PRINCIPIA BIOPHARMA
A SANOFI COMPANY

AMENDED CLINICAL TRIAL PROTOCOL 16

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Protocol Title:	An Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study Investigating the Safety, Pharmacokinetics, and Clinical Activity of Rilzabrutinib (PRN1008), an Oral BTK Inhibitor, in Patients with Relapsed Immune Thrombocytopenia
Protocol No.:	PRN1008-010 (DFI17124)
Amendment No.:	16
Development Phase:	Phase 1/2
Investigational Product:	Rilzabrutinib (PRN1008/SAR444671)
Protocol Date:	15 May 2024, Amended clinical trial protocol 16
Sponsor:	Principia Biopharma Inc. 55 Corporate Drive Bridgewater, NJ 08807 USA
Sponsor's Medical Monitor:	

Regulatory agency identifier number(s):

IND:	132668
EU trial number:	2023-509397-39
NCT:	NCT03395210
WHO:	Not applicable
EUDAMED:	Not applicable
Other	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/ countries impacted by amendment	Date, version	Comments (all global versions except Version 10.1 for Norway)
Amended Clinical Trial Protocol 16	All	15 May 2024, Version 1 (electronic 2.0)	
Amended Clinical Trial Protocol 15	All	19 Mar 2021, Version 1 (electronic 1.0)	
Amended Clinical Trial Protocol 14	All	12 Aug 2020, Version 14.0	Only submitted to United States Food and Drug Administration (FDA); not to sites or other regulatory authorities.
Amended Clinical Trial Protocol 13.1	All	16 Apr 2020, Version 13.1	
Amended Clinical Trial Protocol 13	All	05 Mar 2020, Version 13.0	Only submitted to FDA; not to sites or other regulatory authorities.
Amended Clinical Trial Protocol 12	All	05 Dec 2019, Version 12.0	
Amended Clinical Trial Protocol 11	All	24 Oct 2019, Version 11.0	
Amended Clinical Trial Protocol 10.1	Norway	21 Jan 2020, version 10.1	Norway doesn't participate in Part B, so this is the last protocol version for Norway.
Amended Clinical Trial Protocol 10	All	27 Sep 2019, Version 10.0	
Amended Clinical Trial Protocol 09	All	06 May 2019, version 9.0	
Amended Clinical Trial Protocol 08	All	24 Aug 2018, version 8.0	
Amended Clinical Trial Protocol 07	All	01 Dec 2017, version 7.0	First version under which patients were enrolled
Amended Clinical Trial Protocol 06	All	29 Sep 2017, version 6.0	Submitted to sites, but no patients enrolled under this version.

Country-specific amendments were prepared as needed during study conduct. All country-specific requirements were included in subsequent global amendments.

Previous protocol versions (versions 1.0 [02 Apr 17] through 5.0 [07 Jul 17]) were not submitted to sites. Thus, they are not included in the document history table.

Amended clinical trial protocol 16 (15 May 2024)

This amended protocol (amendment 16) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment (16) to Protocol DFI17124 are to:

- Incorporate language to comply with new EU clinical trial regulations.
- Update overall Benefit-Risk Assessment.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover Page	Removed Principal Investigator (PI) details, added NCT number, and updated with new sponsor address.	To align with new EU CTR guidelines and the latest protocol template language.
2.2 Overall Benefit-Risk Assessment	In the subsection 2.2 "Overall Benefit-Risk Assessment", added details of [redacted] which include [redacted] Added to Benefit assessment section: "Preliminary results of part A and Part B provide evidence that treatment with rilzabrutinib 400 mg BID induces a rapid and durable platelet response and continued to be well-tolerated in patients with ITP" Added to Benefit-risk section: "To date, preliminary analyses of efficacy and safety in patients with ITP support an overall favorable benefit-risk profile, and to continue the development of rilzabrutinib for patients with ITP."	To provide details of [redacted], which are [redacted] of rilzabrutinib, as well as to introduce [redacted] To align with the current version of the IB and provide updated safety information.
4.11 Treatment of Overdose	Added subsection 4.11 to include clear definitions and guidelines for treating overdose with the IMP.	To align with new EU CTR guidelines and per the latest protocol template language
4.12 Concomitant Medications	Modified "per day" to "or equivalent per day" regarding permitted prednisone dosing.	To account for the fact that corticosteroids other than prednisone could be used.
4.12.3 Prohibited	Added below language pertaining to prohibited concomitant medication: • Concomitant use of any immunosuppressant medication, other than corticosteroids, as described in this protocol. Participants who need other immunosuppressant therapy during the study must be withdrawn. See Exclusion Criterion #7 in Section 6.1.2 and Section 6.2.2 for washout periods.	To provide clarification about the prohibited medications and to add the following medications to the prohibited medications list: Immunosuppressants, anti-CD20 medications, new start or increase in doses of TPO-RA, and live vaccines.

Section # and Name	Description of Change	Brief Rationale
	• Rituximab or other anti-CD20 medications, vincristine or immunosuppressants other than corticosteroids, and new starts or increases in doses of eltrombopag, romiplostim, or avatrombopag are not permitted as rescue therapy while the patient is receiving treatment with rilzabrutinib. • **Live vaccines** are not permitted during the study. See Section 6.1.2 and 6.2.2. for Exclusion Criteria #20	
8. List of Study Assessments	Added a new subsection 8.4 to include language pertaining to "Use of biological samples and data for future research".	To allow the use of leftover biological samples and data for future research and to align with new EU CTR guidelines.
9.2 Packaging	Changed to “Rilzabrutinib 100 mg and 300 mg tablets, 35 count per bottle and 400 mg tablets, 70 count per bottle are packaged in white high-density polyethylene (HDPE) bottles with child-resistant induction-sealed caps.”	To be consistent with the recently updated Pharmacist’s Manual v6.0
9.5 Destruction of Investigational 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.” Added “If a site does not have a destruction SOP, study drug can be returned to the depot.”	To be consistent with recently updated Pharmacist’s Manual v6.0
11.7.2 SAE Reporting	Added reference to safety reporting for the EU with direction to Section 16.8.1 Updated to “SAE Reporting Information mailto: ssf.1008010sae@sanofi.com”	To align with new EU CTR guidelines
11.9 Adverse Event of Special Interest	Added this section to include that [redacted] pregnancy, drug overdose, [redacted] are considered adverse events of special interest (AESIs)	To provide a definition of AESIs
11.10 Medication Errors, or Misuses of Medicinal Product	Added section with details on the handling of medication errors and misuse of medicinal product	To align with new EU CTR guidelines
13. Regulatory, Ethical, and Study Oversight Considerations	Section title was updated from “Ethical Aspects” to cover regulatory and study oversight considerations as well. Added section 13.2 on data protection. Updated sections 13.1 and 13.4 to include new language on regulatory and ethical considerations and IRB/IEC review	Updated language to align with the EU-CTR and as per the latest protocol template language .

Section # and Name	Description of Change	Brief Rationale
14.1 Investigator's File/Retention of Records	Updated with new guidelines on the Investigator's retention of records and documents	To align with the EU-CTR on the required retention period of 25 years for all records and documents pertaining to the conduct of this study
14.8 Publication of Data and Protection of Trade Secrets	Added language with further details on the Investigator and Sponsor's responsibilities when publishing data	To expand on proper practices for the protection of trade secrets and guide investigators on the publication of data
16.5 Appendix 5	Added following assessments: ECG (12-lead, single), hemolysis panel, mean platelet volume and immunoglobulins	To align assessments in D169 Appendix 5 with the assessments under Day 169/C1D1_LTE in Appendix 6
	Modified footnote 4 to include "Needed on Day 169 Visit/rollover/C1D1_LTE." Added footnotes 9-13 elaborating on the hemolysis panel, mean platelet volume, immature platelet fraction, immunoglobulins, BTK occupancy, and QOL questionnaires	To clarify the circumstances requiring uses of specific assessments, and the types of assessments used
16.6 Appendix 6	Added footnote 12, "QOL questionnaire includes [redacted] and ITP-PAQ"	To clarify what QOL questionnaires were used as assessments
16.7 Appendix 7	Added figures for [redacted] management algorithm	To guide investigators on the evaluation and reporting of these adverse events.
16.8 Appendix 8	Added EU-specific sub-section	To clarify safety reporting guidelines specific to the European Union
16.9 Appendix 9	Added section on the collection, storage, and future use of data and human biological samples	To direct investigators to where they can find further information on compliance with Member State applicable rules for use of data and biological samples
Throughout the document	Changed the abbreviation of the ITP Bleeding Scale from "ITP-BAT" to "IBLS"	Correction of the ITP Bleeding Scale abbreviation.

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

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PRN1008-010 STUDY SYNOPSIS

Study Title:	An Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study Investigating the Safety, Pharmacokinetics, and Clinical Activity of Rilzabrutinib (PRN1008), an Oral BTK Inhibitor, in Patients with Relapsed Immune Thrombocytopenia
Study Number:	PRN1008-010 (DFI17124)
Indication:	Immune Thrombocytopenia (ITP)
Background and Rationale:	There is preliminary evidence to support the role of Bruton tyrosine kinase (BTK) inhibition in patients with autoimmune cytopenias (2, 3) where sequential episodes of severe autoimmune hemolytic anemia and ITP ceased after initiation of treatment with ibrutinib in patients with chronic lymphatic leukemia (CLL). Rilzabrutinib is a high-affinity inhibitor of BTK. Pertinent to the treatment of ITP, rilzabrutinib treatment results in inhibited human B cell activation and blocked antibody (IgG, IgE) mediated activation of immune cells via Fc receptor signaling. In nonclinical studies, rilzabrutinib demonstrated a significant dose-dependent reduction of platelet loss in a mouse model of immune thrombocytopenia. Rilzabrutinib also showed rapid and significant anti-inflammatory effects in rat collagen-induced arthritis model, rat antibody-mediated arthus model, and spontaneous canine pemphigus disease. Mice in the anti-platelet-driven model of immune thrombocytopenia, dosed with rilzabrutinib at 10, 20, or 40 mg/kg/d had a dose-dependent prevention of platelet loss at 6 hours in comparison to vehicle control treated animals. These doses are generally similar to doses which demonstrated efficacy in the rat CIA model (40 mg/kg/d) when adjusted for body-surface area dosing equivalents from mouse to rat (mouse dose = 50% of rat dose). These results would suggest that doses required for efficacy for ITP and autoimmune indications may be broadly similar (4). The potency of rilzabrutinib in the B-cell activation assay correlated with BTK target occupancy in Phase 1 studies; therefore, [redacted] (4). In the completed Phase 2 study, PRN1008-005 (NCT02704429), a total of 41 patients with pemphigus were enrolled, 27 patients in Part A (12 weeks of rilzabrutinib and 12 weeks of follow-up) and 15 patients in Part B (24 weeks of rilzabrutinib and 4 weeks of follow-up). One patient was enrolled in Part A, then enrolled in Part B 5 months after completing Part A. In Part A, doses ranged from 400 mg to 600 mg BID. In Part B, doses included 400 mg QD, 400 mg BID, and 600 mg BID. In Part A, 51.9% of patients achieved the primary control of disease activity (CDA) endpoint at the Week 5 visit, and 70.4% at the Week 13 visit, further improving to 85.2% after an additional follow up of 12 weeks off rilzabrutinib treatment. Complete response rates were observed beginning at the Week 13 visit in 4 patients, increasing to 6 patients by 20 weeks. In Part B, rilzabrutinib delivered high CDA rates with rapid onset independent of dose with 60.0% of patients achieving CDA at the Week 5 visit and 86.7% within 12 weeks of treatment. Escalation to a dose of 400 mg BID and longer treatment to 24 weeks led to CR rates of 33.3%. Further results are provided in the PRN1008-005 clinical study report (5). [redacted] The proposed study is a dose-finding study that uses an intrapatient dose-escalation design [redacted] in the study and accounts for the biological variation in response in each patient. [redacted]

	[redacted] The dose finding part of the study (Part A) has completed and all newly enrolled patients start active treatment at the recommended 400 mg twice daily (BID) dose of rilzabrutinib. Part B is an expansion of the study that will investigate the safety and efficacy of only the selected dose of 400 mg BID. Part B will enroll patients with ITP who have relapsed or have an insufficient response to prior therapies.
Study Sites:	Part A: Multicenter trial (approximately 30 sites) Part B: Multicenter trial (approximately 30 sites)
Study Phase:	1/2
Study Objectives Part A:	Safety: • To characterize the safety and tolerability of up to four dose levels of rilzabrutinib in patients with ITP Efficacy: • To explore the clinical activity of up to four dose levels of rilzabrutinib in relapsed/refractory patients with ITP • To identify a potential dose regimen to use in future studies of rilzabrutinib in patients with ITP Pharmacokinetics: • To characterize the pharmacokinetics of rilzabrutinib in patients with ITP Exploratory: • To explore effect of rilzabrutinib on [redacted] • To explore effect of rilzabrutinib on [redacted] • To explore effect of rilzabrutinib on thrombopoietin (TPO) levels • To explore effect of rilzabrutinib on quality of life (QOL) using the [redacted]) • To characterize plasma metabolites of rilzabrutinib
Study Objectives Part B:	Safety: • To characterize the safety and tolerability of the selected dose of 400 mg BID of rilzabrutinib in patients with ITP Efficacy: • To further explore the clinical activity and durability of response of the selected dose of 400 mg BID of rilzabrutinib in patients with ITP who have relapsed or have an insufficient response to prior therapies • To evaluate the predictive value of platelet response to rilzabrutinib therapy in the first 8 weeks of active treatment for the achievement of the primary endpoint Pharmacokinetics: • To characterize the pharmacokinetics of rilzabrutinib in patients with ITP Exploratory: • To explore effect of rilzabrutinib on [redacted] • To explore effect of rilzabrutinib on thrombopoietin (TPO) levels • To explore effect of rilzabrutinib on [redacted]ls • To explore effect of rilzabrutinib on quality of life (QOL) using the [redacted]

Study Design Part A:

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

The active treatment period is 24 weeks and the post-treatment follow-up period is 4 weeks.

Once a patient escalates to the 400 mg BID dose, the patient will stay at this dose for 24 weeks (see Section 4.1 of the protocol).

Patients will be monitored with weekly platelet counts and complete blood counts (CBCs) throughout the study; pharmacokinetic (PK) samples will be collected intensively on the first day of each new cycle and at random times following dosing at each on-treatment follow-up visit. Patients will have weekly study visits/laboratory tests throughout the study (Schedule of Assessments, Appendix 3).

Patients may enter the study on stable doses of prednisone and/or TPO receptor agonists. Other [redacted] are not permitted.

Long Term Extension (LTE):

After completing the active treatment period, patients who respond to rilzabrutinib will be allowed to enter the LTE. A platelet response for entering the LTE is defined as platelet count ≥50,000/µL, or ≥30,000/µL and doubling of baseline at ≥50% of the visits during the last 8 weeks of the active treatment period (a minimum of 4 visits per the Schedule of Assessments) will be required. Baseline should be calculated as an average of platelet counts used for enrollment per Inclusion Criterion #4.

A patient may continue in the LTE until:

a) The patient is no longer responding as described in the table below:

Time in the LTE	**'No response' platelet counts defined as <30,000/µL or <20,000/µL above baseline based on:**
C1_LTE through C6_LTE	4 consecutive weekly visits
C7_LTE through C12_LTE	2 consecutive monthly visits
QX_LTE	1 quarterly visit In this case, a second platelet count has to be obtained in one month to confirm lack of response

[redacted]

In the LTE, patients will be monitored weekly for the first 6 months, monthly for an additional 6 months, then once every 3 months with the assessments as outlined in the LTE Schedule of Assessments Appendix 5 and Appendix 6.

Study Design Part B:

This is an open-label study of rilzabrutinib in patients with ITP who have relapsed or have an insufficient response to prior therapies. Eligible patients will have a platelet count <30,000/µL on two occasions no less than 7 days apart, within 15 days before treatment begins and a platelet count of ≤35,000/µL on Study Day 1 (SD1).

The study consists of a 28-day screening period, 24-week active treatment period, and a long-term extension. After the last dose of rilzabrutinib there will be a 4-week safety follow-up period. Patients enrolled with a positive hepatitis B virus (HBV) core

antibody result and hepatitis B virus surface antibody (HBsAb) titer ≥100 IU/L will continue to have HBV DNA monitored monthly for 6 months after treatment has ended.

Patients will have weekly study visits/laboratory tests throughout the study (Schedule of Assessments, Appendix 4).

Long Term Extension (LTE):

After completing the active treatment period, patients who respond to rilzabrutinib will be allowed to enter the LTE. A platelet response for entering the LTE is defined as platelet count ≥50,000/µL, or ≥30,000/µL and doubling of baseline at ≥50% of the visits during the last 8 weeks of the active treatment period (a minimum of 4 visits per the Schedule of Assessments) will be required. Baseline should be calculated as an average of platelet counts used for enrollment per Inclusion Criterion #4.

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QX_LTE	1 quarterly visit In this case, a second platelet count has to be obtained in one month to confirm lack of response

[redacted]

In the LTE, patients will be monitored weekly for the first 6 months, monthly for an additional 6 months, then once every 3 months with the assessments as outlined in the LTE Schedule of Assessments Appendix 5 and Appendix 6.

Dose-Limiting Toxicity, Dose Escalation, and Stopping Rules Part A:

DLT Definition:

Hematologic:

[redacted]

Non-Hematologic:

Any ≥ Grade 3 non-hematologic toxicity per the CTCAE, version 4.0 will be considered a DLT, with the following exceptions:

- Laboratory treatment-emergent adverse events (TEAEs) that are asymptomatic and return to baseline or to Grade 1 within 7 days

- Fatigue
- Nausea, vomiting, or diarrhea that return to baseline or Grade 1 within 7 days
- Systemic reactions (such as fever, headache) that return to baseline or Grade 1 within 7 days

Miscellaneous:

Any toxicity that, at the discretion of the Investigator, is thought to warrant withholding the study drug for more than 7 days.

For laboratory-based AEs, these must be confirmed by repeat testing.

The DLT evaluation period for any patient is defined as the duration of rilzabrutinib dosing until the dose escalation is completed.

Dose Escalation Rules:

Individual:

- Patients will dose-escalate to successive dose levels unless they are withdrawn, have a platelet response at the current dose level, or the next dose level has been determined to be ineligible for further enrollment (see Maximal Administered Dose [MAD], below).
- Patients experiencing a platelet response (as defined for the primary endpoint) will not have their dose escalated at the next cycle. If they do not experience a platelet response during the second cycle of the same dose level, they may dose escalate for the following cycle. If they require rescue medication subsequently because the platelet response was only transient these patients will be discontinued from the study.

Starting Dose Level:

Further dose escalation of cohort starting dose level will not occur if:

- A DLT occurs in two or more patients in a sentinel cohort at the current starting dose level or the dosing level above
- A sustained (3 of 4 counts) platelet response occurs in two or more patients in a sentinel cohort at the current starting dose level
- The Safety Monitoring Committee (SMC) feels that the number and/or severity of TEAEs or laboratory abnormalities occurring do not justify further dose-escalation
- Previously unknown data becomes available to the SMC which raise significant concerns about the potential risk to patients from further dose-escalation

Maximal Administered Dose (MAD) Level:

If any dose level is suspended for safety reasons, that dose level will be considered the MAD, and any continuing patients at the MAD will be de-escalated to the dose level below. Further enrollment will proceed at dosing levels below the MAD. If the MAD is 200 mg QD, the study will be suspended.

Individual Stopping Rules:

- Patients experiencing a DLT will be discontinued from the study.
- Patients requiring rescue therapy during study treatment, will be discontinued from the study.

	• Pregnancy. • [redacted] • Any other situation which, in the opinion of the Investigator or Sponsor, continued study treatment may result in undue safety risk to the patient. Study Stopping Rules: The study will be stopped (no new enrollments and no further study drug administered) if: • [redacted] • The SMC deems the emerging TEAE profile unacceptable to continue the study • The Sponsor elects to stop the study • There is >1 patient with Grade 3 or higher TEAEs (except for platelet count and underlying disease or comorbidity-related events) • Any patient experiences [redacted] except if related to an underlying clinical condition or event (eg, intercurrent illness, cardiovascular event, new sedating medication)
Stopping Rules Part B (also applies to LTE):	Individual Stopping Rules: • Pregnancy • [redacted] • Any other situation which, in the opinion of the Investigator or Sponsor, continued study treatment may result in undue safety risk to the patient. Study Stopping Rules: The study will be stopped (no new enrollments and no further study drug administered) if: • The Sponsor deems the emerging TEAE profile unacceptable to continue the study • The Sponsor elects to stop the study • Two or more life-threatening or CTCAE Grade 4 rilzabrutinib-related TEAEs except for AEs related to the disease under study (lack of efficacy)
Rescue Criteria Guidelines Part A:	Patients may receive another treatment for ITP (one form of intravenous immunoglobulin [IVIg], high-dose steroids, platelet infusion, or anti-D immunoglobulin infusion) if there is a significant safety event requiring “rescue” from a deterioration in the patient’s platelet count that in the opinion of the Investigator puts the patient at significant risk of a safety event.

	[redacted] Patients who receive rescue therapy will be discontinued from the study.
Rescue Criteria Guidelines Part B:	Patients may receive another treatment for ITP (one form of IVIg, high-dose steroids, platelet infusion, or anti-D immunoglobulin infusion) if there is a significant safety event requiring "rescue" from a deterioration in the patient's platelet count that in the opinion of the Investigator puts the patient at significant risk of a safety event. Rituximab or other anti-CD20 medications, vincristine or other immunosuppressants, and new starts or increases in doses of eltrombopag, romiplostim, or avatrombopag are not permitted as rescue therapy while the patient is receiving treatment with rilzabrutinib. Patients who receive rescue therapy will be allowed to continue if none of the stopping rules apply and the Investigator agrees to continue treating the patient with rilzabrutinib.
Study Endpoints Part A:	Safety Endpoints: Safety will be assessed by the incidence, severity, and relationship of TEAEs, including clinically significant changes in physical examination, laboratory tests, electrocardiogram (ECG), and vital signs. Treatment-emergent adverse events in the post treatment follow-up period will also be assessed and examined for possible relationship to the prior rilzabrutinib treatment. Adverse events will be categorized as treatment emergent after the first dose of rilzabrutinib has been received. In addition, safety will be assessed by the following endpoints, • Proportion of patients receiving rescue medication at each dosing level and overall • Proportion of patients with a Grade 2 or higher bleeding event at each dosing level and overall • Bleeding scale (ITP Bleeding Scale [IBLS]) at the end of treatment period for each dosing level Primary Efficacy Endpoint: Proportion of patients able to achieve two or more consecutive platelet counts, separated by at least 5 days, of ≥50,000/μL AND an increase of platelet count of ≥20,000/μL from baseline, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count. Secondary Efficacy Endpoints: • Percent of weeks with platelet counts ≥ 50,000/μL by dose level and overall • Proportion of patients with 4 out of the final 8 platelet counts ≥ 50,000/μL across all dose levels • Change from baseline to the average of the post Day 1 platelet counts by dose level and overall for patients who had >4 weeks of study drug on that given dose level • Number of weeks with platelet counts ≥ 50,000/μL across all dose levels • Number of weeks with platelet counts ≥ 30,000/μL across all dose levels • Time to first platelet count ≥ 50,000/μL across all dose levels Pharmacokinetic Endpoints: Plasma PK parameters of rilzabrutinib in ITP patients will be evaluated in each patient based on frequent sampling on Day 1 of new, higher dosing levels, and sparse sampling at other times.

	Exploratory Endpoints: • Proportion of patients with any two platelet counts ≥50,000/μL AND an increase of platelet count of ≥20,000/μL from baseline during treatment period. • Proportion of patients with any two platelet counts ≥ 50,000/μL AND an increase of platelet count of ≥20,000/μL from baseline during follow-up period (without dose reduction of the concomitant CS or TPO-RA doses) • Proportion of patients able to achieve two or more consecutive platelet counts, separated by at least 5 days, of ≥ 30,000/μL OR an increase of platelet count of ≥20,000/μL from baseline, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count. • Proportion of patients able to achieve any platelet counts ≥100,000/μL. • Time to first of two consecutive platelet counts ≥50,000/μL • Proportion of patients with 4 out of the final 6 platelet counts ≥50,000/μL across all dose levels • Proportion of patients with 8 out of the final 12 platelet counts ≥50,000/μL across all dose levels [redacted] • Effect of rilzabrutinib on TPO levels [redacted]
Study Endpoints Part B:	Safety Endpoints: Safety will be assessed by the incidence, severity, and relationship of TEAEs, including clinically significant changes in physical examination, laboratory tests, ECG, and vital signs. Bleeding TEAEs will be tabulated and a proportion of patients with a Grade 2 or higher bleeding event will be provided. Primary Efficacy Endpoint: Proportion of patients able to achieve platelet counts ≥50,000/μL on at least 8 out of the last 12 weeks of the 24-week treatment period without the use of rescue medication. Secondary Efficacy Endpoints: • Number of weeks with platelet count ≥50,000/μL OR ≥30,000/μL and doubling the baseline in the absence of rescue therapy (platelet counts will be censored for 4 weeks after the use of rescue medication, if given) • Proportion of all treated patients able to achieve two or more consecutive platelet counts, separated by at least 5 days, of ≥50,000/μL AND an increase of platelet count of ≥20,000/μL from baseline without use of rescue medication in the 4 weeks prior to the latest elevated platelet count • Number of weeks with platelet counts ≥30,000/μL and doubling from baseline over the 24-week treatment period (platelet counts will be censored for 4 weeks after the use of rescue medication, if given) • Proportion of patients receiving rescue medication • Change from baseline in ITP Bleeding Scale (IBLS) Exploratory Endpoints: • Proportion of patients who completed 24 weeks of treatment and demonstrated a platelet response defined as platelet counts ≥50,000/μL at 4 out of the last 8 weeks of the active treatment period

	• Proportion of patients who have a platelet count that exceeds 250,000/μL or 450,000/μL (for patients on concomitant TPO-RAs) • Time to first platelet count of ≥50,000/μL • Percentage of time with platelet counts ≥30,000/μL OR ≥20,000/μL above baseline [redacted] [redacted] • Effect of rilzabrutinib on TPO levels • Effect of rilzabrutinib on QOL Pharmacokinetic Endpoints: Plasma PK parameters of rilzabrutinib in ITP patients will be evaluated in each patient based on sparse sampling and population PK modeling.
Planned Number of Patients:	Part A Approximately 60 patients with ITP will be enrolled such that approximately 15 patients complete 24 weeks of dosing and at least 10 patients complete 24 weeks of treatment at a starting dose of 400 mg BID. Patients who drop out for reasons other than TEAEs during the 24-week treatment period may be replaced. Part B The study will enroll approximately 23 patients.
Patient Selection Criteria Part A:	Inclusion Criteria: 1. Male or female patients, aged 18 to 80 years old (**Czech Republic and Norway only**: 18 to 65 years old) 2. Immune-related ITP (both primary and secondary) 3. Refractory or relapsed patients with no available and approved therapeutic options with a platelet count of <30,000/μL on two occasions no less than 7 days apart in the 15 days prior to beginning study treatment. 4. A history of response (two or more platelet counts ≥50,000/μL with an increase of at least 20,000/μL) to at least one prior line of therapy (with splenectomy being considered a line of therapy) 5. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 × 10^9/L, hemoglobin [Hgb] >9 g/dL, AST/ALT ≤1.5 × ULN, albumin ≥3 g/dL, total bilirubin ≤1.5 × ULN, estimated glomerular filtration rate [eGFR] > 60 mL/min (Cockcroft and Gault method) (C1D1 pre-dose may be checked up to Day -3 prior to C1D1) 6. Female patients who are of reproductive potential must agree for the duration of active treatment in the study to use a highly effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, or true abstinence; when this is in line with the preferred and usual lifestyle of the patient). Unless surgically sterile, postmenopausal females should have menopause confirmed by follicle-stimulating hormone (FSH) testing. 7. Able to provide written informed consent and agreeable to the schedule of assessments Exclusion Criteria: 1. Pregnant or lactating women 2. ECG findings of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities

	3. History of current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the trial, with the exception of non-melanoma skin cancer 4. Transfusion with blood or blood products or plasmapheresis within 2 weeks before Day 1 5. Change in corticosteroid and/or TPO agonist dose within 2 weeks prior to Day 1 (more than 10% variation from Day 1 daily doses) 6. Use of rescue medications other than corticosteroids or TPO in Exclusion Criterion #5 in the two weeks before Day 1 7. [redacted] – these drugs should be discontinued for at least 14 days before Day 1 8. Treatment with rituximab or splenectomy within the 3 months prior to Day 1 9. [redacted] 12. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), thienopyridenes (within 14 days of planned dosing through end of follow-up) 13. 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); patient should not be using an investigational device at the time of dosing 14. Current drug or alcohol abuse 15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption 16. History of solid organ transplant 17. Positive screening for human immunodeficiency virus (HIV), hepatitis B (surface antigen and core antibodies unrelated to vaccination), or hepatitis C (anti-HCV antibody confirmed with HCV RNA) 18. History of serious infections requiring intravenous therapy within the last 3 months before Day 1 19. Clinically significant cognitive dysfunction (≥ Grade 1) or medical history suggestive of increased risk for cognitive dysfunction during the study 20. [redacted] 21. Planned surgery in the time frame of the dosing period 22. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with patient safety, study evaluations, and/or study procedures
Patient Selection Criteria Part B:	Inclusion Criteria: 1. Male or female patients, aged 18 to 80 years old 2. Patients with immune-related ITP (both primary and secondary) as defined by current guidelines with at least 3 months duration 3. Patients who had a response (achievement of platelet count ≥50,000/μL) to IVIg/anti-D or corticosteroid that was not sustained and failed at least one other ITP therapy (that was not IVIg or corticosteroid)

4. Patients with a platelet count of <30,000/µL on two occasions no less than 7 days apart in the 15 days before treatment begins, and no platelet count above 35,000/µL on Study Day 1.
5. Patients with adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 × 10^9/L, Hgb >9 g/dL, AST/ALT ≤1.5 × ULN, albumin ≥3 g/dL, total bilirubin ≤1.5 × ULN, eGFR >50 mL/min (Cockcroft and Gault method) (pre-dose may be checked up to Day -3)
6. Female patients who are of reproductive potential must agree for the duration of active treatment in the study to use a highly effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, or true abstinence; when this is in line with the preferred and usual lifestyle of the patient). Unless surgically sterile, postmenopausal females should have menopause confirmed by FSH testing.
7. Able to provide written informed consent and agreeable to the schedule of assessments

Exclusion Criteria:

1. Pregnant or lactating women
2. ECG findings of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities
3. History (within 5 years of SD1) or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the trial, with the exception of non-melanoma skin cancer
4. Transfusion with blood, blood products, IVIg, or plasmapheresis within 2 weeks before SD1
5. Change in corticosteroid and/or TPO agonist dose within 2 weeks prior to SD1 (more than 10% variation)
6. Use of rescue medications in the 4 weeks before SD1
7. Treatment with [redacted] within 2 weeks prior to SD1
8. Treatment with rituximab or splenectomy within the 3 months prior to SD1
   - Patients treated with rituximab within 6 months from screening will have normal B-cell counts prior to enrollment
9. [redacted]
12. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin with the exception of up to 100 mg/day doses, NSAIDs, thienopyridenes (within 2 weeks of planned dosing through end of follow-up)
13. 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); patient should not be using an investigational device at the time of dosing:

	• Patients who previously received treatment with BTK inhibitors within 30 days before receiving the first dose of study medication or who have previously received rilzabrutinib are not eligible for the study 14. Current drug or alcohol abuse 15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption 16. History of solid organ transplant 17. Positive at screening for HIV, hepatitis B (surface antigen, core antibodies), or hepatitis C (anti-HCV antibody confirmed with HCV RNA). • Patients who are HBV surface antigen (HBsAg) positive will not be eligible. • Patients who are HBsAg negative and HBV core 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, patients 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. • Patients who are HBcAb positive, HBsAg negative with HBsAb titer <100 IU/L or negative, are not eligible. 18. [redacted] 19. Myelodysplastic syndrome 20. [redacted] 21. Planned surgery in the time frame of the dosing period 22. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with patient safety, study evaluations, and/or study procedures.
Study Drug and Method of Dosing:	Part A: Rilzabrutinib 100 mg, 300 mg, and 400 mg tablets. Tablets should be taken with a glass (~8 oz.) of water and may be taken [redacted] Part B: Rilzabrutinib 400 mg tablets. Tablets should be taken with a glass (~8 oz.) of water and may be taken [redacted]

Screening Procedures:	Part A and Part B: Up to 28 days before Day 1, patients will be required to sign a consent form, after which screening assessments will be carried out as follows: • Review of medical history including concomitant medications • Review of inclusion and exclusion criteria • Measurement of height and weight • Physical examination • Single 12-lead ECG • Vital signs (blood pressure, heart rate, respiration rate, and temperature) • Laboratory testing per schedule of assessments including two or more platelet counts needed to meet inclusion criteria
Study Assessments (See Schedule~~,~~ Appendix 3, Appendix 4, Appendix 5, and Appendix 6):	Patients will be screened within 28 days of Day 1 and will return for an end-of-study assessment approximately 28 days after receiving their final dose of study drug. During the study, patients will return at specified times on an outpatient basis for assessment of vital signs, abbreviated physical examination, assessment of AEs, concomitant medication use, and laboratory testing. Clinical Assessments: • Medical history, assessment of AEs, periodic vital signs (body temperature, heart rate, blood pressure), and concomitant medication use • Height (screening only), weight, full and abbreviated physical examination • IBLS • QOL assessment[redacted]) • Part B only: ITP-PAQ Laboratory and ECG Assessments: • Complete blood count (CBC) with differential, including reticulocyte count • ABO Blood Type (screening only, historical information is acceptable) • Immature Platelet Fraction (where available) • Mean Platelet Volume (where available) • Coagulation: prothrombin time (PT)/International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) • Serum chemistry: AST, ALT, total, direct, and indirect bilirubin levels, ALP, albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphate, potassium, glucose (random), and creatine phosphokinase (CPK) • FSH for post-menopausal patients who are not surgically sterile • PK: Plasma rilzabrutinib concentration • Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes measured by dip stick or local requirement • Serology: HIV, Hepatitis B, and Hepatitis C • Pregnancy test for women of childbearing potential • Part A only: Quantitative platelet autoantibody panel (Australia only: test excluded) • Hemolysis panel: Coombs test, haptoglobin levels • TPO levels • [redacted]

	• Part B only: [redacted] • Part B only: BTK occupancy (at selected sites) • Part A only: 12-lead ECG: single at screening, triplicate ECGs pre-dose and post-dose on days of intensive PK draws • Part B only: 12-lead ECG: single at screening and at monthly clinical visits
Safety Assessments and Monitoring Part A:	Specific assessments to evaluate treatment safety include the following: the frequency, severity and relationship of AEs, clinical laboratory test changes, physical examination, and vital signs. Patients will remain under observation in the clinic for 6 hours after administration of the first dose at the beginning of each cycle during which time PK sampling will occur. An Independent Safety Data Monitor (IDSM) who is not a study Investigator will be chosen from expert clinicians in the ITP field. A Safety Monitoring Committee (SMC), comprised of the IDSM as Chairperson, lead Investigator, Study Medical Monitor, and Sponsor's Medical Monitor, will closely supervise the conduct of the study. The IDSM will make sentinel cohort safety evaluations. The sentinel patients at each dose level will have their data reviewed by the IDSM, in order to choose the starting dose for additional, new patients. After review, the IDSM may determine that a starting dose for new patients should be dropped for futility (lack of platelet response), increased to the next planned dosing level, kept the same or reduced. New patients entering the study will commence at the dose level determined by the IDSM based on: • If ≥2/3 or ≥2/6 of those sentinel patients have a DLT at any dose level, that level shall be determined the "Maximal Administered Dose" and starting doses (new patients) and continuing doses (patients already on study) set at lower dosing levels (or study suspended if the current sentinel dose cohort was 200 mg QD) • If two or more patients with sustained platelet responses (as defined in the primary endpoint and sustained for at least 3 of 4 consecutive platelet counts) in the sentinel patients are seen at the current starting dose level the starting dose will not be escalated The SMC will meet approximately quarterly and recommend study modification or termination to the Sponsor, based on review of safety and efficacy information.
Safety Assessments and Monitoring Part B:	Specific assessments to evaluate treatment safety include the following: the frequency, severity and relationship of AEs, clinical laboratory test changes, physical examination, and vital signs. The assessments will be conducted as part of ongoing medical monitoring and at Sponsor Quarterly Safety Reviews where safety events and trends across rilzabrutinib studies are considered.
Statistical Methods Part A:	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. Sample Size: The sample size for this study is based on clinical considerations. Assuming an expected efficacy rate for the primary endpoint of 40% (platelet response), with 15 evaluable patients there will be 80% confidence that the true proportion will be 24% and above (80 ±16% confidence interval [CI]) using normal approximation methods. [redacted]

	Analysis Populations: Safety Analysis Population: All patients who have received at least one dose of rilzabrutinib will be included in the safety analysis. The Safety Analysis Population will be defined for all safety analyses. Efficacy Analysis Population: All patients who have enrolled in the study will be included in the Intent to treat (ITT) population. Enrolled patient is defined as a patient who signed the informed consent form and met eligibility criteria. Efficacy analysis will be based on the ITT population. Pharmacokinetic Analysis Population: All patients who have received at least one dose of rilzabrutinib and have at least one measurable plasma concentration value will be included in the pharmacokinetic analysis. Analysis Methods: Efficacy: Qualitative efficacy data will be summarized by frequencies and percentages. Quantitative efficacy data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum). Data will be summarized over time by dose level and overall. The time course of mean changes in platelet count over time will also be described graphically, annotated for dosing levels. Safety and Tolerability: The incidence, severity, and relationship of TEAEs, laboratory tests, rescue treatment usage, and vital signs will be summarized descriptively. Qualitative safety data will be summarized by frequencies and percentages at each dose level. Quantitative safety data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum) at each dose level. Summaries will also be presented for the change from baseline, when appropriate. The proportion of patients with Grade 2 or higher bleeding events will also be summarized. Pharmacokinetics: PK data will be summarized using descriptive statistics, tabulated, and displayed graphically as appropriate. Non-compartmental analysis will be utilized to derive PK parameters for each individual. PK data may also be pooled with the data from other studies for population PK modeling. Individual patient PK values within this study may be used for exploratory analyses of exposure and effect.
Statistical Methods Part B:	A detailed SAP will be developed and finalized before the study database is locked and will supersede the statistical analysis methods described in the protocol. Sample Size: [redacted] Analysis Populations: Safety Analysis Population: All patients who have received at least one dose of rilzabrutinib will be included in the safety analysis.

	Efficacy Analysis Population: All patients who have enrolled in the study will be included in the Intent to treat (ITT) population. Enrolled patient is defined as a patient who signed the informed consent form and met eligibility criteria. Efficacy analysis will be based on the ITT population. Pharmacokinetic Analysis Population: All patients who have received at least one dose of rilzabrutinib and have at least one measurable plasma concentration value will be included in the pharmacokinetic analysis. Analysis Methods: Efficacy: Qualitative efficacy data will be summarized by frequencies and percentages. Quantitative efficacy data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum). The time course of mean changes in platelet count over time will also be described graphically. Other efficacy analyses: • Estimate the predictive value of platelet count to achieve the primary endpoint for each of the three predictors separately or in combination: o ≥30,000/μL on Study Day 8 o ≥20,000/μL above baseline on Study Day 8 o ≥50,000/μL at any time over first 8 weeks of the treatment period Safety and Tolerability: The incidence, severity, and relationship of TEAEs, laboratory tests, rescue treatment usage, and vital signs will be summarized descriptively. Qualitative safety data will be summarized by frequencies and percentages at each dose level. Quantitative safety data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum). Summaries will also be presented for the change from baseline, when appropriate. The proportion of patients with Grade 2 or higher bleeding events will also be summarized. Pharmacokinetics: PK data will be summarized using descriptive statistics, tabulated, and displayed graphically as appropriate. PK data will be pooled with the data from other studies for population PK modeling, with the results reported outside the main clinical study report.
Study Duration:	Part A: Approximately 18 months from the first patient treated to last patient completing, and approximately 32 weeks per patient. For patients who receive additional treatment cycles to complete 24 weeks at the 400 mg BID dose, the study duration could be up to 55 weeks. Part B: Approximately 28 months from the first patient treated to last patient completing. The study duration for each patient will be approximately 32 weeks. Long Term Extension (LTE) Part A and Part B: Study duration for the patients who enter the LTE will be determined by the durability of the platelet response, the occurrence of DLTs, and/or other criteria as described in the Study Design section of the Study Synopsis.

GLOSSARY OF ABBREVIATIONS AND TERMS

ABBREVIATION OR TERM	DEFINITION
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice daily (morning and evening)
BP	blood pressure
BTK	Bruton tyrosine kinase
CA	Competent Authority
CBC	complete blood count
CDA	control of disease activity
CI	confidence interval
CL/F	apparent total clearance of the drug from plasma after oral administration
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CPK	creatine phosphokinase
CRF	case report form
CRO	Contract Research Organization
CS	corticosteroid
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
D	day
[redacted]	
DLT	dose-limiting toxicity
EC	Ethics Committee
ECG	electrocardiogram
EDC	electronic data capture
eGRF	estimated glomerular filtration rate
[redacted]	
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H2	histamine two (receptor)
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure

ABBREVIATION OR TERM	DEFINITION
IBLS	Idiotic Thrombocytopenic Purpura Bleeding Scale
ICH	International Council for Harmonisation
IDSM	Independent Data Safety Monitor
IR	immediate release
IRB	Institutional Review Board (Human Research Ethics Committee)
ITP	Immune thrombocytopenia
ITP-PAQ	Idiopathic Thrombocytopenic Purpura Patient Assessment Questionnaire
ITT	Intent-to-treat
IVIg	intravenous immunoglobulin
LPLV	last patient last visit
LTE	long term extension
MAD	Maximal Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
NK	natural killer (cell)
NSAID	non-steroidal anti-inflammatory drug
OTC	over the counter
PK	pharmacokinetic
PT/INR	prothrombin time/international normalized ratio
PV	pemphigus vulgaris
PVG	pharmacovigilance
QD	once daily
QOL	Quality of Life
QTcF	QT interval corrected for heart rate (Fridericia Correction)
RR	resting rate
SAE	serious adverse event
SAP	Statistical Analytical Plan
SI	Système international d'unités (International system of units)
SMC	Safety Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
T_{max}	time of observed maximum plasma concentration
TPO	thrombopoietin
t½	elimination half-life
ULN	upper limit of normal
USUBJID	unique patient identifier
VAS	visual analog scale
V/F	apparent volume of distribution of the drug after oral administration
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

1 BACKGROUND

1.1 Scientific Rationale for Treatment of ITP with Rilzabrutinib

Idiopathic thrombocytopenic purpura, now more commonly referred to as 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, intravenous immunoglobulin [IVIg], or anti-D) is used for symptomatic patients with low platelet counts for reducing platelet destruction. While a majority of patients respond initially to corticosteroids, 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 (6) are approved for the treatment of patients with chronic ITP who have not had sufficient responses to corticosteroids, IVIg, or splenectomy. Novel, safe, and effective oral treatments in this setting to maintain platelet counts would be a significant therapeutic advantage. Thus, there remains a high unmet medical need for novel, safe, and effective oral therapies for ITP.

There is preliminary evidence to support the role of Bruton tyrosine kinase (BTK) inhibition in patients with autoimmune cytopenias (2, 3), where sequential episodes of severe autoimmune hemolytic anemia and ITP ceased after initiation of treatment with ibrutinib, a BTK/EGFR/ITK inhibitor, in patients with chronic lymphatic leukemia (CLL).

Rilzabrutinib is a high-affinity inhibitor of BTK. [redacted] rilzabrutinib treatment *in vitro* profoundly inhibited human B cell activation and blocked antibody (IgG, IgE) mediated activation of immune cells via Fc receptor signaling. In nonclinical studies, rilzabrutinib demonstrated a significant dose dependent reduction of platelet-loss (consumption) in a mouse model of immune thrombocytopenia. Rilzabrutinib also showed rapid and significant anti-inflammatory effects in rat collagen-induced arthritis model, rat antibody mediated arthus model, spontaneous canine pemphigus foliaceus and human pemphigus vulgaris (PV).

1.2 Summary of Rilzabrutinib Clinical Experience

To date, rilzabrutinib has been administered to more than 170 healthy volunteers and patients in Phase 1 and Phase 2 studies. Rilzabrutinib has been generally well tolerated. In the completed Phase 2 study, PRN1008-005 (NCT02704429), a total of 41 patients with pemphigus were enrolled, 27 patients in Part A (12 weeks of rilzabrutinib and 12 weeks of follow-up) and 15 patients in Part B (24 weeks of rilzabrutinib and 4 weeks of follow-up). One patient was enrolled in Part A, then enrolled in Part B 5 months after completing Part A. In Part A, doses ranged from 400 mg to 600 mg BID. In Part B, doses included 400 mg QD, 400 mg BID, and 600 mg BID. In Part A, 51.9% of patients achieved the primary control of disease activity (CDA) endpoint at the Week 5 visit, and 70.4% at the Week 13 visit, further improving to 85.2% after an additional follow up of 12 weeks off rilzabrutinib treatment. Complete response rates were observed beginning at the Week 13 visit in 4 patients, increasing to 6 patients by 20 weeks. In Part B, rilzabrutinib delivered high CDA rates with rapid onset independent of dose with 60.0% of patients achieving CDA at the Week 5 visit and 86.7% within 12 weeks of treatment.

Escalation to a dose of 400 mg BID and longer treatment to 24 weeks led to CR rates of 33.3%. Further results are provided in the PRN1008-005 clinical study report (5). Preliminary results of PRN1008-010 after 47 patients were enrolled (05 May 2020 data cutoff) were presented at European Hematology Association annual meeting (7).

Analysis of hematology and coagulation measurements in prior healthy volunteer studies showed [redacted]

1.3 Clinical Pharmacokinetics and Pharmacodynamics of Rilzabrutinib

Rilzabrutinib is rapidly absorbed following oral administration, with a fast half-life (3–4 hours), and variable pharmacokinetics (PK). [redacted]

[redacted]

Rilzabrutinib demonstrates a slow BTK off-rate, with BTK occupancy observed for more than 24 hours after plasma concentrations are undetectable. With multiple dosing, equivalent doses of 428 mg of the immediate-release (IR) tablet and above (QD or BID) appear to achieve near maximal peak BTK occupancy, however twice daily dosing regimens maintained higher occupancy at trough compared to once daily dosing.

2 DOSE RATIONALE AND STUDY DESIGN

2.1 Rationale for the Study Design

An adaptive, open-label, dose-finding study of 15 patients, using rule-based intrapatient dose escalation, is an appropriate Phase 1/2 design to evaluate the safety and effect of rilzabrutinib in patients with ITP – a relatively rare autoimmune disease. This study [redacted] and is similar in design to one used to study the initial efficacy and safety of fostamatinib in ITP (8).

Patients enrolled in this study will have low platelet counts having relapsed on or been refractory to prior therapies with no available and approved therapeutic options, and may continue corticosteroids and/or thrombopoietin mimetics during the study. Compared to a sequential group dose-escalation study, this design will not expose the initial cohorts of patients to ineffective dose levels for a prolonged period and will thus potentially minimize the use of rescue medication. [redacted]

The active treatment period of 24 weeks and the post-treatment follow up period of 4 weeks and the Long Term Extension (LTE) are justified by safety and efficacy seen to date in human and animal studies. The "sentinel cohorts" at each dose level consist of the first 3 patients, or 6, if 3 extra are added for a dose-limiting toxicity (DLT) or platelet response (as defined in the primary endpoint and sustained for at least 3 of 4 consecutive counts over one or two 28-day cycles). To be evaluable in a sentinel cohort, patients must have ≥75% compliance over the 28-day dosing period. The sentinel cohort data is reviewed for by the Independent Data Safety Monitor (IDSM, who is also Chairperson of the Safety Monitoring Committee [SMC]), in order to choose the starting dose for additional, new patients entering the study. After safety review, the IDSM may determine that a starting dose for new patients should be dropped for futility (lack of platelet response), increased to the next planned dosing level, kept the same or reduced (Section 4.4).

Patients will be monitored frequently by weekly platelet counts and complete blood counts (CBCs) throughout the active treatment period and will continue in the LTE weekly for 6 months, then monthly for six months, and every three months thereafter. PK samples will be collected intensively on the first day of each new, higher dose level and at random times following dosing at each on-treatment follow up visit. The other clinical and laboratory assessments used in this study are standard and used in clinical practice for assessment of patients with ITP. The bleeding assessment (Idiopathic Thrombocytopenic Purpura Bleeding Scale [IBLS]) (9) has been used in prior studies.

2.1.1 Rationale for Doses Used and Duration of Study Part A

[redacted]

[redacted] Dosing above 400 mg BID is thought unlikely to result in greater target inhibition.

Pemphigus vulgaris is an autoantibody-driven disease like ITP. In Study PRN1008-005 a rapid onset of clinical effect was seen in most pemphigus patients within 4 weeks, with continued improvement to very low levels of skin inflammation by the end of 12 weeks of therapy. Therefore 28-day cycles to assess the initial platelet response, and trigger intrapatient dose-escalation are appropriate. A 24-week overall treatment period is preferred for this dose-finding study to enable all patients to potentially dose-escalate to the higher doses and be fully evaluated at those doses.

A 24-week treatment period and the LTE are supported by completed long term Good Laboratory Practice (GLP) animal safety toxicology studies, and a favorable risk benefit profile observed in completed and ongoing human studies (4).

2.1.2 Rationale for Doses Used and Duration of Study Part B

The dose-finding portion of the study (Part A) has been completed. All doses were evaluated and the 400 mg BID dose has been selected as a safe and efficacious dose for further investigation in Part B. Similar to Part A, there will be a 24-week treatment period to assess the primary endpoint and an LTE for patients who demonstrate a platelet response.

The primary endpoint in Part B will assess the durability of response in the last 12 weeks of the 24-week treatment period, and a key secondary endpoint will assess the [redacted] platelet response in the first 8 weeks of treatment for the achievement of the primary endpoint.

2.2 Overall Benefit-Risk Assessment

Safety Profile

Rilzabrutinib was well tolerated in the clinical development program, including single and multiple doses. The most common treatment-emergent adverse events (TEAEs) were [redacted] The majority of TEAEs were mild to moderate in severity.

Until 02 January 2024, no SUSAR has been reported in the ITP Phase 2 PRN1008-010 Study. There was one SUSAR of serious infection reported in the ongoing ITP Phase 3 Study (PRN1008-018), and a causal association with blinded IMP (rilzabrutinib/placebo) was deemed

unlikely by the Sponsor. No major bleeding events occurred in the clinical experience with rilzabrutinib. Refer to the Investigator's Brochure for additional and updated information.

Risk Assessment

Based on the review of the cumulative data, as of 2 January 2024, with an estimated exposure of 1137 participants who received at least one dose of rilzabrutinib or placebo (826 participants on rilzabrutinib with approximately 545 patient-years, estimated based on randomization ratio) across multiple disease conditions, there are [redacted]for rilzabrutinib.The following are considered as important potential risks for rilzabrutinib:

- [redacted]

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

Table 1 - Risk assessment

[redacted]

[redacted]

Benefit assessment

Patients with ITP were expected to only transiently benefit from rilzabrutinib with the initial dose escalation scheme and 12-weeks of treatment, although anecdotal evidence from the Phase 2 study of rilzabrutinib in pemphigus suggests a durable effect post-treatment may occur in some patients. The additional non-clinical data supported longer treatment durations enabling amending to 24 weeks of treatment and allowing dose escalation to the highest dose level, as well as an LTE for patients with platelet response.

Preliminary review of the efficacy data in Part A of this study demonstrated a dose response and that patients with ITP who failed multiple treatments were able to achieve a fast and durable platelet response at the 400 mg BID dose of rilzabrutinib. Patients treated with once daily doses were less likely to achieve fast platelet response and the primary endpoint (10). This evidence of

treatment effect supports initiation of Part B of the study that will focus on further investigating this dose of rilzabrutinib in this patient population. Preliminary results of Part A and Part B provide evidence that treatment with rilzabrutinib 400 mg BID induces a rapid and durable platelet response and continued to be well tolerated in patients with ITP (11, 12).

Benefit-risk: To date, preliminary analyses of efficacy and safety in patients with ITP support an overall favorable benefit-risk profile, and to continue the development of rilzabrutinib for patients with ITP.

3 OBJECTIVES AND OUTCOME MEASURES OF THE STUDY

3.1 Objectives of the Study: Part A

3.1.1 Safety Objective

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

3.1.2 Efficacy Objectives

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

3.1.3 Pharmacokinetics Objective

- To characterize the pharmacokinetics of rilzabrutinib in patients with ITP

3.1.4 Exploratory Objectives

[redacted]

- To explore effect of rilzabrutinib on thrombopoietin (TPO) levels
- To explore effect of rilzabrutinib on quality of life (QOL) using the [redacted]
- [redacted] of rilzabrutinib

3.2 Objectives of the Study: Part B

3.2.1 Safety Objective

- To characterize the safety and tolerability of 400 mg BID dose of rilzabrutinib in patients with ITP

3.2.2 Efficacy Objectives

- To further explore the clinical activity and durability of response of the selected dose of 400 mg BID of rilzabrutinib in patients with ITP who have relapsed or have an insufficient response to prior therapies
- To evaluate the predictive value of platelet response to rilzabrutinib therapy in the first 8 weeks of active treatment for the achievement of the primary endpoint

3.2.3 Pharmacokinetics Objective

- To characterize the pharmacokinetics of rilzabrutinib in patients with ITP

3.2.4 Exploratory Objectives

- [redacted]
- To explore effect of rilzabrutinib on thrombopoietin (TPO) levels
- [redacted]
- To explore effect of rilzabrutinib on quality of life (QOL) using the [redacted] and Idiopathic Thrombocytopenic Purpura Patient Assessment Questionnaire (ITP-PAQ)

3.3 Outcome Measures of the Study: Part A

3.3.1 Primary Safety Endpoints

Safety will be assessed by the incidence, severity, and relationship of TEAEs, including clinically significant changes in physical examination, laboratory tests, and vital signs. Treatment-emergent adverse events in the post treatment follow-up period will also be assessed and examined for possible relationship to the prior rilzabrutinib treatment. Adverse events (AEs) will be categorized as treatment emergent after the first dose of rilzabrutinib has been received.

3.3.2 Primary Efficacy Endpoint

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

Secondary efficacy endpoints are described in Section 10.

3.4 Outcome Measures of the Study: Part B

3.4.1 Primary Safety Endpoints

Safety will be assessed by the incidence, severity, and relationship of TEAEs, including clinically significant changes in physical examination, laboratory tests, and vital signs. Bleeding TEAEs will be tabulated and a proportion of patients with a Grade 2 or higher bleeding event will be provided.

3.4.2 Primary Efficacy Endpoint

Proportion of patients able to achieve platelet counts ≥50,000/μL on at least 8 out of the last 12 weeks of the 24-week treatment period without the use of rescue medication after 10 weeks of active treatment.

Secondary efficacy endpoints are described in Section 10.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan Part A

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

The active treatment period is 24 weeks and the post-treatment follow up period is 4 weeks.

Once a patient escalates to the 400 mg BID dose in the active treatment period, the patient will stay at this dose for 24 weeks.

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

The “sentinel cohorts” at each dose level consist of the first 3 patients, or 6, if 3 extra are added for a DLT or platelet response (as defined in the primary endpoint and sustained for at least 3 of 4 consecutive platelet counts at any dose level). To be evaluable in a sentinel cohort, patients must have ≥75% compliance over the 28-day dosing period. The sentinel cohort data is reviewed by the IDSM, in order to choose the starting dose for additional, new patients entering the study. After review, the IDSM may determine that a starting dose for new patients should be dropped for futility (lack of platelet response), increased to the next planned dosing level, kept the same or reduced (Section 4.4).

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

Adaptive Cohort Dosing Table

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

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

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

Dose down-titration is permitted where, in the opinion of the Investigator, tolerability is poor and a satisfactory platelet response was seen in that patient on a lower dose previously studied or as mandated by the SMC. Otherwise, patients with clinically significant intolerance to rilzabrutinib should be discontinued from the study.

Patients experiencing a DLT or requiring rescue therapy for low platelet counts must be discontinued from the study.

Patients will be monitored with weekly platelet counts and CBCs throughout the study; PK samples will be collected intensively on the first day of each new, higher dose level and at random times following dosing at each on-treatment follow up visit. Patients will have weekly study visits/laboratory tests throughout the Part A of the study (Schedule of Assessments, Appendix 3).

Patients may enter the study on stable doses of prednisone and/or TPO receptor agonists (TPO-RAs). Other [redacted] are not permitted.

Long Term Extension (LTE) Part A and Part B

After completing the active treatment period, patients who respond to rilzabrutinib will be allowed to enter the LTE. A platelet response is defined as platelet count ≥50,000/μL, or ≥30,000/μL and doubling of baseline at ≥50% of the visits during the last 8 weeks of the active treatment period (a minimum of 4 visits per the Schedule of Assessments) will be required. Baseline should be calculated as an average of platelet counts used for enrollment per Inclusion Criterion #4.

A patient may continue in the LTE until:

a) The patient is no longer responding as described in the table below:

Time in the LTE	'No response' platelet counts defined as <30,000/µL or <20,000/µL above baseline based on:
C1_LTE through C6_LTE	4 consecutive weekly visits
C7_LTE through C12_LTE	2 consecutive monthly visits
QX_LTE	1 quarterly visit In this case, a second platelet count has to be obtained in one month to confirm lack of response

[redacted]

Patients who continue into the LTE will be monitored with weekly platelet counts and CBC's for the first 6 months, and then monthly for an additional 6 months, then once every 3 months with the assessments as outlined in the LTE Schedule of Assessments (Appendix 5 and Appendix 6).

4.2 Overall Study Design and Plan Part B

Part B is an open-label study of rilzabrutinib in patients with ITP who have relapsed or have an insufficient response to prior therapies. Eligible patients will have a platelet count <30,000/µL on two occasions no less than 7 days apart, within 15 days before treatment begins, and a platelet count of ≤35,000/µL on Study Day 1 (SD1).

The study consists of a 28-day screening period, 24-week active treatment period, and a long-term extension. After the last dose of rilzabrutinib there will be a 4-week safety follow-up period. Patients enrolled with a negative hepatitis B virus (HBV) DNA result and hepatitis B virus surface antibody (HBsAb) titer ≥100 IU/L will continue to have HBV DNA monitored monthly for 6 months after treatment has ended.

Patients will have weekly study visits/laboratory tests throughout the Part B of the study (Schedule of Assessments, Appendix 4).

Long Term Extension (LTE)

After completing the active treatment period, patients who respond to rilzabrutinib will be allowed to enter the LTE. A platelet response is defined as platelet count ≥50,000/µL, or ≥30,000/µL and doubling of baseline at ≥50% of the visits during the last 8 weeks of the active treatment period (a minimum of 4 visits per the Schedule of Assessments) will be required. Baseline should be calculated as an average of platelet counts used for enrollment per Inclusion Criterion #4.

A patient may continue in the LTE until:

a) The patient is no longer responding as described in the table below:

Time in the LTE	'No response' platelet counts defined as <30,000/µL or <20,000/µL above baseline based on:
C1_LTE through C6_LTE	4 consecutive weekly visits
C7_LTE through C12_LTE	2 consecutive monthly visits
QX_LTE	1 quarterly visit In this case, a second platelet count has to be obtained in one month to confirm lack of response

[redacted]

In the LTE, patients will be monitored weekly for the first 6 months, monthly for an additional 6 months, then once every 3 months with the assessments as outlined in the LTE Schedule of Assessments Appendix 5 and Appendix 6.

4.3 Dose-Limiting Toxicity (DLT) Part A Only

Hematologic:

[redacted]

Non-Hematologic:

Any ≥ Grade 3 non-hematologic toxicity per the CTCAE, version 4.0 will be considered a DLT, with the following exceptions:

- Laboratory TEAEs that are asymptomatic and return to baseline or to Grade 1 within 7 days
- Fatigue

- Nausea, vomiting or diarrhea that return to baseline or Grade 1 within 7 days
- Systemic reactions (such as fever, headache) that return to baseline or Grade 1 within 7 days.

Miscellaneous:

Any toxicity that, at the discretion of the Investigator, is thought to warrant withholding the study drug for more than 7 days.

For laboratory-based AEs, these must be confirmed by repeat testing.

The DLT evaluation period for any patient is defined as the duration of rilzabrutinib dosing until the dose escalation is completed.

4.4 Dose Escalation Rules Part A Only

Individual:

- Patients will dose-escalate to successive dose levels unless they are withdrawn, have a platelet response at the current dose level, or the next dose level has been determined to be ineligible for further enrollment (see Maximal Administered Dose [MAD], below)
- Patients experiencing a platelet response (as defined for the primary endpoint) will not have their dose escalated at the next cycle. If they do not experience a platelet response during the second cycle of the same dose level they may dose escalate for the following cycle. If they require rescue medication subsequently because the platelet response was only transient, these patients will be discontinued from the study.

Starting Dose Level:

Further dose-escalation of cohort starting doses will not occur if:

- A DLT occurs in two or more patients in a sentinel cohort at the current starting dose level or the dosing level above
- A sustained platelet response (3 of 4 counts) occurs in two or more patients in a sentinel cohort at the current starting dose level
- The SMC feels that the number and/or severity of TEAEs or laboratory abnormalities occurring do not justify further dose-escalation
- Previously unknown data becomes available to the SMC which raise significant concerns about the potential risk to patients from further dose-escalation.

Maximal Administered Dose (MAD) Level:

If any dose level is suspended for safety reasons, that dose level will be considered the MAD, and any continuing patients at the MAD will be de-escalated to the dose level below. Further enrollment will proceed at dosing levels below the MAD. If the MAD is 200 mg QD, the study will be suspended.

4.5 Stopping Rules Part A (also applies to LTE)

4.5.1 Individual Stopping Rules

- Patients experiencing a DLT will be discontinued from the study.
- Patients requiring rescue therapy during study treatment will be discontinued from the study.
- Pregnancy.
- [redacted]
- Any other situation which, in the opinion of the Investigator or Sponsor, continued study treatment may result in undue safety risk to the patient.

4.5.2 Study Stopping Rules

The study will be stopped (no new enrollments and no further study drug administered) if:

- The MAD is determined to be 200 mg QD
- The SMC deems the emerging TEAE profile unacceptable to continue the study
- The Sponsor elects to stop the study
- There is >1 patient with Grade 3 or higher TEAEs (except for platelet count and underlying disease or comorbidity-related events)
- [redacted]

4.6 Stopping Rules Part B (also applies to LTE)

4.6.1 Individual Stopping Rules

- Pregnancy.
- [redacted]
- Any other situation which, in the opinion of the Investigator or Sponsor, continued study treatment may result in undue safety risk to the patient.

4.6.2 Study Stopping Rules

The study will be stopped (no new enrollments and no further study drug administered) if:

- The Sponsor deems the emerging TEAE profile unacceptable to continue the study
- The Sponsor elects to stop the study
- Two or more life-threatening or CTCAE Grade 4 rilzabrutinib-related TEAEs except for AEs related to the disease under study (lack of efficacy).

4.7 Number of Patients

Part A:

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

Part B:

The study will enroll approximately 23 patients.

4.8 Study Duration and Duration of Patient Participation

Part A:

Patients will receive rilzabrutinib treatment for 24 weeks, starting on Day 1 and ending on Study Day 169, followed by 4 weeks of post-treatment safety follow-up. The expected study duration is approximately 18 months from the first patient treated to the last patient completing, and approximately 32 weeks per patient.

Patients who are dose escalated to 400 mg BID will continue in the active treatment period until 24 weeks of treatment at the 400 mg BID dose is completed.

Part B:

After a screening period of up to 4 weeks, patients will receive rilzabrutinib treatment for up to 24 weeks, starting on Study Day 1. All patients will complete 4 weeks of post-treatment safety follow-up.

The expected study duration is approximately 28 months from the first patient treated to last patient completing. Study duration for individual patient is approximately 32 weeks.

The duration of the LTE will be determined by the rules outlined in Section 4.6.

4.9 End of Study Definition (Part A and Part B)

The end of the study is defined as the date of the final safety follow-up visit after the last patient's last visit (LPLV).

4.10 Rilzabrutinib Administration (Part A and Part B)

Rilzabrutinib [redacted]

4.11 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 should:

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

4.12 Concomitant Medications

4.12.1 Allowed Part A

- All patients may receive, but are not required to be taking, concomitant corticosteroids. The dose should be fixed (±10%) for at least 2 weeks before Day 1 and remain unchanged throughout the study unless rescue criteria are triggered. If the patient requires rescue treatment or concomitant ITP drug increases of more than 10% of the Day 1 daily dose, the patient will be discontinued from the study and receive rescue treatment per standard of care. These drugs may not have their dose increased as part of "rescue" medication.
- Patients who continue in the LTE period will be able to taper corticosteroid dose if platelet counts are ≥100,000/µL. Tapering 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.

- All patients may receive, but are not required to be taking, eltrombopag or romiplostim. The dose should be fixed for at least 2 weeks before Day 1 and remain constant (10% variation from Day 1 daily dose is allowed) throughout the study unless there are safety concerns related to those drugs. These drugs may not have their dose increased as part of "rescue" medication.
- [redacted]

4.12.2 Allowed Part B

- All patients may receive, but are not required to be taking, concomitant corticosteroids. The dose should be fixed (±10%) for at least 2 weeks before Day 1 and remain unchanged throughout the active treatment period of the study unless rescue criteria are triggered or patient experiences corticosteroid-associated adverse events that require a reduction of steroid dose. Patients who continue in the LTE period will be able to taper corticosteroid dose if platelet counts are ≥100,000/µL. Tapering 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

- All patients may receive, but are not required to be taking, eltrombopag, romiplostim, or avatrombopag. The dose should be fixed for at least 2 weeks before Day 1 and remain constant (10% variation from Day 1 daily dose is allowed) throughout the study unless there are safety concerns related to those drugs.
- Patients may receive another treatment for ITP (one form of IVIg, high-dose steroids, platelet infusion, or anti-D immunoglobulin infusion) if there is a significant safety event requiring "rescue" from a deterioration in the patient's platelet count that in the opinion of the Investigator puts the patient at significant risk of a safety event. Patients who receive rescue therapy will be allowed to continue if none of the stopping rules apply (Section 4.6) and the Investigator agrees to continue treating the patient with rilzabrutinib.
- [redacted]

4.12.3 Prohibited

- [redacted]

[redacted]

- Concomitant use of any ***immunosuppressant medication***, other than corticosteroids, as described in this protocol. Participants who need other immunosuppressant therapy during the study must be withdrawn. See Exclusion Criterion #7 in Section 6.1.2 and Section 6.2.2 for washout periods.
- Rituximab or other anti-CD20 medications, vincristine or other immunosuppressants, and new starts or increases in doses of eltrombopag, romiplostim, or avatrombopag are not permitted as rescue therapy while the patient is receiving treatment with rilzabrutinib.
- **Live vaccines** are not permitted during the study. See Section 6.1.2 and Section 6.2.2 for Exclusion Criterion # 20.

5 PROTOCOL DEVIATIONS

The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. Principia does not allow intentional or prospective deviations from the protocol unless necessary to eliminate an immediate hazard to study patients. The Principal Investigator is responsible for immediately (within 24 hours) notifying the CRO of a major protocol deviation to permit Principia to determine the impact of the deviation on the patient and/or the study.

The Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities. The contract research organization (CRO) Clinical Monitors will notify the Sponsor.

6 STUDY POPULATION

6.1 Part A

6.1.1 Inclusion Criteria

1. Male and female patients, aged 18 to 80 years old (**Czech Republic and Norway only**: aged 18 to 65 years old)

2. Immune-related ITP (both primary and secondary)

3. Refractory or relapsed patients with no available and approved therapeutic options with a platelet count of count <30,000/μL on two occasions no less than 7 days apart in the 15 days prior to beginning study treatment

4. A history of response (two or more platelet counts ≥50,000/μL with an increase of ≥20,000/μL) to at least one prior line of therapy (with splenectomy being considered a line of therapy)

5. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 × 10^9/L, hemoglobin [Hgb] >9 g/dL, AST/ALT ≤1.5 × ULN, albumin ≥3 g/dL, total bilirubin ≤1.5 × ULN, estimated glomerular filtration rate [eGFR] >60 mL/min (Cockcroft and Gault method) (C1D1 pre-dose may be checked up to Day 3 prior to C1D1)

6. Female patients who are of reproductive potential must agree for the duration of active treatment in the study to use a highly effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormonereleasing system, bilateral tubal ligation, vasectomized partner, or true abstinence: when this is in line with the preferred and usual lifestyle of the patient). Unless surgically sterile, postmenopausal females should have menopause confirmed by follicle-stimulating hormone (FSH) testing.

7. Able to provide written informed consent and agreeable to the schedule of assessments.

6.1.2 Exclusion Criteria

1. Pregnant or lactating women

2. Electrocardiogram (ECG) findings of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities

3. History or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the trial, with the exception of non-melanoma skin cancer

4. Transfusion with blood or blood products or plasmapheresis within 2 weeks before Day 1

5. Change in corticosteroid and/or TPO agonist dose within 2 weeks prior to Day 1 (more than 10% variation from Day 1 daily doses)

6. Use of rescue medications other than corticosteroids or TPO in Exclusion Criterion #5 in the two weeks before Day 1

7[redacted]

8. Treatment with rituximab or splenectomy within the 3 months prior to Day 1

9.[redacted]

12. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), thienopyridenes (within 14 days of planned dosing through end of follow-up)

13. 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); patient should not be using an investigational device at the time of dosing

14. Current drug or alcohol abuse

15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption

16. History of solid organ transplant

17. Positive for screening for human immunodeficiency virus (HIV), hepatitis B (surface antigen and core antibodies unrelated to vaccination), or hepatitis C (anti-HCV antibody confirmed with HCV RNA)

[redacted]

20. [redacted]

21. Planned surgery in the time frame of the dosing period

22. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with patient safety, study evaluations, and/or study procedures.

6.2 Part B

6.2.1 Inclusion Criteria

1. Male or female patients, aged 18 to 80 years old

2. Patients with immune-related ITP (both primary and secondary) as defined by current guidelines with at least 3 months duration

3. Patients who had a response (achievement of platelet count ≥50,000/μL) to IVIg/anti-D or corticosteroid that was not sustained and failed at least one other ITP therapy (that was not IVIg or corticosteroid)

4. Patients with a platelet count of <30,000/μL on two occasions no less than 7 days apart in the 15 days before treatment begins, and no platelet count above 35,000/μL on Study Day 1.

5. Patients with adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 × 10^9/L, Hgb >9 g/dL, AST/ALT ≤1.5 × ULN, albumin ≥3 g/dL, total bilirubin ≤1.5 × ULN, eGFR >50 mL/min (Cockcroft and Gault method) (pre-dose may be checked up to Day -3)

6. Female patients who are of reproductive potential must agree for the duration of active treatment in the study to use a highly effective means of contraception (hormonal contraception methods that inhibits ovulation, intrauterine device, intrauterine hormonereleasing system, bilateral tubal ligation, vasectomized partner, or true abstinence; when this is in line with the preferred and usual lifestyle of the patient). Unless surgically sterile, postmenopausal females should have menopause confirmed by FSH testing.

7. Able to provide written informed consent and agreeable to the schedule of assessments.

6.2.2 Exclusion Criteria

1. Pregnant or lactating women

2. ECG findings of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic patients or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities

3. History (within 5 years of SD1) or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the trial, with the exception of non-melanoma skin cancer

4. Transfusion with blood, blood products, IVIg, or plasmapheresis within 2 weeks before SD1

5. Change in corticosteroid and/or TPO agonist dose within 2 weeks prior to SD1 (more than 10% variation)

6. Use of rescue medications in the 4 weeks before SD1

7. Treatment with [redacted] within 2 weeks prior to SD1

8. Treatment with rituximab or splenectomy within the 3 months prior to SD1

   - Patients treated with rituximab within 6 months from screening will have normal B-cell counts prior to enrollment.

9. [redacted]

10. [redacted]

11. [redacted]

12. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin with the exception of up to 100 mg/day doses, NSAIDs, thienopyridenes (within 2 weeks of planned dosing through end of follow-up)

13. 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); patient should not be using an investigational device at the time of dosing

    - Patients who previously received treatment with BTK inhibitors within 30 days before receiving the first dose of study medication or who have previously received rilzabrutinib are not eligible for the study

14. Current drug or alcohol abuse

15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate study drug absorption

16. History of solid organ transplant

17. Positive at screening for HIV, hepatitis B (surface antigen, core antibodies), or hepatitis C (anti-HCV antibody confirmed with HCV RNA).

    - Patients who are HBV surface antigen (HBsAg) positive will not be eligible.

    - Patients who are HBsAg negative and HBV core 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, patients 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.

    - Patients who are HBcAb positive, HBsAg negative with HBsAb titer <100 IU/L or negative, are not eligible.

18. [redacted]

19. Myelodysplastic syndrome

20. [redacted]

21. Planned surgery in the time frame of the dosing period

22. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with patient safety, study evaluations, and/or study procedures.

7 STUDY ASSESSMENTS

The Schedule of Assessments is presented in Appendix 3 for Part A, Appendix 4 for Part B, and for the LTE in Appendix 5 and Appendix 6. All patients must sign and date the most current IRB/IEC-approved written informed consent form before any study specific assessments or procedures are performed. An original signed consent form will be retained by the Investigator and the patient will be given a copy of the signed consent form.

Patients must fulfill all entry criteria to be enrolled into the study. Patients who fail to meet the entry criteria may be rescreened once at the discretion of the Investigator after informing the study Medical Monitor. A record of eligibility screening documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria, including screen failures, is to be completed and signed by the Investigator or designee. Ethnicity of patients will be recorded, since this information might be important to evaluate a potential impact of ethnic factors on drug properties; see ICH Guideline E5 (R1).

8 LIST OF STUDY ASSESSMENTS

The Schedule of Assessments is presented in Appendix 3 for Part A, Appendix 4 for Part B, and for the LTE in Appendix 5 and Appendix 6.

- Study procedures and their timing are summarized in the Schedule of Assessments. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Clinical Assessments

- Medical history
- Concomitant medications
- Physical examination
- Weight, height
- Vital signs
- IBLS
- QOL assessment [redacted]
- Part B: ITP-PAQ
- Safety assessments.

8.2 Laboratory & ECG Assessments

Note: Laboratory assessments will be performed at both central and local laboratories, if required.

- CBC with differential, including reticulocyte count
- ABO Blood Type (screening only, historical information is acceptable)
- Immature Platelet Fraction (where available)
- Mean Platelet Volume (where available)
- Coagulation: prothrombin time (PT)/International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT)
- 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, glucose (random), and creatine phosphokinase (CPK)

- FSH for post-menopausal patients who are not surgically sterile
- PK: plasma rilzabrutinib concentration
- Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocytes measured by dip stick or local requirement
- Serology: HIV, Hepatitis B, and Hepatitis C
- Pregnancy test for women of childbearing potential
- Part A only: quantitative platelet autoantibody panel (Australia Only: test excluded)
- Hemolysis panel: Coombs test, haptoglobin levels
- TPO levels
- [redacted]
- Part B only: BTK occupancy (at selected sites)
- Part A only: 12-lead ECG: single at screening, triplicate ECGs pre-dose and post-dose on days of intensive PK draws
- Part B only: 12-lead ECG: single at screening and at monthly clinical visits.

8.3 Safety Assessments

Safety assessments include the following: the frequency, severity and relationship of AEs, clinical laboratory test changes, physical examination, ECGs, and vital signs.

Part A:

Patients will remain under observation in the clinic for 6 hours after administration of the first dose at the beginning of each new, higher dosing level while having intensive PK sampling performed.

Part B:

Patients will remain under observation in the clinic for 2 hours after administration of the first dose on Study Day 1, Study Day 29, and Study Day 57 for PK sampling.

8.4 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 13.3) and, when applicable, further information on the future research will be 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.

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 13.2).

Use of leftover samples and additional samples for future research

Leftover samples from the study will be used only after the end of main treatment period of both Part A and Part B. 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. 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.

9 IDENTITY OF INVESTIGATIONAL PRODUCT

9.1 Formulation

[redacted]

9.2 Packaging

Rilzabrutinib 100 mg and 300 mg tablets, 35 count per bottle and 400 mg tablets, 70 count per bottle are packaged in white high-density polyethylene (HDPE) bottles with child-resistant induction-sealed caps.

9.3 Storage and Handling

The bottles of 100 mg and 300 mg tablets are stored at 2–8°C. The bottles can be transported without ice at room temperature and can be kept at room temperature conditions for up to 2 weeks.

The bottles of 400 mg tablets are stored at 2–25°C. The bottles can be kept at room temperature conditions.

9.4 Drug Accountability

The Investigator or his/her designated representatives will dispense study drug per the Schedule of Assessments (Appendix 3 for Part A, Appendix 4 for Part B, and for the LTE in Appendix 5 and Appendix 6).

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 drug must be maintained. The Investigational Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the patient to whom the study drug was dispensed (for example patient identification number, patient initials, and date of birth)
- the date(s), quantity, and lot number(s) of the study drug dispensed to the patient
- the identification of the person who dispensed the study drug.

All records and drug supplies must be available for inspection by the Study Monitor at every monitoring visit. When the study is completed, the Investigator will return any used and unused study drug (eg, empty, partially used, and unused containers), occluded labels (or the equivalent) to the Sponsor as requested, or the drug may be destroyed at the site with Sponsor approval. The completed Drug Dispensing Log and Drug Return Record(s) will be returned to the Local

Sponsor. The Investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to the Sponsor.

9.5 Destruction of Investigational Product

Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study center staff to destroy dispensed investigational product before a monitoring inspection, provided that written authorization is obtained from the Sponsor before destruction, and 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.

Study drug that has not been stored properly or is damaged should not be destroyed until the final temperature excursion or packaging and storage deviation report has been completed, and Sponsor approval for drug destruction is obtained.

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 investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed the investigational products.

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

10 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

10.1 Primary Safety Endpoints

Safety will be assessed by the incidence, severity, and relationship of TEAEs, including clinically significant changes in physical examination, laboratory tests, ECG, and vital signs. Treatment-emergent adverse events in the post treatment follow-up period will also be assessed and examined for possible relationship to the prior rilzabrutinib treatment. Adverse events will be categorized as treatment emergent after the first dose of rilzabrutinib has been received.

10.2 Primary Efficacy Endpoints

Part A:

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

Part B:

Proportion of patients able to achieve platelet counts ≥50,000/μL on at least 8 out of the last 12 weeks of the 24-week treatment period without the use of rescue medication.

10.3 Secondary Endpoints

10.3.1 Safety Endpoints

In addition, safety will be assessed by the following endpoints,

- Proportion of patients receiving rescue medication at each dosing level and overall
- Proportion of patients with a Grade 2 or higher bleeding event at each dosing level and overall
- Bleeding scale (IBLS) at the end of treatment period for each dosing level

10.3.2 Efficacy Endpoints

Part A:

- Percent of weeks with platelet counts ≥50,000/μL by dose level and overall
- Proportion of patients with 4 out of the final 8 platelet counts ≥50,000/μL across all dose levels
- Change from baseline to the average of the post Day 1 platelet counts by dose level and overall for patients who had >4 weeks of study drug on that given dose level

- Number of weeks with platelet counts ≥50,000/μL across all dose levels
- Number of weeks with platelet counts ≥30,000/μL across all dose levels
- Time to first platelet count ≥50,000/μL across all dose levels

Part B:

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

10.3.3 Pharmacokinetic Outcome Measures

Plasma PK parameters (maximum observed plasma concentration [C_{max}], T_{max}, area under the plasma concentration-time curve [AUC], elimination half-life [$t_{½}$], apparent volume of distribution of the drug after oral administration [V/F], apparent total clearance of the drug from plasma after oral administration [CL/F]) of rilzabrutinib in ITP patients will be evaluated in each patient based on frequent sampling on Day 1 of a new, higher dosing level and reported by dose (Part A only) and, if relevant, overall. Results will be reported by descriptive statistics. Exploratory analyses will pool these data with the data from other studies of rilzabrutinib.

10.4 Exploratory Measures

Part A:

- Proportion of patients with any two platelet counts ≥50,000/μL AND an increase of platelet count of ≥20,000/μL from baseline during treatment period.
- Proportion of patients with any two platelet counts ≥50,000/μL AND an increase of platelet count of ≥20,000/μL from baseline during follow-up period (without dose reduction of the concomitant CS or TPO-RA doses)
- Proportion of patients able to achieve two or more consecutive platelet counts, separated by at least 5 days, of ≥30,000/μL OR an increase of platelet count of ≥20,000/μL from baseline, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count.

- Proportion of patients able to achieve any platelet counts ≥100,000/μL.
- Time to first of two consecutive platelet counts ≥50,000/μL
- Proportion of patients with 4 out of the final 6 platelet counts ≥50,000/μL across all dose levels
- Proportion of patients with 8 out of the final 12 platelet counts ≥50,000/μL across all dose levels
- Effect of rilzabrutinib on platelet autoantibody levels

[redacted]

- Effect of rilzabrutinib on QOL using [redacted]
- Plasma metabolite analysis.

Part B:

- Proportion of patients who completed 24 weeks of treatment and demonstrated a platelet response defined as platelet counts ≥50,000/μL at 4 out of the last 8 weeks of the active treatment period
- Proportion of patients who have a platelet count that exceeds 250,000/μL or 450,000/μL (for patients on concomitant TPO-RAs)
- Time to first platelet count of ≥50,000/μL
- Percentage of time with platelet counts ≥30,000/μL OR ≥20,000/μL above baseline
- [redacted]
- Effect of rilzabrutinib on [redacted]
- Effect of rilzabrutinib on TPO levels
- Effect of rilzabrutinib on QOL.

10.5 Determination of Sample Size

Part A

The sample size for this study is based on clinical considerations. Assuming an expected efficacy rate for the primary endpoint of 40% (platelet response), with 15 evaluable patients there will be 80% confidence that the true proportion will be 24% and above (80 ±16% confidence interval [CI]) using normal approximation methods.

The results from this study will be used to [redacted]

Part B

The sample size is designed to provide an estimate the true response rate. Part B will enroll approximately 23 patients. If 5 responders are observed out of 23 treated patients, the observed response rate is [redacted] which is the historical standard of care response rate estimated from a pooled analysis of 8 randomized studies in ITP patients.

10.6 Analysis Populations (Part A and Part B)

10.6.1 Safety Analysis Population

All patients who have received at least one dose of rilzabrutinib will be included in the safety analysis. The Safety Analysis Population will be used for all safety analyses.

Part A only:

For assessment of safety by the IDSM, with regard to dropping a dose level for futility, 3 evaluable patients, defined as compliance of ≥75% of doses for that dose level, are required. Patients will be replaced if necessary to fulfill this requirement.

10.6.2 Efficacy Analysis Population

All patients who have enrolled in the study will be included in the Intent to treat (ITT) population. Enrolled patient is defined as a patient who signed the informed consent form and met eligibility criteria. Efficacy analysis will be based on the ITT population.

10.6.3 Pharmacokinetic Analysis Population

All patients who have received at least one dose of rilzabrutinib and have at least one measurable plasma concentration value will be included in the PK analysis. The Pharmacokinetic Analysis Population will be used for all PK analyses.

10.7 Patient Numbers and Treatment Assignments

As they are enrolled in the study, patients will be assigned a unique consecutive number. The site, in conjunction with the Sponsor, will be responsible for assignment of all unique patient numbers and dose assignments.

10.8 Patient Disposition, Patient Replacement, and Demographics and Baseline Characteristics

10.8.1 Disposition

The numbers of patients enrolled, completing, and withdrawing, along with reasons for withdrawal, will be tabulated. The number of patients in each analysis population will be reported.

10.8.2 Replacement of Patients

Patients prematurely discontinued from the study, for reasons other than TEAEs, may be replaced at the discretion of the Sponsor to ensure adequate numbers of evaluable patients. Each patient who provides informed consent will be assigned a unique patient identifier (USUBJID). Patients recruited to be replacement patients will be assigned the next available patient identifier.

10.8.3 Demographics and Baseline Characteristics

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

Prior and concomitant medications will be listed, classified using World Health Organization Drug Dictionary (WHODD) Anatomical Therapeutic Chemical classes and preferred terms.

Baseline demographics and patient characteristics will be summarized for the Safety Population.

10.9 Efficacy and Exploratory Analysis

Part A

Qualitative efficacy data will be summarized by frequencies and percentages. Quantitative efficacy data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum). Data will be summarized over time by dose level and overall. The time course of mean changes in platelet count over time will also be described graphically, annotated for dosing levels. All analyses will be based on the Intent-to-treat (ITT) Population.

Full details of the analyses for Part A will be provided in the Statistical Analysis Plan (SAP).

Part B

Qualitative efficacy data will be summarized by frequencies and percentages. Quantitative efficacy data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum). The time course of mean changes in platelet count over time will also be described graphically. All analyses will be based on the ITT Population.

Full details of the analyses for Part B will be provided in the SAP.

10.10 Safety and Tolerability Analysis

The incidence, severity, and relationship of TEAEs, laboratory tests, rescue treatment usage, and vital signs will be summarized descriptively. Qualitative safety data will be summarized by frequencies and percentages at each dose level, using the time boundaries of that dosing level (Part A only). Quantitative safety data will be summarized by descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum) at each dose level (Part A only) and overall for Part B. Summaries will also be presented for the change from baseline, when

appropriate. The proportion of patients with a Grade 2 or higher bleeding event will also be summarized. Non-TEAEs will be described in separate listings.

10.10.1 Adverse Events

The original verbatim AE terms recorded on the patient's case report form (CRF) by the Investigator will be standardized by assigning preferred terms and system organ classes from the most recent available version of the Medical Dictionary for Drug Regulatory Affairs (MedDRA).

Adverse events will be codified using the NCI CTCAE v5.0, which provides a mechanism for grading the severity of the AE.

Treatment emergent adverse events include all AEs that start on or after the first dose of study medication, or AEs that are present prior to the first dose of study medication, but worsen after the first dose of study medication up to and including the final study medication dosing date. Adverse events that occur after the first dose of study medication or worsen after the first dose of study medication are treatment-emergent adverse events (TEAEs). Adverse events that occur prior to the first dose of study medication are pre-treatment adverse events (ie, non-TEAEs). The number and percent of patients with any TEAEs will be displayed by system organ class and preferred term by dosing level and overall. Within each preferred term, patients will be counted only once if they had more than one event reported during the dosing period. The same summary will be performed for all serious TEAEs and all TEAEs causing discontinuation of study drug.

Treatment-emergent adverse events will also be summarized by greatest reported severity grade (Grades 1–5) for each event/preferred term. Counts will indicate patients reporting one or more TEAEs that map to the severity grade classification for each preferred term. At each level of summarization (system organ class or event preferred term) patients are only counted once. TEAEs will be summarized by greatest reported relationship in a similar manner. A listing will be produced for all patients who reported serious TEAEs or who discontinued study medication due to TEAEs.

All TEAEs will be listed individually by patient. In addition, a separate listing will be produced for AEs that are not treatment-emergent.

10.10.2 Clinical Laboratory Tests

All clinical laboratory data will be stored in the database in the units in which they were reported. Normal ranges for the local laboratory parameters must be provided to Principia/designee before the study starts. Patient listings and summary statistics at each assessment time, including change from baseline, will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before analysis.

<u>Part A</u>

Clinical laboratory results will be summarized descriptively for baseline and each time point. The numerical change from baseline to each time point will be computed. Exploratory analysis

of the relationship between dose level and laboratory changes will be explored if any are seen in the initial analyses. In addition, laboratory shift tables will be provided for all laboratory parameters where low/normal/high or abnormal/normal status can be ascertained for shift from baseline to each time point. Listings of individual laboratory parameters by visit with normal ranges and abnormality assessments will also be completed by patient.

Part B

Clinical laboratory results will be summarized descriptively for baseline and each monthly clinic visit. The numerical change from baseline to each visit will be computed. Laboratory shift tables will be provided for all laboratory parameters where low/normal/high or abnormal/normal status can be ascertained for shift from baseline to each monthly clinic visit. Listings of individual laboratory parameters by visit with normal ranges and abnormality assessments will also be completed by patient.

Part A and Part B

[redacted]

10.10.3 Vital Signs

Vital signs data will be presented by individual listings. Systolic blood pressure values <90 or >140 mmHg and diastolic blood pressure values <60 or >80 mmHg will be flagged as outside the normal range. Resting heart rate <40 or >100 beats per minute will be flagged as outside the normal range. Descriptive statistics of values and changes from baseline (mean, median, standard deviation) will be reported for quantitative variables separately for each dosing level, using the time boundaries for that level in Part A and overall in Part B. In addition, tabular and graphical summaries will be used, as appropriate.

10.10.4 Rescue Medication, DLTs, and Bleeding Scale Scores

The percentage of patients receiving rescue medication at each dosing level (Part A only) and at any time during dosing for Part A, and at any time during dosing for Part B.

The percentage of patients with a DLT will be summarized at each dosing level, overall for Part A, and overall for Part B.

Bleeding scale (IBLS) scores will be summarized over time at each dosing level, overall for Part A, and overall for Part B.

10.10.5 Concomitant Medications

The original terms recorded on the patients' CRF by the Investigator for concomitant medications will be standardized by assigning preferred terms from the WHODD drug terms dictionary for treatments or coded via generic name of the concomitant medication.

Concomitant medications will be presented in summary tables and listings.

10.11 Pharmacokinetics Analyses

Part A

Pharmacokinetic data will be summarized using descriptive statistics, tabulated, and displayed graphically as appropriate. Non-compartmental analysis will be utilized to derive PK parameters for each individual. Pharmacokinetic data may also be pooled with the data from other studies for population PK modeling. Individual patient PK values within this study may be used for exploratory analyses of exposure and effect.

Part B

Pharmacokinetic data will be summarized using descriptive statistics, and tabulated, and displayed graphically as appropriate. Pharmacokinetic data may also be pooled with the data from other studies for population PK modeling.

10.12 Statistical Analysis Plan

A detailed SAP will be developed and finalized before the study database is locked, which will supersede the statistical analysis methods described in the protocol.

11 SAFETY AND TOXICITY MANAGEMENT

This section provides detailed information on reporting requirements and interpretation of safety assessments for AEs and reporting requirements for SAEs. Guidance and reporting requirements for pregnancy are also outlined below.

11.1 Independent Data Safety Monitor (IDSM) and Safety Monitoring Committee (SMC)

Part A

An IDSM who is not a study Investigator will be chosen from expert clinicians in the ITP field. A Safety Monitoring Committee (SMC), comprised of the IDSM as Chairperson, lead Investigator, Study Medical Monitor, and Sponsor's Medical Monitor, will closely supervise the conduct of the study. The IDSM will make "sentinel cohort" safety evaluations.

The "sentinel patients" for each dose level will have their data reviewed by the IDSM, in order to choose the starting dose for additional, new patients. After review, the IDSM may determine that a starting dose for new patients should be dropped for futility (lack of platelet response), increased to the next planned dosing level, kept the same, or reduced. New patients entering the study will commence at the dose level determined by the IDSM based on:

- If ≥2/3 or ≥2/6 of those sentinel patients have a DLT at any dose level, that level shall be determined the "Maximal Administered Dose" and starting doses (new patients) and continuing doses (patients already on study) set at lower dosing levels (or study suspended if the current sentinel dose cohort was 200 mg QD)
- If two or more sustained platelet responses (3 of 4 counts) in the sentinel patients are seen at the current starting dose level the starting dose will not be escalated.

The SMC will meet approximately quarterly and recommend study modification or termination to the Sponsor, based on review of safety and efficacy information. Any SMC findings that impact the safety of patients in this study will be immediately reported to the local Competent Authority (CA) and IRB/EC.

An SMC Charter outlining the SMC composition and responsibilities will be in place prior to the first scheduled meeting.

Part B

There will be no independent SMC in Part B.

Specific assessments to evaluate treatment safety include the following: the frequency, severity and relationship of AEs, clinical laboratory test changes, physical examination, and vital signs. The assessments will be conducted as part of ongoing medical monitoring and at Sponsor Quarterly Safety Reviews where safety events and trends across rilzabrutinib studies are considered.

11.2 Adverse Event Collection Period

The AE Collection Period begins at the time of the first screening/eligibility assessment and ends at the end of the study for each patient.

11.3 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient 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 investigational product, whether or not considered related to the product. All AEs encountered during the clinical study will be recorded in detail in the source documents and entered in the CRF from the date of patient consent throughout the study follow-up period. Pre-existing conditions that worsen during a study are reported as AEs, with the expectation 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 CRF unless the event meets the definition of an SAE or is not consistent with the typical clinical course of the patient's disease as established by the patient'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.**

11.4 Adverse Event Relationship to Study Drug

Investigators should use their knowledge of the study patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE may be considered as related to the study drug, indicating "yes" or "no" accordingly.

The following information should be considered:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (if applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the study patient 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.

11.5 Treatment and Follow-Up of Adverse Events

Adverse events, especially those for which the severity is Grade 3 or higher, should be followed up until stabilization or until 4 weeks post last dose (considered as the last follow up), based on the PK profile of the drug.

11.5.1 Laboratory and ECG Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the CRF or merged electronically with the CRF data, and will appear on electronically produced laboratory reports provided to the Investigator. Data will be reported to Principal Investigators in laboratory reports and merged with CRF data on the back end. Some laboratory data may be manually entered, if necessary.

Any treatment-emergent abnormal laboratory or ECG result that 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 CRF:

- Accompanied by clinical symptoms
- Leading to a change in study drug (eg, dose modification, 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 must be reported as such, in addition to being recorded as an AE in the CRF.

11.6 Adverse Event Intensity Grading

All clinical AEs encountered during the clinical study will be reported on the AE page of the CRF. Intensity of AEs will be graded based on the NCI CTCAE, version 4.0 or higher and reported in detail as indicated on the CRF. For any AEs not found in the CTCAE, a description of intensity grading can be found 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.

Any life-threatening events or any event with an outcome of death should be reported as a serious adverse event as outlined in Section 11.7.

11.6.1 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 and 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 CRF.

11.7 Serious Adverse Event (SAE) Reporting

11.7.1 SAE Definitions

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death*
- is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

**Note that the term "sudden death" is only used when the cause is of a cardiac origin as per* standard *definition. The terms "death" and "sudden death" are clearly distinct and are not used interchangeably.*

11.7.2 SAE Reporting

For the European Union, safety reporting to the agency is described in Section 16.8.1.

Any adverse event that is *serious* and occurs during the course of the study (as defined above), occurring from the signing of the informed consent (start of study screening procedures), and including long term follow up must be reported:

- In the Medidata RAVE EDC **within 24 hours** of the Investigator becoming aware of the event (expedited reporting)
- The investigational site’s IRB by the Investigator in accordance with their regulations.

If the EDC is unavailable the SAE must be reported by the Investigator on an SAE Reporting Form **within 24 hours** of Investigator's awareness to Principia Pharmacovigilance:

SAE Reporting Information

mailto:

ssf.1008010sae@sanofi.com

The 4 minimum criteria for a valid SAE report include:

- Identifiable reporter
- Single identifiable patient
- Adverse event term
- Suspect medicinal product.

The Investigator should not wait to receive additional information to document fully the event before notification of a SAE. As soon as the 4 minimum mentioned above criteria are fulfilled, the Investigator must report the SAE within 24 hours of awareness. In addition, all further information requested on the SAE Reporting Form should be completed and sent to PVG contact as soon as possible.

Receipt of the initial notification of an SAE will be confirmed in writing within 24 hours from the time the investigational team first becomes aware of the event, if possible.

Copies of paper SAE report forms must be retained in the Investigator Site File.

Any further information, including SAE follow-up information should be documented within the RAVE system.

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention must be reported within 24 hours (eg, SAEs related to invasive screening procedures such as biopsies, medication washout, or no treatment run-in). After first study medication, all SAEs must be reported within 24 hours.

Related SAEs ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated SAEs must be collected and reported during the study and/or for up to 30 days after the last dose of study medication, whichever is longer.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to Investigators at each site and associated IRB when the following conditions occur:

- The event is a SAE
- There is a reasonable possibility that the event is an adverse reaction caused by the administered drug
- The adverse reaction is unexpected, that is to say, not listed in the Investigator's Brochure
- Individual SUSAR reports will be forwarded to the site and its associated IRB on an expedited basis.

Individual SUSARs considered a significant safety issue and/or which result in a change to the informed consent form will be reported in an expedited manner to all Investigators and IRBs.

Reporting of any SAEs to applicable regulatory authorities will be the responsibility of the Local Sponsor in compliance with local regulations.

11.7.3 Other Safety Findings Requiring Expedited Reporting

Significant safety findings will be reported to the Investigator by Principia or designee as obtained. The Investigator is responsible for reporting to the investigational site's IRB in accordance with their regulations. Reporting to applicable regulatory authorities will be the responsibility of Principia (or designee) in compliance with local regulations.

Investigators will report all potential DLT events to the Medical Monitor within 24 hours from the time the investigational team first becomes aware of the event.

11.8 Pregnancy

Pregnancy in a Female Clinical Trial Patient: If a female clinical trial patient becomes pregnant during the study, she must be instructed to stop taking the study drug and immediately inform the Investigator. Pregnancies occurring up to 4 weeks after the completion of the study drug must also be reported to the Investigator. The patient should be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until the outcome of the pregnancy is known. The Investigator should report all pregnancies in clinical trial patients to the Sponsor within 24 hours of becoming aware of them, using the Clinical Trial Pregnancy Reporting Form.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor.

11.9 Adverse Event of Special Interest

An adverse event of special interest (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 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 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 Section 11.7).
  - 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 (Section 11.8)
- Symptomatic overdose (serious or non-serious) with IMP
- Increase in alanine transaminase (ALT): >3 × ULN (refer to the flow chart, Section 16.7.)
- Any Grade 4 or 5 infection where the participant is hospitalized ≥24 hours and/or requires emergency care and/or requires IV antibiotics.
- [redacted]

11.10 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.

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 CRF against the Investigator's records by the study monitor (source document verification), and the maintenance of a study drug dispensing log by the Investigator.

Data for this study will be recorded in the study Electronic Data Capture (EDC) CRFs. The data will be entered by the study center from the source documents into the CRF or will be loaded from electronic files (eg, safety lab data). In no case is the CRF 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 all data entered in the database will be independently compared with the original Investigator's records.

12.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned to the original terms recorded on the CRF, using the MedDRA for AEs, diseases and surgical and medical procedures, and the WHODD for drug and herbal treatments as specified in the SAP.

13 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

This section provides information for the Investigator on the ethics requirements for the study, including patient informed consent, IRB/EC 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.

13.1 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.

13.2 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 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 are expected to 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 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.

- The participant must be informed that his/her 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.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The 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 of the Sponsor's studies. In case the professionals have already been involved in a ~~s~~study with this Sponsor, 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 company 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,
  - The Sponsor'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 thirty (30) 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 once for all 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 Sanofi 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).

13.3 Patient Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator [if acceptable by local regulations], to obtain signed and dated informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The CRFs for this study contain a field for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

13.4 Institutional Review Board and Ethics Committee Review

- The protocol, protocol amendments, ICF, Investigator's Brochure, 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:
  - 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
  - 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 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.
- 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 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

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 clinical trial 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.

13.5 Conditions for Modifying the Protocol

Any protocol modifications must be prepared and approved by a representative of The Sponsor.

All protocol modifications must be submitted to the appropriate IRB/IEC for information and/or approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study patients, or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor[s], change of telephone number[s]).

13.6 Conditions for Terminating the Study

The Sponsor, the Investigator, and the IRB responsible for the study reserve the right to terminate the study at any time. Should this be necessary, the parties will consult and arrange the termination procedures on an individual study basis. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IRB/IEC and Regulatory Agencies should be informed accordingly.

13.7 Financial Disclosure

The Investigator(s) will provide the Sponsor with sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The Investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

14 STUDY DOCUMENTATION, MONITORING, CASE REPORT FORMS, AND RECORD RETENTION REQUIREMENTS

14.1 Investigator's File/Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) patient clinical source documents.

The Investigator's Study File will contain the protocol/amendments, CRF data and Discrepancies, IRB and regulatory authority approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

Patient clinical source documents independent of the CRF would include patient hospital/clinic records, physician's and nurse's notes, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrollment logs.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies or by agreement with the Sponsor require a different retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

14.2 Source Documents and Background Data

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

14.3 Audits and Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Sponsor or its designees, or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

14.4 Case Report Forms

The data collected in the source documents for this study will be entered into the study EDC CRF. 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 patient enrolled, a CRF must be completed and signed by the Principal Investigator or authorized delegate from the study staff. If a patient withdraws from the study, the reason must be noted in the CRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, 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 CRFs and in all required reports.

14.5 Study Monitoring

It is understood that the responsible Sponsor study monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (CRFs and other pertinent data) provided that patient confidentiality is maintained in accordance with local requirements.

It will be the monitor's responsibility to inspect the EDC CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the patient received the assigned dose. The monitor should have access to laboratory test reports and other patient records needed to verify the entries in the EDC CRF. The Investigator (or deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

14.6 Confidentiality of Clinical Trial Documents and Patients' Medical Records

The Investigator must assure that patients’ anonymity will be maintained and that their identities are protected from unauthorized parties. In the EDC CRF or other documents submitted to the Sponsor, patients must not be identified by their names, but by an identification code.

The Sponsor already maintains rigorous confidentiality standards for clinical studies by “coding” (ie, assigning a unique patient identification [ID] number at the Investigator site) all patients enrolled in Sponsor clinical studies. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

14.7 Clinical Study Report

A Clinical Study Report will be submitted to relevant IRB/EC and regulatory authorities in accordance with local requirements.

14.8 Publication of Data and Protection of Trade Secrets

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

15 STUDY ADMINISTRATIVE PROCEDURES

This section provides additional information on study-related administrative procedures, definitions, requirements, and record-keeping activities related to the study assessments described in Section 8.

15.1 Patient Recruitment Procedures

Patients will be identified for potential recruitment by the Investigator, possibly including activities such as, but not limited to, a listing from study center, patient database, newspaper/radio/internet advertisement, or mailing list.

15.2 Patient Enrollment Procedures

Patients cannot commence enrollment procedures until all entry criteria have been fulfilled. Where the clinical significance of an abnormal screening test result (lab or any other tests) is uncertain, the test may be repeated.

The Investigator or designee will enter data for each enrolled patient in the study CRF and enter the corresponding number for allocation to the treatment groups in the appropriate place on each patient's CRF. A patient enrollment and Identification Code List must be maintained by the Investigator or Pharmacist, or designee.

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

15.3 Patient Premature Withdrawal – Definition

A patient who withdraws from the study before the planned end of study visit is considered to have withdrawn from the study early.

15.4 Procedures for Patients Who Withdraw from the Study

Patients have the right to withdraw from the study at any time for any reason. In the event that a patient decides to discontinue from the study, he/she should be asked if he/she will complete the Early Withdrawal/Unscheduled Visit and be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the Investigator without the patient's consent. The Investigator may withdraw patients from the study in the event of intercurrent illness, AEs, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures or any other reasons where the Investigator feels it is in the best interest of the patient to be terminated from the study.

Reasons for withdrawal must be documented and explained to the patient. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible, particularly the follow-up examinations.

The Investigator should contact the patient or a responsible relative either by telephone (followed by registered mail) or through a personal visit to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an AE, the principal specific event must be recorded on the CRF. The patient should be followed until the AE is resolved, if possible.

15.5 Treatment Compliance

Accountability and patient compliance will be assessed by maintaining adequate study drug dispensing records and medication counts. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. See Section 9.4 for instructions on Drug Accountability procedures.

15.6 Recording of AEs on the CRF

All AEs encountered during the clinical study will be reported in detail in the source documents and documented in the CRF, from the date of patient consent throughout the follow-up visit. All AEs, especially Grade 3 or higher, should be followed up until they have returned to the baseline status or stabilized. If the cause of the AE is established, it should be described in detail, including supporting information, in the source documents and on the CRF.

15.7 Physical Examination Procedures

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

An abbreviated physical examination will consist of checking the normality or abnormality of the following body systems: general appearance, skin, abdomen, and cardiorespiratory examination.

The results of the physical examination will be summarized as normal/abnormal. In case of abnormality, details will be recorded in the patient notes and in the CRF.

Height will be recorded at screening only.

15.8 Vital Signs Procedures

Blood pressure (BP), pulse rate, body temperature, and respiratory rate will be recorded at the time points specified in the Schedule of Assessments (Appendix 3 for Part A, Appendix 4 for Part B, and for the LTE in Appendix 5 and Appendix 6).

15.9 Body Weight

Body weight should be measured on the same digital clinic scale, after checking for accurate zero calibration each time. Weight is recorded in kg to one decimal place.

15.10 ECG Procedures

Single 12-lead ECG assessments will be obtained as specified in the Schedule of Assessments (Appendix 3 for Part A, Appendix 4 for Part B, and for the LTE in Appendix 5 and Appendix 6) to confirm eligibility and to ensure real time safety evaluation of the patients in the study, as specified in the Schedule of Assessments.

Patients should be in a resting position for at least 10 minutes prior to any measurement. Body position should also be consistently maintained for each ECG evaluation. In particular, changes in heart rate should be avoided. There should be no environmental distractions (TV, radio, conversation) during the pre-ECG rest and the ECG recording time.

Heart rate (HR), QRS duration, RR interval, and QT intervals will be recorded. Changes of the T-wave and U-wave morphology and overall ECG interpretation will be documented.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements.

For triplicate ECG assessments, three interpretable ECG recordings (without artifacts) must be collected per time point within a ±10 minute period per time point.

For safety monitoring purposes, the Investigator must review, sign and date all ECG tracings. Paper copies will be kept at the study center with the patient's clinical file as part of the permanent record. The ECG intervals and interpretation will be recorded on the CRF.

15.11 Laboratory Test Procedures

The laboratory assessments will be performed at a central laboratory, with the provision for occasional local laboratory testing, if required. Laboratory safety tests shall be collected at time points specified in the Schedule of Assessments (Appendix 3 for Part A, Appendix 4 for Part B, and for the LTE in Appendix 5 and Appendix 6).

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before Day 1 to confirm eligibility. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated

immediately and followed up until they have returned to the normal range, are considered to be clinically stable, and/or an adequate explanation of the abnormality is found.

15.11.1 Recording of Laboratory Test Results on the CRF

Results of clinical laboratory testing will be recorded on the CRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory, if applicable.

The procedures for the collection, handling and shipping of laboratory samples will be specified in the Sample Collection, Handling, and Logistics Manual.

15.12 Recording of Concomitant Medications on the CRF

All medications (prescription and over-the-counter [OTC]) taken within 28 days prior to study screening (reference Exclusion Criteria) will be recorded in the CRF.

16 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

16.1 Appendix 1:

	Strong	Moderate

16.2

16.3 Appendix 3: Schedule of Assessments (Part A)

	Screening (D-28 to D-1)	On-treatment clinic visits, treatment cycles of 28days, X≤6[14]					Weekly lab visit between clinic visits[13]	Early Withdrawal/ Unscheduled visit
		C1D1 only	CXD1 (first day of each cycle)[12]	CXD15	D169 (last day of active rilzabrutinib treatment)	End of Study D197 / 4 weeks post last dose		
Clinic visits[1]	X		X	X	X	X		X
Laboratory Only Visits for Hematology, differential & retics							X	
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X[1]						
AEs	X	X	X	X	X	X		X
Concomitant Medications	X		X	X	X	X		X
Dose-escalation points[2]			X					
Height	X							
Weight	X		X		X	X		X
Physical exam/med history[3]	X		X	X	X	X		X
ECG (12-lead, single)	X					X		X
ECG (12-lead, triplicate)[4]			X					
Vital Signs	X		X	X	X	X		X
Urinalysis	X		X	X	X	X		X
Hep B &C, HIV	X							
Pregnancy test[5]	X		X		X	X		X
FSH[6]	X							
ABO and Rh Blood Type	X							
Serum Chem	X		X		X	X		X
Hematology, differential, retics.	X		X	X	X	X		X
[redacted]	[redacted]							
PT/INR PTT	X		X		X	X		
TPO levels			X		X	X		
Hemolysis panel[7]			X		X			
Platelet Auto antibodies[8]		X			X			X
Mean platelet volume			X					
Immature platelet fraction			X					
PK sample & metabolites[9]			X	X	X			X[10]

	Screening (D-28 to D-1)	On-treatment clinic visits, treatment cycles of 28days, X≤6[14]					Weekly lab visit between clinic visits[13]	Early Withdrawal/ Unscheduled visit
		C1D1 only	CXD1 (first day of each cycle)[12]	CXD15	D169 (last day of active rilzabrutinib treatment)	End of Study D197 / 4 weeks post last dose		
QOL	X		X		X	X		
IBLS[11]	X		X	X	X	X		X
[redacted]								

16.4 Appendix 4: Schedule of Assessments (Part B)

	Screening (D-28 to D-1)	Active Treatment Period for 24 Weeks and 4 Week Follow Up Period[1]								Weekly Lab Visits Between Clinic Visits[1]	Early Withdrawal/ Unscheduled visit
		Enrolment Week 1 SD1	Week 5 SD29	Week 9 SD57	Week 13 SD85	Week 17 SD113	Week 21 SD141	Last Day of Treatment Week 25 SD169	End of Study SD197 / 4 weeks post last dose		
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X1									
AEs	X	X	X	X	X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X		X
Height	X										
Weight	X	X	X	X	X	X	X	X	X		X
Physical exam/med history[2]	X	X	X	X	X	X	X	X	X		X
ECG (12-lead, single)	X	X	X	X	X	X	X	X	X		X
Vital Signs	X	X	X	X	X	X	X	X	X		X
Urinalysis	X	X	X	X	X	X	X	X	X		X
Hep B & C, HIV[12]	X										
Pregnancy test[3]	X	X	X	X	X	X	X	X	X		X
FSH[4]	X										
ABO and Rh Blood Type[5]	X										
Serum Chemistry	X	X	X	X	X	X	X	X	X		X
Hematology, differential, reticulocytes	X	X	X	X	X	X	X	X	X	X	X
[redacted]											
PT/INR PTT	X	X	X	X	X	X	X	X	X		
TPO levels		X	X	X	X	X	X	X	X		
Hemolysis panel[7]		X	X	X	X	X	X	X	X		
Mean platelet volume[13]		X	X	X	X	X	X	X	X		
Immature platelet fraction[13]											
[redacted]											
BTK Occupancy[9]		X	X	X				X			
PK sample[10]		X	X	X							

	Screening (D-28 to D-1)	Active Treatment Period for 24 Weeks and 4 Week Follow Up Period[1]								Weekly Lab Visits Between Clinic Visits[1]	Early Withdrawal/ Unscheduled visit
		Enrolment Week 1 SD1	Week 5 SD29	Week 9 SD57	Week 13 SD85	Week 17 SD113	Week 21 SD141	Last Day of Treatment Week 25 SD169	End of Study SD197 / 4 weeks post last dose		
QOL Questionnaires[11]	X	X	X	X	X	X	X	X	X		
IBLS	X	X	X	X	X	X	X	X	X		X

[redacted]

16.5 Appendix 5: Schedule of Extension Period – First 6 Months (Part A and Part B)

	Day 169 Visit/rollover[redacted]	On-treatment clinic visits, treatment cycles of 28days, X≤6 [redacted]				Early Withdrawal/ Unscheduled visit
Clinic visits[1]	X	X				X
Laboratory Only Visits for Hematology, differential & retics			X	X	X	
AEs	X	X				X
Concomitant Medications	X	X				X
Weight	X	X				X
Physical Exam[7]	X	X				
ECG (12-lead, single)	X					

	Day 169 Visit/rollover/C1D1_LTE	On-treatment clinic visits, treatment cycles of 28days, X≤6				Early Withdrawal/ Unscheduled visit
		CXD1_LTE (first day of each cycle)	CXD8_LTE	CXD15_LTE	CXD22_LTE	
Vital Signs	X	X				X
Urinalysis	X	X				X
Pregnancy test[2]	X	X				X
Serum Chem	X	X				X
Hematology, differential, retics.	X	X				X
[redacted]	[redacted]					
PT/INR PTT[4]	X	X				
TPO levels	X	X				
Hemolysis panel[9]	X					
Mean platelet volume[12]	X					
Immature platelet fraction[12]	X					
Immunoglobulins[10]	X					
BTK Occupancy[11]	X					
Platelet Auto antibodies[5]	X					X
PK sample & metabolites[6]	X	X				X
QOL questionnaire[13]	X	X				
IBLS	X	X				X
HBV[8]	X	X				X

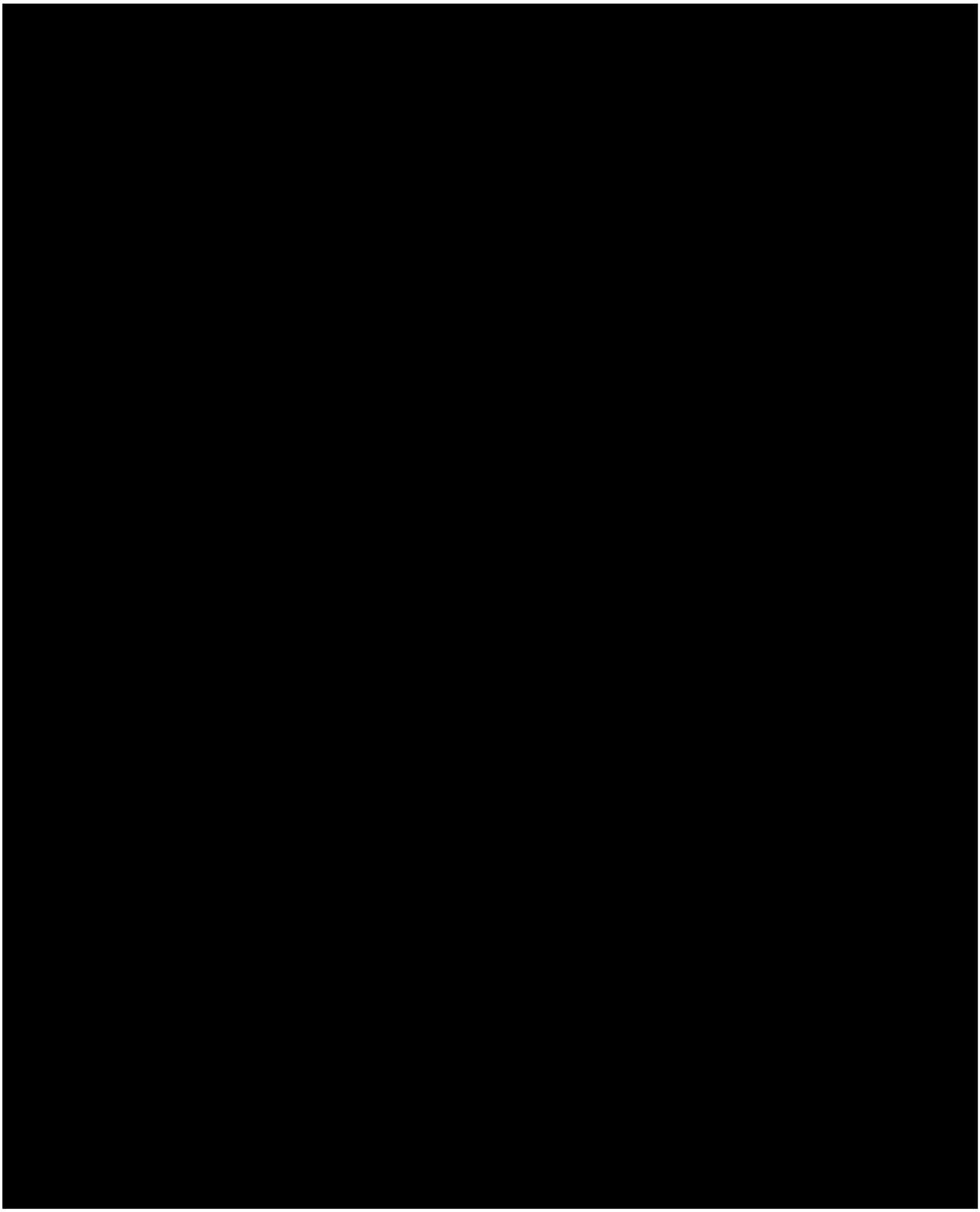
[redacted]

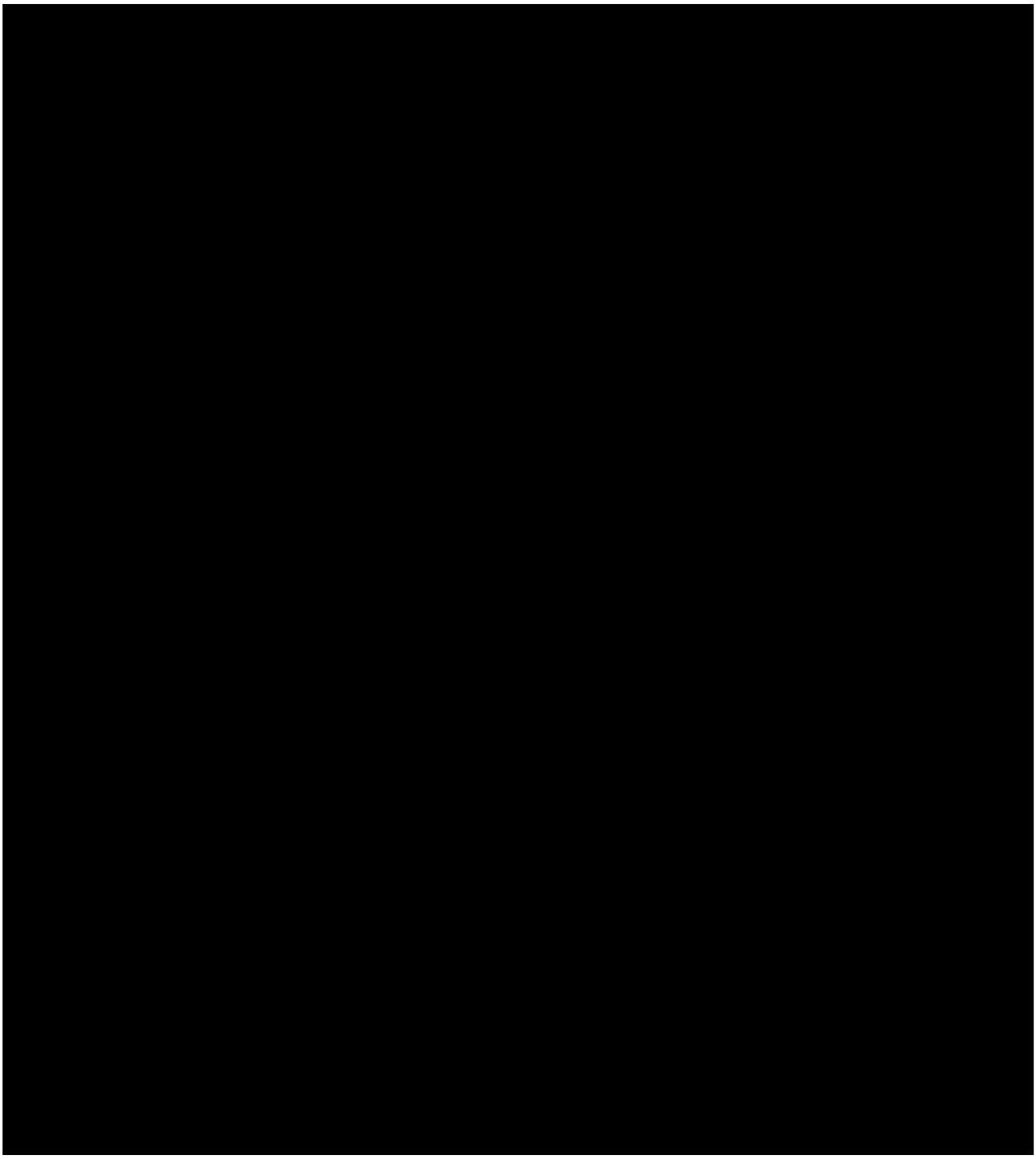
16.6 Appendix 6: Schedule of Assessments – Extension Period Continued (Part A and Part B)

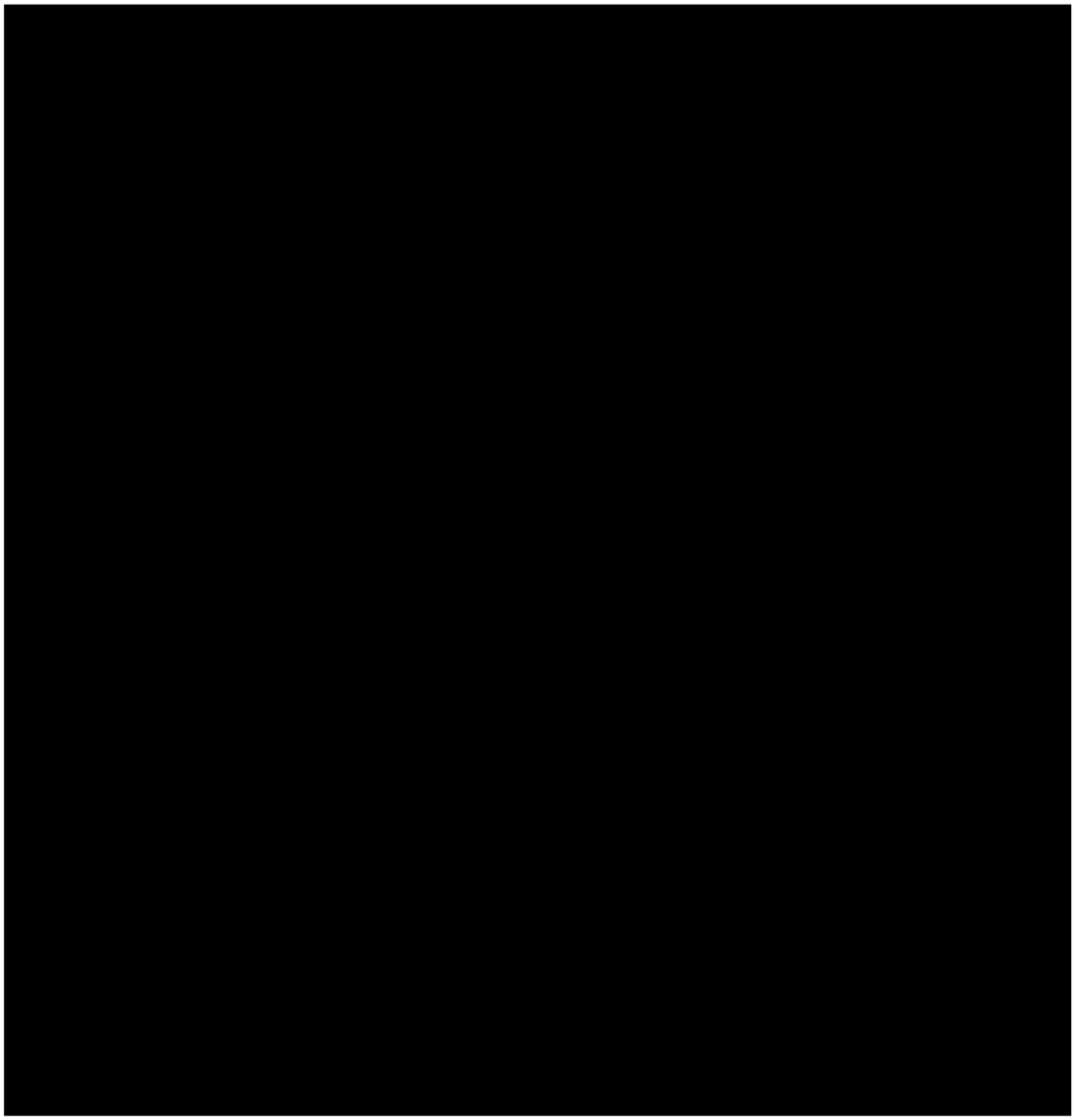
	On-treatment clinic visits, visits every 28 days for 6 months, then every 3 months[8]				
	[redacted] (first day of each cycle) Every 28 days for 6 months	Every 3 Months [redacted]	Last day of active rilzabrutinib treatment	End of Study (4 week post last dose)	Early Withdrawal/ Unscheduled visit
Clinic visits[1]	X	X	X	X	X
AEs	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
Weight	X	X	X	X	X
Physical Exam[7]	X	X	X	X	
Vital Signs	X	X	X	X	X
Urinalysis	X	X	X	X	X
Pregnancy test[2]	X	X	X	X	X
Serum Chem	X	X	X	X	X
Hematology, differential, retics.	X	X	X	X	X
[redacted]	[redacted]				
PT/INR PTT[4]	X	X	X	X	
TPO levels	X	X	X	X	
Platelet Auto antibodies[5]			X		X
PK sample & metabolites[6]	X	X	X		X
QOL questionnaire[10]	X	X	X	X	
IBLS	X	X	X	X	X
HBV[9]	X	X		X	X

1. [redacted]

16.7 Appendix 7: [redacted]







16.8 Appendix 8: Country-specific/region requirements

16.8.1 European Union

16.8.1.1 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.

16.9 Appendix 9: Collection, storage and future use of data and human biological samples

16.9.1 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.

16.9.2 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.

16.10 Appendix 10: Protocol Amendment History

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

Amended protocol 15.0: (19 Mar 2021)

This amended protocol (amendment 15) 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 number to include "(DFI17124)"; added amendment number "15"; updated protocol version and date; added "SAR444671" to header; added "a Sanofi Company" after "Principia Biopharma"; added company logo.	Administrative and per Sanofi template.
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 protocol acceptance page.	For consistency with current Sanofi protocol template and processes. A separate signature page will be available.

Section # and Name	Description of Change	Brief Rationale
Protocol amendment summary of changes	Inserted document history table and protocol amendment summary of changes table.	Per Sanofi protocol template and process.
PRN1008-010 Study synopsis, Background and Rationale; Section 1.2, Summary of rilzabrutinib clinical experience	Updated the paragraph regarding PRN1008-005 study results and added cross-reference to the PRN1008-005 Clinical Study Report.	Update.
PRN1008-010 Study synopsis, Study Design Part B, Patient selection criteria Part B; Section 4.2, Overall study design and plan Part B; Appendix 4, Schedule of assessments (Part B); Appendix 5, Schedule of extension period – first 6 months (Part A and Part B); Appendix 6, Schedule of assessments extension period continued (Part and Part B)	Corrected units for HBsAb titer from IU/mL to IU/L.	Correction.
PRN1008-010 Study synopsis, Study stopping rules; Section 4.6.2, Study stopping rules	Revised third bullet from “3 or more life-threatening (Grade 4) rilzabrutinib-related TEAEs” to “Two or more life-threatening or CTCAE Grade 4 rilzabrutinib-related TEAEs except for AEs related to the disease under study (lack of efficacy).”	Health authority request and consistency with other Principia Biopharma Phase 3 immune thrombocytopenia (ITP) protocols.
PRN1008-010 Study synopsis, Study endpoints Part A; Section 10.3.1, Safety endpoints	Added additional safety endpoints.	Consistency with Statistical Analysis Plan (SAP).
PRN1008-010 Study synopsis, Study endpoints Part A; Section 10.3.2, Efficacy endpoints	Revised secondary efficacy endpoints.	Consistency with SAP.
PRN1008-010 Study synopsis, Study endpoints Part A, Exploratory endpoints; Section 10.4, Exploratory measures, Part A	Added additional exploratory endpoints.	Consistency with SAP.
PRN1008-010 Study synopsis, Study Drug and Methods of Dosing; Section 4.10, Rilzabrutinib administration (Part A and Part B)	Added sentence to state that [redacted]	Clarification to align with Investigator’s Brochure.
PRN1008-010 Study synopsis, Study assessments (Laboratory and ECG assessments) ; Section 8.2, Laboratory and ECG assessments	Bullet 3: Added “(where available)” to bullet for immature platelet fraction.	Correction, previously removed in error.
PRN1008-010 Study synopsis, Study assessments (Laboratory and ECG assessments); Section 8.2, Laboratory and ECG assessments	Bullet 15: Removed Part A only: monocytes counts and B-cell subsets.	[redacted]

Section # and Name	Description of Change	Brief Rationale
Appendix 3, Schedule of Assessments (Part A)	[redacted] removed footnote 7.	[redacted]
PRN1008-010 Study synopsis, Statistical methods Part A, Statistical methods Part B; Section 10.6.2, Efficacy Analysis Population	Text revised to specify that all efficacy analysis will be based on the ITT population, and added definition of the ITT population.	Consistency with SAP.
Section 1.2, Summary of rilzabrutinib clinical experience	Updated text regarding preliminary results of PRN1008-010 and added cross reference to Kuter 2020.	Update.
Section 3.3, Outcome measures of the study: Part A; Section 3.4, Outcome measures of the study: Part B	Revised headings to specify primary safety and primary efficacy endpoints.	Clarification.
Section 4.11.1, Allowed Part A; Section 4.11.2, Allowed Part B; Section 4.11.3, Prohibited	Added text (last bullet) regarding the use of clinically relevant drugs that are[redacted] to Section 4.11.1 and Section 4.11.2; removed previous corresponding text from Section 4.11.3.	Update based on new drug-drug interaction data.
Section 6.2.2, Exclusion Criteria (Criterion #17)	Corrected HBsAb units from IU/mL to IU/L; corrected to read “HBsAb titer “is “≥” 100 IU/L (rather than “>100 IU/L”).	Correction.
Section 10.9, Efficacy and exploratory analysis, Part A, Part B	Replaced “ITT-E” population with “ITT” population.	Correction and consistency with SAP.
Section 11.6, Adverse event intensity grading	Corrected NCI CTCAE version back to 4.0 from 5.0.	Correction, previously changed in error.
Section 11.8, Pregnancy	Revised text to state that pregnancies occurring up to 4 weeks (rather than 90 days) after completion of the study drug must also be reported to the Investigator.	Consistency with current standard text in other Principia BioPharma ITP protocols and is supported by reproductive toxicity data.
	Added information regarding reporting pregnancy AEs/SAEs, including complication or elective termination, abnormal pregnancy outcomes. and post-study pregnancy related SAEs.	Clarification.
Section 16, References	Added reference for Kuter 2020.	Per update in Section 1.2.
	Added reference for PRN1008-005 CSR.	Per update in Synopsis, Background and Rationale.
Appendix 3, Schedule of Assessments (Part A); Appendix 4, Schedule of Assessments (Part B)	In header, clarified that end of study is 4 weeks post last dose.	Clarification.
Appendix 4, Schedule of assessments (Part B)	Removed Hep B & C and HIV testing except at screening.	Clarification as to when Hep B & C and HIV testing is needed.

Section # and Name	Description of Change	Brief Rationale
Appendix 7, Protocol Amendment History	Added new appendix to include protocol amendments history.	Per Sanofi template and process.
Protocol header throughout document	Updated header.	Per Sanofi template.
Throughout document	Replaced “PRN1008” with “rilzabrutinib” as applicable. Added Sanofi study number “DFI17124” as applicable.	Administrative update.

Amended protocol 14.0: (12 Aug 2020)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Study sites	Updated Part B from “approximately 50 sites” to “approximately 30 sites.”	Update to number of study sites in Part B.
Synopsis, Study Design Part A; Section 4.1, Overall study design and plan Part A	LTE: Updated text to further define the response criteria for entrance into the LTE from Part A, and the patient monitoring frequency.	Clarification.
Synopsis, Study design Part B; Section 4.2, Overall study design and plan Part B	LTE: Updated to further define the response criteria for entrance into the LTE from Part A, and the patient monitoring frequency.	Clarification to Part B assessments.
Synopsis, Study design Part B; Section 4.2, Overall study design and plan Part B	Updated to reflect requirements for HBV DNA monitoring of affected Part B patients as specified in Exclusion Criterion #17.	Clarification to Part B assessments.
Synopsis, Study design Part B; Section 4.2, Overall study design and plan Part B	Updated to further define the response criteria for entrance into the LTE from Part B, and the patient monitoring frequency.	Clarification to Part B assessments.
Synopsis, Dose limiting toxicity, dose escalation, and stopping rules Part A	Added text as follows: The DLT evaluation period for any patient is defined as the duration of rilzabrutinib dosing until the dose escalation is completed.	Harmonization of synopsis text with text in the protocol body.
Synopsis, Study stopping rules Part B; Section 4.6.2, Study stopping rules	Revised text to specify that the study will be stopped if the Sponsor (rather than the SMC) deems the emerging TEAE profile unacceptable to continue the study.	As the treatment-emergent adverse event profile is acceptable for continuation of the study, there will not be a Safety Monitoring Committee in Part B. Safety in Part B will be monitored via Sponsor Quarterly Safety Reviews established after the original protocol was implemented.

Section # and Name	Description of Change	Brief Rationale
		Sponsor Quarterly safety reviews will include analyses of safety events and trends across rilzabrutinib studies.
Synopsis, Study endpoints Part B; Section 10.2, Primary efficacy endpoint	Text revised to specify that patients who used rescue medications are not considered responders.	Updated to reflect discussion with FDA.
Synopsis, Study endpoints Part B; Section 10.3, Secondary efficacy endpoints	Text moved to Statistical Methods Part B section of synopsis.	Per analysis population definition in Section 10.7.2.
Synopsis, Planned number of patients; Section 4.7, Number of patients	Revised text to specify enrollment of "approximately 60 patients" in Part A and "approximately 23 patients" in Part B.	Clarification of expected enrollment.
Synopsis, Patient selection Part A; Section 6.1.2, Exclusion criteria	Updated exclusion text to specify "hepatitis B (surface **antigen** and core antibodies unrelated to vaccination)."	Updated to clarify intended exclusion for Hepatitis B surface antigen.
Synopsis, Patient Section Criteria Part B; Section 6.2.2 Exclusion criteria	Criterion 17: Revised text intent for exclusion or inclusion of patients meeting hepatitis B virus serology, and follow-up for those patients who are enrolled with stated conditions.	Clarification of intent for exclusion of patients.
Synopsis, Safety assessments and monitoring Part B	Revised text to state that "The assessments will be conducted as part of ongoing medical monitoring and at Sponsor-Quarterly Safety Reviews where safety events and trends across rilzabrutinib studies are considered." Removed text regarding independent SMC.	As the treatment-emergent adverse event profile is acceptable for continuation of the study, there will not be a Safety Monitoring Committee in Part B. Safety in Part B will be monitored via Sponsor Quarterly Safety Reviews established after the original protocol was implemented. Sponsor Quarterly safety reviews will include analyses of safety events and trends across rilzabrutinib studies.
Synopsis, Statistical methods Part A	Revised text as follows: "The proportion of patients with ~~a Grade 2 or higher~~ bleeding events will also be summarized."	Updated to reflect decision to summarize all bleeding events.
Synopsis, Statistical methods Part B; Section 10.6, Determination of sample size Part B	Updated text to reflect revised sample size estimate. Updated to reflect changes to the efficacy analysis and the revised sample size (deleted text), and to reflect the move of the inserted text from the Study Endpoints Part B section of the synopsis. Updated to reflect decision to summarize all bleeding events.	Updates to reflect revised sample size estimate, efficacy analysis, and summarization of all bleeding events.
Section 1.1, Scientific rationale for treatment of ITP with rilzabrutinib (PRN1008)	Added text as follows: Idiopathic thrombocytopenic purpura, **now more commonly referred to as immune thrombocytopenia** (ITP) . . . "	Updated to reflect American Society of Hematology guidelines of indication name.

Section # and Name	Description of Change	Brief Rationale
Section 2.2, Overall benefit risk assessment	Revised safety profile text.	Updated text to reflect revised information in the Investigator's Brochure v11.
Section 4.3, Dose limiting toxicity (DLT) Part A only	Harmonized text in the protocol body with text in the synopsis.	Revised for protocol consistency.
Section 4.11.1, Allowed Part A	Updated text o address corticosteroid taper in Part A LTE.	Clarification.
Section 4.11.2, Allowed Part B	Updated text o address corticosteroid taper in Part B LTE. Harmonization of text in the protocol body with text in the Rescue Criteria Guidelines Part B section of the synopsis.	Clarification and protocol consistency.
Original Section 10.7.1, Screening population	Orphaned unused section header removed, and all subsequent level 3 header numbers adjusted.	Administrative.
Section 10.7.2, Efficacy analysis population	Revised text to remove legacy analysis population and harmonize text with the synopsis for the efficacy analysis population.	Administrative and protocol consistency.
Section 10.10, Efficacy and exploratory analysis	Part A: Text updated to remove unneeded analysis. Part B: Text updated to remove unneeded analysis.	Consistency with other revisions. Unneeded analysis as a result of revised sample size.
Section 11.1, Independent data safety monitor (IDSM) and safety monitoring committee (SMC)	Text added to specify that there will no independent SMC in Part B; details regarding SMC removed. Added text specifying that safety in Part B will be monitored via Sponsor Quarterly Safety Reviews established after the original protocol was implemented.	As the TEAE profile is acceptable for continuation of the study, there will not be a Study Monitoring Committee in Part B. Sponsor Quarterly safety reviews will include analyses of safety events and trends across rilzabrutinib studies.
Section 13.1, Local regulations/declaration of Helsinki	Revised text to clarify ethical requirements.	Clarification.
Appendix 3, Schedule of assessments (Part A)	Footnote 3 updated to provide clarification of intent regarding physical examination at Cycle 1 Day 1.	Clarification
Appendix 4, Schedule of assessments (Part B)	Footnote 2 updated to provide clarification of intent regarding physical examination at Cycle 1 Day 1. Footnote 12 updated to reflect requirement noted in Part B exclusion criterion #17 for monthly monitoring of affected patients.	Clarification Clarification and consistency with other protocol revisions.
Appendix 5, Schedule of extension period - first 6 months (Part A and Part B	Removed "informed consent form" row from table. Added row for HBV testing and added footnote 8 with HBV testing details.	Consent for LTE is included within the main consent form. Updated to reflect requirement noted in Part B Exclusion Criterion #17 for monthly monitoring of affected patients.
Appendix 6, Schedule of extension period – extension period continued (Part A and Part B	Added row for HBV testing and added footnote 9 with HBV testing details.	Updated to reflect requirement noted in Part B Exclusion Criterion #17 for monthly monitoring of affected patients.

Section # and Name	Description of Change	Brief Rationale
Protocol title and throughout the document.	**Rilzabrutinib (**PRN1008**)** – in protocol title, first use, and when referring to the physical tablets **Rilzabrutinib** or **rilzabrutinib** PRN1008 – elsewhere in the protocol	Updated with recommended name by the World Health Organization (WHO) International Nonproprietary Names (INN) Committee as well as the United States Adopted Names (USAN) Council.
	Replaced" participants" with "patients."	Administrative change to terminology.

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

Amended protocol 13.1: (16 April 2020)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Participant selection criteria Part B : inclusion criteria; Section 6.2.1, Inclusion criteria	Criterion #4: Revised to specify that patients must have platelet count of <30,000/µL on two occasions no less than 7 days apart in the 15 days before treatment begins, and **no** (rather than "a") platelet count **above** (rather than "of") 35,000/µL on Study Day 1.	Clarification.
Synopsis, Participant selection criteria Part B : Exclusion criteria ; Section 6.2.2, Exclusion Criteria	Criterion #17: Revised sentence as follows: "If HBV DNA is negative and HBsAb titer is >100 IU/ml, patients may be enrolled in study." To "If HBV DNA is negative and HBsAb titer is ≥100 IU/ml or negative, patients may be enrolled in study."	Clarification.
Synopsis, Study assessments; Section 8.2, Laboratory & ECG assessments	Revised text to specify that monocyte counts and B-cell subsets assessments will be done for Part A only.	Clarification to Part A assessments.
Appendix 4, Schedule of assessments (Part B); Appendix 5, Schedule of extension period – first 6 months (Part A and Part B); Appendix 6, Schedule of extension period continued (Part A and Part B)	Removed monocytes from [redacted] assessments.	Clarification to Part B assessments.
Appendix 5, Schedule of extension period – first 6 months (Part A and Part B); Appendix 6, Schedule of extension period continued (Part A and Part B)	Specifies that the platelet autoantibody panel to be collected at D169, last day of treatment and early withdrawal will not be performed in Australia.	Clarification to Part A assessments.

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

Amended protocol 13: (05 Mar 2020)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page (study title) and throughout the document	Revised title: replaced "thrombocytopenic purpura" with "thrombocytopenia."	Updated indication name to reflect American Society of Hematology guidelines.
Synopsis, Background and rationale	Added text to indicate the status of ongoing study and introduce addition of Part B.	The dose escalation part of the study has been completed and all patient currently enrolling start the study at the 400 mg BID dose, [redacted] Part B will assess the 400 mg BID dose in patients who had initial response to IVIg or corticosteroids that was not sustained and failed at least one other ITP therapy
Synopsis, Study sites	Revised to the following: Part A: Multicenter trial (approximately 30 sites) Part B: Multicenter trial (approximately 30 sites)	Addition of new sites to participate in Part B.
Synopsis, Study Objectives Part B; Section 3.2, Objectives of the study: Part B	Added new text for Part B safety, efficacy, pharmacokinetics, and exploratory objectives.	Addition of objectives specific or for Part B/
Synopsis, Study design	Part A; Updated requirements for continuing in the LTE part of the study.	Clarification.
	Part B: Deleted text regarding dose-escalation part of the study.	The dose-escalation part of the study has been completed.
Synopsis, Stopping rules Part B; Section 4.6, Stopping rules Part B (also applies to LTE)	Section 4.6.1, Individual stopping rules and Section 4.6.2 Study stopping rules: Added text for Part B stopping rules.	Inclusion of Part B of the study.
Synopsis, Rescue criterial guidelines for Part B	Added text to reflect rescue criteria for Part B, which allows patients who need rescue medication to continue the study.	Inclusion of Part B of the study.
Synopsis, Study endpoints Part B; Section 3.4, Outcome measures of the study: Part B	Added text for safety, primary efficacy, secondary efficacy, exploratory, and pharmacokinetic endpoints.	Addition of study endpoints specific for Part B patient population which will enable assessment of both the primary endpoint and clinically meaningful endpoints for this difficult to treat patient population.
	Secondary efficacy endpoints: Added secondary efficacy endpoint for analyzing patients in the LTE.	Addition of LTE to study design.
Synopsis, Planned number of participants	Added "Part A" before previous text in this section. Added new text for Part B.	Added the maximum number of participants in Part B.
Synopsis, Participant selection criteria Part B	Added inclusion and exclusion criteria for Part B.	Inclusion of Part B of the study.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Study drug and method of dosing.	Added "Part A" before previous text. Added text for Part B.	Addition of only 400mg tablets to be used for Part B with the same method of dosing as Part A [redacted]
Synopsis, Study assessments	Addition of assessments: (immunoglobulin levels, ITP-PAQ tool, BTK occupancy at selected sites) for Part B. Minor revisions to multiple Part A assessments.	Addition of assessments specific for Part B and clarifications for Part A assessments.
Synopsis, Safety Assessments and monitoring Part B; Section 11.1, Independent data safety monitor (IDSM) and safety monitoring committee (SMC)	Added new section.	Addition of Part B safety assessments and monitoring with adjustments made for the end of dose escalation.
Synopsis, Statistical methods Part B; Section 10.12, Pharmacokinetics analysis	New section added.	Addition of Part B statistical methods to incorporate historical standard of care.
Synopsis, Study Duration	Added "Part A" before previous text. Added new text for Part B. Added "Long Term Extension (LTE) Part A and Part B" before text regarding the LTE.	Platelet autoantibody panel cannot be completed on patients in Australia due to stability and shipment timelines.
Section 1.2, Summary of PRN1008 Clinical Experience	Updated text to include preliminary data from the ongoing studies in alignment with the data presented at ASH 2019 (Kuter 2019).	Addition of available data.
Section 1.3, Clinical Pharmacokinetics and Pharmacodynamics of PRN1008	Updated text to include additional information from pharmacology studies.	Addition of available data.
Section 2.2.1, Rationale for doses used and duration of the study	Added new Section 2.2.2, Rationale for doses used and duration of study Part B.	Addition of Part B dose and duration [redacted] In addition, to reflect the change in primary endpoint to allow for better assessment of durability of platelet response.
Section 2.3, Overall benefit-risk assessment, Safety profile	Revised text to state: "Importantly, there were no related thrombin or major bleeding events in the clinical experience with PRN1008 up to date."	Updated clinically relevant safety information.
Section 2.3, Overall benefit-risk assessment, Efficacy	Added text from preliminary review of the efficacy data in Part A.	[redacted]
Section 4.1, Overall study design and plan Part A, Long term extension; Section 4.2, Overall study design and plan Part B	Updated criteria to better define the population that may receive clinical benefit of the study drug. Delete text to reflect the completion of the dose escalation part of the study. Addition of Part B overall study design and plan.	Clarification, updates related to completion of the dose-escalation part of the study, addition of Part B to the study.

Section # and Name	Description of Change	Brief Rationale
Section 4.7, Number of participants	Added text for Part B	Addition of the maximum number of participants in Part B.
Section 4.8, study duration and duration of patient participation	Added text for Part B.	Addition of Part B study duration and duration of patient participation.
Section 4.11, Concomitant medications, Section 4.11.2, Allowed Part B	Added permitted concomitant medications for Part B.	Inclusion of Part B of the study.
Section 8.3, Safety assessments	Added “Part A” before existing text. Added text for Part B.	Addition of Part B PK sampling information.
Section 10.7.1, Screening population	This section was deleted.	There will no longer be an analysis of the screening population as it is the same as the ITT population.
Section 10.9.3, Reconsenting of patients	This section was deleted.	Requirement for reconsenting removed.
Section 10.10, Efficacy and exploratory analysis	Added text for Part B statistical analysis.	Inclusion of Part B of the study.
Section 10.11, Safety and tolerability analysis	Text revised.	Clarification.
Section 10.11.1, Adverse events	Updated text to define the reported AEs that start before the first dose of study drug as pre-treatment events and those events that start after the first dose of study drug or worsen after the first dose of study drug as TEAEs.	Clarification.
Section 10.11.2, Clinical laboratory tests	Added text for Part B.	Inclusion of Part B of the study.
Section 10.11.3, Vital signs	Text revised.	Addition of Part B changes regarding only 1 dose to be used in Part B.
Section 10.11.4, Rescue medication, DLTs, and bleeding scale scores	Revised text to clarify that the history of rescue medication collection in Part A was not limited to 12 weeks and that Part B will assess only 1 dose of PRN1008.	Clarification; inclusion of Part B of the study.
Section 11.3, Clinical adverse events	Updated text regarding pre-existing conditions to be reported as AEs.	The platelet count is part of the assessment of efficacy in the ITP patients. As such it is expected to fluctuate and is captured in the efficacy assessments. Text updated in this section to clarify that the disease under study is only recorded as an event if it meets serious criteria or is not consistent with the typical clinical course for that patient.
Section 11.7.1, SAE definitions	Text revised.	Text streamlined for operational ease of use to locate the definition of an SAE.
Section 11.7.2, SAE reporting	Revised text specifying the 4 minimum criteria for a valid SAE report.	Streamlined text for operational ease and reconciliation with the safety database.

Section # and Name	Description of Change	Brief Rationale
	Revised text for SUSAR reporting.	Clarified that expectedness for a SUSAR is based upon what is listed in the IB. Clarified that individual SUSARs are sent to all sites which is expected until the site is officially closed for the study.
Section 16, references.	Reference added for Kuter DJ et al, 2019.	Addition of ASH reference in support of preliminary data provided in protocol Section 2.3.
Appendix 3, Schedule of assessments (Part A)	Footnote 10 revised.	Updated for clarify and for operational ease.
Appendix 4, Schedule of assessments (Part B)	New table added.	Inclusion of Part B of the study.
Throughout document	Global changes to headings and appendix numbering as follows: Revised heading titles to identify Part and the addition of new headings for Part B. Appendix numbers revised to accommodate the addition of the schedule of assessment for Part B (Appendix 4).	Editorial changes.

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

Amended protocol 12: (5 December 2019)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Planned number of participants and interim analysis	Number of patients revised from “up to 40” to “up to 60.”	Increase in number of patients to be enrolled.
Synopsis, Study drug and method of dosing; Section 9.1, Formulation	Text revised to allow for patients to take 400 mg BID in any dosage form (100 mg + 300 mg tables or 400 mg tablet).	More flexible dosing.

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

Amended protocol 11: (24 October 2019)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Screening procedure, Study Assessment; Section 8.1, Clinical Assessments; Section 8.3, Safety Assessments; Section 15.7, Physical examination procedure	Removed Cogstate testing.	[redacted]

Section # and Name	Description of Change	Brief Rationale
Section 16 References	Removed reference Cataland SR et al, 2011.	Removal of Cogstat testing.
Appendix 3, Schedule of assessments; Appendix 4, Schedule of assessments – extension period – first 6 months	Removal of footnote 15 regarding cognitive testing.	Removal of Cogstat testing.
Appendix 6, Description of computerized cognitive monitoring	Removed table.	Removal of Cogstat testing.

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

Amended protocol 10.1 (Norway): (21 January 2020)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Participant selection criteria: Inclusion criteria	Criterion #4: Revised to specify that patients must have "A history of response (**2** [rather than 1] or more platelet counts of ≥50,000/µL with an increase of at least 20,000/ µL) to at least 1 prior line of therapy (with splenectomy being considered a line of therapy)	Correction as synopsis and body of protocol did not match.
Synopsis, Participant selection criteria: Inclusion criteria	Criterion 67: Updated text regarding sexual abstinence to "true abstinence; when this is in line with the preferred and usual lifestyle of the patient)."	Updated to define abstinence in line with a request from the MHRA.
Synopsis, Study drug and method of dosing	Updated text to read "PRN1008 100 mg, 300 mg, and 400 mg tablets."	Updated to introduce the 400 mg tablets.
Section 4.1, Overall study design and plan	Paragraph regarding dose down-titration inserted.	Paragraph copied from synopsis into Section 4.1 for consistency.
Section 9.1 Formulation	Paragraph was revised to include the 400 mg drug substance and to describe the 400 mg tablet.	Updated to introduce the 400 mg tablets.
Section 9.3, Storage and handling	Text updated to specify storage for [redacted] tables, and storage for [redacted] tablets, separately.	Updated to include the [redacted] tablet storage conditions.

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

Amended protocol 10: (27 September 2019)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Inclusion criteria	Criterion 4: Definition of history of response was updated from "one or more" to "two or more" platelet counts ≥50,000/µL with an increase of at least 20,000/µL)	Correction to match inclusion criterion 4 in the body of the protocol.
	Criterion 6: Revised text regarding highly effective means of contraception, specifically abstinence.	Updated in line with a request from the MHRA.
Synopsis, Study drug and method of dosing; Section 9.1, Formulation	Added text regarding 400 mg tablets that will be administered to patients who enter the LTE.	Addition of 400 mg tablets for LTE.
Appendix 4, Schedule of assessments – extension period – first 6 months	Footnote 1: Changed clinical/laboratory visit windows from ±7 days to ±3 days for all dosing period and lab visits.	Correction as visits in the first 6 months are weekly.

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

Amended protocol 9: (6 May 2019)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Page updates to clarify that EudraCT number, not CTN number is listed. Company address and Principia medical monitor information updated.	Administrative change.
Protocol signature page	Updated to reflect new Chief Medical Officer at Principia.	Administrative change.
Synopsis, Background and rationale	Revised text.	Updated to reflect the final data for the PRN1008-005 Part A study, to update the number of exposed patients per IB, and to refer investigators to the IB version 10 for the current updates on the preclinical studies.
Synopsis, Study sites	Revised "approximately 25 sites" to "approximately 30 sites."	Updated to reflect additional sites.
Synopsis, Study Design	Added text to allow patients who received lower doses to receive 24 weeks of treatment at the [redacted] dose level. Added text regarding the LTE for patients who responded to continue to receive [redacted] study drug beyond 24 weeks of treatment.	Text added to reflect updated study design.
	Long Term Extension: Added text regarding monitoring of LTE patients.	Added to describe the frequency of study visits for responders who enter the LTE.
Synopsis, Dose-limiting toxicity, dose escalation and stopping rules	Individual stopping rules: [redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Synopsis, Rescue criterial guidelines	Added a statement that the rescue medications listed are not permitted while the patient is receiving treatment with PRN1008.	Clarification.
Synopsis, Outcome measures	Added text specifying that AEs will be categorized as treatment-emergent after the first dose of PRN1008 has been received..	Clarification of safety endpoint.
	Secondary efficacy endpoints: Added secondary efficacy endpoint for analyzing patients in the LTE.	Addition of LTE to study design.
Synopsis, Planned number of participants and interim analysis	Number of participants updated from 24 to 40; added text that at least 10 patients complete 24 weeks of treatment at a starting dose of [redacted]	Updated to the new number of patients to be enrolled and completed.
Synopsis, Exclusion criteria	Removed “fish oil supplements (within 30 days of planned dosing through end of follow-up).”	Updated to reflect current understanding of drug-drug interactions with PRN1008 as there are no expected interactions with fish oil supplements.
Synopsis, Study duration	Added text to describe the duration of treatment expected for those patients who receive up to 6 cycles of [redacted] and duration of the LTE	Addition of LTE to study.
Section 4.9.2, Allowed concomitant medication	Text revised.	Clarification.
Section 5, Protocol Deviations	Removed specific Principia contacts.	The site is responsible to notify the CRA and CRO of the protocol deviations. The CRO is then responsible for notifying Principia.
Section 6.1, Inclusion criteria	Criterion 3: Updated text.	Correction so text is consistency with inclusion criterion 3 in the synopsis.
Section 8.2, Laboratory and ECG assessments	Added text to specify that platelet antibody panel will not be done for patients in Australia.	Platelet autoantibody panel cannot be completed on patients in Australia due to stability and shipment timelines.
Section 10.7.3, Efficacy population	ITT Population: Text revised to define an ITT population and to clarify that there is only 1 population, not different populations for each dose.	Clarification.
Section 10.9.3, Reconsenting of patients	Text revised to add reconsent for additional treatment cycles of [redacted] and entry into LTE.	Addition of LTE to study design.
Section 10.10, Efficacy and exploratory variables	Added analysis of primary endpoint.	Correction, previously missing.
Section 11.5, Treatment and follow-up of adverse events	Updated to reflect the practice of following any AEs of Grade 3 or higher regardless of relationship to study drug.	Clarification.
Section 11.7.2, SAE reporting	Updated text to reflect that SAE reporting is now done directly in the EDC system Medidata RAVE. If the	Update to reflect new electronic reporting of SAEs of the party responsible to Principia Biopharma.

Section # and Name	Description of Change	Brief Rationale
	system in not available, a paper form can be sent directly to Principia Biopharma.	
Section 12.1, Assignment of preferred term and original terminology	Updated text to specify that the SAP will contain information regarding the version of MedDRA and WHO used in the study.	This is no longer specified in the protocol.
Section 15.3, Patient premature withdrawal - definition	Text revised to clarify that any patient who leaves the study before the planned of study visit is considered to be an early withdrawal.	Clarification.

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

Amended protocol 8 (24 August 2018)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Background and rationale; Section 1.2, Summary of PRN1008 clinical experience	Updated to include safety data from N= 27 PV patients and current numbers of healthy volunteers and patients treated.	Updates to add new safety data.
Synopsis, Study sites	Revised “up to 15” to “approximately 25 sites.”	Updated to allow for a greater number of sites.
Synopsis, Study Design	Revised text.	Updated to reflect the change in study drug treatment and post-treatment follow-up from 12 weeks to 24 weeks, and 12 weeks to 4 weeks respectively and to clarify the definition of a sustained platelet response.
	Revised Adaptive Cohort Dosing Table.	Updated to reflect the change in study drug treatment from 12 weeks to 24 weeks, clarify the dose escalation rules after the first cycle and to clarify the definition of a sustained platelet response.
Synopsis, Dose-limiting toxicity, dose escalation and stopping rules	Revised dose-escalation rules, individual.	Updated to clarify the dose escalation rules after the first cycle and to clarify the definition of a sustained platelet response.
	Revised starting dose level by adding “sustained (3 or 4 counts).”	Updated to clarify the definition of a sustained platelet response.
	Revised individual stopping rules.	Updated to harmonize country specific requests into one protocol.
Synopsis, Outcome measures	Revised safety endpoints by replacing “12-week” with “post-treatment” follow-up period.	Updated to reflect the shorter post-treatment follow-up period.
Synopsis, Planned number of participants and interim analysis.	Revised “12” to “24” weeks of dosing.	Updated to reflect the change in study drug treatment from 12 weeks to 24 weeks.
Synopsis, Inclusion criteria	Criterion 1: added aged 18 to 65 years old for Czech Republic only.	Updated to reflect a Czech Republic only request (creation of a global protocol).

Section # and Name	Description of Change	Brief Rationale
	Criterion 5: Added text to specify that C1D1 pre dose may be checked up to Day -3 prior to C1D1.	Updated to clarify that Inclusion Criteria lab values may be drawn up to 3 days before the Cycle 1 Day 1 enrollment visit.
	Revised criterion 6 (female contraception requirements); removed previous criterion 7 (male contraception requirements).	Updated based to reflect data in IB Version 9 regarding the reproductive toxicity data which support change in inclusion criteria with text conforming with current ICH guidance (Heads of Medicines Agencies Clinical Trial Facilitation Group [HMA CTFG] Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials).
Synopsis, Study assessments	Revised end-of-study assessment approximately 28 (rather than 84) days after receiving final does of study drug.	Updated to reflect the change in study drug treatment from 12 weeks to 24 weeks and of follow up for 12 weeks to 4 weeks.
	Clinical assessments: Text added to urinalysis assessment so specify by dip stick “or local regulations.”	Updated to allow for urinalysis as measured by dipstick or through sites laboratory as sites local rules require.
Synopsis, Safety assessments	Revised text to specify that patients will remain under observation in the clinic for 6 hours (rather than 8) after administration of the first dose.	Updated to remove the 8-hour post-dose PK timepoint as the timing exceeds an 8 hour day and places undue burden on participants.
	Revised text regarding sentinel patients.	Updated to clarify the definition of a sustained platelet response.
Synopsis, Study Duration	Revised text to specify that study duration will be approximately 32 (rather than 28) weeks per subject.	Updated to reflect the change in study drug treatment from 12 weeks to 24 weeks and of follow up for 12 weeks to 4 weeks.
Section 2.1.1, Rationale for doses used and duration of study	Revised text.	Updated to describe the rationale for increasing treatment from 12 weeks to 24 weeks.
Section 2.2, Overall benefit risk assessment	Efficacy text revised.	Text revised with the new extension of treatment to 24 weeks.
Section 3, Objectives and outcome measures of the study	Added Section 3.5, Safety Endpoints; added Section 3.6, Primary Efficacy Endpoint.	In addition to information in Section 10.0, the primary and secondary endpoints were added to the objectives Section 3.0.
Section 5, Protocol deviations	Updated contact details as appropriate.	Administrative change.
Section 10.2, Primary efficacy endpoint	Text revised.	Correction to match the wording of the primary endpoint in the Synopsis.
Section 10.9.3, Reconsenting of subjects	New section added.	Added to confirm that subjects currently in the 12-week treatment period when the protocol is approved can reconsent to receive 24 weeks of treatment
Section 10.11.2, Clinical Laboratory Tests	Added text for clinical laboratory tests believed to be the [redacted]	Added per country-specific requirement.
Section 10.11.3, Vital signs	Replaced “abnormal” with “outside the normal range.”	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 11.6, Adverse Events Intensity grading	Revised text.	Updated to clarify intensity grading scale if an event is not included in the Common Toxicity Criteria (CTCAE).
Section 11.8, Pregnancy	Removed text regarding pregnancy in the partner of a male clinical trial participant.	Text is no longer relevant with new reproductive toxicity data as outlined in IB Version 9.0.

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

Amendment 7: (1 December 2017)

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Synopsis, Study objectives	Deleted Idiopathic Thrombocytopenic Purpura Patient Assessment (ITP-PAQ) from the exploratory study objectives.	The ITP-PAQ questionnaire is not available for licensing from Amgen.
Section 6.2, Exclusion criteria	Criteria reordered to be consistent with order in the Synopsis.	Correction.
Section 8.2, Laboratory and ECG assessments	First bullet: Deleted “Serum pregnancy texts at screening, urine pregnancy tests at other visits.”	Correction as the bullet is duplicate within the same section.
Appendix 3, Schedule of assessments – weekly lab visit between clinic visits	Added subscript 14 to this column.	Clarification – footnote added to clarify when the weekly lab visits between in clinic visits are to take place.
Appendix 3, Schedule of assessments – laboratory only visits	Added subscript 1 to this line.	Clarification to make it clear that footnote 1 visit windows apply to this laboratory visit.
Appendix 3, Schedule of assessments – pregnancy test	Added pregnancy test assessment to the Early withdrawal/unscheduled visit.	Clarification to allow for unscheduled pregnancy testing.
Appendix 3, Schedule of assessments – platelet auto antibodies	Removed platelet auto antibodies from Screening, [redacted] text added to C1D1.	Collection timepoints updated to reduce burden on subjects as the test requires 40 mL of blood per timepoint.

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

Amended protocols 1-6: (3 April 2017 - 7 July 2017)

Protocol versions (versions 1.0 [2 Apr 17] through 5.0 [7 Jul 17]) were not submitted to sites. Thus, they are not detailed here.

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