - Blinded Treatment Period, Table 2: Schedule of Assessments - Open Label Period, Table 3: Schedule of Assessments - Long-Term Extension	"(Optional) sample for vaccine-specific IgG" was added in Table 1. Table 2 and Table 3. Footnotes "s", "n" and "i" were added to Table 1, 2 and 3, respectively, to clarify the requirements regarding the optional sample for vaccine-specific IgG: "**Optional collection of 2 blood samples for vaccine-specific IgG in rum (see Section 7.7.9 for a list of routine vaccines). The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine-specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded**".	
Section 4.1.2 Blinded Treatment Period (Weeks 1 to 24), Section 4.1.3 Open Label Period (Weeks 25 to 53), Section 4.1.4 End of Study visit (Four Weeks post last dose of study drug), Section 4.1.5 Long-Term Extension (LTE)	Added "(Optional) vaccine-specific IgG response" as one of the collected exploratory laboratory blood samples.	
Section 7.7.9 Vaccine IgG (optional)	Section 7.7.9 was developed for optional Vaccine IgG collection and requirements.	
Section 8.1 Specification of the Efficacy Parameters	Added "optional vaccine IgG levels" as one of the planned laboratory assessments in Section 8.1.	

Section # and Name	Description of Change	Brief Rationale
Synopsis: Exploratory Endpoints, and Section 3.2.4 Exploratory Endpoints	Refer to Appendix 10 Country-specific requirements for China-specific endpoints after the exploratory endpoints listing.	Changes made to comply with Sanofi standards and to clarify country-specific requirements for participants in China.
Synopsis: Table 1: Schedule of Assessments - Blinded Treatment Period, Table 2: Schedule of Assessments - Open Label Period, Table 3: Schedule of Assessments - Long-Term Extension	Footnotes “r”, “m”, and “h” were added for in Table 1, Table 2 and Table 3, respectively, referring to Appendix 10 for country-specific requirements.	
Section 4.1.2 Blinded Treatment Period (Weeks 1 to 24), Section 4.1.3 Open Label Period (Weeks 25 to 53), Section 4.1.4 End of Study visit (Four Weeks post last dose of study drug), Section 4.1.5 Long-Term Extension (LTE)	For each bullet point “Collect exploratory laboratory blood samples” reference to **Appendix 10 country-specific requirements)** has been added.	
Section 7.7.8 Bruton’s Tyrosine Kinase (BTK) Occupancy, Section 7.7.9 Vaccine IgG (optional), Section 8.1 Specification of the Efficacy Parameters	Refer to Appendix 10 country-specific requirements as these 3 sections contains assessments that are not applicable for participants in China.	
Appendix 10.5 China country-specific requirements	This entire section was added to outline country specific requirements for participants from China, such as exploratory biomarker samples and optional blood samples for vaccine-specific IgG response will not be collected for participants in China; exploratory endpoints regarding BTK occupancy, biomarker levels, and (optional) vaccine-specific IgG response are not applicable to participants in China, and specific requirement was mentioned for biological samples handling and disposal.	
Synopsis: Pharmacokinetics and Section 10.3.12 Pharmacokinetic Analysis (PK)	Added “**metabolites, if applicable”** as part of the analytes in plasma samples.	To allow PK assessment of relevant metabolites of rilzabrutinib.
Section 7.7.7 Pharmacokinetic Assessments	Added the following text: “**Plasma samples will be obtained for PK characterization of rilzabrutinib as outlined in the SoA (see Table 1, Table 2 and Table 3). If applicable, residual plasma samples could be utilized to assess PK of relevant metabolites of rilzabrutinib (eg, PRN834 & PRN4400). Concentrations at each time point will be reported.** **Pharmacokinetic samples could be used for testing analytical method performance such as comparability**.”	

Section # and Name	Description of Change	Brief Rationale
Synopsis: Table 1: Schedule of Assessments - Blinded Treatment Period	Added footnote "t" to "inform consent" at Screening. **"t. Participants enrolled into the adolescent portion of the trial will still be considered as part of the adolescent group with all the planned assessments when they turn 18 years old, unless specified, and they should be re-consented with an adult consent."**	Clarification
Synopsis: Table 1: Schedule of Assessments - Blinded Treatment Period, Section 4 Study Design	Added following text to both Table 1 footnote "w" and Section 4: "**During the blinded treatment period (Week 13 to Week 24): Participants who discontinue from the blinded treatment period due to safety or other reasons and choose to join the open label period will undergo the Week 25 assessments at their next scheduled visit."** Added the following text in Section 4: "**Participants who discontinue the blinded treatment period and choose not to join the open label period, should attend an ET visit as shown in the SoA (Table 1) for collection of data at the time of study discontinuation and for follow-up and any further evaluations that need to be completed.**"	To clarify the study design and visits/assessments to be performed for patients who discontinue from the blinded treatment period.
Synopsis: Table 1: Schedule of assessments - Blinded Treatment Period, Table 2: Schedule of assessments - Open Label Period	Added footnote "u" and "s" in Table 1 and Table 2, respectively, to clarify hematology samples collected at weekly lab visits are only for platelet count collection. **"This is only for collecting platelet count and can be conducted on-site or at home during a nurse visit."** Footnote "o" and "p" in Table 1, and footnote "j" and "k" in Table 2 were revised to clarify time window information for PK and BTK occupancy sampling.	Clarification and include time window for PK sampling time points
Synopsis: Table 1: Schedule of Assessments - Blinded Treatment Period, Table 2: Schedule of Assessments - Open Label Period, Table 3: Schedule of Assessments - Long-Term Extension	Added a row for "paper diary" to be collected at the same time of the rilzabrutinib dispensation.	Implement paper diary to document IMP administration information.
Synopsis: Table 3: Schedule of Assessments - Long-Term Extension	QOL questionnaires footnote "g" was revised to include ITP-KIT for adolescent patients and PGIC assessments for adult patients.	Correction

Section # and Name	Description of Change	Brief Rationale
Synopsis: Table 1: Schedule of Assessments - Blinded Treatment Period, Table 2: Schedule of Assessments - Open Label Period, Table 3: Schedule of Assessments - Long-Term Extension, and Appendix 10.2 Germany country-specific requirements	The previous footnotes "r", "m" and "f" were removed from the Table 1, 2 and 3, respectively. Added footnote "r" to refer to Appendix 10.2 Country-specific requirements in Table 1 and added a row for "SARS-CoV-2 test" with new footnotes "m" and "h" referring to Appendix 10 for country-specific requirements for Germany in Table 2 and Table 3. The following specific requirements was revised in Appendix 10.2 Germany country- specific requirements: "Participants in Germany must be tested… **The test may no longer be required** (with approval from the ethics committee) if the local regulations change with control of the **SARS-CoV-2** pandemic".	Update SARS-CoV-2 test language according to Germany regulations, and the SoA (Table 1, Table 2 and Table 3) were rearranged to better present this specific assessment.
Synopsis: Table 2: Schedule of Assessments - Open Label Period	In column title, "SD169" and "SD365" were corrected to "First" day of WK25 and WK53, respectively. Footnotes "o", "p" and "q" were added: **"o. Week 25/SD169 visit is the last visit of the blinded treatment period and also serve as the start of the open label period.** **p. For patients who will enter the open label period directly after 12 weeks of blinded treatment, they will attend the Week 13/SD85 visit which corresponds to the Week 25/SD169 visit (Table 2), this would be their last visit of the blinded treatment period and also the start of the open label period. They will follow the open label period SoA from Week 29 (Table 2) starting at their next scheduled visit.** **q. For patients who will enter the open label period directly after 12 weeks of blinded treatment, the last day (EOT visit) in open label period will occur on Week 41/SD281."**	Correction and clarification
Synopsis: Table 2: Schedule of Assessments - Open Label Period, and Section 4.1.3 Open Label Period (Weeks 25 to 53)	In synopsis Table 2: "ECG (12-lead, single), PK sample, and BTK Occupancy (at selected sites)" were ticked at Week 41. Footnote "r" was added clarifying the fact that these assessments will be performed "**only for patients who will join the open label part at Week 13**". Updated Section 4.1.3, "ECG (12-lead, single), PK sample, and BTK Occupancy (at selected sites)" were added into Week 41 assessments.	Update to add ECG, PK and BTK occupancy assessments at Week 41 for patients that will join the open label period at Week 13.

Section # and Name	Description of Change	Brief Rationale
Synopsis: Table 3: Schedule of Assessments - Long-Term Extension, and Section 4.1.5 Long-Term Extension (LTE)	In synopsis Table 3: "ECG (12-lead, single)", "hemolysis panel", and "immunoglobulin levels" were added and ticked at End of Study visit. Updated Section 4.1.5, refer to Section 4.1.4 for the end of study visit assessments in the LTE.	Update to align the end of study visit assessments in open-label period and LTE.
Section 2.4 Clinical Experience	Updated clinical experiences as per new data included in the latest IB with the data cut-off date of 22 April 2021.	Update and consistency
Section 2.4.1 Safety	Updated clinical safety results as per new data included in the latest IB with the data cut-off date of 22 April 2021.	To implement new clinical safety results based on updated IB and to develop sections regarding benefit and risk assessments as per Sanofi standard.
Section 2.7 Overall Risk-Benefit Assessment, Section 2.7.1 Risk assessment, Section 2.7.2 Benefit assessment, and Section 2.7.3 Overall benefit: risk conclusion	Section 2.7 Overall Risk-Benefit Assessment was revised. Three subsections "Section 2.7.1 Risk assessment, Section 2.7.2 Benefit assessment, and Section 2.7.3 Overall benefit: risk conclusion" were developed under Section 2.7 to implement new findings in the updated IB.	
Synopsis: Table 3: Schedule of Assessments - Long-Term Extension	Added footnote "a" for concomitant medication to indicate the taper of corticosteroid (CS) and/or thrombopoietin receptor agonist (TPO- RA) is permitted.	Updated text to address corticosteroid taper in LTE.
Section 4 Study Design	Added text: **"In the LTE part, reductions in the doses or withdrawal of concomitant ITP medications (an oral CS and/or a TPO-RA) will also be permitted if the participant achieves platelet count of ≥50,000/µL in three scheduled visits (over 12 weeks). Retreatment with the same medication(s) and doses of ITP concomitant medication(s) used at baseline (an oral CS and/or a TPO-RA), changing the dose or initiation of new ITP medications (an oral CS and/or a TPO-RA) will also be allowed. Tapering of concomitant CS should be performed in accordance with the schedule in Section 6.6.2."**	
Section 6.6.2 Particular Permissible Medications	The corticosteroid tapering rules added	
Section 4 Study Design: Figure 1: Study Design Flow Chart	Updated study schema to better present the study design.	Correction and consistency
Section 4.1.2 Blinded Treatment Period (Weeks 1 to 24), and Section 4.1.3 Open Label Period (Weeks 25 to 53)	"PK blood sample" was rearranged as a separate bullet from the exploratory laboratory blood samples.	Correction

Section # and Name	Description of Change	Brief Rationale
Section 6.4.2 Destruction of Investigational Product	Revised as "When the study is completed, any used and unused study medication (eg, empty, partially used, and unused containers) **will be destroyed on-site or returned** to the **depot of destruction** as requested."	Clarified to match Sanofi standard process of IMP destruction.
Section 6.5 Treatment of Overdose	Section 6.5 Treatment of Overdose was developed. Overdose of rilzabrutinib is defined, and the information of handling and reporting of rilzabrutinib overdose was implemented.	To implement definition and handling procedures of rilzabrutinib overdose to align with other rilzabrutinib protocols.
Section 6.6.1 Prohibited Medications, and Appendix 10.2	Revised text specifying that all patients who need other immunosuppressant therapy during the study **must** be withdrawn. In Appendix 10.2, the country-specific language related to Section 6.6.1 was therefore removed.	Correction and consistency
Section 7.7.10 Immune Thrombocytopenia (ITP) Assessment Tools (IBLS, ITP-PAQ, ITP KIT) and throughout the protocol	Section 7.7.10 was updated to introduce the ITP Bleeding Scale (IBLS). Throughout the protocol, "ITP-BAT" was corrected as "ITP Bleeding Scale" or "IBLS".	Correction as previously the IBLS was referred to as ITP-BAT by mistake.
Section 9.3.9 Adverse events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting, Appendix 12 AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The entire Section 9.3.9 was updated and replaced with Sanofi standard process regarding AE, SAE, and other safety reporting. New subsections were developed, the definition of adverse event of special interest (AESI) was introduced. Appendix 12 was added as part of standard appendices in Sanofi protocol template.	Updated section per Sanofi protocol template and process. The definition of AESI was added to align across rilzabrutinib clinical development program.
Section 10.3.4 Pharmacokinetic (PK) population	The definition of pharmacokinetic population was updated to "All patients who receive at least one dose of study medication **in the safety population** and have sufficient data for PK analysis."	Correction
Section 10.3.8 Safety and Tolerability Analysis	Included AESIs in the planned safety statistical analysis.	Consistency
Appendix 1 ITP Disease Activity - ITP Bleeding Scale (IBLS) Appendix 2 ITP Disease Activity - ITP-PAQ Appendix 3 ITP Disease Activity - ITP-KIT Appendix 4 General Quality of Life Evaluation: EQ-5D-5L Appendix 5 Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)	Updated questionnaires with watermarks and copyright information (where applicable).	Updated questionnaires that comply with Sanofi standard.

Section # and Name	Description of Change	Brief Rationale
Appendix 6 Strong-to-Moderate CYP3A Inhibitors and Inducers and Sensitive CYP3A Substrates	The table of Strong-to-Moderate CYP3A Substrates, Inhibitors and Inducers and Sensitive CYP3A Substrates were updated.	Updated the Appendix 6 according to updated information from US Food and Drug Administration websites.
Appendix 11: Protocol Amendment History	This entire section was updated with the protocol amendment01 summary of changes table.	Changes made to comply with Sanofi standards.

In addition, other minor editorial changes (eg, grammatical, stylistic, references, and minor typographical error corrections) were implemented throughout the protocol.

Appendix 11.14 Amended Clinical Trial Protocol 03 (11 August 2022)

The primary reasons for this amendment to Amended Clinical Trial Protocol 02:

- To modify the primary endpoint and objective to specify participants having 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. This change does not apply to the EU (EEA countries) and the UK.
- To require conducting platelet count testing at local laboratories.
- To provide guidelines for temporary discontinuation of study medication.
- To move the IBLS assessment from the Secondary to the Exploratory endpoints (not applicable for the EU [EEA countries] and UK).
- To introduce a fatigue assessment using Item 10 of the ITP-PAQ, as a Key Secondary endpoint.
- To provide new instructions for the long-term extension duration and study visit schedule.
- To add efficacy objectives and endpoints to the open label and long-term extension periods.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Sponsor address revised from “220 E Grand Avenue South San Francisco CA 94080, USA” to “55 Corporate Drive Bridgewater, NJ 08807”	To provide the new address of Principia Biopharma Inc.
Protocol Amendment Summary of Changes: Document History; Appendix 11: Protocol Amendment History	Expanded the table to include previous country-specific protocol amendments and added the relevant changes to the protocol history in Appendix 11.	To comply with the Sanofi template

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis: Duration of Study Participation, Investigational Plan: Study Design; Section 4.1: Duration of study participation	Changed the duration of participation for participants who enter the long-term extension (LTE) to indicate that they will continue to receive treatment until the time expected for the last participant who enters the LTE to complete 12 months.	Duration of long-term extension changed to allow participants who respond to the study medication to continue on treatment, and to evaluate the long-term safety and efficacy of treatment with rilzabrutinib
Section 1 Synopsis: Number of Study Sites	Revised the number of study sites from approximately 125 sites to approximately 150 sites worldwide.	Number of sites increased due to an increase in study sample size in the adult population and inclusion of new countries (China and Japan) and to help achieve the enrollment goals
Section 1 Synopsis: Objectives, Primary Efficacy Objective Blinded Treatment Period); Endpoints, Primary Efficacy Endpoint; Section 3.1.1 Efficacy Objectives, Primary Efficacy Objective; Section 3.2.1 Primary Efficacy Endpoint	The primary objective and endpoint for the blinded treatment period was revised to specify that the assessment will be based on the durability of 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. See Appendix 10.7 for efficacy EU (EEA countries) and UK-specific requirements.	Correction to better define the primary objective (durable platelet response) and the criteria for meeting the primary efficacy objective/endpoint and to reflect the feedback from FDA pertaining to the definition of platelet durable response. Considering the EMA feedback, the durable platelet response will be defined based on the previous definition of the primary endpoint (proportion of adult 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) will be applicable to EU (EEA countries) and UK only, See Appendix 10.7.
Section 1 Synopsis: Objectives, Key Secondary Efficacy Objectives (Blinded Treatment Period); Section 3.1.1 Efficacy Objectives, Key Secondary Efficacy Objectives (Blinded Treatment Period)	Added the following key secondary efficacy objective evaluated during the blinded treatment period: "To evaluate the effect of rilzabrutinib versus placebo on the change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (≥18 years) at Week 13" Deleted: "To evaluate the effect of rilzabrutinib versus placebo on the change from baseline in Idiopathic Thrombocytopenic Purpura Bleeding Scale (IBLS) assessment". This revision is not applicable to EU (EEA countries) and the UK as per RA (EMA) feedback (See Appendix 10.7).	To position Item 10 of the ITP-PAQ instrument within the key secondary objectives. Included "rilzabrutinib versus placebo", to be clear about the comparison. To re-position the change in IBLS to be an exploratory endpoint except in the EU (EEA countries) and the UK as per RA

Section # and Name	Description of Change	Brief Rationale
	The second key secondary efficacy objective in the blinded treatment was revised to: 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.	(EMA) feedback (See Appendix 10.7). To be consistent with the endpoint below.
Section 1 Synopsis: Endpoints, Key Secondary Efficacy Endpoints (Blinded Treatment Period); Key Secondary Efficacy Analyses Section 3.2.2 Key Secondary Efficacy Endpoints; Section 10.3.10 Key Secondary Efficacy Analysis	Revised the Key Secondary Efficacy endpoints for the blinded treatment period as follows: • Inserted an endpoint assessing change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (≥18 years) at Week 13 • Deleted the endpoint evaluating the change from baseline in IBLS assessment at Week 25 The second, key secondary efficacy endpoint in the blinded treatment was 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.	Fatigue endpoint added to key secondary endpoints. IBLS assessment moved to exploratory endpoints except for EU (EEA countries) and the UK as per RA (EMA) feedback; see Appendix 10.7. Correction to the endpoint to include responders with platelet count ≥30,000 /μL and at least doubled from baseline. The platelet count <50,000 /μL was removed because it excludes patients with platelet response of ≥50,000 /μL from the analysis.
Section 1 Synopsis: Endpoints; Section 3 Objectives and Endpoints	Added new subsections to specify exploratory endpoints that will be evaluated during the open label period and long-term extension to distinguish them from those assessed during the blinded treatment period.	To clarify the exploratory endpoints that will be evaluated during the open label and long-term extension periods.
Section 1 Synopsis: Objectives, Other Secondary Objectives; Endpoints, Other Secondary Endpoints; Section 3.1.2 Other Secondary Objectives; Section 3.2.3 Other Secondary Endpoints	Added the following other secondary efficacy objective and endpoint, respectively: • To evaluate the stability of platelet response of rilzabrutinib. • 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).	To include a long-term efficacy endpoint that can be evaluated at the blinded treatment period, open label period and the long-term extension.

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis: Inclusion criteria #3; Section 5.1: Inclusion criteria #3	IC #1 revised to: Patients will be male and female with primary ITP with duration of >6 months in pediatric participants aged 12 to <18 years (pediatric participants aged 10 to <12 years will be enrolled in the EU [EEA countries] only; refer to Appendix 10.2, Appendix 10.3 and Appendix 10.7 for country-specific requirements) and duration of >3 months in adults aged ≥18 years.	Revision to indicate specific age criteria for the EU (EEA countries)
	IC #3 revised to: An average of 2 platelet counts at least 5 days apart of <30,000/µL during the screening period, and no single platelet count >35,000/µL within 14 days prior to the first dose of study drug • Pediatric participants must additionally be determined to need treatment for ITP as per clinical assessment by the Investigator (see Appendix 10.7 for EU [EEA countries] specific criteria)	In accordance to EMA feedback, country-specific requirement (body weight limit) was included to ensure that the exposure to the IMP among pediatric participants 10 to >12 years old is comparable to pediatric participants ≥ 12 years old.
Section 1 Synopsis: Endpoints, Exploratory Endpoints (Blinded Treatment Period); Section 3.2.4 Exploratory Endpoints	Revised the Exploratory endpoints in the blinded treatment period as follows: Inserted: "Change from baseline in Idiopathic Thrombocytopenic Purpura Bleeding Scale (IBLS) assessment at Week 13 and Week 25" Specified that the change in all ITP-PAQ domains will be assessed from baseline to Week 25 and from Week 13 to Week 25. In addition, specified that the change in all but Item 10 (Fatigue Scale) will be assessed from baseline to Week 13 as an exploratory endpoint.	IBLS assessment moved to exploratory endpoints except for EU (EEA countries) and the UK as per RA (EMA) feedback; see Appendix 10.7. Assessment of fatigue moved from exploratory to key secondary endpoints.
Section 1 Synopsis: Endpoints, Exploratory Endpoints (Blinded Treatment Period); Section 3.2.4.1 Blinded Treatment Period; Section 7.9 Study Assessments; Appendix 5: Patient Global Impression of [Fatigue] Severity (PGIS-Fatigue), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC)	Added an exploratory endpoint assessing "disease-related fatigue using the PGIS-Fatigue scale". Added a subsection 7.9.12 with a description of the PGIS-Fatigue and the questionnaire to Appendix 5.	To add an assessment that focuses on fatigue severity.
Section 1 Synopsis: Study Design; Section 4: Study Design	Added the following paragraph: 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 factors used for stratification (for adult participants) or balance (for pediatric participants) are splenectomy status (yes/no), and by severity of thrombocytopenia (Inclusion Criteria 3 platelet counts <15,000/µL or ≥15,000/µL).	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis: Sample Size; Section 10.1 Determination of Sample Size	Revised text: A sample size of approximately 194 (129 versus 65 adult participants in the rilzabrutinib versus placebo arms, respectively) will provide 86% power to detect a 20% difference in response rates as defined in the primary endpoint (Section 3.2.1) between the 2 arms (25% vs 5%, in the rilzabrutinib versus placebo arms, respectively), using the Fisher's Exact test with a 0.01 two-sided significance level. Added paragraph to Section 10.1: 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 (Bussel 2018). The participants who are not evaluable for primary efficacy due to dropout or missing data will be considered as non-responders.	To clarify the assumptions and rationale of the study sample size calculation.
Section 1 Synopsis: Primary Efficacy Analysis, Section 10.3.9: Primary Efficacy Analysis	Revised text: The primary analysis will compare the proportion of participants in the adult ITT population who achieve durable platelet response defined as 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 medication (provided that at 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) between rilzabrutinib and placebo with a Cochran-Mantel-Haenszel test using the two stratification factors at a 2-sided alpha level of 0.01. Participants who do not respond in the first 12 weeks and enter the open label period will be treated as non-responders in the primary analysis. Added: "The primary endpoint will be analyzed for adult and pediatric participants separately. Platelet counts conducted locally will be used for the primary endpoint analysis. Platelet counts conducted centrally at Clinic Visits will be used as a back-up for missed or non-analyzable local lab samples."	Consistency with primary endpoint modification. Clarify that platelet count assessments for the primary endpoint should be conducted at the local laboratories.
Section 1 Synopsis: Other statistical considerations; Section 10 Statistical methods; Section 10.4 Interim Analysis	New section added to further clarify the separate analyses for adult and pediatric participants due to different enrollment expectations, and to clarify that additional analyses may be performed at the Sponsor's discretion for purposes of regulatory filings, publications, or future planning after the early analysis.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis: Table 1, Table 2, and Table 3; Section 4.1 Duration of Study Participation	The term "Paper Diary" has been revised to "Patient Medication Diary" and the collection of this diary newly specified in Section 4.1.	To align with correct naming of the document.
Section 1 Synopsis: Table 1, and Footnote a	Added the following text to footnote a: "The screening period can be up to -31 days of Study Day 1."	Clarification
Section 1 Synopsis: Table 1, Footnote d	Added: Medical history should include vaccine history.	Clarification
Section 1 Synopsis: Table 1, Footnote l; Table 2: Footnote g	Text added to footnote: Local laboratories will be used for platelet analysis required at ALL visits (ie, Clinic Visits and Weekly Lab Visits in between Clinic Visits). The central laboratory will be used for the analyses required at Clinic Visits including hematology, differential, and reticulocytes. The results of hematology, differential and reticulocytes obtained at local laboratories will be used only if the central lab results of Clinic Visits are missing due to any reason. Central platelet counts assessed at Clinic Visits will be used if local platelet results are missing for any reason.	Hematology footnote modified to clarify that platelet counts should be conducted at the local laboratories.
Section 1 Synopsis: Table 1, Footnote o	Revised this footnote to exclude the Week 25 assessment (included with Table 2), and deleted the last sentence: "At Week 53 and ET, random timepoint samples will be collected and the time of sample and time of the last dose of rilzabrutinib or placebo will be captured."	Clarification to align with SoA
Section 1 Synopsis: Table 1, Footnote p	Deleted the Week 25 assessment (included in Table 2) and removed below text from footnote p: "At Week 53 a random timepoint sample will be collected and the time of draw and time of the last dose of rilzabrutinib or placebo will be captured."	Clarification to align with SoA
Section 1 Synopsis: Table 1, Footnote q	Added: The PGIC will be collected starting after Day 1.	The PGIC asks the participant to describe disease-related symptoms since starting the study medication.
Section 1 Synopsis: Table 1 Footnote u, Table 2 Footnote r	Revised: Table 1 Footnote u to: "This visit is for platelet count assessment and can be conducted on-site or remotely. After the end of treatment (EOT) visit, weekly platelet count assessment is not required; however, it is up to the Investigator to decide whether to conduct weekly platelet assessments using unscheduled visits, if deemed necessary for participant safety."	Clarification

Section # and Name	Description of Change	Brief Rationale
	Table 2 Footnote r (previously footnote s) to: "This visit is for platelet count assessment and can be conducted on-site or remotely. Lab visits will occur weekly from Week 25 to Week 53. The Investigator can request that the participant visits the clinic for additional platelet monitoring during unscheduled visits if needed. After the end of treatment (EOT) visit, weekly platelet count assessment is not required; however, it is up to the Investigator to decide whether to conduct weekly platelet assessments using unscheduled visits, if deemed necessary for participant safety."	
Section 1 Synopsis: Table 1	Added annotation and corresponding footnote x to indicate the end of study visit for participants who discontinue treatment during the blinded treatment period. "All participants who discontinue treatment during the blinded or open-label period need to have an ET visit as specified in Table 1 and an End of Study visit (4 weeks after last IMP intake) as specified in the End of Study visit in Table 2 (See End of Study Table 2)."	Clarification of end of study visit for early termination during blinded treatment period
Section 1 Synopsis: Table 2	Deleted ECG, PK and BTK assessments at Week 41 and the ECG assessment at Week 29.	To decrease the study burden as assessments at these visits are not needed.
Section 1 Synopsis: Table 2, Footnote c	Added the following text to footnote c: "Adult participants are also required to complete ECG at Week 25."	Clarification
Section 1 Synopsis: Table 2, Footnote j	Revised footnote j to: "At Week 25 visit, PK samples for participants aged 18 years or older will be collected Predose (within 1.5 hours predose) and 2 hours postdose (±15 mins). At the Week 25 visit, PK samples for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (±5 mins), 2 hours (±5 mins) and 4 hours (±15 mins), 6 hours (±15 mins). At these visits, participants will wait to take their morning dose until they complete the blood draw of pre-dose sample. At Week 53 and ET visits, a random timepoint PK samples will be collected and the time of sample and time of the last dose of rilzabrutinib will be captured."	Clarification to align with SoA
Section 1 Synopsis: Table 2, Footnote k	Revised footnote k to: "At Week 25 visit, BTK occupancy samples for participants aged 18 years or older will be collected Predose (within 1.5 hours predose) and 2 hours postdose (±15 mins). At Week 25 visit, BTK Occupancy samples for pediatric participants (see Appendix 10.7 for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (±5 mins), 2 hours (±5 mins) and 4 hours (±15 mins), 6◦hours (±15 mins). At these visits, participants will wait to take their	Clarification to align with SoA

Section # and Name	Description of Change	Brief Rationale
	morning dose until they complete the blood draw of pre-dose sample. At Week 53, a random timepoint BTK occupancy sample will be collected and the time of sample and time of the last dose of rilzabrutinib will be captured"	
Section 1 Synopsis: Table 2, Footnote p	Added the below text to footnote p: "for a total of 28 weeks"	Clarification
Section 1 Synopsis: Table 2, Footnote q	Revised footnote q to: "For participants who will enter the open label period directly after 12 weeks of blinded treatment, they will follow the open-label extension SoA (**Week 25 to Week 53**) which means that they will be treated on the open-label part for a total of 28 weeks. After Week 53, the participants will follow the SoA according to their eligibility for the LTE period."	To clarify the end-of-treatment visit for participants entering the open-label extension.
Section 1 Synopsis: Table 2	Footnote "r" in Amended Clinical Trial Protocol 02 was deleted. The previous footnote "s" is now footnote "r".	No longer needed
Section 1 Synopsis: Table 2, Footnote s	Revised footnote "r" (previously footnote "s"): "This visit is for platelet count assessment and can be conducted on-site or remotely. Lab visits will occur weekly from Week 25 to Week 53. The Investigator can request that the participant visits the clinic for additional platelet monitoring during unscheduled visits if needed. "	Clarification
Section 1 Synopsis: Table 3; Section 4.1.5. Long-Term Extension (LTE)	Revised the clinic visit schedule for participants in the long-term extension. Column header of Table 3 revised to: "Clinic Visits Every 28 Days for the first year of LTE then every 3 months thereafter". Deleted "visits every 28 days for 12 months" from the main header.	Clarification of frequency of clinic visits for participants in the long-term extension
Section 1 Synopsis: Table 3	Deleted the PK assessment at the ET/Unscheduled visit Added check marks and annotation "m" to specify physical exam and ECG assessments, collection of medication diary and performance of SARS-CoV-2 test at the ET visit, and a footnote "m" to indicate that the assessment is for the ET visit only. Added an ECG assessment at the Week 53 visit and a footnote 'n' to indicate that assessments performed at the Open Lapel period Week 53 visit will be used at the starting visit (Week 53) of the LTE.	Assessment not needed Assessment needed Clarification
Section 1 Synopsis: Table 3	Added annotation c, e, f, m and n and corresponding footnotes in the table and annotations of other footnotes changed accordingly.	Clarification and consistency with other schedules of assessments
Section 2.4 Clinical Experience	Deleted details of studies in patients.	Refer reader to the Investigator's Brochure instead

Section # and Name	Description of Change	Brief Rationale
Section 2.4.3 Pharmacokinetics and Pharmacodynamics	Revised text for the first 2 paragraphs: "Rilzabrutinib is rapidly cleared from the plasma, with a terminal half-life of approximately 4 hours, maximum concentration time of approximately 2 hours after ingestion, and a volume of distribution of 149 L after intravenous administration. No significant accumulation was observed after multiple dosing. Approximately 3% of rilzabrutinib is excreted unchanged in the urine. Rilzabrutinib is available in a tablet formulation for investigation in-patient populations in clinical studies. Food delays the time of observed maximum plasma concentration (Tmax) by 1.5 h and decreases AUC and Cmax of rilzabrutinib by 20% and 30%, respectively, which is not considered to be clinically relevant**.** Rilzabrutinib showed approximately linear increases in exposure between doses of 150 mg and 600 mg."	Updated clinical pharmacology reference data
Section 2.4.4 Drug-Drug Interaction Potential	Text revised to: "Rilzabrutinib is a substrate of the CYP3A isoenzyme. In clinical drug-drug interaction studies, the CYP3A inhibitor ritonavir increased plasma rilzabrutinib concentrations (PRN1008-014**)** and the CYP3A inducer rifampin decreased plasma rilzabrutinib concentration (PRN1008-024); therefore, concomitant use of strong and moderate CYP3A inhibitors or inducers should be avoided. Rilzabrutinib is also a substrate of P-gp from in-vitro studies. However, the P-gp inhibitor quinidine didn't change plasma concentrations of rilzabrutinib (PRN1008-024); thus, rilzabrutinib could be administered with P-gp inhibitors clinically."	Updated clinical pharmacology reference data
Section 2.6 Dose Rationale	Paragraph added to provide a dosing rationale for pediatric participants 10 to <18 years of age.	Provide a rationale for the selected dosing in this population.
Section 2.7.1 Risk Assessment Table 4	Revised mitigation strategy text for infection to: "Documented vaccinations per local guidelines are required. Serum immunoglobulin levels will be monitored throughout the study. Participants who received live vaccine within 28 days before first dose will be excluded. Live vaccines are not allowed during treatment. Participants with evidence suggestive of active TB are excluded. Participants with history of serious infections requiring intravenous therapy with the potential for recurrence are excluded."	Changed the duration in which participants may receive a live vaccine prior to first dose from 12 weeks to 28 days.
Section 4 Study Design	Figure 1 inserted, which describes the decision process for assessing response in participants who have completed 12 weeks in the study.	Insertion of a visual aid to show the decision process for assessing response
Section 4.1.1 Screening (Day -28 to Study Day -1 Predose)	Added the below text to screening visit: "Perform SARS-CoV-2 molecular test (if COVID- 19 testing is required per local guidelines to be determined for each site)."	To add COVID-19 testing requirements per local guidelines.
Section 4.1 Duration of Study Participation	Collection of Patient Medication Diary added to the following Visits: Week 5 to Week 53 and the LTE visits.	Consistency with schedules of assessments

Section # and Name	Description of Change	Brief Rationale
Section 6.4.4 Treatment Blinding/Unblinding	Added the following bullets after "Allocation of participants to treatment groups will proceed through the use of an interactive web response system (IRT/IWRS) that is accessible 24 hours a day, 365 days a year.": • The randomized intervention kit number list is generated centrally by the IRT/IWRS. • The randomization and intervention allocation are performed centrally by the IRT/IWRS. The IRT/IWRS generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it. • A randomized participant is a participant from the screened population who has been allocated to a randomized intervention by the IRT/IWRS regardless of whether the intervention was received or not. Added a paragraph to specify who may unblind the data in the case of a reported SUSAR. Added a paragraph to document that the blind will be broken prior to database lock (DBL) and access provided to designated individual(s) to allow initiation of PK analyses prior to DBL.	Sponsor template and standard operating procedure requirements
Section 6.6.1 Prohibited Medications	Added "live vaccines" to the list of prohibited medications.	Live vaccines are not permitted during the study.
Section 7.3 Temporary Discontinuation; Section 7.4 Rechallenge	Two new subsections added (7.3 and 7.4) and numbering of subsections in Section 7 updated accordingly. These new subsections describe when temporary discontinuation of IMP may be considered, how to manage it, reinitiate it and what defines it.	Added to permit temporary discontinuation of IMP under certain circumstances.
Section 7.5.1 Individual Participant Stopping Rules	Added a new stopping rule related to abnormal liver tests: "Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Appendix 15 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant."	To comply with Sanofi protocol requirements.
Section 7.5.1.1 Individual Long-Term Extension Participant Stopping Rule	Section 7.5.1.1 is added for participants who may withdraw from the study if no longer responding in the LTE.	Clarification
Section 7.9.9 Vaccine IgG (optional)	The following vaccinations were removed from the list of those allowed during the study: measles (alone or in combination), or shingles (varicella zoster virus).	These are live vaccines and are therefore not permitted during the study.

Section # and Name	Description of Change	Brief Rationale
	Clarified the optional collection of vaccine-specific IgG samples applies to participants who have received at least 6 weeks of rilzabrutinib or placebo at the time of scheduled vaccination and is applicable to the blinded treatment and open label periods and long-term extension.	Clarified who the optional collection of IgG samples is intended for.
Section 7.9.10 Immune Thrombocytopenia (ITP) Assessment Tools (IBLS, ITP-PAQ, ITP-KIT)	Added a paragraph describing intention of ITP treatments and real-world evidence of the burden of fatigue in patients with ITP.	To provide a rationale for promoting fatigue assessment from an exploratory to a key secondary efficacy endpoint.
Section 7.9.15 Use of biological samples and data for future research	New section added comprising Sanofi template standard language that explains Sponsor's intent to store biological samples for research purposes from consenting participants.	Clarification and consistency with template requirements
Section 7.9.16 Overdose, medication errors, misuses or abuses of medicinal product	New section added to provide definition and instruction for reporting of overdoses, medication errors, misuses or abuses of medicinal product.	EU CTR requirement
Section 9.3.9 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting	Revised instructions for AE reporting: "The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up AEs, particularly those that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7.5).	Clarification and consistency with template requirements
Section 9.3.9.5 Pregnancy	Specified that only pregnancies reported after the first dose of the IMP, will be recorded by the Investigator and submitted to the Sponsor within 24 hours of learning of the pregnancy. Revised the timeframe of collection of details of all pregnancies from 7 days to 28 days after the last dose of study intervention: "Details of all pregnancies will be collected after the start of study intervention and until 28 days after the last dose of study intervention." Added the below text: "While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE."	Clarification to align with the SoA and Sanofi template requirements.
Section 9.3.9.6 Adverse Events of Special Interest	The "symptomatic overdose with IMP" qualifier was updated to include both serious and nonserious overdoses. Specified the immediate notification timeframe to be within 24 hours.	Clarification

Section # and Name	Description of Change	Brief Rationale
	The following text was revised: Pregnancy of a female participant entered in a study and received at least one dose of the IMP as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP.	
Section 12.2 Informed Consent	Added: Participants enrolled into the pediatric portion of the trial will still be considered as part of the pediatric group with all the planned assessments when they turn 18 years old. They should be re-consented with an adult consent when they become an adult per country-specific requirements.	Clarification
Appendix 10: Country-Specific Requirements	Added Appendix 10.6 Italy country-specific requirements: "For pediatric participants (10 to <18 years old) enrolled in Italy, eGFR will be calculated using the Bedside Schwartz Equation." Added Appendix 10.7 to 1) describe primary and key secondary endpoints specific to the EU (EEA countries) and the UK, 2) allow inclusion of children ≥10 to <18 years of age (EU [EEA] countries only) and 3 specify a body weight lower limit for pediatric participants.	Country-specific requirement Added to describe primary and secondary endpoints specific to the region and to specify new agreement with RA (EMA) to include pediatric participants ≥10 to <18 years (previously adolescents ≥12 years to <18 years).
Appendix 11: Protocol Amendment History	This entire section was updated with the country specific protocol amendments summary of changes tables.	Changes made to comply with Sanofi standards.
Appendix 11: Protocol Amendment History	This entire section was updated with the Amended Clinical Trial Protocol 02 summary of changes table.	Changes made to comply with Sanofi standards.
Appendix 12.3 Recording and follow-up of AE and/or SAE	Assessment of Intensity definitions modified to reflect NCI-CTCAE grading system.	Consistency with grading definitions in Section 9.3.3
Appendix 14: Patient Medication Diary	"Blank Patient Medication Diary" added to the appendices.	Added for reference.
Appendix 15: Liver Safety: Suggested Actions and Follow-up Assessments	Liver safety follow-up guidelines added.	Added to provide guidance on actions and follow-up assessments for ALT increase.
Throughout	1) The term "patient" was revised to "participant". 2) The term "caplet" was replaced with "tablet". 3) In most instances the term adolescent was replaced with pediatric. The term adolescent was retained in the protocol title.	1) To reflect common terminology in the template, 2) To correct naming of the formulation and 3) To reflect that participants 10 to <12 years may be enrolled in the EU (EEA countries).

In addition, other minor editorial changes (eg, grammatical, stylistic, references, and minor typographical error corrections) were implemented throughout the protocol.

Amended Clinical Trial Protocol 04 (24 July 2023)

This amended clinical trial protocol 04 (Amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment are to:

- Update the 2-sided significance level from 0.01 to 0.05 for the hypothesis testing of the primary efficacy end point.
- Clarify distinct durations of participation in the long-term extension (LTE) for the adult and pediatric populations.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page, Protocol Amendment Summary of Changes, and headers throughout	Amendment number has been revised to "04".	Administrative change to comply with Sanofi standard format.
Protocol Amendment Summary of Changes: Document History; Appendix 11: Protocol Amendment History	Expanded the table to include previous country-specific protocol amendments and added the relevant changes to the protocol amendment history in Appendix 11.	To comply with the Sanofi template.
Section 1 Synopsis: Sample size and Primary Efficacy Analysis; Section 10.1: Determination of Sample Size; Section 10.3.9: Primary Efficacy Analysis; Section 16 Appendix 10.7: EU (EEA Countries) and UK-specific Requirements	Updated the 2-sided significance level from 0.01 to 0.05 for the hypothesis testing (ie, Cochran-Mantel-Haenszel test) of the primary efficacy end point.	To align with health authority common standard, in response to the feedback received from health authority.
Section 1 Synopsis: Sample size, and Section 10.1 Determination of Sample Size	Updated the study power from 86% to 95% to reflect the update of the 2-sided significance level from 0.01 to 0.05.	Revised to reflect the impact of changing the 2-sided significance level from 0.01 to 0.05 on the study power.
	In the following sentence "up to" has been added before "30 participants": "The pediatric sample size of up to 30 participants (20 participants on rilzabrutinib and 10 participants on placebo) was determined based on clinical practice and is adequate to descriptively describe the safety and efficacy in pediatric participants."	To clarify that 30 participants is the maximum number of pediatric participants planned to be enrolled.

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis: Duration of Study Participation; Section 4.1: Duration of Study Participation	Revised text to specify that: For adult participants, the maximum duration of the long-term extension (LTE) period will be 12 months from the date of the last adult participant to enter the LTE. For pediatric participants, the maximum duration of the LTE period will be 12 months from the date of the last pediatric participant to enter the LTE.	To clarify the duration of participation in the LTE separately for adults and pediatrics. Due to low enrollment rate of pediatric population compared to adults, last participant in (LPI) of pediatrics expected to occur much later than LPI of adults.
Section 1 Synopsis: Table 1 (Schedule of assessments-Blinded Treatment Period), footnote d, Table 2 (Schedule of assessments-Open Label Period), footnote b, and Table 3 (Schedule of assessments-Long-Term Extension Period), footnote b; Sections 4.1.2: Blinded Treatment Period (Weeks 1 to 25); Section 4.1.3: Open Label Period (Weeks 25 to 53); Section 4.1.4: End of Study Visit (Four Weeks post last dose of study drug); Section 4.1.5: Long-Term Extension (LTE); Section 7.9.2: Physical Examination	Added cross references to Section 16 Appendix 10.6, Italy-specific requirement for details concerning Tanner staging in pediatric participants.	Health authority requirement to assess pubertal status in pediatric participants.
Section 1 Synopsis: Table 1 - Schedule of Assessments-Blinded Treatment Period	Added cross reference in footnote b to Figure 1, Decision tree for assessing response at Week 13 for details on calculating baseline platelet count.	To clarify how to calculate platelet count at baseline.
Section 1 Synopsis: Investigational plan; Section 4 Study Design	Updated the following text on calculating baseline platelet count: "The baseline value of platelet count is defined as the average of all the participant's Predose platelet counts (Screening and Study Day 1)."	To clarify how to calculate platelet count at baseline.
Section 4 Study Design	Added a footnote for Figure 1 on calculating baseline platelet count as below: "The baseline value of platelet count is defined as the average of all the participant's Predose platelet counts (Screening and Study Day 1). In case of availability of 3 platelet counts, the baseline platelet count will be the average of the 2 qualifying platelet counts during Screening and within 14 days before the first dose and the platelet count at Week 1 (Study Day 1). In case the second qualifying platelet count is collected at the Study Day 1 prior to the first dose, the baseline platelet count will be the average of the 2 qualifying platelet counts."	

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis: Inclusion criteria #3 Section 5.1: Inclusion Criteria # 3 Section 16 Appendix 10: Country -Specific Requirements, 10.7 EU (EEA countries) and UK-specific requirements	For the following sentence, the comma is removed after "screening period" and a comma is added before the word "within": "An average of 2 platelet counts at least 5 days apart of <30,000/µL during the screening period and no single platelet count >35,000/µL, within 14 days prior to the first dose of study drug"	To clarify that both the qualifying platelet counts as well as the criterion of "no single platelet count >35,000/µL" should be evaluated within 14 days prior to the first dose of the study drug.
Section 1 Synopsis: Exclusion criteria #22 Section 5.2: Exclusion Criteria # 22	The following text has been added: "known allergy to any of the study medication, their analogues, or excipients in the various formulations of any agent (please see Section 6.1.1 for information on excipients)"	To exclude participants with history of known allergy to any of the study medication, their analogues, or excipients.
Section 2.5: Study Design Rationale	Deletion of the sentence related to remote site monitoring not available in Germany.	To align with Germany health authority requirements.
Sections 4.1.2: Blinded Treatment Period (Weeks 1 to 25); Section 4.1.3: Open Label Period (Weeks 25 to 53); Section 4.1.4: End of Study Visit (Four Weeks post last dose of study drug); Section 4.1.5: Long Term Extension (LTE); Section	Mean platelet volume has been added to hematology and the word "random" is added for glucose test.	For consistency with the rest of the protocol.
Section 6.1.1: Rilzabrutinib/Placebo	The following text has been added to the section describing the study intervention: "Each tablet is coated with a light orange film coat (Opadry II 85F130006) containing polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and FD&C yellow #6."	To provide additional information on excipients.
Section 9.3.9.5: Pregnancy	In the following sentences the word "will/should" has been replaced with "must": "Any female participant who becomes pregnant while participating in the study must discontinue study intervention or be withdrawn from the study."	To ensure participant's safety and to comply with regulatory guidance.
Section 9.3.9.6: Adverse Events of Special Interest	"In the event of pregnancy in a female participant, IMP must be discontinued"	
Section 12.2: Informed Consent	The following statement has been added to the section about signing a specific informed consent form (ICF) for female partners: "for male participants, in case of pregnancy of your partner, your partner will be asked to provide consent for collection of the pregnancy data."	To provide information on signing a specific ICF for the partners of the male participants.
Section 16 Appendix 8: Guidelines to Sites for Delayed Participant Visits or Missed Visits due to travel restrictions and any foreseeable impacts of COVID-19	Cross-references referring to Appendix 10.2 and Appendix 10.7 have been added.	As per addition of text in Appendix 10.2 and Appendix 10.7.
	Deletion of the sentence related to remote site monitoring not available in Germany.	To align with Germany health authority requirements.

Section # and Name	Description of Change	Brief Rationale
Section 16 Appendix 10: Country-Specific Requirements, 10.2 Germany country-specific requirements.	Deletion of the text: "Section 2.5, Study design rationale; Appendix 8, Remote site monitoring: During the coronavirus (COVID-19) pandemic, remote site monitoring is not available in Germany" Added the following text: "Direct to participant shipment is only allowed until 31 December 2023, as long as the ordinance "Ordinance to ensure the supply of medically necessary products to the population in the event of an epidemic caused by the SARS-CoV-2 Coronavirus (Ordinance to Ensure the Supply of Medicines)" is in place in Germany."	To align with Germany health authority requirements.
Section 16 Appendix 10: Country-Specific Requirements, 10.6 Italy country-specific requirement	Added the following text: "For the pediatric population, Tanner staging should be performed at W1, W25, W53, end of study (EOS)/early termination (ET), and every 1 year during the LTE period until the end of the trial or until the participant reaches Tanner stage V (whichever comes first). Self-reported Tanner staging or records from pediatric assessments in standard-of-care settings are considered acceptable." Included the following statement: "Details regarding risk mitigation measures for exceeding blood sample volumes are provided in the Laboratory Manual."	Health authority requirement to assess pubertal status in adolescent participants. To provide information on risk mitigation measures for exceeding blood sample volumes
Section 16 Appendix 10: Country-Specific Requirements, 10.7 EU (EEA countries) and UK-specific requirements	Deleted the word "adult" Sub-section: EU (EEA countries) only, added contingency measures for the COVID-19 pandemic.	Correction and consistency To provide additional information on contingency measures and data management during the pandemic.
Section 16 Appendix 11: Protocol Amendment History	Added the summary of changes from the prior amendment.	To comply with the Sanofi template.
Section 16 Appendix 12.1 Definition of AE, Events meeting the AE definition	Added the following to the lists of events meeting an adverse event (AE) criterion: "Signs, symptoms, or the clinical sequelae of any medication errors, misuse and abuse with the investigational medicinal product (IMP). An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie, intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, "getting high" (euphoria)."	To comply with the Sanofi template.

In addition, other minor editorial changes (eg, grammatical, stylistic, abbreviations, references, and minor typographical error corrections) were implemented throughout the protocol.

Appendix 12 AE and SAEs: Definitions and procedures for Recording evaluating, Follow-up, and Reporting

Appendix 12.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/LAR who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants/LAR will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participants/LARs will be collected during interview with the participants/LARs and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse, and abuse with the IMP. An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie, intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, "getting high" (euphoria).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Appendix 12.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)

- Convulsions (seizures, epilepsy, epileptic fit, absence, etc).

- Development of drug dependence or drug abuse
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

Appendix 12.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The NCI-CTCAE Version 5.0 will be used to assess the severity of AEs/SAEs.

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

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences; urgent intervention indicated: by definition also a SAE.

Death will not be recorded as a Grade 5 severity - rather the underlying condition will be recorded, and its severity graded, with death regarded as an outcome.

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

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Appendix 12.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator Study File.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Study File.

Appendix 13 Contraceptive and Barrier Guidance

Appendix 13.1 Definitions

A **woman is considered WOCBP** (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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

Women in the following categories are considered WONCBP:

1. Any female with permanent infertility due to one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.
2. Postmenopausal female

   A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
   - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.

- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Appendix 13.2 Contraception guidance

Participants should be given advice about donation and cryopreservation of germ cells prior to the start of the study intervention, in line with the fact that study intervention may affect ova up to 4 weeks and sperm up to 13 weeks (see inclusion criteria).

If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.* • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly effective methods[b] that are user dependent Failure rate of <1% per year when used consistently and correctly. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable Progestogen-only hormone contraception associated with inhibition of ovulation[c] • Oral • injectable Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

Appendix 14 Patient Medication Diary

Patient Medication Diary
PRN1008-018 (EFC17093) / Site Number: _____

LUNA

THIS SPACE IS FOR THE SITE PATIENT LABEL IF NEEDED

Patient Study ID Number:		Treatment Period:	Week ____ to Week ____
Site Staff Contact Information:			

General information:

- Please fill out the diary every day and keep it in a safe, convenient place. You will complete entries for each dose of study medication
- **Always bring this diary and your study medication (in the original container) to each study visit (even if empty)**
- Do not share your supply of study medication tablets

How to take your study medication:

- You will take the study medication **twice each day** (take the first tablet before 10 am and the second tablet after 6 pm) for approximately **28 days**, before returning to the clinic for your next monthly study visit
- The study medication should be taken with a glass (8 oz or 250 mL) of water and can be taken with or without food. We recommend that you should take the study medication with food to reduce the probability of gastrointestinal adverse events (e.g., nausea, vomiting), and their impact (intensity, duration) should they occur
- The study medication tablets should not be crushed, chewed or dissolved in water, since this can affect how the medication is absorbed by your body
- Do not take consecutive study medication doses within 8 hours of each intake
- If you forget to take your dose it can be taken up to 4 hours after your usual time
- If you miss a dose on any dosing day, do not take an extra dose the next day to compensate for the missed dose; just record the missed dose in this medication diary
- If you vomit within one hour after taking a dose, record this in your medication diary

Completion of the diary, one page is provided for each week of study medication dosing:

- Record the date when you take each dose of study medication
- Remember the dose is only one tablet each time you take the study medication
- Check Yes or No for the morning and evening dose. If you miss a dose, specify why in the **comments column**
- If you vomit after taking the study drug, record the date and time when you vomited and whether the medication was taken with or without food in the **comments column**

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Patient Medication Diary
PRN1008-018 (EFC17093) / Patient Study ID Number: _____

LUNA 3

THIS SPACE IS FOR THE SITE PATIENT LABEL IF NEEDED

Day 1 Date: _____	Day 2 Date: _____	Day 3 Date: _____	Day 4 Date: _____	Day 5 Date: _____	Day 6 Date: _____	Day 7 Date: _____
Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No
Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No
Comments:	Comments:	Comments:	Comments:	Comments:	Comments:	Comments:

Patient Medication Diary
PRN1008-018 (EFC17093) / Patient Study ID Number: _____

LUNA 3

THIS SPACE IS FOR THE SITE PATIENT LABEL IF NEEDED

Day 8 Date: _____	Day 9 Date: _____	Day 10 Date: _____	Day 11 Date: _____	Day 12 Date: _____	Day 13 Date: _____	Day 14 Date: _____
Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No
Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No
Comments:	Comments:	Comments:	Comments:	Comments:	Comments:	Comments:

Patient Medication Diary
PRN1008-018 (EFC17093) / Patient Study ID Number: _____

LUNA 3

THIS SPACE IS FOR THE SITE PATIENT LABEL IF NEEDED

Day 15 Date: _____	Day 16 Date: _____	Day 17 Date: _____	Day 18 Date: _____	Day 19 Date: _____	Day 20 Date: _____	Day 21 Date: _____
Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No
Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No
Comments:	Comments:	Comments:	Comments:	Comments:	Comments:	Comments:

Patient Medication Diary
PRN1008-018 (EFC17093) / Patient Study ID Number: _____

LUNA 3

THIS SPACE IS FOR THE SITE PATIENT LABEL IF NEEDED

Day 22 Date: _____	Day 23 Date: _____	Day 24 Date: _____	Day 25 Date: _____	Day 26 Date: _____	Day 27 Date: _____	Day 28 Date: _____
Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No
Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No
Comments:	Comments:	Comments:	Comments:	Comments:	Comments:	Comments:

Patient Medication Diary
PRN1008-018 (EFC17093) / Patient Study ID Number: _____

LUNA 3

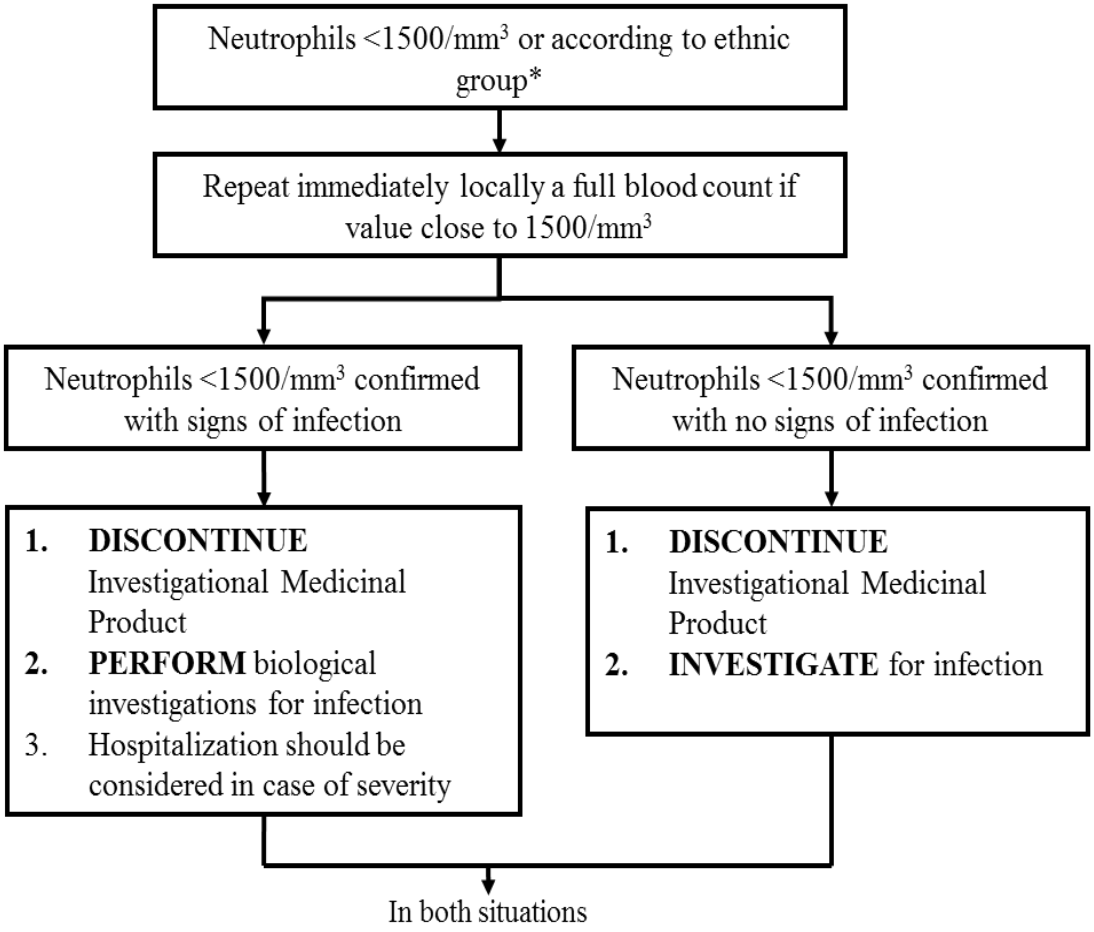
THIS SPACE IS FOR THE SITE PATIENT LABEL IF NEEDED

Back-up week only if clinic visits are not exactly 28 days apart						
Day 29 Date: _____	Day 30 Date: _____	Day 31 Date: _____	Day 32 Date: _____	Day 33 Date: _____	Day 34 Date: _____	Day 35 Date: _____
Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No	Have you taken your Morning Dose? ☐ Yes ☐ No
Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No	Have you taken your Evening Dose? ☐Yes ☐No
Comments:	Comments:	Comments:	Comments:	Comments:	Comments:	Comments:

PRN1008-018 Patient Medication Diary V3 | 23JUL2021 Page 6 of 6

Appendix 15 Liver AND OTHER Safety: Suggested Actions and Follow-up Assessments

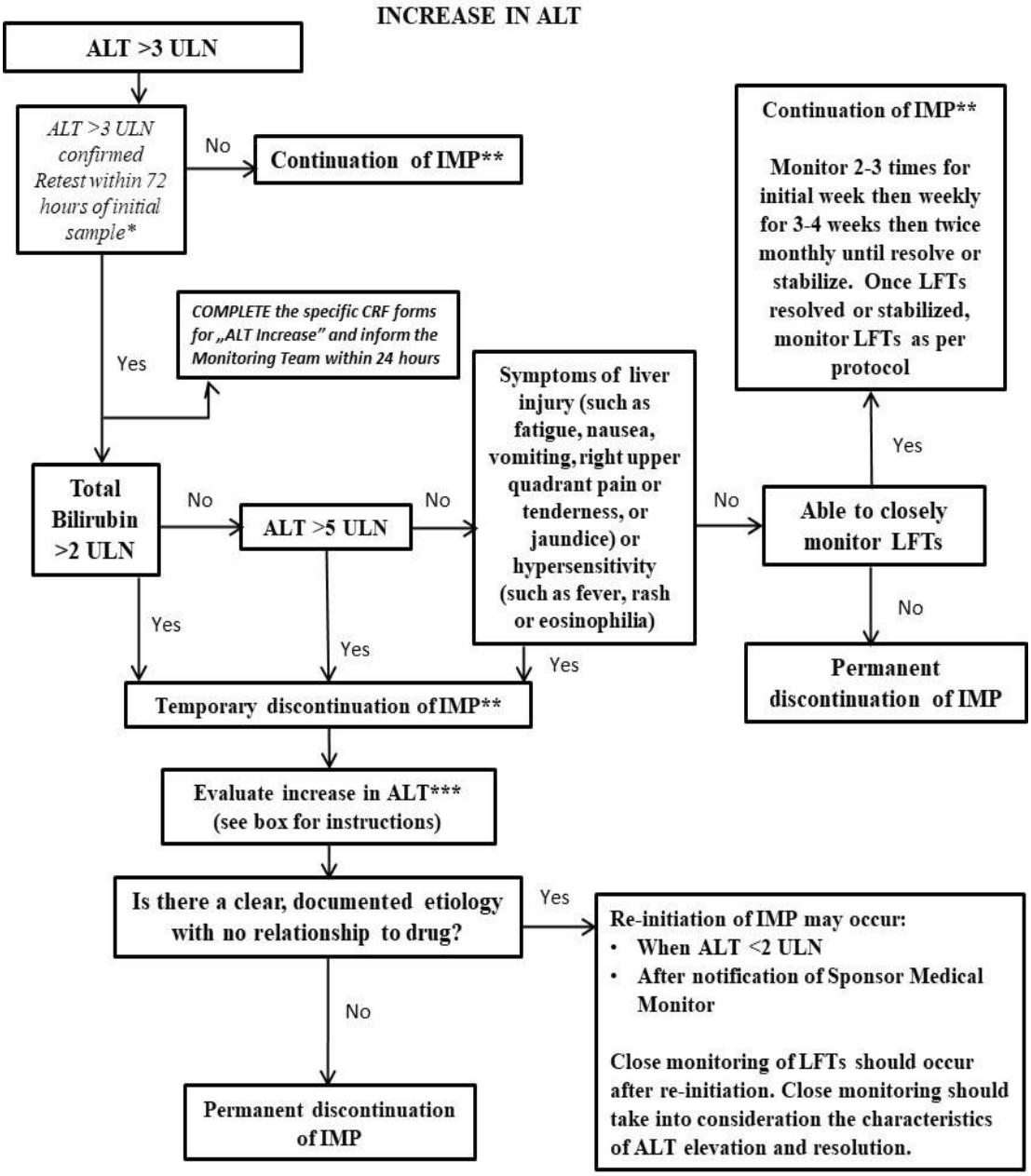
NEUTROPENIA



3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 9.3 is met.



*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

** Unless a protocol-defined criterion for permanent discontinuation is met

*** See box below

Note:

- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 9.3 or guidance on safety reporting.

Evaluate Increase in ALT***

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any recent alcohol use or travel
4. **INVESTIGATE** if any use of non-prescription medications including herbal or dietary supplements
5. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, GGT, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
6. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
7. **CONSIDER** iron, ferritin and transferrin
8. **CONSIDER** biomarkers for alcohol use (eg, urine ethyl glucuronide (EtG)]
9. **CONSIDER** consulting with hepatologist
10. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
11. **MONITOR LFTs after discontinuation of IMP:**
    - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to ≤ULN, baseline value (if baseline >ULN) or clinical resolution.
12. **FREEZE** serum sample (5ml x 2)
13. **In case of suspicion of GILBERT Syndrome**, a DNA diagnostic test should be done

Appendix 16 Collection, storage and future use of data and human biological samples

- Compliance with Member State applicable rules for the collection, storage, and future use of human biological samples (Article 7.1h)
    - This appendix is provided separately.

- Compliance with Member State applicable rules for the collection, storage, and future use of (personal) data (article 7 (1 d) of EU Regulation 536/2014)
    - This appendix is provided separately.

Signature Page for VV-CLIN-0592484 v9.0
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