

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219685Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	219685
Priority or standard	Standard
Submit date(s)	8/29/2024
Received date(s)	8/29/2024
PDUFA goal date	8/29/2025
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	8/29/2025
Established/proper name	Rilzabrutinib
(Proposed) proprietary name	WAYRILZ
Pharmacologic class	Kinase inhibitor
Other product name(s)	PRN1008
Applicant	Genzyme Corporation
Dosage form(s)/formulation(s)	TABLET
Dosing regimen	400 mg orally twice daily
Applicant-proposed indication(s)/population(s)	Treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment.
SNOMED CT code for proposed indication disease term(s)¹	2897005 Immune thrombocytopenia (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	400 mg orally twice daily
Approved indication(s)/population(s) (if applicable)	WAYRILZ is indicated for the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
SNOMED CT code for approved indication disease term(s)¹	2897005 Immune thrombocytopenia (disorder)

¹ For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BID	twice daily
BSEP	bile salt export pump
BTK	Bruton's tyrosine kinase
BTKI	Bruton's tyrosine kinase inhibitor
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CLCr	creatinine clearance
C _{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease of 2019
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
EAIR	exposure adjusted incidence rate
ECAC	Executive Carcinogenicity Assessment Committee
ECG	electrocardiogram
EEA	European Economic Area
E-R	exposure-response
F1	first filial
FcγR	fragment crystallizable gamma receptor
FDA	Food and Drug Administration
FTC	fumitremorgin C
GD	gestation day
GFAP	glial fibrillary acidic protein
GLP	good laboratory practice
HBcAb	hepatitis B core antigen antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HD	high dose
hERG	human ether-à-go-go related gene

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HI	hepatic impairment
HIV	human immunodeficiency virus
HLM	human liver microsomes
HPLC	high performance liquid chromatography
IBA-1	ionized calcium binding adapter protein 1
IBLS	ITP Bleeding Scale
IC ₅₀	half maximal inhibitory concentration
ICH	International Council for Harmonisation
I _{gut}	intestinal luminal concentration of the interacting drug
IMP	investigational medicinal product
IND	investigational new drug
iPSP	initial Pediatric Study Plan
IR	immediate release
ISP	integrated safety population
ITP	immune thrombocytopenia
ITT	intent-to-treat
IVIG	intravenous immunoglobulin
LS	Least squares
LTE	long-term extension
MATE	multidrug and toxin extrusion protein
MD	mid dose
MDCK	Madin-Darby canine kidney
MDR1	multidrug resistance mutation 1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effect model with repeated measures
MRHD	maximum recommended human dose
NDA	new drug application
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
ODD	Orphan Drug Designation
OCMQ	OND Custom Medical Query
OL	open-label
PAQ	Patient Assessment Questionnaire
PD	pharmacodynamic
P-gp	P-glycoprotein
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Prescribing Information
PIND	pre-investigational new drug
PK	pharmacokinetic
PMR	postmarketing requirement
PopPK	population PK
PPI	proton pump inhibitor
PRO	patient-reported outcome

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PT	preferred term
QD	once daily
QOL	quality-of-life
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SEE	substantial evidence of effectiveness
SOC	system organ class
SPA	special protocol assessment
TB	tuberculosis
TEAE	treatment-emergent adverse event
Tg-RasH2	transgenic-RasH2
T _{max}	time to maximum concentration
TPO-RA	thrombopoietin-receptor agonist
TQT	thorough QT
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
USPI	United States Prescribing Information

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

On August 29, 2025, Genzyme Corporation (Applicant) submitted a new drug application (NDA) for rilzabrutinib for the proposed indication of the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment.

Rilzabrutinib was granted Orphan Drug Designation (ODD) on October 15, 2018, for the treatment of ITP, and Fast Track designation for rilzabrutinib for the treatment of ITP on October 15, 2020.

The Applicant submitted results from one Phase 3 Study (LUNA 3) to establish the superiority of rilzabrutinib compared to placebo in adults with chronic or persistent primary ITP. LUNA 3 included a 24-week randomized, double blind treatment period. An initial assessment was performed after the first 12 weeks of blinded treatment (Week 13). Participants who had a platelet response during the first 12 weeks continued blinded treatment for a total of 24 weeks. The primary efficacy endpoint was durable platelet count, in the absence of rescue medication, assessed between Weeks 12 and 24. Participants who discontinued blinded treatment at Week 13 were considered nonresponders. Analysis of efficacy data for adults enrolled to LUNA 3 found a higher percentage of participants in the rilzabrutinib arm achieved a durable platelet response (23% [95% confidence interval (CI), 16.12% to 30.49%]) compared to no participants in the placebo arm. Rilzabrutinib also demonstrated superiority for the first four key secondary endpoints, which included assessments of number of weeks with platelet response, time to first response, and proportion of participants not requiring rescue therapy during the 24-week blinded treatment.

These findings of efficacy are supported by platelet response data from Study PRN1008-010 (LUNA 2), a two-part dose finding with cohort expansion study of adults with primary or secondary ITP who had relapsed or had an insufficient response to prior therapies. The platelet response rate in the dose finding portion of the study was 40%. The durable platelet response rate in the cohort expansion part was 35% (95% CI: 17, 56).

Assessment of risk was based primarily on data from the 202 participants (133 in the rilzabrutinib arm and 69 in the placebo arm) who received blinded treatment for up to 24 weeks on LUNA 3.

NDA 219685 was reviewed by the multidisciplinary review team. Each discipline recommends approval of rilzabrutinib for the treatment of adult patients with persistent or chronic immune thrombocytopenia who have had an insufficient response to a previous treatment, and I, the signatory authority for this application, concur with those recommendations. The overall benefit-risk is favorable as described in the Benefit-Risk Framework below. For detailed information

supporting the basis for this approval, please refer to the detailed reviews included in this integrated review.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

Chronic ITP is a rare, serious, and potentially life-threatening disease, and it is reasonable in this situation to establish effectiveness based on one adequate and well-controlled study plus confirmatory evidence. The one adequate and well controlled trial was Study PRN1008-018 (LUNA 3), a multicenter, randomized, placebo-controlled study conducted in 202 adults with chronic ITP. The results for the primary endpoint of durable platelet count provided compelling evidence of superiority of rilzabrutinib over placebo. These findings were supported by the first four key secondary endpoints which evaluated number of weeks with platelet responses, time to first platelet response, and use of rescue medication. For these secondary endpoints, rilzabrutinib also demonstrated superiority over placebo.

The Applicant also conducted Study PRN1008-010 (LUNA 2), an open-label dose-finding with cohort expansion study in patients with ITP who have relapsed or have an insufficient response to prior therapies, which provides confirmatory evidence of effectiveness for rilzabrutinib based on the observed pharmacodynamic effects. Spontaneous sustained increases in platelet count in patients with chronic ITP would not be expected. Therefore, it is reasonable to consider the durable responses observed in this single-arm study as evidence of activity related to rilzabrutinib and confirmatory evidence supporting the findings from LUNA 3.

Together the data from LUNA 3 with confirmatory evidence from Study LUNA 2 establish substantial evidence of effectiveness of rilzabrutinib in adults with chronic ITP.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Immune thrombocytopenia (ITP), also known as immune or idiopathic thrombocytopenic purpura, is an autoimmune disorder characterized by immunologic destruction of platelets and decreased platelet production. - The resulting thrombocytopenia predisposes to bleeding, bruising or petechiae. - Bleeding may be fatal or life threatening - Acute ITP often resolved spontaneously within 3 months. - Persistent ITP is defined as a condition lasting between 3 and 12 months after diagnosis, while chronic ITP is defined as lasting longer than 12 months. - The estimated incidence of ITP among adults in the United States is 3.3/100,000 per year.	ITP is an uncommon autoimmune disorder that can cause bleeding, which may be fatal or life threatening.
Current treatment options	- The goal of treatment in ITP is to increase and sustain platelet counts to a level that limits bleeding episodes and allows the patient to continue or resume normal activities of daily living. The platelet count need not be a normal platelet count to achieve these goals. The following are currently available ITP treatments: - Decrease the rate of platelet destruction: - Corticosteroids - Immunoglobulins - Anti-D immunoglobulin - Splenectomy - Fostamatinib (Tavalisse) (oral administration) FDA approved - Reduce B-cell antibody production - Corticosteroids - Rituximab (anti-CD20) (intravenous administration) - Increase platelet production - Romiplostim (Nplate) (intravenous administration) FDA approved - Eltrombopag (Promacta) (oral administration) FDA approved	There is no cure for ITP. Although there are other treatment options for patients with ITP, there remain patients for whom currently available therapies are not effective or do not provide sustained benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- Evidence of benefit is derived primarily from LUNA 3, a multicenter, randomized, double-blind, placebo-controlled study in 202 adults with ITP who had had an unsustained response to treatment with intravenous immunoglobulins (IVIG), anti-D therapy, or corticosteroids. Participants were enrolled and randomized 2:1 to receive rilzabrutinib 400 mg orally twice daily or placebo equivalent. Randomization was stratified by splenectomy status and severity of thrombocytopenia. The primary assessment was based on a 24-week blinded period. An initial assessment was performed during after the first 12-weeks of blinded treatment. Participants who had a platelet response during the first 12 weeks continued blinded treatment for a total of 24 weeks. - The participants were generally heavily pretreated with 71% of all participants having received ≥ 3 prior unique ITP treatments and 46% having received at least 5 prior unique ITP treatments. - After 24 weeks of treatment, rilzabrutinib was superior to placebo on: - Proportion of participants achieving a durable platelet response¹, with 23.3% in the rilzabrutinib arm ([95% CI, 16.12% to 30.49%]) compared to no responses in the placebo arm, resulting in a risk difference of 23.1% [95%CI, 15.95, 30.31], p-value<0.0001. - Number of weeks with platelet response², with an LS Mean³ of 7.18 (SE: 0.747) weeks in the rilzabrutinib arm compared to 0.72 (SE: 0.350) weeks in the placebo arm, yielding an LS Mean difference versus placebo of 6.46 (95% CI: 4.923, 7.990), p<0.0001. - Number of weeks with platelet counts $\geq 30,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy with an LS Mean of 6.95 (SE: 0.749) weeks in the rilzabrutinib arm compared with 0.64 (SE: 0.337) weeks in the placebo arm, yielding an LS mean difference versus placebo of 6.31 (95% CI: 4.787, 7.831), p<0.0001. - Time to first platelet count of $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and doubled from baseline with median of 36 days (95% CI: 22, 44) in the rilzabrutinib arm compared to NA in the placebo arm (HR 3.1 [95% CI: 1.945, 4.934], p<0.0001. - Proportion of participants requiring rescue therapy during the 24-week blinded treatment period, with 33.1% in the rilzabrutinib arm compared to 58.0% in the placebo arm requiring rescue therapy, with a median time to first use of rescue not reached in the rilzabrutinib arm compared to 56 days in the placebo arm.	The benefit of rilzabrutinib for the treatment of adult patients with ITP with insufficient response to previous treatment was demonstrated by an increased and sustained platelet counts in Study PRN1008-018. The submitted evidence shows durable platelet response in approximately 23% of participants who received rilzabrutinib compared to 0 participants in the placebo arm. The majority of enrolled population was heavily pretreated having received at least 3 prior types of ITP treatments. An increase and sustained platelet response to a level that limits bleeding episodes and allows the patient to pursue normal activities of daily living is a clinical benefit increase. Fewer participants who received rilzabrutinib required rescue therapy during the first 24 weeks of treatment compared to participants who received placebo.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	- The safety profile of rilzabrutinib in ITP was established primarily based on experience in 202 adults (133 who received rilzabrutinib at the approved dosage and 69 who received placebo) during the randomized, double-blind period of LUNA 3. - The mean duration of exposure for this primary safety population was 17.4 weeks for rilzabrutinib versus 13.5 weeks for placebo. Of participants treated with rilzabrutinib, 37% remained on treatment at 24 weeks compared to only 13% of those who received placebo. - Key safety findings were: - There was one death in the pooled integrated safety population occurring during the double-blind (DB) period of LUNA 3 in a participant receiving rilzabrutinib. The fatal TEAE was pulmonary aspergillosis and was assessed by the review team as related to rilzabrutinib. - During the DB period, the frequency of SAEs was similar between arms. 9% of participants in the rilzabrutinib arm had at least one SAE. After review of narratives, only 4 participants (3%) were assessed as having had a serious adverse reaction (SAR). These SARs were all related to infection. - Adverse events leading to permanent discontinuation occurred in 6% of participants in the rilzabrutinib arm and no participant in the placebo arm. These included pneumonia (fatal), neutropenia, peripheral embolism, erythema nodosum, and multijoint pain, each occurring in one participant. Multiple TEAEs occurred in three additional patients leading to discontinuation of rilzabrutinib. They were diarrhea, nausea, abdominal discomfort; esophageal varices hemorrhage hepatic enzyme increased; and heartburn, headache, and leg pain. - Important adverse reactions of special interest and clinical interest occurring in participants while receiving rilzabrutinib on clinical trials included: infections, and neutropenia. - The most common adverse reaction, occurring in at least 5% of participants in the rilzabrutinib arm and at least 3% more than in the placebo arm are: diarrhea (32%, nausea (20%), headache(18%), COVID-19 (14%), arthralgia (9%), dizziness (8%), abdominal pain (8%), nasopharyngitis (7%), vomiting (7%), abdominal pain upper (5%), dyspepsia (5%), and cough (5%). - Evaluation of an integrated safety population comprising 276 participants with ITP who received at least one dose of rilzabrutinib at 400 mg orally twice daily in clinical trials LUNA 3 and PRN1008-010 Parts A and B did not identify a new or more serious safety signal than identified in DB period of LUNA 3.	The safety data submitted were sufficient to characterize the toxicity profile of rilzabrutinib. Studies showed the safety profile was acceptable in the studied population. The observed safety profile was generally consistent with other approved BTKIs and possibly less toxic. Warnings and precautions in the USPI will include increased risk of infections as well as BTKi class labeling for hepatotoxicity (b) (4). Although these events were not observed in the pooled population of ITP patients treated with rilzabrutinib on clinical trials, the size of the population and extent of exposure is small. Adverse reactions seen in the clinical trials were generally manageable with monitoring, dose interruption and appropriate clinical management.

¹Durable platelet response was defined as platelet counts $\geq 50,000/\mu\text{L}$ for $\geq$ two-thirds of at least 8 nonmissing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 nonmissing weekly scheduled platelet measurements were at or above $50,000/\mu\text{L}$ during the last 6 weeks of the 24-week blinded treatment period.

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² For the first key secondary endpoint, platelet response at Week 24 was defined as a platelet count $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period, in the absence of rescue therapy.

³ Mixed-effect model with repeated measures on longitudinal binary data with treatment group, stratification factors, week (Weeks 2 to 25), treatment-by-week interaction as fix effects. Abbreviations: BID, twice daily; BTKi; Bruton's tyrosine kinase inhibitor; CI, confidence interval; COVID-19, coronavirus disease of 2019; HR, hazard ratio; LS, least squares; PT, preferred term; SE, standard error; SOC; system organ class; TEAE, treatment-emergent adverse event; USPI, United States Prescribing Information

2.2. Conclusions Regarding Benefit-Risk

Chronic immune thrombocytopenia is an uncommon acquired autoimmune disorder characterized by low platelet count that can result in a significant risk of bleeding. Goals of treatment are to prevent bleeding and maintain platelet count above a safe level to reduce the risk of bleeding. There are approved therapies for the treatment of ITP, but there remain patients for whom currently available therapies are not effective or do not provide sustained benefit.

Overall, the benefit-risk analysis of rilzabrutinib for the treatment of chronic or persistent ITP is favorable. The LUNA 3 study was an adequate and well-controlled trial that demonstrated rilzabrutinib as an effective treatment for chronic and persistent ITP as demonstrated by durable platelet count and reduction in use of rescue medications. The risks associated with rilzabrutinib based on LUNA 3 were manageable and can be adequately described in labeling.

II. Interdisciplinary Assessment

3. Introduction

Rilzabrutinib (proposed proprietary name, WAYRILZ), is a new molecular entity and small-molecule, selective, covalent, reversible kinase inhibitor targeting Bruton's tyrosine kinase (BTK). Rilzabrutinib mediates its therapeutic effect in ITP through immune modulation including inhibition of B cell activation, and interruption of antibody-coated cell phagocytosis by fragment crystallizable gamma receptor (FcγR) in spleen and liver.

The proposed indication is for treatment of adults with persistent or chronic ITP who have had an insufficient response to a previous treatment. The proposed dosing regimen for rilzabrutinib is 400 mg orally twice daily.

ITP is an autoimmune disorder characterized by immunologic destruction of platelets resulting in thrombocytopenia with a predisposition to bleeding, bruising, and petechiae. The estimated incidence of ITP among adults in the United States is 3.3/100,000 per year. The decision to start treatment is determined by severity of bleeding, bleeding risk, activity level, and patient preference. Treatments of chronic ITP including agents intended to decrease the rate of platelet destruction e.g., corticosteroids, intravenous immunoglobulin (IVIG), fostamatinib, and splenectomy, reduce the production of B-cell antibodies, including antiplatelet antibodies e.g., corticosteroids, rituximab, or increase platelet production e.g., thrombopoietin-receptor agonists (TPO-RAs).

The single study submitted to support approval of rilzabrutinib in adults with chronic or persistent ITP, LUNA 3, was a multicenter, randomized, placebo-controlled trial designed to demonstrate superiority of rilzabrutinib over placebo on durable platelet response.

This review serves as the interdisciplinary assessment for the original NDA for rilzabrutinib in chronic and persistent ITP and includes assessments from nonclinical related to safety and toxicity in nonclinical studies, clinical pharmacology related to safety and dosing based on clinical studies, statistics related to efficacy, and clinical related to efficacy and safety.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. High Dropout Prior to Completion of the 24-Week Double-Blind Treatment Period

A minority of participants in both the rilzabrutinib arms completed the 24-week double-blind period, 46.6% (62 of 133) and 14.5% (10 of 69) in the rilzabrutinib and placebo arms respectively. The high level of dropout raises concerns regarding the interpretability of the efficacy results.

3.1.2. Key Safety Review Issues

None.

3.2. Approach to the Clinical Review

[Table 3](#) provides an overview of the clinical studies submitted to support the benefit-risk assessment for rilzabrutinib for patients with persistent or chronic ITP. The pivotal study, LUNA 3, was the primary source of evidence to support the finding of efficacy, with confirmatory evidence from uncontrolled, open-label, Study LUNA 2 Parts A and B.

The assessment of benefit was based on a comparison of efficacy data from the double-blind treatment period of LUNA 3 where participants with persistent and chronic ITP were randomized 2:1 to receive rilzabrutinib or placebo. The assessment of risk was based primarily on the data derived from LUNA 3 during the double-blind treatment period. This was supported by analysis of an integrated pool comprised of participants with persistent or chronic ITP who received at least one dose of rilzabrutinib at the intended dose on LUNA 3 DB, open-label (OL), and long-term extension (LTE) periods and the main and long-term treatment periods of LUNA 2 Parts A and B.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how SEE was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

WAYRILZ is indicated for the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)
 - a. Adequate and well-controlled clinical investigation(s):
 - i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
 - ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

- c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)²

3. Complete response, if applicable

- a. ☒ SEE was established
b. ☐ SEE was not established (*if checked, omit item 2*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* ([January 2020](#))

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* ([August 2018](#))

³ FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*

Table 3. Clinical Studies Submitted¹ in Support of Efficacy and Safety Determinations for Rilzabrutinib

Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Participants Planned; Actual Randomized	No. of Centers and Countries
PRN1008-018 (Phase III)	Adults with persistent or chronic immune thrombocytopenia	Control Type: Placebo concurrent Randomization: Stratified permuted block Randomization Ratio: 2:1 Blinding: Double-blind Biomarkers: Biomarker as confirmatory evidence Innovative design features: None	Drug: Rilzabrutinib Dose: 400 mg BID Number treated: 198 Duration (quantity and units): 24 weeks (blinded) 28 weeks (open-label) 28+ weeks (long-term extension)	Primary: - Durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for $\geq$ two-thirds of at least 8 nonmissing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 nonmissing weekly scheduled platelet measurements are at or above 50,000/μL during the last 6 weeks of the 24-week blinded treatment period - Durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy Secondary: - Number of weeks with platelet count $\geq$50,000/μL OR between $\geq$30,000/μL and <50,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy. - Number of weeks with platelet counts $\geq$30,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.	Planned: 393 Actual: 202	Centers: 154 Countries: 26

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Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Participants Planned; Actual Randomized	No. of Centers and Countries
PRN1008-010 (Part A) (Phase I/II)	Patients with relapsed immune thrombocytopenia.	Control Type: None	Drug: Rilzabrutinib	Primary: The proportion of patients able to achieve 2 or more consecutive platelet counts, separated by at least 5 days, of $\geq 50,000/\mu\text{L}$ AND an increase of platelet count of $\geq 20,000/\mu\text{L}$ from baseline, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count	Planned: 60	Centers: 34
		Randomization: N/A	Dose: 200 mg QD (N=9) 400 mg QD (N=1) 300 mg BID (N=5) 400 mg BID (N=45)	Secondary: - Percent of weeks with platelet counts $\geq 50,000/\mu\text{L}$ by dose level and overall - Proportion of patients with 4 out of the final 8 platelet counts $\geq 50,000/\mu\text{L}$ 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	Actual: 60	Countries: 8
PRN1008-010 (Part B) (Phase II)	Patients with relapsed immune thrombocytopenia	Control Type: None	Drug: Rilzabrutinib	Primary Efficacy: The proportion of participants able to achieve platelet counts $\geq 50,000/\mu\text{L}$ 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	Planned: 23	Centers: 28
		Randomization: N/A	Dose: 400 mg BID Number treated: 26	Primary Safety: - The incidence, severity and relationship of treatment-emergent adverse events (TEAE), including clinically significant changes in physical examination, laboratory tests, electrocardiogram (ECG), and vital signs - TEAEs in the post treatment follow-up period and their possible relationship to prior rilzabrutinib treatment	Actual Enrolled 26	Countries: 7
		Blinding: None	Duration (quantity and units): 24 weeks (active treatment period) 24+ weeks (long term extension)			
		Biomarkers: Biomarker as confirmatory evidence				
		Innovative design features: None				

Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Participants Planned; Actual Randomized	No. of Centers and Countries
				Secondary: - Number of weeks with platelet count $\geq 50,000$ OR $\geq 30,000/\mu\text{L}$ and doubling the baseline in the absence of rescue therapy (platelet counts were censored for 4 weeks after the use of rescue medication, if given) - Proportion of all treated participants able to achieve 2 or more consecutive platelet counts, separated by at least 5 days of $\geq 50,000/\mu\text{L}$ AND an increase of platelet count of $\geq 20,000/\mu\text{L}$ from baseline without use of rescue medication in the 4 weeks prior to the latest elevated platelet count Number of weeks with platelet counts $\geq 30,000/\mu\text{L}$ and doubling from baseline over the 24-week treatment period (platelet counts were censored for 4 weeks after the use of rescue medication, if given)		
PRN1008-023	Healthy participants	XX	Drug: Rilzabrutinib Dose: Japanese cohort 100 mg Day 1 200 mg day 5 400 mg BID X 4 Days 9-12 and morning day 13 Caucasian cohort: 400 mg BID x 4 days and morning dose Day 5	Objectives: To evaluate the pharmacokinetics (PK) of rilzabrutinib in Japanese and Caucasian healthy participants following single and multiple doses Endpoints: PK parameters	Planned: 23 Actual: 23	Centers: 1

Source: Reviewer.

¹ Includes all submitted clinical studies, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.

Abbreviations: BID, twice daily; N, number of participants; N/A, not applicable; No., number; QD, once daily

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Section 6.2.1.4.5
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

The Applicant submitted patient-reported outcome (PRO) data for ITP- Patient Assessment Questionnaire (PAQ) item-10 score. The Division of Clinical Outcomes Assessment found the instrument was not fit for purpose (see Section [6.2.1.4.5](#)).

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

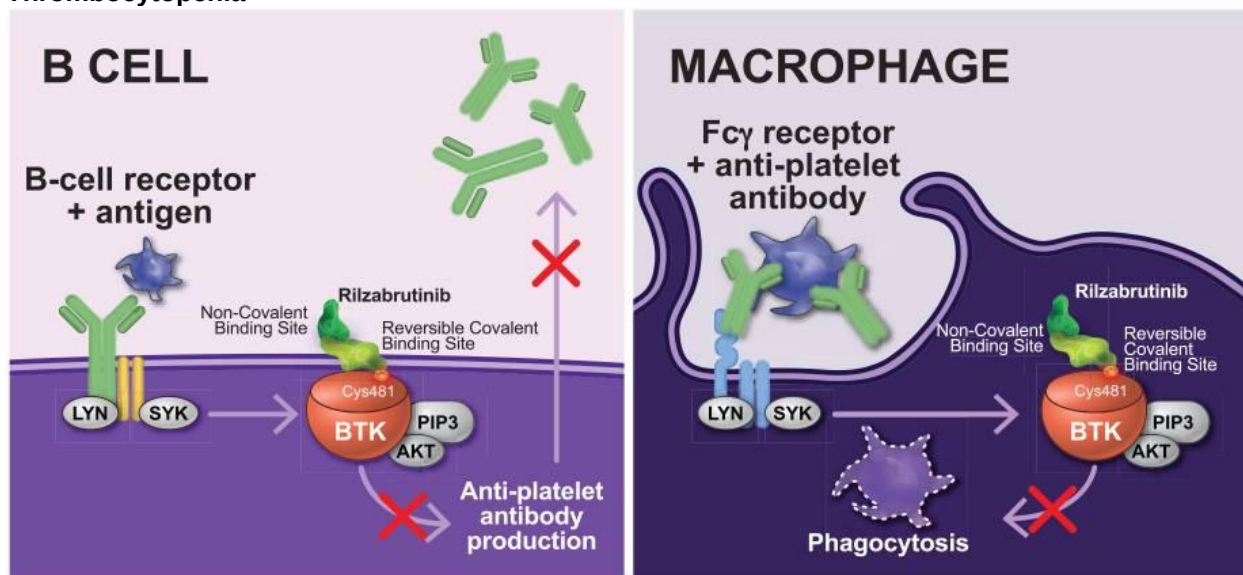
Primary Pharmacology

Autoantibodies targeting platelets play a central role in the pathogenesis of ITP, simultaneously enhancing platelet clearance and suppressing thrombopoiesis. Bruton's tyrosine kinase is an enzyme and signaling molecule expressed in B cells, myeloid lineage cells (monocytes,

macrophages, mast cells, and neutrophils), osteoclasts, platelets, and some cells of neural origin (neurons and astrocytes). Bruton's tyrosine kinase is a key component of the B cell receptor (BCR) that plays a role in B cell development, and it is involved in signaling pathways in myeloid cells, such as Toll-like receptor and Fc receptor signaling primarily through FcγR and FcεR. Upon antigen binding, BTK activation occurs downstream through a cascade involving lymphocyte-specific protein tyrosine kinase (Lck)/yamaguchi sarcoma virus oncogene (yes)-related protein tyrosine kinase (Lyn kinase) and spleen tyrosine kinase, leading to phosphatidylinositol-3,4,5-triphosphate kinase/protein kinase B (PI3K/AKT) strain transforming kinase pathway activation and phosphatidylinositol-3 kinase generation, which facilitates BTK recruitment and activation ([Figure 1](#)). By inhibiting BTK, rilzabrutinib blocks these downstream signaling pathways, thereby reducing antiplatelet antibody production and platelet destruction in ITP.

Rilzabrutinib is an orally administered BTK inhibitor that decreases signaling downstream of the B-cell receptor in B-cells, leading to decreased antiplatelet antibody production and B-cell development. Rilzabrutinib also interrupts antibody-coated cell Fc receptor-mediated phagocytosis pathways in cells of myeloid lineage ([Figure 1](#)). Given both mechanisms contribute to platelet destruction in immune thrombocytopenia, a plausible scientific rationale for the development of rilzabrutinib for the treatment of immune thrombocytopenia is supported.

Figure 1. Mechanism of Action Relevant to Reduction in Platelet Loss of Rilzabrutinib in Immune Thrombocytopenia



Source: ([Kuter et al. 2023](#))

Abbreviations: AKT, Akt strain transforming kinase; serine-threonine kinase; BTK, Bruton's tyrosine kinase; FcγR, Fc gamma receptor; LYN, Lck/yes-related protein tyrosine kinase; PI3K, phosphatidylinositol-3 kinase; PIP3, phosphatidylinositol-3,4,5-triphosphate kinase; SYK, spleen tyrosine kinase

The Applicant conducted in vitro studies evaluating the effect of rilzabrutinib on the potency and selectivity for BTK, binding characterization and its kinetic profile, the inhibition of BTK function, and proof of concept in vivo studies using a mouse model of ITP and other animal models of BTK-related autoimmune disorders.

5.1.1. In Vitro BTK Binding

Rilzabrutinib exhibits high-affinity binding to BTK with a half maximal inhibitory concentration (IC_{50}) of 1.3nM in competitive inhibition with adenosine triphosphate (ATP). The binding affinity of rilzabrutinib is inversely correlated with ATP concentration (IC_{50} s were 1.3, 3.0, and 9.8nM at ATP concentrations of 16, 160 and 800 μ M, respectively). The binding kinetics of rilzabrutinib are characterized by rapid association and very slow (reversible-covalent) dissociation rates, resulting in an extended residence time with a dissociation half-life of approximately 7 days. This kinetic behavior contributes to sustained target engagement, with >85% occupancy observed at 24 hours postinitial binding. Rilzabrutinib forms a covalent bond with BTK, as demonstrated through controlled trypsin digestion studies. Following incubation of rilzabrutinib with excess recombinant BTK and subsequent protein denaturation via trypsin digestion, 137% $\pm$ 37% (mean; n=2) of rilzabrutinib was recovered, indicating reversibility of the covalent interaction upon protein degradation.

5.1.2. In Vitro Pharmacology

Rilzabrutinib exhibited inhibitory effects on B cell activation in human whole blood from healthy volunteers with an IC_{50} of 123nM, while BCR-induced B cell proliferation was suppressed at an IC_{50} of 5nM. Additionally, rilzabrutinib inhibited IgG-mediated monocyte activation with an IC_{50} of 55.7nM. These findings collectively underscore rilzabrutinib's efficacy in modulating key cellular processes, including B cell activation, proliferation, and Fc γ R-mediated monocyte activation. The potency differences are considered to reflect differences in the experimental conditions and the IC_{50} s are not directly comparable.

The specificity of rilzabrutinib for BTK-expressing cells was demonstrated by its minimal cytotoxic effects on HCT-116 cells, a BTK-negative human colorectal carcinoma cell line, with an IC_{50} of 16,000nM. This observation suggests cells lacking BTK expression are protected.

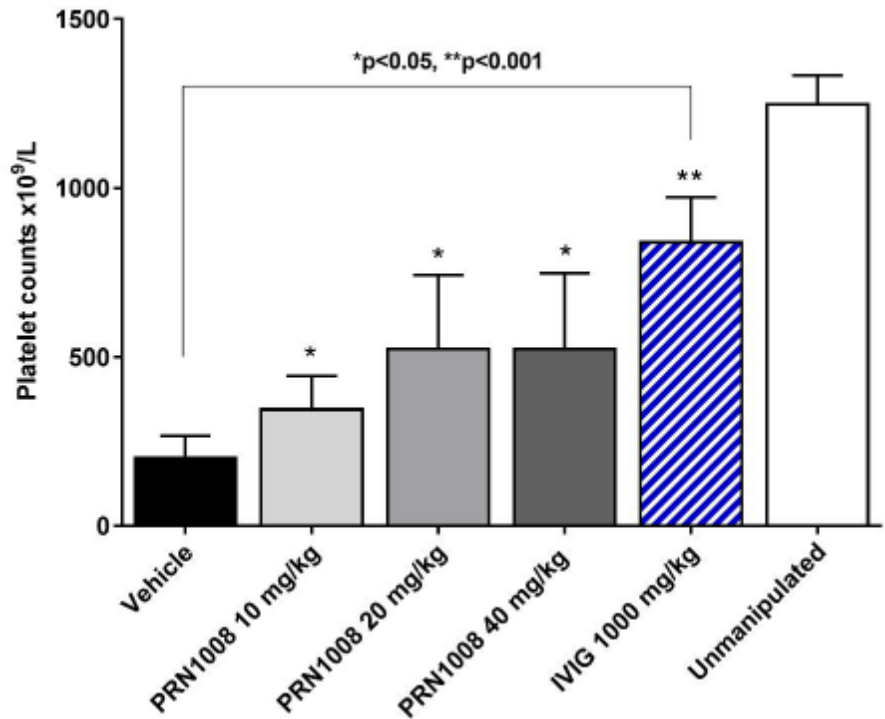
Furthermore, in vitro platelet aggregation assays were conducted to evaluate the impact of rilzabrutinib on platelet function. These studies were performed using blood samples from both healthy volunteers and patients with ITP at rilzabrutinib concentrations meant to mimic anticipated plasma concentrations (i.e., 0.3 μ M or 1 μ M). Notably, rilzabrutinib did not significantly affect platelet aggregation in blood from either population.

5.1.3. In Vivo Proof-of-Concept Animal Model Data

A proof-of-concept study was conducted using male BALB/c mice dosed with rilzabrutinib or control vehicle once daily for three consecutive days before induction of thrombocytopenia using anti-cluster of differentiation (CD)41 antibodies after the last dose. CD41 (integrin α IIb) is a platelet-specific surface glycoprotein commonly targeted by autoantibodies in patients with ITP. Upon injection of anti-CD41 antibodies, platelets are marked for destruction by macrophages through Fc receptor-mediated phagocytosis, mimicking the autoimmune platelet destruction seen in ITP. Analysis of platelet counts six hours post anti-CD41 injection revealed that rilzabrutinib exhibited dose-dependent protective effects against platelet loss compared to vehicle-treated control ([Figure 2](#)). Results provide evidence for rilzabrutinib's capacity to mitigate antibody-induced thrombocytopenia via modulation of macrophage activity, decreasing the efficiency with

which they recognized and destroyed antibody-coated platelets. A durable platelet response was observed after oral administration of rilzabrutinib in adults and adolescents with persistent or chronic immune thrombocytopenia highlighting the translational value of the in vitro and in vivo evidence.

Figure 2. Effect of Rilzabrutinib on Platelet Counts in the Mouse ITP Model



Source: Study report DVR0288
Platelet counts in mice (n=5/group) at 6 hours following induction of ITP via anti-CD41 injection
Abbreviations: ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin injection for infusion

5.2. Clinical Pharmacology/Pharmacokinetics

Rilzabrutinib's clinical pharmacology characteristics, including absorption, distribution, metabolism, and elimination, are summarized in the following table ([Table 5](#)).

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Kinase inhibitor
Mechanism of action	Rilzabrutinib is a small-molecule, covalent, reversible kinase inhibitor targeting Bruton's tyrosine kinase (BTK). Rilzabrutinib mediates its therapeutic effect in ITP through immune modulation including 1) inhibition of B cell activation, and 2) interruption of antibody-coated cell phagocytosis by Fcγ receptor (FcγR) in spleen and liver. In vitro, rilzabrutinib reduced autoantibody signaling mediated through the FcγR pathway, blocked B cell signaling, and decreased autoantibody generation through effects on B cell activation.
Active moieties	Rilzabrutinib
QT prolongation	A thorough QT (TQT) study demonstrated that rilzabrutinib did not cause QTc interval prolongation (i.e., >10 msec) after a single dose of 400 mg with ritonavir (strong CYP3A inhibitor). A single dose of 400 mg administered with ritonavir adequately covers the worst-case clinical exposures. However, a concentration-dependent QTcF shortening was observed. Following a single dose of rilzabrutinib 400 mg, the mean maximum QTcF decrease of -7 msec (90% confidence interval: -9 msec to -5 msec) was observed at 2 hours postdose. The mean maximum QTcF decrease at exposures 4-fold the highest recommended dose i.e., 400 mg BID, was -10 msec (90% confidence interval: -12 msec to -8 msec) at 2 hours postdose.

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Characteristic	Drug Information
	General Information
Bioanalysis	Plasma rilzabrutinib concentrations were measured using validated turbo ion spray liquid chromatography-mass spectrometry (LC-MS/MS) methods.
Healthy subjects versus patients	There is no clinically relevant difference in the pharmacokinetics of rilzabrutinib between patients with ITP and healthy subjects, as evaluated by population pharmacokinetic (PopPK) analysis.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Parameter: Mean (CV%) (400 mg, twice daily) AUC _{ss} (ng·h/mL): 928 (45.6%) C _{max,ss} (ng/mL): 259 (48%) (Simulated exposure for patients with ITP using PopPK model)
Range of effective dose(s) or exposure	400 mg, twice daily (BID).
Maximally tolerated dose or exposure	A maximum single dose of 1200 mg was studied in healthy subjects in Study PRN1008-001 (oral liquid formulation) and Study PRN1008-014 (tablet formulation).
Dose proportionality	Rilzabrutinib exposure (C _{max} and AUC) increased in a nearly dose proportional manner (50 – 600 mg) manner, however, increasing the dose from 600 to 1200 mg did not change the exposure of rilzabrutinib.
Accumulation	Limited accumulation (1.5- to 1.8-fold) at steady state was observed after multiple dosing of 300 mg and 450 mg BID and 600 mg once daily (QD) in healthy participants. In ITP population, accumulation of up to 1.3-fold was estimated following dosing at 400 mg BID using PopPK analysis.
Time to achieve steady-state	Because there is no significant accumulation upon repeat dosing, along with the short elimination half-life, the steady state exposures of rilzabrutinib can be expected to be achieved within 3 days.
Bridge between to-be-marketed and clinical trial/study formulations	N/A. To-be-marketed tablets were used in the pivotal Phase 3 trial.
	Absorption
Bioavailability	The absolute bioavailability of rilzabrutinib immediate release (IR) tablet is 4.7%. The relative bioavailability of rilzabrutinib IR tablet is 70% compared to the liquid formulation.
T _{max}	The median time to peak plasma concentrations of rilzabrutinib is approximately 1.5 hours in the fasted state (ranging from 0.5 to 2 hours).
Food effect (fed/fasted) Geometric least square mean and 90% CI	The effect of a high-fat meal on rilzabrutinib pharmacokinetics was tested with 400 mg to-be-marketed tablets in Study PRN1008-025.

Characteristic	Drug Information								
	Table 6. Effect of High-Fat Meal on Rilzabrutinib PK Parameters <table><tr><th>Food Effect</th><th>AUC_{0-last}, GMR (90% CIs)</th><th>C_{max}, GMR (90% CIs)</th><th>T_{max}, Median (Range)</th></tr><tr><td>Fed/Fasted</td><td>82% (90% CI: 69.4, 96.3)</td><td>69% (90% CI: 55.4, 86.1)</td><td>3 h (0.75, 6.1)</td></tr></table> Source: Summary of Applicant's analysis PRN1008-025 report Abbreviations: AUC_{0-last}, area under the concentration-time curve from time 0 to last measurable concentration of the drug; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; h, hours; PK, pharmacokinetic; T_{max}, time to maximum concentration The pivotal clinical study was conducted by administering the drug without regards to food. The product can be taken without regards to food.	Food Effect	AUC _{0-last} , GMR (90% CIs)	C _{max} , GMR (90% CIs)	T _{max} , Median (Range)	Fed/Fasted	82% (90% CI: 69.4, 96.3)	69% (90% CI: 55.4, 86.1)	3 h (0.75, 6.1)
Food Effect	AUC _{0-last} , GMR (90% CIs)	C _{max} , GMR (90% CIs)	T _{max} , Median (Range)						
Fed/Fasted	82% (90% CI: 69.4, 96.3)	69% (90% CI: 55.4, 86.1)	3 h (0.75, 6.1)						
Volume of distribution Plasma protein binding Drug as substrate of transporters	Distribution The mean volume of distribution is 149 L. Rilzabrutinib is approximately 97.5% bound to human plasma proteins. Rilzabrutinib is a substrate of P-gp.								
Mass balance results	Elimination Following administration of 300 mg [¹⁴C]-rilzabrutinib, less than 5% of the dose is recovered in urine and 86% is recovered in feces. Unchanged rilzabrutinib represented about 9% of the administered dose in feces and <1% in urine (Study PRN1008-015).								
Clearance	The clearance of rilzabrutinib is not time-dependent. Following multiple doses of 400 mg BID rilzabrutinib in patients with ITP, mean CL/F ranged from 246 to 911 L/h. Based on the PopPK analysis in patients with ITP, the mean CL/F was 516 L/h.								
Half-life	Mean t_{1/2} of rilzabrutinib ranged from 1.5 to 4 hours after single dose administration of 50 or 1200 mg, and 3.8 and 4.5 hours after multiple dose administration of 300 or 600 mg.								
Metabolic pathway(s) Primary excretion pathways (% dose)	Rilzabrutinib is primarily metabolized by CYP3A4, with minor contribution from CYP2D6. Approximately 92.9% of the dose administered orally (300 mg liquid formulation) was recovered, in which approximately 5% and 86% of the dose were recovered in the urine and the feces, respectively.								

Characteristic	Drug Information
	<i>Intrinsic Factors and Specific Populations</i>
Body weight	Based on PopPK analyses, body weight is a statistically significant covariate. However, the changes in rilzabrutinib exposures due to body weight are not clinically significant.
Age	Based on PopPK analyses, age is not a statistically significant covariate on rilzabrutinib exposure.
Renal impairment	A dedicated renal impairment study was not conducted. Renal elimination is not expected to be the major elimination pathway of rilzabrutinib. Less than 5% was recovered in urine in the mass balance study with unchanged rilzabrutinib only in trace amounts. PopPK analysis showed no significant difference in systemic exposure of rilzabrutinib between patients with mild or moderate renal impairment and normal renal function. The effect of severe renal impairment including effect of dialysis is unknown.
Hepatic impairment	Mild hepatic impairment did not appear to significantly affect the total systemic exposure of rilzabrutinib. There was approximately 4.5-fold higher exposure of total rilzabrutinib in participants with moderate hepatic impairment compared to subjects with normal hepatic function.
	<i>Drug Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism	In vitro studies show rilzabrutinib is an inhibitor and inducer of CYP3A4. In vivo evaluation: Coadministration of rilzabrutinib with midazolam, a CYP3A4 substrate, increased the exposure of midazolam by 2.4-fold (AUC) upon administration with a single dose of 600 mg rilzabrutinib. PBPK simulation: Modeling of coadministration of rilzabrutinib with midazolam also significantly increased the exposure of midazolam upon administration with rilzabrutinib at 400 mg BID for 14 days. Please see Section 14.5.3 for details.
Inhibition/induction of transporter systems	In vitro studies show rilzabrutinib is a potential inhibitor of P-gp, BCRP and OATP1B3. In vivo evaluation: No clinical DDI studies were conducted to evaluate the inhibitory effect of rilzabrutinib towards P-gp, BCRP or OATP1B3. PBPK simulation: PBPK analyses of transporter related drug interactions are considered inadequate. For risk assessment only, the simulation results cannot rule out the potentially significant interactions of rilzabrutinib on the pharmacokinetics of substrates of these transporters. Please see Section 14.5.3 for details.

Source: FDA Summary of Clinical Pharmacology Studies

Abbreviations: AUC, area under the concentration-time curve; AUC_{ss}, area under the concentration-time curve over a dosage interval at steady state; BCRP, breast cancer resistance protein; CI, confidence interval; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; C_{max,ss}, maximum plasma concentration at steady state; CV, coefficient of variation; CYP2D6, cytochrome P450 2D6, CYP3A4, cytochrome P450 3A4; DDI, drug-drug interaction; ITP, immune thrombocytopenia; N/A, not available; OATP1B3, organic anion transporting polypeptide 1B3; PBPK, Physiologically based pharmacokinetic; P-gp, P-glycoprotein; PopPK, population PK; QT, QT interval; QTc, corrected QT interval; QTcF, corrected QT interval using Fridericia's formula; t_{1/2}, half-life

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

6.1.1. Applicant's Proposed Dosing Regimen

The proposed dosing regimen of rilzabrutinib is 400 mg taken orally twice daily.

This dose and dosing regimen is the same as used in LUNA 3: Selection of Dosing Regimen for Phase 3 Studies.

The phase 1 study, PRN1008-001, suggested rilzabrutinib was well-tolerated up to 600 mg once daily (QD) and 450 mg twice daily (BID). Rilzabrutinib was evaluated in the Phase 1/2 Study, LUNA 2, which was conducted in two parts in individuals with ITP. Part A consisted of inpatient dose escalation using a 3+3 design, where treatment was initiated with 1 of 4 doses: 200 mg QD, 400 mg QD, 300 mg BID, or 400 mg BID. Inpatient dose escalation was allowed every 28 days if the participant did not experience a platelet response, as defined in the primary endpoint, or a dose-limiting toxicity (DLT) at that dose level. Once a participant escalated to the 400 mg BID dose, they remained at that dose. Part B was an open-label study that investigated the selected dose of 400 mg BID in a new cohort. In both parts A and B, the active treatment period was 24 weeks.

Based on BTK occupancies in the mouse model of antiplatelet driven immune thrombocytopenia, the top dose of 40 mg/kg/day resulted in a maximum BTK occupancy of 91%, matching the expected peak occupancies with the maximum 400 mg QD and 400 mg BID doses. The 400 mg BID dose was expected to produce higher trough, or predose BTK occupancies relative to QD dosing, while having similar peak values. Dosing above 400 mg BID was thought unlikely to result in greater target inhibition. In Part A of LUNA 2, among patients who initiated and maintained rilzabrutinib doses of 400 mg BID throughout the main treatment period, 40.0% achieved the primary platelet response ([Table 7](#)). Primary platelet response was defined as ≥ 2 consecutive platelet counts, separated by at least 5 days of $\geq 50,000/\mu\text{L}$ and increased $\geq 20,000/\mu\text{L}$ from baseline without requiring rescue medication. [Table 8](#) summarizes primary platelet response by dose level (dose attributed to/before the response) and overall, for the main treatment period. From the dose finding part of Study LUNA 2, the 400 mg rilzabrutinib BID dosing regimen was also associated with a faster and more pronounced increase in platelet count compared to lower doses. Based on the data from this dose-finding portion of the study, the 400 mg BID dose was selected for further investigation in Part B of LUNA 2.

Table 7. Primary Platelet Response by Starting Dose and Overall, Main Treatment Period, ITT Population, Part A

	Starting Dose 200 mg QD (N = 9)	Starting Dose 400 mg QD (N = 1)	Starting Dose 300 mg BID (N = 5)	Starting Dose 400 mg BID (N = 45)	Overall (N = 60)
Responder - n (%)	4 (44.4)	0 (0.0)	2 (40.0)	18 (40.0)	24 (40.0)
- 95% CI	13.70, 78.80	0.00, 97.50	5.27, 85.34	25.70, 55.67	27.56, 53.46

Source: Clinical study report PRN1008-010 (DFI17124), Table 15, Page 42

Percentages are based on the number of ITT participants in each starting dose level and overall.

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of participants; n, number of responders; QD, once daily

Table 8. Primary Platelet Response by Dose Level* and Overall, Main Treatment Period, ITT Population, Part A

	200 mg QD (N = 9)	400 mg QD (N = 8)	300 mg BID (N = 12)	400 mg BID (N = 52)	Overall (N = 60)
Responder - n (%)	1 (11.1)	2 (25.0)	4 (33.3)	20 (38.5)	24 (40.0)
- 95% CI	0.28, 48.25	3.19, 65.09	9.92, 65.11	25.30, 52.98	27.56, 53.46

Source: Clinical study report PRN1008-010 (DFI17124), Table 16, Page 42

Percentages are based on the number of ITT participants in each dose level and overall.

Participants are evaluable in the dose level(s) if the dose level was received during main treatment period. A given participant can be classified into multiple dose levels.

*Participants are classified into different dose levels according to the dose they received at the visit prior to the start of the platelet response.

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of participants in treatment arm; n, number of responders; QD, once daily

In Part B (400 mg BID), of the 26 participants evaluated for efficacy in the ITT population, 9 participants (34.6%) met the primary efficacy endpoint of durable platelet response which was defined as the proportion of participants able to achieve platelet counts $\geq 50,000/\mu\text{L}$ 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 ([Table 9](#)).

Table 9. Platelet Overall Response During 24-Week Treatment Period, ITT Population, Part B

	Rilzabrutinib 400 mg BID (N=26)
At least 8 out of the last 12 platelet counts $\geq 50,000/\mu\text{L}$	
n (%)	9 (34.6)
95% CI ^a	17.21 to 55.67

Source: Clinical study report PRN1008-010b (DFI17124), Table 12, Page 34

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of participants in treatment arm; n, number of responders

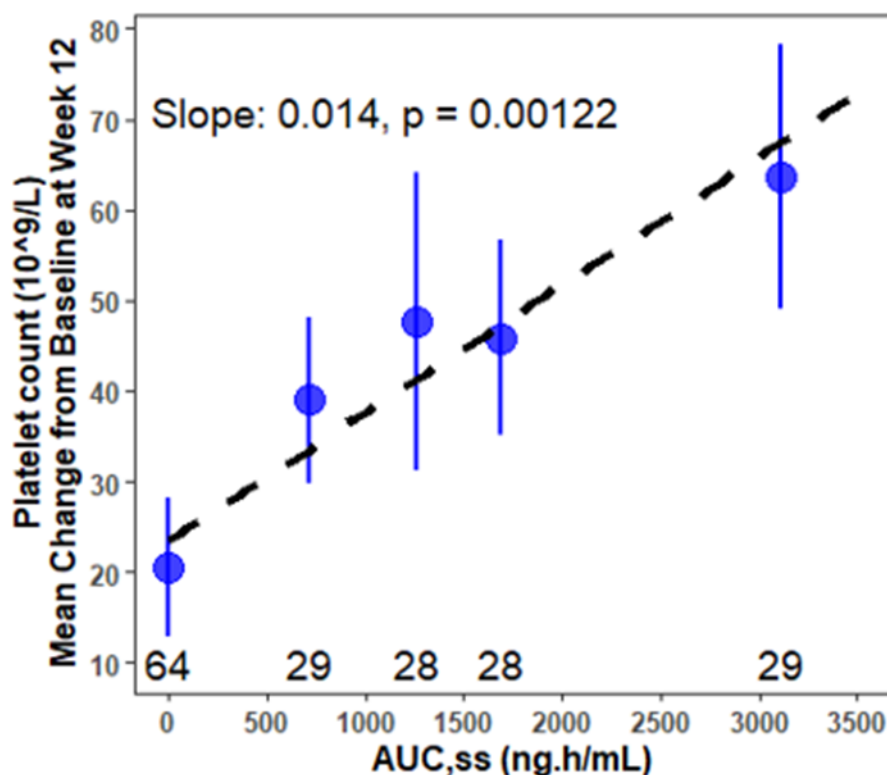
Based on results from LUNA 2, the Applicant selected 400 mg BID rilzabrutinib for further evaluation in the pivotal Phase 3 study PRN1008-018. As noted earlier, a dosing regimen higher than 400 mg BID were not expected to result in any meaningful increase in BTK receptor occupancy. Moreover, systemic exposure of rilzabrutinib reaches a plateau beyond 600 mg.

6.1.1.1. Exposure-Response for Efficacy and Safety

Exposure-response (E-R) analyses of efficacy were conducted using data from study LUNA 3 based on the repeated-measures endpoints (longitudinal platelet counts) and rilzabrutinib exposure metrics ($C_{\text{max,ss}}$, $C_{\text{min,ss}}$, and area under the concentration-time curve (AUC_{ss}). In

addition, exploratory analyses were performed using studies LUNA 2 and LUNA 3 to determine the exposure response relationship for three adverse events (AEs) (nausea, diarrhea, and anemia). The results of the E-R analyses ([Figure 3](#)) show a trend for greater increase in platelet counts from baseline with higher rilzabrutinib exposure (AUC_{ss}). However, response rate as defined by the primary endpoint of LUNA 3, i.e., durable platelet response, did not appear to depend on exposure over the range at 400 mg BID ([Table 10](#)). In addition, participants with higher rilzabrutinib exposures (AUC_{ss} and $C_{min,ss}$) had relatively higher rates of diarrhea and nausea events, [Figure 4](#) and [Figure 5](#)). See detail in Section [14.5.2](#).

Figure 3. E-R Analysis of Efficacy Explored Between Rilzabrutinib Exposure (AUC_{ss}) and the Mean Change From Platelet Count Baseline at Week 12



Source: Reviewer's analysis

Note: The black dash line represents model-predicted platelet count changes from baseline at Week 12 by rilzabrutinib exposure. Error bars with blue dots represent observed response rate (median with 95% CrI) in each exposure quartile bin, which contain the placebo bin.

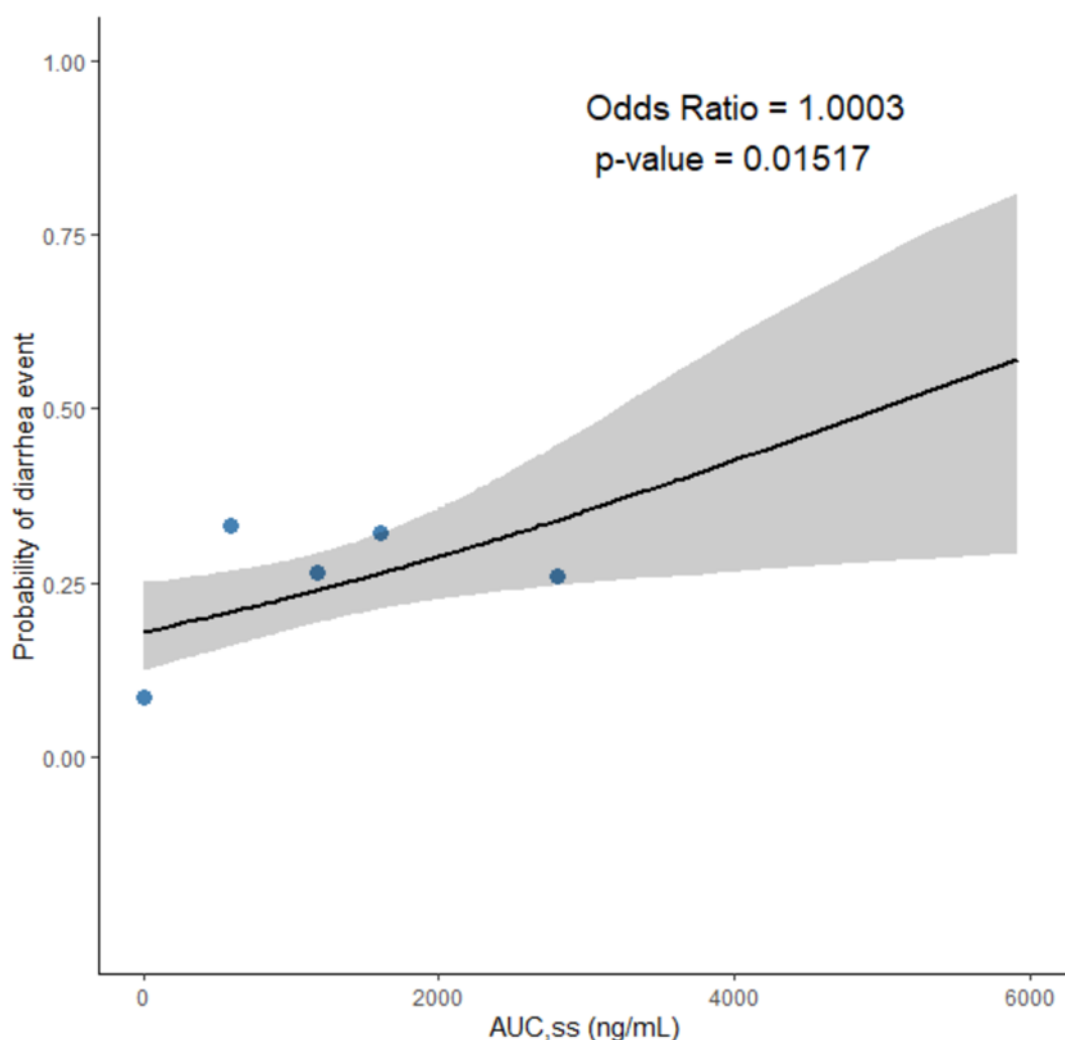
Abbreviations: AUC_{ss} , area under the concentration-time curve at steady state; CrI: credible interval; E-R, exposure-response

Table 10. Observed Primary Endpoint Response Rate by AUC_{ss} Exposure Quartiles in LUNA 3

AUC _{ss} quartile	AUC _{ss} range (h*ng/mL)	Total (n)	Responders (n)	Response rate (%)
1	[171, 948]	34	9	26.5
2	[948, 1340]	33	7	21.2
3	[1340, 1850]	33	8	24.2
4	[1850, 5820]	33	7	21.2

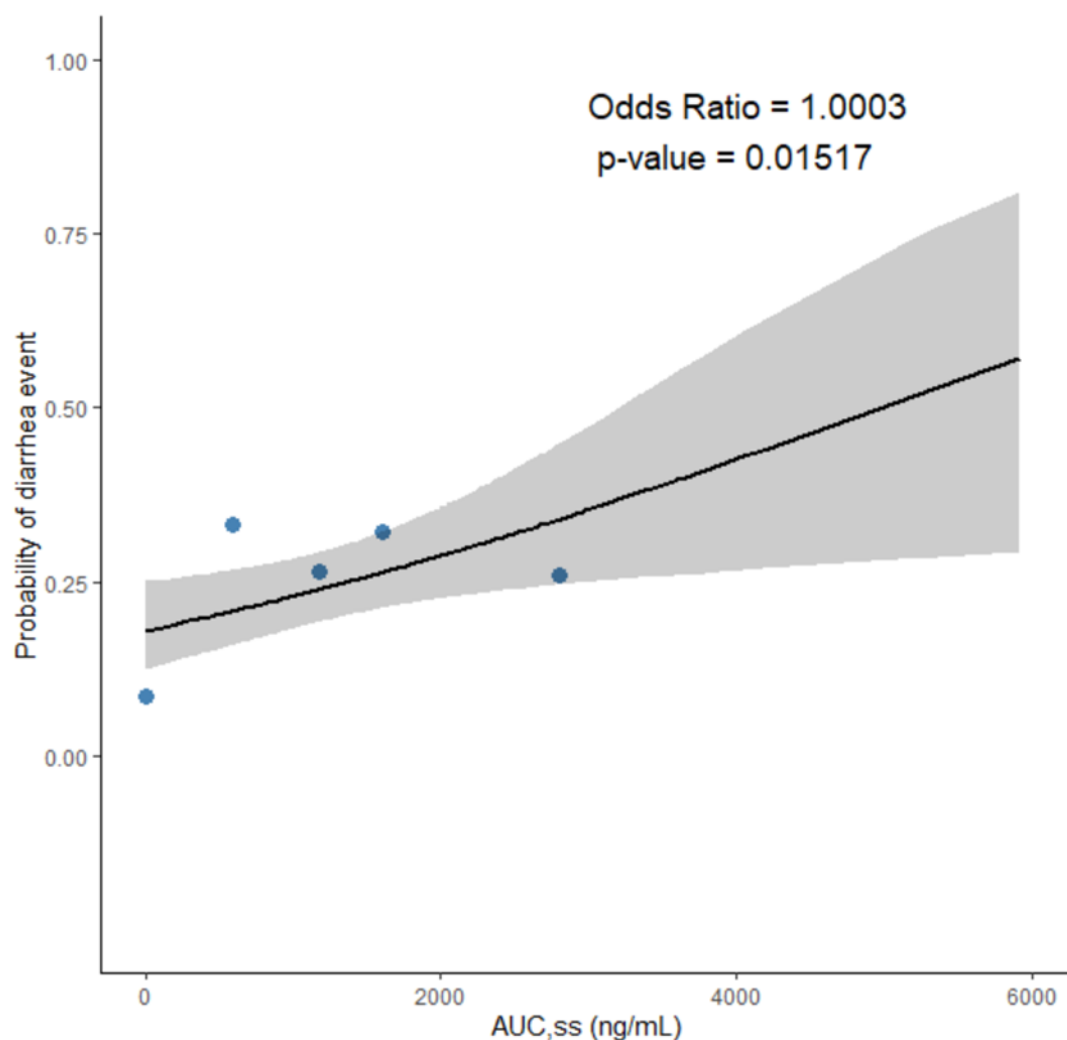
Source: Exposure-response analyses report (Report Number: SAN3001-Report-v1.0-Final), Table S7, Page 115
 Quartiles of AUC_{ss} in adult participants from Group 18.2 in Study PRN1008-018
 Abbreviations: AUC_{ss}, area under the concentration-time-curve at steady state

Figure 4. Predicted Probability of a Nausea Event vs. C_{min,ss} Exposure



Source: Reviewer's analysis
 The black line indicates the mean E-R relationship, and the shaded blue area indicates the 95% CrI. blue dots represent observed response rate (median with 95% CrI) in each exposure quartile bin, which contain the placebo bin.
 Abbreviations: AUC_{ss}: area under the concentration-time curve at steady state; C_{min,ss}: minimum concentration in the dosing interval at steady state; CrI: credible interval; E-R, exposure-response

Figure 5. Predicted Probability of a Diarrhea Event vs. AUC_{ss} Exposure



Source: Reviewer's analysis

The black line indicates the mean E-R relationship, and the shaded blue area indicates the 95% CrI. blue dots represent observed response rate (median with 95% CrI) in each exposure quartile bin, which contain the placebo bin.

Abbreviations: AUC_{ss} : area under the concentration-time curve at steady state; CrI: credible interval; E-R, exposure-response

Overall, based on the efficacy and safety data from LUNA 3 and the available exposure-response relationships, the Applicant's proposed dosing regimen is acceptable.

6.2. Clinical Studies/Studies Intended To Demonstrate Efficacy

6.2.1. LUNA 3 Study

6.2.1.1. Design, LUNA 3

The study design of LUNA 3 is shown in [Figure 6](#).

LUNA 3 was a global, multicenter randomized, parallel-group, double-blind, placebo-controlled trial in approximately 194 adults⁴ with ITP who had had an unsustained response to either intravenous immunoglobulin (IVIG), anti-D, or CS. Participants were randomized 2:1 to receive rilzabrutinib 400 mg taken orally twice daily or matching placebo. Randomization was stratified by splenectomy status (yes/no) and severity of thrombocytopenia (platelet count <15,000/ μ L or $\geq$ 15,000/ μ L). Concomitant ITP medications (an oral CS and/or a TPO-RA) were permitted.

The primary assessment was performed on a 24-week blinded treatment period, which was followed by a 28-week open-label period during which all participants received rilzabrutinib. An initial assessment for platelet response was performed after 12 weeks of blinded treatment (Week 13). Participants who had a platelet response⁵ during the first 12 weeks continued blinded treatment for a total of 24 weeks. Participants who did not have a platelet response⁶ could discontinue from the study or enter the 28-week OL period.

The primary objective of the study was to demonstrate the efficacy of rilzabrutinib versus placebo in participants with refractory/relapsed ITP.

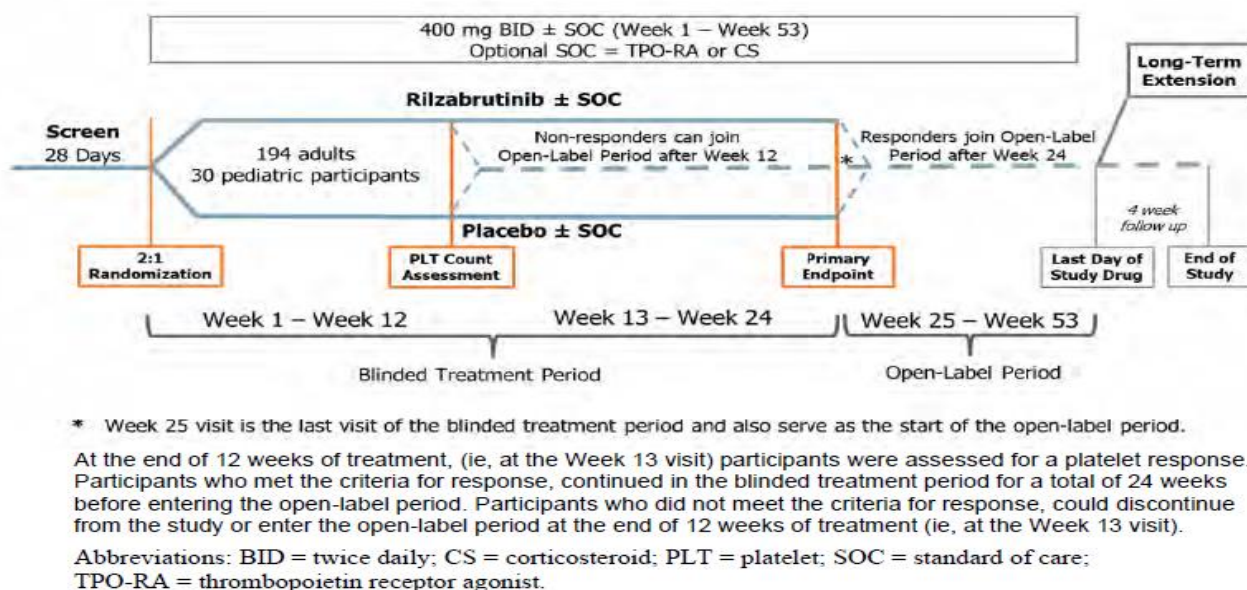
The primary efficacy endpoint was durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 50,000/ μ L for $\geq$ two-thirds of at least 8 nonmissing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 nonmissing weekly scheduled platelet measurements were at or above 50,000/ μ L during the last 6 weeks of the 24-week blinded treatment period.

⁴ Although the study enrolled both adult and adolescent participants, only data from adult (defined as age at least 18) participants is the subject of this review and all information in this section should be assumed as related to adults.

⁵ Platelet response for assessment at Week 13 is defined as achieving a platelet count of $\geq$ 50,000/ μ L OR a platelet count $\geq$ 30,000/ μ L and < 50,000/ μ L and at least doubled from baseline at any time during the first 12 weeks AND the absence of rescue medication in the 4 weeks prior to platelet count that meets the Week 13 response criterion.

⁶ Ibid.

Figure 6. Study Design, LUNA 3



Source: Study LUNA 3 Clinical Study Report, Figure 1

6.2.1.2. Eligibility Criteria, LUNA 3

Important eligibility criteria are summarized below, and the full criteria are available in Section [15.1.1](#)

Inclusion Criteria

1. Male and female participants with primary ITP with a duration of >3 months
2. Response (achievement of platelet count $\geq 50,000/\mu\text{L}$) to intravenous immunoglobulin (IVIg), anti-D, or corticosteroids (CSs) that was not sustained and documented intolerance, insufficient response, or any contraindication to any appropriate courses of standard of care ITP therapy
3. An average of 2 platelet counts at least 5 days apart of $< 30,000/\mu\text{L}$ during the screening period, and no single platelet count $> 35,000/\mu\text{L}$, within 14 days prior to the first dose of study drug

Exclusion Criteria

1. Participants with secondary ITP
2. Change in CS and/or TPO-RA dose within 14 days prior to Study Day 1 (more than 10% variation from current doses)
3. Treatment with rituximab or splenectomy within the 3 months prior to Study Day 1

Participants treated with rituximab were required to have normal B-cell counts prior to enrollment.

6.2.1.3. Statistical Analysis Plan, LUNA 3

In the final statistical analysis plan (SAP) version 3, dated March 18, 2024, the primary efficacy analysis compared rilzabrutinib to placebo using the Cochran-Mantel-Haenszel test adjusted by randomization stratification factors based on the ITT population which included all participants who are randomized. Participants were analyzed according to the intervention allocated by randomization. The Mantel-Haenszel estimate of common risk difference in response rates and its associated 95% CI based on Mantel-Haenszel stratum weights and the Sato variance estimator were reported. The observed response rate for each treatment group was presented along with its associated 95% asymptotic CI.

The key secondary endpoints included in the statistical testing hierarchy and analysis methods are summarized below.

1. Number of weeks with platelet count $\geq 50,000/\mu\text{L}$ or between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy. The mixed-effect model with repeated measures (MMRM) approach was used to analyze the longitudinal binary platelet response data across visits in the ITT population.
2. Number of weeks with platelet counts $\geq 30,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy. The MMRM approach was used to analyze the longitudinal binary platelet response data across visits in the ITT population.
3. Time to first platelet count of $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and doubled from baseline. The log-rank test adjusted by randomization stratification factors was used. Hazard ratio and its 95% CI were modeled using Cox regression model with treatment and randomization stratification factors as covariates.
4. Proportion of participants requiring rescue therapy during the 24-week blinded treatment period. The log-rank test adjusted by randomization stratification factors was used. Hazard ratio and its 95% CI were modeled using Cox regression model with treatment and randomization stratification factors as covariates.
5. Change from baseline on Item 10 of the Immune Thrombocytopenia-Patient Assessment Questionnaire (ITP-PAQ) (i.e., physical fatigue) in adult participants (≥ 18 years) at Week 13. The analysis was based on the analysis of covariance (ANCOVA) model with the treatment group, randomization stratification factors, and geographic region as fixed effects and baseline Item 10 score as a covariate.

For additional SAP details see [16.1.1](#).

6.2.1.4. Results of Analyses, LUNA 3

6.2.1.4.1. Patient Disposition

[Table 11](#) summarizes participant disposition for adult participants. In LUNA 3, a total of 393 participants were screened and 202 were randomized: 133 who received rilzabrutinib 400 mg twice daily and 69 who received placebo. Most participants completed 12 weeks of the double-blind period in both the rilzabrutinib group (121 [91.0%] participants) and the placebo group (66 [95.7%] participants). The percentage of participants who completed the 24-week double-blind

period was higher in the rilzabrutinib group compared with the placebo group (62 [46.6%] participants versus 10 [14.5%] participants, respectively). The most frequent reason for discontinuation of treatment in the double-blind period was lack of response, which was lower in the rilzabrutinib group compared with the placebo group (55 [41.4%] participants and 55 [79.7%] participants, respectively).

Table 11. Participant Disposition, Adults Screened for LUNA 3

Disposition	Placebo N=69 n (%)	Rilzabrutinib 400 mg BID N=133 n (%)	All Screened N=393 n (%)
All screened			393
Screened but not randomized			191
Exposed and not randomized	0	0	0
Randomized	69 (100)	133 (100)	202 (100)
Randomized and not exposed	0	0	0
Randomized and exposed	69 (100)	133 (100)	202 (100)
Entered the 24-week double-blind period	69 (100)	133 (100)	202 (100)
Completed the 24-week period	10 (14.5)	62 (46.6)	72 (35.6)
Discontinued the 24-week period	59 (85.5)	71 (53.4)	130 (64.4)
Reason for discontinuation			
Lack of response	55 (79.7)	55 (41.4)	110 (54.5)
Participant decision ¹	2 (2.9)	7 (5.3)	9 (4.5)
Adverse event	0	8 (6.0)	8 (4.0)
Participant noncompliance	1 (1.4)	0	1 (0.5)
Sponsor discretion	1 (1.4)	0	1 (0.5)
Other	0	1 (0.8)	1 (0.5)

Source: Reviewer table Study LUNA 3 Clinical Study Report, Table 5 (p.32), adsl.xpt.

¹ Participant's decision in rilzabrutinib arm recorded as: "...found job outside the region...", "... thought efficacy was not enough...", "... time conflict...", "personal decision", "... nausea after taking IP", "... not able to come to weekly blood test", "... could not continue to receive rescue medication... was experiencing symptoms".

Abbreviation: BID, twice daily, N, number of participants in study arm; n, number of participants with disposition

6.2.1.4.2. Baseline Demographics and Disease Characteristics

Baseline demographic characteristics are presented in [Table 12](#) and disease characteristics in [Table 13](#). The baseline demographics are generally balanced between arms with slightly higher percentage of male participants in the rilzabrutinib arm compared to placebo.

The baseline disease characteristics are similar between arms for duration of ITP, prior exposure to corticosteroids, IVIG, TPO-RA, and use of concomitant medications. Broadly speaking there are no major differences between prior lines of therapy and the reliability of the results as the population enrolled in the trial represents a chronic ITP population with majority having ITP over three years that is unresponsive to initial therapy.

Table 12. Baseline Demographics, LUNA 3

Characteristic	Rilzabrutinib 400 mg BID N=133	Placebo BID N=69	All N=202
Age (years), Median (min, max)	46.8 (18, 80)	46.0 (19, 79)	47.0 (18; 80)
Sex, n (%)			
Female	78 (58.6)	49 (71.0)	127 (62.9)
Male	55 (41.4)	20 (29.0)	75 (37.1)
Race, n (%)			
White	85 (63.9)	40 (58.0)	125 (61.9)
Black or African American	1 (0.8)	0	1 (0.5)
Asian	40 (30.1)	24 (34.8)	64 (31.7)
Not reported	1 (0.8)	2 (2.9)	3 (1.5)
Other	3 (2.3)	2 (2.9)	5 (2.5)
Geographic region, n (%)			
Asia/Pacific	44 (33.1)	26 (37.7)	70 (34.7)
West Europe	33 (24.8)	16 (23.2)	49 (24.3)
South America	24 (18)	11 (16)	35 (17.3)
East Europe	19 (14.3)	13 (18.8)	32 (15.8)
North America	13 (9.8)	3 (4.3)	16 (7.9)

Source: LUNA 3 Clinical Study Report, Table 7 (p.39); FDA Reviewer Verified

Abbreviation: BID, twice daily, N, number of participants in study arm; n, number of participants with characteristic

Table 13. Baseline Disease Characteristics, LUNA 3

Characteristic	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)
Duration of ITP		
<1 year	10 (8)	5 (7)
>1 year to <3 years	21 (16)	14 (20)
>3 years	102 (77)	50 (72)
Min; max (years)	0.31;52.2	0.29;35.8
Baseline platelet count ^a		
<15,000/μL	71 (53)	32 (46)
>15,000/μL	62 (47)	37 (54)
Median platelet count (k/μL)	15.3	15.3
Min, max (k/μL)	0.6;32	1;54
Prior ITP medication by type ^b		
Corticosteroids	127 (95.5)	66 (95.7)
TPO-RA	88 (66.2)	51 (73.9)
IVIg	70 (52.6)	39 (56.5)
Anti-D immunoglobulin	6 (4.5)	3 (4.3)
Anti-CD20 monoclonal antibody/rituximab	42 (31.6)	29 (42.0)
Fostamatinib	17 (12.8)	7 (10.1)
Immunosuppressant and other immunomodulators	67 (50.4)	42 (60.9)
Dapsone	13 (9.8)	4 (5.8)
Danazol	12 (9.0)	7 (10.1)
Investigational ITP medications	7 (5.3)	6 (8.7)
Other	26 (19.5)	20 (29.0)
Number of prior unique ITP treatments including splenectomy ^c		
1 to 2	43 (32.2)	15 (21.7)
3 to 4	33 (24.8)	18 (26.1)
≥5	57 (42.9)	36 (52.2)

	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)
Characteristic		
Concomitant ITP medication group	86 (65)	47 (68)
Neither CS nor TPO-RA	53 (40)	23 (33)
CS but no TPO-RA	34 (26)	20 (29)
TPO-RA but no CS	25 (19)	12 (17)
Both CS and TPO-RA	21 (16)	14 (20)

Source: adsl.xpt. FDA reviewer analysis

^a Baseline platelet count is defined as average of 1st, 2nd qualifying screening platelet counts, and Week 1 (Study day 1) platelet count.

^b LUNA CSR Table 8.

^c Unique ITP therapy is identified using standard medication term AND different corticosteroids counted as one therapy (from CSR LUNA Table 8).

Abbreviations: Anti-D, Rh (D); CS; corticosteroid; CSR, clinical study report; ITP, immune thrombocytopenia; max, maximum; Min, minimum; N, number of participants in study arm; n, number of participants with characteristic; TPO-RA, thrombopoietin-receptor agonist

6.2.1.4.3. Efficacy Results of the Primary Endpoint

The proportion of participants achieving durable platelet response was higher in the rilzabrutinib group (31 (23.3%) participants [95% CI, 16.12% to 30.49%]) compared with the placebo group (0 participants) [Table 14](#). The Mantel-Haenszel risk difference for the rilzabrutinib group versus placebo was 23.1% [95% CI, 15.95, 30.31], with a p-value<0.0001.

Table 14. Primary Analysis for Durable Platelet Response (Primary Endpoint), LUNA 3

Parameter	Placebo N=69	Rilzabrutinib 400 mg BID N=133
n (%)	0 (0.0)	31 (23.3)
95% CI ^a	0.00, 0.00	16.12, 30.49
Risk difference (95% CI) vs. placebo ^b		23.1 (15.95, 30.31)
p-value ^c		<0.0001

Source: Study LUNA 3 Clinical Study Report, Table 10 (p.51), confirmed by FDA statistical reviewer

^aAsymptotic confidence interval.

^bMantel-Haenszel estimate based on Mantel-Haenszel stratum weights and the Sato variance estimator.

^cCochran-Mantel-Haenszel test adjusted by stratification factors; Stratification factors include randomization strata of splenectomy status (yes, no) and randomization strata of severity of thrombocytopenia (platelet counts <15,000/μL, ≥15,000/μL).

Abbreviation: BID, twice daily; CI, confidence interval; N, number of participants in study arm; n, number of participants with response

Two sensitivity analyses (SA), alternative assumption of missing data (tipping point analysis) and modified primary estimand (missing due to Covid-19 imputed with participant's median value), were conducted to assess the robustness of the results ([Table 15](#)). These sensitivity analyses showed findings consistent with that the primary efficacy results ([Table 14](#)).

Table 15. Sensitivity Analyses for Primary Endpoint, ITT, LUNA 3

Sensitivity Analyses	Difference (95% CI)	p-Value (Nominal) ^a
SA 1 ^b		
SA 2 ^c	23.1 (15.95 to 30.31)	<0.001

Source: Study LUNA 3 Efficacy response data 12.2.6, statistical reviewer's analysis

^a p-Value =0.0003 under the least favorable scenario for rilzabrutinib for SA1 where missing data imputed as response in the placebo group and nonresponse in the rilzabrutinib group. All p-values in SA 1 are less than 0.001. See Section 6.3.1 for further details.

^b Sensitivity analysis 1 (tipping point analysis) was to explore the plausibility of missing data assumptions under which the conclusion changes, i.e., under which there is no longer evidence of a treatment effect. missing considered due to missing data, or discontinuation not due to related Adverse Events or lack of response.

^c Sensitivity analysis 2 missing platelet count due to COVID-19 was imputed using the participant's median value of available weekly platelet counts as an alternative handling of missing data.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease of 2019; ITT, intent-to-treat; SA, sensitivity analysis

6.2.1.4.4. Subgroup Analysis of the Primary Endpoint

Subgroup analyses were conducted to assess the potential for differences in the treatment effect of rilzabrutinib compared to placebo based on durable platelet response across various demographic and clinical characteristic groups. Overall, the treatment effect was consistent across baseline subgroups and demonstrated positive trend in favor of rilzabrutinib (Figure 28). Since these subgroup analyses are limited by the small numbers of subjects, the results should be interpreted with caution.

6.2.1.4.5. Efficacy Results for the Key Secondary Endpoints

The five key secondary efficacy endpoints, described above, were tested in the prespecified hierarchical order. For the first four, favorable results are shown below in Table 16, Table 17, Table 18, and Table 19. The PRO endpoint is discussed separately.

Table 16. Primary Analysis for Number of Weeks With Platelet Response (First Key Secondary Endpoint)^a, LUNA 3

Parameter	Placebo N=69	Rilzabrutinib 400 mg BID N=133
LS mean (SE) ^b	0.72 (0.350)	7.18 (0.747)
LS mean difference (95% CI) vs. placebo ^b		6.46 (4.923, 7.990)
p-Value ^b		<0.0001

Source: LUNA 3 Clinical Study Report, Table 10 (p.51); FDA statistical reviewer verified

^a Number of weeks with platelet count $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $<50,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.

^b Mixed-effect model with repeated measures on longitudinal binary data with treatment group, stratification factors, week (Weeks 2 to 25), treatment-by-week interaction as fix effects. Platelet counts assessed within 4 weeks of rescue medication intake are considered as no response. Missing weekly platelet counts due to any reasons are considered as no response.

Abbreviations: BID, twice daily; CI, confidence interval; LS, least squares; N, number of participants in study arm; SE, standard error

Table 17. Primary Analysis for Number of Weeks With Platelet Response (Second Key Secondary Endpoint),^a LUNA 3

Parameter	Placebo N=69	Rilzabrutinib 400 mg BID N=133
LS mean (SE) ^b	0.64 (0.337)	6.95 (0.749)
LS mean difference (95% CI) vs. placebo ^b		6.31 (4.787, 7.831)
p-Value ^b		<0.0001

Source: LUNA 3 Clinical Study Report, Table 10 (p.51); FDA statistical reviewer verified

^a Number of weeks with platelet counts $\geq 30,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.

^b Mixed-effect model with repeated measures on longitudinal binary data with treatment group, stratification factors, week (Weeks 2 to 25), treatment-by-week interaction as fix effects. Platelet counts assessed within 4 weeks of rescue medication intake are considered as no response. Missing weekly platelet counts due to any reasons are considered as no response.

Abbreviations: BID, twice daily; CI, confidence interval; LS, least squares; N, number of participants in study arm; SE, standard error

Table 18. Primary Analysis for Time-to-First Platelet Response (Third Key Secondary Endpoint), LUNA 3

Parameter	Placebo N=69	Rilzabrutinib 400 mg BID N=133
Time (days) to first response (95% CI)		
1st quartile (25 th percentile)	65.0 (36.00, NA)	10.0 (8.00, 15.00)
Median (50 th percentile)	NA (NA, NA)	36.0 (22.00, 44.00)
Hazard ratio (95% CI) vs. placebo ^a		3.10 (1.948, 4.934)
p-Value ^b		<0.0001

Source: Study LUNA 3 Clinical Study Report, Table 10 (p.51); FDA statistical reviewer verified

^a Cox regression model with treatment group and stratification factors as covariates.

^b Log-rank test adjusted by stratification factors.

Abbreviation: BID, twice daily; CI, confidence interval; N, number of participants in study arm; NA, not available

Table 19. Primary Analysis for Proportion of Participants Requiring Rescue Therapy (Fourth Key Secondary Endpoint),^a LUNA 3

Parameter	Placebo N=69	Rilzabrutinib 400 mg BID N=133
Participants requiring rescue therapy, n (%)	40 (58.0)	44 (33.1)
Median time to first use of rescue therapy (days)	56	NA ^b

Source: Study LUNA 3 Clinical Study Report, Table 10 (p.51); FDA statistical reviewer verified

^a The fourth key secondary endpoint was to compare proportion of participants requiring rescue therapy (via the time to event analysis due to the expected high rate of treatment discontinuation) during the 24-week blinded treatment period between the Rilzabrutinib and placebo.

^b The median time to first use of rescue therapy was not reached in the WAYRILZ group.

Abbreviation: BID, twice daily; N, number of participants in study arm; n, number of participants requiring rescue therapy

Evaluation of the PRO

The fifth key secondary endpoint was change from baseline on Item 10 of ITP-PAQ (i.e., physical fatigue) in adult participants (≥ 18 years) at Week 13.

The Division of Clinical Outcomes Assessment (DCOA), after review of all relevant information provided by the Applicant, concluded that there was insufficient evidence to support that ITP-PAQ Item 10 is fit-for-purpose for the context of this development program. For complete details, see COA review memo dated March 27, 2025 (DARRTS Reference ID: 5558745).

Key concerns with the instrument include the following:

1. The ITP-PAQ uses only one item (Item 10) to assess physical fatigue over the past 4 weeks. A single item cannot sufficiently measure fatigue, which is multidimensional (physical fatigue, mental fatigue). In addition, Item 10 measures both disease and treatment-related

symptoms, making it a double-barreled question (measures more than one concept, e.g., it asks, “In the past 4 weeks, how often did ITP or its treatment cause you to feel physically fatigued?”) which leads to unwanted variability in the data. Combining these concepts into one question makes it unclear what is being measured.

2. The Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) anchor scales to assess the threshold for meaningful within-patient score change in the ITP-PAQ Fatigue domain score limit the interpretability of the clinically meaningfulness of the statistical results, as they do not align with the ITP-PAQ Item 10. Specifically, the concept measured in the PGIS and PGIC items is generic (disease-related symptoms; disease-related fatigue) and is not fully aligned with the concept of the ITP-PAQ item 10 (physical fatigue). Likewise, the recall period of the PGIS items (“past week”) does not align with the assessment time period of the prespecified ITP-PAQ Item 10 endpoint (“past 4 weeks”). Furthermore, while ITP-PAQ Item 10 measures symptom frequency, the PGIS items measure symptom severity.

(b) (4)

6.2.2. Confirmatory Evidence of Effectiveness

Chronic ITP is a rare, serious, and potentially life-threatening disease. It is reasonable in this situation to establish effectiveness based on one adequate and well-controlled study plus confirmatory evidence. LUNA 3 is an adequate and well-controlled study that provides strong evidence of rilzabrutinib’s effectiveness. LUNA 2, an open-label dose-finding with cohort expansion study in participants with ITP who have relapsed or have had an insufficient response to prior therapies, provides confirmatory evidence of effectiveness for rilzabrutinib based on the observed PD effects.

6.2.2.1. Confirmatory Evidence, LUNA 2

Study Design

Refer to Section [15.2](#)

Enrolled Population

Part A enrolled 60 participants with 95% having a diagnosis of primary ITP and 5% with secondary ITP. The mean duration of ITP was 11.3 years (standard deviation (SD): 13.41) with a median of 6.3 years (range: 0.4, 52.5). The median baseline platelet count was $14.75 \times 10^9/L$ (range: 0.4, 33.3) with 50% of participants having a platelet count $<15,000/\mu L$. The median number of prior unique ITP therapies (including splenectomy) was 3 (range: 1, 14).

Part B enrolled 26 participants with a diagnosis of primary ITP. The mean duration of ITP was 13.1 years (SD: 12.3) with a median of 10.3 years (range: 0.7, 48.2). The median baseline platelet count was $13.2 \times 10^9/L$ (range: 1.7, 23.7) with 54% of participants having a platelet count $<15,000/\mu L$. The median number of prior unique ITP therapies (including splenectomy) was 6 (range: 3, 17).

Analysis of the Primary Efficacy Endpoint

Efficacy endpoints in LUNA 2 Parts A and B were assessed during the 24-week treatment period using descriptive statistics. See Section [6.1](#).

In Part A, of the 60 participants evaluated for efficacy, cumulatively across dosages, 24 participants (40.0%) had a platelet response as defined above ([Table 8](#)).

In Part B, of the 26 participants evaluated for efficacy in the ITT population, 9 participants (34.6%) had a durable platelet response, as defined above ([Table 9](#)).

Conclusions

Spontaneous increases in platelet count, particularly sustained increases as defined for the primary endpoint in Part B, in heavily pretreated participants with chronic ITP would not be expected. Therefore, it is reasonable to consider the responses observed in this single arm study as evidence of activity related to rilzabrutinib and confirmatory evidence supporting the findings from LUNA 3.

6.3. Key Efficacy Review Issues

6.3.1. High Dropout Prior to Completion of the 24-Week Double-Blind Treatment Period

Issue

A minority of participants in both the rilzabrutinib arms completed the 24-week double-blind period, 46.6% (62 of 133) and 14.5% (10 of 69) in the rilzabrutinib and placebo arms respectively. The high level of dropout raises concerns regarding the interpretability of the efficacy results.

Background

The design of LUNA 3 included an assessment at Week 13, and participants who did not respond during the first 12 weeks of blinded treatment were unblinded and allowed to switch to other treatments, i.e., crossing over to rilzabrutinib arm for nonresponders in the placebo arm or discontinuing study to receive other treatments off study. This design element is consistent with the clinical approach to treating participants with low platelets where therapies are assessed for a limited period and switched to something else, given the risk for serious bleeding. This approach is also similar to other clinical studies in ITP.

Assessment

The Applicant and review team conducted multiple sensitivity analyses under varying assumptions to assess the impact of missing data and dropouts to ensure the robustness of the primary efficacy findings of the evaluation of rilzabrutinib's effectiveness.

Durable Platelet Response During the 12-Week Double-Blind Period

To explore the consistency of treatment effect over the first 12-week duration compared to the second 12-weeks, the statistical review team examined durable platelet response through Week 12 and found that 25 (18.8%) participants, (95% CI: 12.16%, 25.44%) in the rilzabrutinib group achieved durable response, compared to one (1.4%) participant, (95% CI: 0.00, 4.27%) in the placebo group. The Mantel-Haenszel risk difference was 17.0% [95% CI: 9.92, 24.12], with a p-value of 0.005. This result is consistent to the primary analysis results for the primary endpoint, which assessed durable platelet count between Week 12 and 24.

Sensitivity Analyses: Durable Platelet Response During the 12-Week and 24-Week Double-Blind Periods

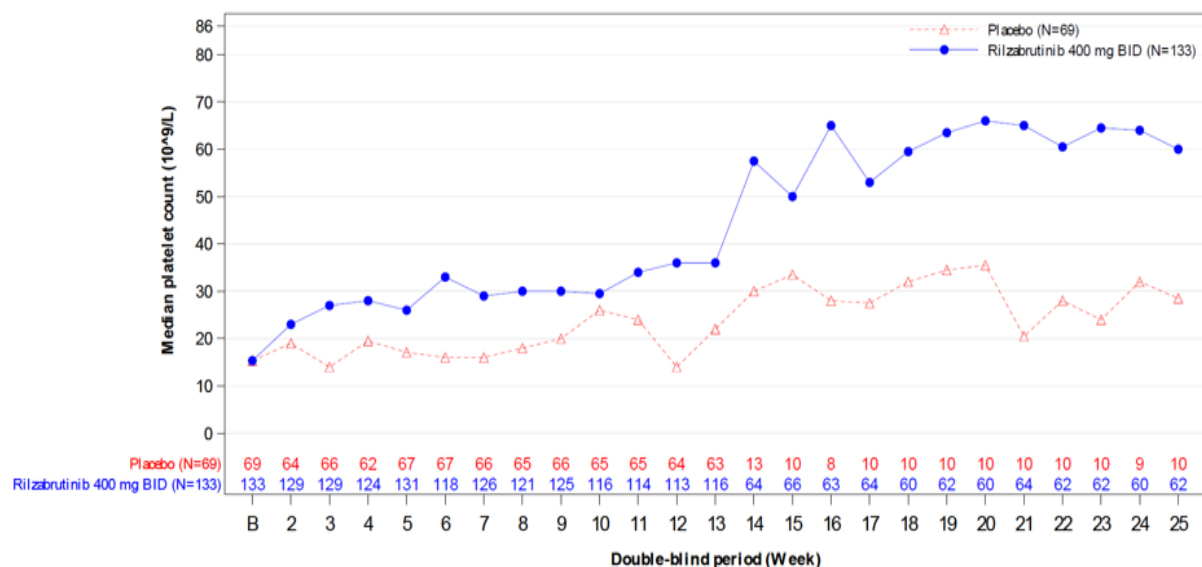
The Applicant conducted multiple sensitivity analyses per FDA statistical review team requests to handle all types of missing data regardless of the reasons for missing data or dropouts rather than only treated lack of response or related AE as nonresponder. [Table 116](#) and [Table 117](#) present tipping point analyses for the 12-week and 24-week periods, respectively. In these analyses, participants with missing response data were imputed as responders at varying probabilities—denoted as p_0 for the placebo group and p_1 for the rilzabrutinib group. The values of p_0 and p_1 were incrementally increased from 0% to 100% in 10% steps to evaluate the impact of different imputation assumptions on the treatment effect.

[Table 116](#) and [Table 117](#) showed that the statistical significance of the treatment effect was lost when the assumed response rate among missing participants is relatively high in the placebo group (p_0 close to 0.2) and relatively low in the rilzabrutinib group (p_1 close to 0). For example, when $p_0=0.2$, the p-value is no longer significant if $p_1=0$ or 0.1. In this study, the placebo group had a durable response rate below 5%, indicating that assuming a higher p_0 is not consistent with the observed data. Overall, the tipping point results demonstrated that the primary analyses results for rilzabrutinib on durable platelet response during the 12-week and 24-week double-blind period remain robust (see Section [16.1.2](#)).

Over Time Performance

Over time analyses of platelet count change from baseline further support the primary analysis. [Figure 7](#) shows the median platelet count by visit during the 24-week double-blind treatment period. Mann-Whitney tests were performed to assess the distribution of platelet counts at Week 2 through Week 25 between the rilzabrutinib arm and the placebo arm ([Table 20](#)). [Figure 7](#) and [Table 20](#) show that the platelet counts in the rilzabrutinib arm were higher than those in the placebo arm across Week 2 to Week 25, with all nominal p-values ≤ 0.05 .

Figure 7. Plot of Median Platelet Count by Visit During the 24-Week Double-Blind Treatment Period, LUNA 3



Source: LUNA 3 Efficacy Response Data
Abbreviations: BID, twice daily; N, number of participants in study arm

Table 20. Mann-Whitney Test on Platelet Counts by Visit During the 24-Week Double-Blind Treatment Period, Adult ITT Population, LUNA 3

Visit	p-Value (Nominal)	Visit	p-Value (Nominal)	Visit	p-Value (Nominal)
Week 2	0.025	Week 10	0.0362	Week 18	0.0072
Week 3	<0.001	Week 11	0.0051	Week 19	0.0488
Week 4	0.0046	Week 12	<0.0001	Week 20	0.0020
Week 5	0.0011	Week 13	0.0002	Week 21	0.0003
Week 6	<0.0001	Week 14	0.0030	Week 22	0.0139
Week 7	0.0022	Week 15	0.0068	Week 23	0.0043
Week 8	<0.0001	Week 16	0.0084	Week 24	0.0016
Week 9	0.0003	Week 17	0.0003	Week 25	0.0002

Source: Applicant response to FDA information request dated January 3, 2025; FDA reviewer verified
Abbreviation: ITT, intent-to-treat

Conclusion

To address the high amount of missing data in both treatment arms, multiple sensitivity analyses were conducted to assess the impact of missing data and dropouts on the primary endpoint. Tipping point analyses were also performed by varying imputation of the assumed performance in both treatment groups. Results showed that statistical significance was generally maintained unless implausibly high response rates were assumed in the placebo group. In addition, analyses of platelet count over time from baseline to Week 25 showed consistently higher platelet counts in the rilzabrutinib group compared to placebo, with nominal p-values ≤ 0.05 at all visits. The review team determined that missing data did not meaningfully change the conclusion of effectiveness of rilzabrutinib for the treatment of ITP in adults.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

A comprehensive toxicological evaluation in healthy animals revealed that rilzabrutinib primarily affected the liver in dogs, the gastrointestinal tract in dogs and rats, and brain in rats. Refer to Section [13.1.5](#) for detailed study descriptions.

Hepatotoxicity

Liver findings in the chronic 39-week study in dogs included reversible increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), with additional increases in ALP observed in females. The changes in liver enzymes were coincident with microscopic hepatic findings including Kupffer cell hypertrophy and pigment accumulation. Kupffer cell hypertrophy was noted at ≥ 30 mg/kg/day females and 50 mg/kg/day males and increased Kupffer cell pigmentation at 50 mg/kg/day in both males and females with exposures ranges approximating the clinical exposures, respectively, the clinical exposures at the maximum recommended dose (MRHD) based on AUC. While Kupffer cell hypertrophy with increased pigmentation can indicate phagocytic uptake of foreign materials or cellular debris that may occur during pathogenic processes and ALT/AST and/or ALP increases were observed, it is important to note that no significant histopathological impacts on hepatocytes were observed. No significant hepatic findings were observed in rats in studies of durations up to 26 weeks.

The issue of hepatotoxicity in humans for various BTK inhibitors is well known and described in literature and product labeling. However, available data indicate that animal studies are poor predictors of the type of idiosyncratic drug-induced liver injury (DILI) observed in patients treated with BTK inhibitors. Idiosyncratic DILI typically has a complex, immune-related etiology, in contrast to direct toxicity to hepatocytes. Given that rilzabrutinib may be associated with infrequent idiosyncratic DILI events in humans based on observations with this class of drugs, this risk is better characterized by clinical trial data.

Gastrointestinal Toxicity

Findings in the chronic 26-week rat study were observed in the gastrointestinal (GI) tract, which occurred primarily at doses ≥ 150 mg/kg/day that resulted in exposures ≥ 5 times the clinical exposures at the MRHD, based on AUC. Findings consisted of hemorrhage in duodenum, esophagus, and stomach in the presence of mixed cell and neutrophil inflammation. Findings in dogs consisted of mild increases in intraepithelial lymphocytes with mucosal atrophy at 50 mg/kg/day in males with exposures approximating the clinical exposures at the MRHD, based on AUC, indicative of gastritis. GI side effects are not uncommon with this class of drugs.

Brain Findings

While acute oral doses (single or 3 daily exposures) of rilzabrutinib to Wistar Han rats up to 500 mg/kg (21 times the clinical exposure, based on AUC) did not affect the gross behavioral, physiological, or neurological state of the animals, repeated oral administration of rilzabrutinib at 500 mg/kg/day caused minimal to mild neutrophilic inflammation in the meninges and neuropil

and increased ionized calcium binding adaptor molecule 1 (IBA-1) positivity (indicating microglial activation) in brain. With repeated dosing for ≥ 13 weeks (including the 26-week chronic study), minimal to mild neutrophil infiltration in the meninges and perivascular spaces, as well as alterations in IBA-1 expression in specific brain regions were observed at 5 times the clinical exposures, based on AUC, indicative of microgliosis. Concurrent increases in glial fibrillary acidic protein (GFAP) expression, indicative of astrocyte activity, were observed in similar areas at all doses tested. Rilzabrutinib-induced changes in IBA-1 and GFAP expression showed partial resolution at the end of recovery periods.

While rilzabrutinib induced inflammatory changes (neutrophil infiltration, microglial activation) in rat brains during chronic toxicology studies, importantly, these effects occurred without evidence of neuronal damage or degeneration. The occurrence of microgliosis in the absence a direct effect on neurons is consistent with the reported BTK expression pattern in the brain (higher microglial expression, lower neuronal expression), although rilzabrutinib brain penetration was shown to be limited. This implies these brain effects are secondary to some other process (e.g., interaction with the gut-brain axis). No similar findings were observed in dogs.

While the clinical risk of microgliosis remains uncertain, the findings occurred only at clinical exposure margins in excess (≥ 5 times) of the clinical exposures, with no evidence of findings at the clinical exposures.

Reproductive Toxicology

Refer to Section [8.4](#).

Genetic Toxicology and Carcinogenicity

There are no concerns for malignancy based on negative results of genetic toxicology and carcinogenicity studies with rilzabrutinib, see Sections [13.1.7](#) and [13.1.8](#).

Nonclinical Recommendation

Overall, there are no nonclinical safety issues that would preclude approvability for the treatment of persistent or chronic ITP and no postmarketing requirements (PMRs) are recommended.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

There are currently three FDA approved irreversible Bruton's tyrosine kinase inhibitors (BTKIs)⁷ and one reversible BTKI⁸. All are approved only in oncology indications. Across the class of BTKIs, the following risks are identified in Section 5, Warnings and Precautions: Infection, Hemorrhage, Cardiac arrhythmia/failure, Hypertension, Cytopenias, (Second) malignancy, Hepatotoxicity. These risks represent both on-target, off-target, and combination effects. Observation of these risks with rilzabrutinib may differ from the approved BTKIs given it is a more selective BTKI, and based on non-clinical studies, exhibits a rapid "on-rate" and a slow

⁷ Ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa).

⁸ Pirtobrutinib (Jaypirca).

“off-rate” for BTK, ensuring prolonged target occupancy even with low systemic exposure, favoring lower off target effect.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Rilzabrutinib is not currently approved or marketed in the United States or in any country.

7.3.1. Adverse Events Identified in Postmarket Experiences

Rilzabrutinib is not currently approved or marketed in the United States or in any country.

7.4. FDA Approach to the Safety Review

The safety assessment for the intended population of patients with chronic or recurrent ITP is based on data derived from a total of 276 unique participants who received at least one dose of the proposed dosage of rilzabrutinib (400 mg orally twice daily) while enrolled in LUNA 3 or LUNA 3. A description of these studies is provided in [Table 3](#). The data cutoff for LUNA 3 was March 14, 2024, and for LUNA 2 Part A, May 4, 2021, and Part B, January 31, 2023.

The primary safety profile for the proposed dosing regimen of rilzabrutinib 400 mg twice daily in adults with persistent or chronic ITP is based on analysis of safety data from the double-blind (DB) 24-week treatment period of LUNA 3. Additional analyses were performed on pooled ITP populations (See Section [17.1](#) for description)

The application also included safety data from Study PRN 1008-023 (See [Table 3](#)), a phase 1 pharmacokinetics and tolerability study in healthy subjects, review of which did not identify any additional potential safety signals.

Clinical study data were independently analyzed by the Agency. Clinical data scientists from the Division of Biomedical Informatics who generated the safety tables and figures. These include safety tables and figures for participants disposition, exposure data, AEs, and serious adverse events (SAEs). Frequency analyses were performed based on preferred term (PT) and based using Office of New Drug Custom Medical Queries (OCMQ) (narrow). Additional exploration and analysis of AEs were performed by the clinical reviewers using JMP, JMP Clinical, and the Office of Computational Science Medical Dictionary for Regulatory Activities (MedDRA)-based Adverse Event Diagnostics tool.

No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant’s translations of verbatim terms to MedDRA lowest level term for the events reported in LUNA 3 were reviewed and found to be acceptable. Treatment-emergent AEs (TEAEs) were protocol-defined as adverse events that developed, worsened, or became serious during the treatment-emergent period (after the first dose of rilzabrutinib had been administered and until the end of study visit [4 weeks after the last dose of study intervention]). Serious adverse events were defined as any untoward medical occurrence that, at

any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect. All AEs in the reviewed studies were graded using common terminology criteria for adverse events (CTCAE) version 5.0 ([CTEP 2017](#)).

Review of safety was based upon:

- Clinical Study Report for studies.
- Protocol for studies.
- Datasets for populations noted above.
- Summary of clinical safety.
- 120-day safety update.
- Patient narratives.
- Case report forms.
- Case report forms and narratives were provided and reviewed for deaths, SAEs, adverse events of special interest, and discontinuations associated with AEs.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for the comprehensive safety assessment of rilzabrutinib for the proposed indication, patient population, dosage regimen, and duration. [Table 21](#) summarizes the duration of exposure during the double-blind treatment period in LUNA 3. The mean duration of exposure for rilzabrutinib was 17.4 weeks versus 13.5 weeks for placebo. Nearly 37% of participants treated with rilzabrutinib remained on treatment at 24 weeks compared to only 13% of those who received placebo.

Table 21. Duration of Exposure, Safety Population, LUNA 3

Parameter	Rilzabrutinib N=133	Placebo N=69
Duration of treatment, weeks		
Mean (SD)	17.4 (6.7)	13.5 (4.7)
Median (Q1, Q3)	14 (12, 24)	12 (12, 12.3)
Min, max	3.1, 26	2.4, 24.7
Total exposure (person years)	44	18

Parameter	Rilzabrutinib N=133	Placebo N=69
Patients treated, by duration, n (%)		
<4 weeks	2 (1.5)	1 (1.4)
≥4 to <8 weeks	6 (4.5)	1 (1.4)
≥8 to <12 weeks	13 (9.8)	13 (18.8)
≥12 to <16 weeks	47 (35.3)	44 (63.8)
≥16 to <20 weeks	1 (0.8)	0
≥20 to <24 weeks	14 (10.5)	1 (1.4)
≥24 to <26 weeks	49 (36.8)	9 (13.0)
≥26 weeks	1 (0.8)	0

Source: adex.xpt and adsl.xpt; Software: R; FDA reviewer analysis

Duration is the 24-week double-blind treatment period

Abbreviations: max, maximum; Min, minimum; N, number of participants in treatment arm; n, number of participants with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

In the Integrated Safety Population (see Section [17.1](#), the mean (SD) and median (min, max) rilzabrutinib exposure were 29.4 (15.7) weeks and 28 weeks (1.4, 53), respectively. Among participants in the ISP, 50% were exposed to rilzabrutinib for 6 months or longer, and 15% were exposed for over 1 year.

7.6. Safety Results

Overall Summary

The safety profile of rilzabrutinib in patients with ITP is based primarily on analysis of data from the DB period of LUNA 3 with additional evaluation of safety assessments and reporting from the open-label periods of LUNA 3 and LUNA 2 Parts A and B.

The overall safety profile of rilzabrutinib at the proposed dose regimen for the treatment of adult patients with persistent and chronic ITP is acceptable. Key findings are:

- There was one death on LUNA 3, which occurred during the DB period in a participant receiving rilzabrutinib. The fatal TEAE was pulmonary aspergillosis and was assessed by the review team as related to rilzabrutinib.
- The frequency of serious adverse events was similar between arms. In the rilzabrutinib arm, 9% of participants had at least one SAE. After review of the narratives, four participants in the rilzabrutinib arm (3%) were assessed as having had at least one SAE (considered at least possibly related to rilzabrutinib). These SAEs were all infection related.
- Adverse events leading to permanent discontinuation occurred in 6% of participants in the rilzabrutinib arm and no participants in the placebo arm. These included pneumonia (fatal), neutropenia, peripheral embolism, erythema nodosum, and multijoint pain, each occurring in one participant. Multiple TEAEs occurred in three additional patients leading to discontinuation of rilzabrutinib. They were diarrhea, nausea, abdominal discomfort; esophageal varices hemorrhage hepatic enzyme increased; and heartburn, headache, and leg pain. No TEAE at the PT level occurred in more than one participant.
- Important adverse events of special interest occurring in participants while receiving rilzabrutinib on clinical trials are: infections, neutropenia, and second malignancies.

- The most common adverse events at the system organ class (SOC) level occurring in $\geq 20\%$ of participants in the rilzabrutinib arm and more frequently than in the placebo arm are Gastrointestinal disorders (54% in rilzabrutinib arm compared to 23% in placebo arm), Infections and Infestations (33% in rilzabrutinib arm compared to 20% in placebo arm), Musculoskeletal and Connective Tissue Disorders (20% in rilzabrutinib arm compared to 12% in placebo arm), and Nervous System Disorders (24% in rilzabrutinib arm compared to 12% in placebo arm).
- The most common adverse reaction, occurring in at least 5% of participants in the rilzabrutinib arm and at least 3% more than in the placebo arm are: diarrhea (32%, nausea (20%), headache (18%), COVID-19 (14%), arthralgia (9%), dizziness (8%), abdominal pain (8%), nasopharyngitis (7%), vomiting (7%), abdominal pain upper (5%), dyspepsia (5%), and cough (5%).
- Evaluation of an integrated safety population comprising 276 participants with ITP who received at least one dose of rilzabrutinib at 400 mg orally twice daily in LUNA 3 and LUNA 2 Parts A and B did not identify any new or more serious safety signal, including for rare but serious events that may be detectable only in a larger dataset.

The 120-day safety update was reviewed and found consistent with the original safety analysis.

7.6.1. Safety Results, LUNA 3

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Double-Blind Treatment Period, LUNA 3

[Table 22](#) presents a high-level summary of TEAEs based on frequency analysis of the DB treatment period for LUNA 3

During the DB treatment period, 84% of participants treated with rilzabrutinib compared to 75% of those treated with placebo experienced at least one TEAE. Most TEAEs in the rilzabrutinib arm were Grade 1 or 2 in severity, with 11% of participants having at least one Grade ≥ 3 TEAE. One participant treated with rilzabrutinib died due to *Aspergillus* pneumonia. SAEs were reported in 12 (9%) participants treated with rilzabrutinib as compared to 8 (12%) of placebo treated participants. Permanent discontinuation due to TEAE was reported in eight (6%) of rilzabrutinib treated participants, while no placebo treated participants discontinued treatment due to AEs. Dose interruption due to TEAEs was reported for seven (5.3%) rilzabrutinib treated participants compared to two (2.9%) placebo treated participants.

Table 22. Overview of Treatment-Emergent Adverse Events, Double-Blind Treatment Period, LUNA 3

Event Category	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
SAE	12 (9.0)	8 (11.6)	-2.6 (-13.0, 5.8)
SAEs with fatal outcome	1 (0.8)	0	0.8 (-4.6, 4.1)
Life-threatening SAEs	3 (2.3)	2 (2.9)	-0.6 (-7.9, 4.1)
SAEs requiring hospitalization	11 (8.3)	8 (11.6)	-3.3 (-13.7, 4.9)
SAEs resulting in substantial disruption of normal life functions	1 (0.8)	0	0.8 (-4.6, 4.1)
Other	1 (0.8)	0	0.8 (-4.6, 4.1)
AE leading to permanent discontinuation of study drug	8 (6.0)	0	6.0 (0.6, 11.4) *
AE leading to dose modification of study drug	7 (5.3)	2 (2.9)	2.4 (-5.2, 8.1)
AE leading to interruption of study drug	7 (5.3)	2 (2.9)	2.4 (-5.2, 8.1)
AE leading to reduction of study drug	0	0	0.0 (-5.3, 2.8)
AE leading to dose delay of study drug	0	0	0.0 (-5.3, 2.8)
Any AE	111 (83.5)	52 (75.4)	8.1 (-3.2, 20.8)
Grade ≥3	15 (11.3)	10 (14.5)	-3.2 (-14.4, 6.0)
Grade 2	49 (36.8)	25 (36.2)	0.6 (-13.6, 14.2)
Grade 1	47 (35.3)	17 (24.6)	10.7 (-3.0, 23.1)

Source: adae.xpt; Software: R; FDA reviewer analysis

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator based on CTCAE version 5.0 ([CTEP 2017](#))

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, LUNA 3

Double-Blind Period

One participant had a TEAE leading to death during the 24-week DB period. This death occurred in a participant who received rilzabrutinib and died due to pneumonia. Summary narrative for this death is provided below. The Division assessed the event as at least possibly related to rilzabrutinib based on the mechanism of action of rilzabrutinib and the association with other BTKIs with an increased risk of infection.

Participant (b) (6) was a 75-year-old white female with chronic ITP and long-term corticosteroid use who received rilzabrutinib and developed pneumonia on Study Day 61. Bronchoalveolar lavage culture grew cytomegalovirus, candidiasis, *Aspergillus fumigatus* and *nocardia spp* and *Aspergillus fumigatus*. Rilzabrutinib was permanently discontinued due to the event of pneumonia with last dose of rilzabrutinib administered on Day 72. During time on study the participant continued to concomitantly receive corticosteroids. On Day 76 the participant died due to pneumonia.

The Investigator and Applicant assessed the death as unrelated to rilzabrutinib. The review team did not agree and assessed the event as at least possibly related to rilzabrutinib. Although the participant had a long-standing history of corticosteroid use, which is a risk factor for development of fungal infections including *Aspergillus spp.*, BTKIs, including rilzabrutinib, can impact immune cell function and response and can increase susceptibility to infections and fatal

and non-fatal infections (including bacterial, viral or fungal) have been occurred in patients treated with Bruton Tyrosine Kinase inhibitors.

Open-Label and Long-Term Extension Periods

As of the cutoff dates, no adverse event leading to death had occurred in the OL or the LTE periods.

7.6.1.3. Serious Adverse Events, LUNA 3

Double-Blind Period

A frequency-based analysis of SAEs during the DB period, by MedDRA PT, is provided in [Table 23](#). The frequency of SAEs was similar between arms (12 [9%] rilzabrutinib versus 8 [12%] in placebo). Analysis using OCMQ (narrow) did not identify any safety signal not already captured in analysis by preferred term (see [Table 118](#)). At the PT level, no PT occurs more than once in an arm. At the SOC level, the most commonly occurring SAE in participants who received rilzabrutinib is Infections and Infestations, which occurred more frequently in participants in the rilzabrutinib arm (3%) compared to placebo (0%); however, SAEs in this SOC are still rare, and the observed difference between arms may be due to chance.

A total of 15 SAEs were reported in 12 participants in the rilzabrutinib group during the DB period. The PTs of immune thrombocytopenia, thrombocytopenia, and platelet count decreased each occurred in one participant and are considered related to the underlying disease. The PTs of periorbital hematoma ((b) (6)), vaginal hemorrhage ((b) (6)), and epistaxis ((b) (6)) each occurred in one participant. At the time of each of these events, the participant's platelet count was less than $10 \times 10^9/L$. These events are considered related to the underlying disease. The PT of esophageal varices hemorrhage is discussed below with narrative for Participant ((b) (6)).

The remaining eight SAEs not considered related to ITP occurred in six participants. Narrative for the fatal SAE of pneumonia occurring in Participant ((b) (6)) is discussed with Deaths. Narratives for the remaining participants having at least one SAE are presented below.

Based on the narratives, the Division assessed the following SAEs as at least possibly related to rilzabrutinib: pneumonia (Participant ((b) (6))); urinary tract infection and renal abscess (Participant ((b) (6))); wound infection (Participant ((b) (6))); coronavirus disease of 2019 (COVID-19) infection (Participant ((b) (6))).

Table 23. Frequency of Serious Adverse Events by System Organ Class and Preferred Term, Double-Blind Treatment Period, LUNA 3

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Any SAE	12 (9.0)	8 (11.6)	-2.6 (-13.0, 5.8)
Blood and lymphatic system disorders (SOC)	2 (1.5)	3 (4.3)	-2.8 (-10.7, 1.8)
Immune thrombocytopenia	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Thrombocytopenia	1 (0.8)	2 (2.9)	-2.1 (-9.3, 1.7)
Eye disorders (SOC)	0	1 (1.4)	-1.4 (-7.8, 1.4)
Conjunctival hemorrhage	0	1 (1.4)	-1.4 (-7.8, 1.4)

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Gastrointestinal disorders (SOC)	1 (0.8)	2 (2.9)	-2.1 (-9.3, 1.7)
Esophageal varices hemorrhage	1 (0.8)	0	0.8 (-4.6, 4.1)
Hematemesis	0	1 (1.4)	-1.4 (-7.8, 1.4)
Mouth hemorrhage	0	1 (1.4)	-1.4 (-7.8, 1.4)
Hepatobiliary disorders (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Hepatic cirrhosis	1 (0.8)	0	0.8 (-4.6, 4.1)
Infections and infestations (SOC)	4 (3.0)	0	3.0 (-2.3, 7.5)
COVID-19	1 (0.8)	0	0.8 (-4.6, 4.1)
Pneumonia	1 (0.8)	0	0.8 (-4.6, 4.1)
Renal abscess	1 (0.8)	0	0.8 (-4.6, 4.1)
Urinary tract infection	1 (0.8)	0	0.8 (-4.6, 4.1)
Wound infection	1 (0.8)	0	0.8 (-4.6, 4.1)
Injury, poisoning and procedural complications (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Periorbital haematoma	1 (0.8)	0	0.8 (-4.6, 4.1)
Investigations (SOC)	2 (1.5)	0	1.5 (-3.8, 5.3)
Hepatic enzyme increased	1 (0.8)	0	0.8 (-4.6, 4.1)
Platelet count decreased	1 (0.8)	0	0.8 (-4.6, 4.1)
Reproductive system and breast disorders (SOC)	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Vaginal haemorrhage	1 (0.8)	0	0.8 (-4.6, 4.1)
Heavy menstrual bleeding	0	1 (1.4)	-1.4 (-7.8, 1.4)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Epistaxis	1 (0.8)	0	0.8 (-4.6, 4.1)
Skin and subcutaneous tissue disorders (SOC)	0	1 (1.4)	-1.4 (-7.8, 1.4)
Purpura	0	1 (1.4)	-1.4 (-7.8, 1.4)
Vascular disorders (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Peripheral embolism	1 (0.8)	0	0.8 (-4.6, 4.1)

Source: adae.xpt; Software: R; FDA reviewer analysis

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease of 2019; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SOC, system organ class

Narratives

- **Participant** (b) (6) is a 50-year-old female with chronic ITP and history of iliac artery stenosis, peripheral artery occlusive disease (ongoing for 3.5 years prior to study start), artery bypass, and stent insertion who was receiving concomitant eltrombopag and experienced the SAE of **peripheral embolism**. On Day 32 of the blinded treatment period with rilzabrutinib, the participant was hospitalized for grade 3 peripheral embolism of the left lower leg. Magnetic resonance imaging demonstrated occlusion of the previously known bypass at the left lower leg. Platelet count was 112,000 cells/microliter. The participant underwent thrombolysis. Rilzabrutinib was permanently discontinued due to the event and last administered on Day 31. The event was reported as recovered on Day 36.
- The investigator's assessment of causality was related to the rilzabrutinib and concomitant use of thrombopoietin receptor agonist. The Applicant assessed the event as was not related to rilzabrutinib. Based on rilzabrutinib's mechanism of action, platelet count at

the time of the event, and the participant's history of prior arterial occlusion, bypass and stent placement. The review team agreed with the Applicant's assessment that the event was not related to rilzabrutinib.

- **Participant** (b) (6) is a 58-year-old white male with a history of chronic ITP and fungal skin infection at baseline who was randomized to the rilzabrutinib treatment group and continued concomitant prednisone.
 - The SAE of **urinary tract infection (Grade 3)** was reported on treatment Day 54 and required hospitalization. Laboratory assessments were significant for elevations in creatinine, C-reactive protein (426 mg/L) white blood cell (33.26x10⁹/L), erythrocyte sedimentation rate (77 mm/hr), and low platelets of 6x10⁹/L. Urine culture was negative. The participant was treated with IV antibiotics followed by oral to Day 62. Corticosteroid dose was initially increased due to urinary infection but then decreased for the kidney abscess. Rilzabrutinib was interrupted on Day 55 and resumed on Day 79.
 - The SAE of **renal abscess (Grade 3)** occurred on Day 84 and required hospitalization. Platelets at time were 8x10⁹/L. Treatment included drainage and culture (Klebsiella pneumoniae) of the abscess and IV antibiotics. IVIg was administered on Day 84 for platelet count less than 20x10⁹/L and need for procedure. Rilzabrutinib was interrupted from Day 84 to Day 94.
 - The Investigator's and Applicant's assessments of causality for the SAEs of urinary tract infection and renal abscess was not related to rilzabrutinib. Based on the mechanism of action and known risk of infection associated with BTKIs, the review team did not agree and assessed the event as *at least possibly related* to rilzabrutinib.
- **Participant** (b) (6) is a 70-year-old white male with history of chronic ITP, obesity, hypertension, hyperlipidemia, and a cat bite to left wrist (4 months prior to study) with a subsequent skin graft (one month prior to study) who was randomized to treatment with rilzabrutinib. He continued concomitant treatment with prednisolone 10 mg daily. On Day 21 the SAE of **wound infection (Grade 2)** occurred. The participant required hospitalization from received oral antibiotics. Day 20 (Week 4) platelet count was 40 x10⁹/L. During hospitalization, the laboratory values included elevated C-reactive protein 87.4 mg/L, persistently elevated leukocytes 14.2 x10⁹/L (baseline value: 17 to 48x10⁹/L [normal range: 3.9 to 10.50x10⁹/L], normal range: 3.5 to 11.0x10⁹/L), and platelet count at 33x10⁹/L (baseline value: 19x10⁹/L, normal range: 150 to 370x10⁹/L). No action was taken with rilzabrutinib. T
 - The Investigator's and Applicant's assessments of causality was not related to rilzabrutinib. Based on the mechanism of action and known risk of infection associated with BTKIs, the review team did not agree and assessed the event as *at least possibly related* to rilzabrutinib.
- **Participant** (b) (6) is a 74-year-old white male with chronic ITP, diabetes mellitus, hepatic cirrhosis, esophageal varices status post bleeding episode, obesity, and hypertension, randomized to receive rilzabrutinib and continued weekly romiplostim and daily prednisone. Baseline liver function values (AST, ALT, and bilirubin) were normal.
 - On Day 29 he was admitted to the hospital for the SAEs of **esophageal variceal hemorrhage (Grade 3)** and **hepatic cirrhosis (Grade 3)**. His platelets at the time of hospital admission were 50x10⁹ K/ μ L. He underwent lower variceal esophageal bleeding

band ligation, was administered intravenous (IV) terlipressin, oral lactulose, IV ceftriaxone, and blood transfusion. No action was taken with rilzabrutinib. He was discharged from the hospital.

- On Day 49 he was re-admitted to the hospital with **recurrent esophageal variceal hemorrhage (Grade 4)**, hemorrhagic shock, a decrease in hemoglobin to 4 g/dL (baseline value: 12.5 g/dL), and SAE of **hepatic enzyme increased Grade 3** (ALT elevation [11x(upper limit of normal) ULN], AST elevation [11x ULN], and normal bilirubin). His platelet count on Day 42 was $56 \times 10^9/L$, Day 49 was $274 \times 10^9/L$. The only intervention was discontinuation of rilzabrutinib on Day 43.
 - The Investigator's and Applicant's assessments of causality was these events were not related to rilzabrutinib.
 - For the SAE of hepatic cirrhosis and hepatic enzyme increased, the review team agreed based on the participant's past medical history these events were *not related* to rilzabrutinib.
 - For the SAE of esophageal variceal hemorrhage, the review team also considered the events as *unlikely to be related* to study drug given the history of esophageal variceal hemorrhage. However, given the association of other BTKIs with hemorrhage, the review team considered that rilzabrutinib could have contributed to the severity of the bleeding, although this is confounded by the thrombocytopenia at the time of the events.
- **Participant** (b) (6) is a 19-year-old Asian male with chronic ITP who was randomized to receive rilzabrutinib and continued concomitant prednisolone 20 mg daily. On Day 34, the participant had an SAE of **COVID-19 (Grade 3)**. He was admitted to the hospital. Platelet counts were $7 \times 10^9/L$ (local lab, normal range: $140-450 \times 10^9/L$, baseline value: $3 \times 10^9/L$ [local lab] and $15 \times 10^9/L$ [central lab, normal range: $140-400 \times 10^9/L$). He received treatment with IV remdesivir daily for 4 days and platelet transfusion on Day 37. No action was taken with rilzabrutinib.

The Investigator's and Applicant's assessments of causality for the event of COVID-19 was not related to rilzabrutinib. Based on the mechanism of action and known risk of infection associated with BTKi, the review team disagreed with the Applicant and assesses the event as *at least possibly related* to rilzabrutinib.

Open-Label and Long-Term Extension Periods

Serious adverse events occurring during the OL and the LTE periods are presented in [Table 119](#). Notable SAEs not related to ITP nor observed during the DB period are: pulmonary embolism and deep vein thrombosis experienced during the open-label period for one participant ((b) (6)) and paresthesia experienced during the OL period and peripheral motor neuropathy experienced during the LTE period reported in one participant ((b) (6)), and peripheral sensory neuropathy reported in one participant ((b) (6)) during the LTE period.

Narratives

- **Participant** (b) (6) is a 23-year-old white female with chronic immune thrombocytopenia, ulcerative colitis, and vitamin D deficiency who was randomized to receive rilzabrutinib. She continued no concomitant medications for ITP.
 - On Day 243 the participant had a TEAE of sarcoidosis (Grade 1, nonserious) with no action with rilzabrutinib taken. On Day 256 the participant had a TEAE of facial paralysis (Grade 2) Oral methylprednisolone was administered and the participant recovered on Day 268. No action was taken with rilzabrutinib. On Day 274, the participant had a SAE of **paraesthesia (Grade 3)**, concerning for neurosarcoidosis and required hospitalization. The participant's platelet count was 226 (nl:150 to 400)x10⁹/L. Electromyography and lumbar puncture were normal. No action was taken with rilzabrutinib. The participant was reported as recovered from the event on Day 282.
 - On Day 365 the participant had the SAE of **peripheral motor neuropathy (Grade 2)** requiring hospitalization. Participant was treated with immunoglobulins (Days 367 to 371). The rilzabrutinib was interrupted due to the event and permanently discontinued on Day 367 due to participant's decision. The participant recovered from the peripheral motor neuropathy on Day 372 (28 days after the last dose of rilzabrutinib).
 - The investigator and the Applicant assessed the SAEs as not related to rilzabrutinib. The review team agreed assessing the events as *not related* but more likely related to the diagnosis of sarcoidosis.
- **Participant** (b) (6) is a 61-year-old white Asian male with chronic immune thrombocytopenia, hypertension, and Cushingoid habitus who was randomized to receive placebo and continued eltrombopag and prednisolone. He withdrew from the double-blind period treatment at Week 13 due to Sponsor discretion and started rilzabrutinib during the OL period on Day 86 and continued in the LTE period from Day 310 of the study.
 - On Day 498 of rilzabrutinib, the participant had a TEAE of peripheral sensory neuropathy (Grade 2, nonserious). On Day 501 of rilzabrutinib, the **peripheral sensory neuropathy was considered serious** since it required hospitalization.. Magnetic resonance imaging showed bilateral medial motor, sensory neuropathy, with compression at the wrist, endplate signal abnormality at C5-6. On Day 550 the participant underwent right hand/wrist carpal tunnel surgery. On day 607 peripheral sensory neuropathy (sensory neuropathy of bilateral hands) improved to Grade 1.No action was taken with the rilzabrutinib.
 -
 - The Investigator and the Applicant assessed the event as not related to rilzabrutinib. The review team agreed, assessing the neuropathy as more likely related to the diagnosis of carpal tunnel syndrome.
- **Participant** (b) (6) is a 36-year-old female with chronic ITP, overweight, hepatic steatosis, anemia, and hypophosphatemia who was randomized to treatment with rilzabrutinib and continued treatment with prednisone and avatrombopag. On Day 309 the participant experienced the SAEs of **pulmonary embolism (Grade 3)** and the next day **deep vein thrombosis (Grade 3)**. She was hospitalized. Imaging by ultrasound revealed deep vein thrombosis from the common femoral vein to the popliteal vein with occlusion of the femoral vein. Imaging by computed tomography and angiography of the chest revealed thrombi of the

middle and bilateral lower lobar pulmonary arteries and distal branches. Her platelet count on Day 309 was $79 \times 10^9/L$ (normal range: 150 to $400 \times 10^9/L$, baseline value: $3 \times 10^9/L$). Treatment included enoxaparin sodium and endoxaban tosilate monohydrate. No action was taken with the rilzabrutinib. The investigator's assessment of causality of deep vein thrombosis and pulmonary embolism was not related to rilzabrutinib and related to thrombopoietin receptor agonist. The Applicant's assessment of causality was not related to rilzabrutinib. The review team assessed the event as unlikely to be related to rilzabrutinib given the platelet count was only $79 \times 10^9/L$ (nl: 150 to $400 \times 10^9/L$) and the higher risk of thrombosis with TPO-RAs.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation and Interruptions, LUNA 3

Double-Blind Treatment Period

Frequency analysis of TEAEs leading to permanent discontinuation is shown in [Table 24](#). Adverse events leading to permanent discontinuation of rilzabrutinib during the DB treatment period occurred in eight (6%) participants, compared to no participant in the placebo arm. These included pneumonia (fatal), neutropenia, peripheral embolism, erythema nodosum, and multijoint pain, each occurring in one participant. Multiple TEAEs occurred in three additional patients leading to discontinuation of rilzabrutinib. They were diarrhea, nausea, abdominal discomfort; esophageal varices hemorrhage hepatic enzyme increased; and heartburn, headache, and leg pain. No TEAE at the PT level occurred in more than one participant. The most common AE leading to discontinuation at the SOC level was gastrointestinal disorders, cumulatively occurring in three (2.3%) participants.

Table 24. Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, LUNA 3

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Any AE leading to discontinuation	8 (6.0)	0	6.0 (0.6, 11.4) *
Blood and lymphatic system disorders (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Neutropenia	1 (0.8)	0	0.8 (-4.6, 4.1)
Gastrointestinal disorders (SOC)	3 (2.3)	0	2.3 (-3.1, 6.4)
Abdominal discomfort	1 (0.8)	0	0.8 (-4.6, 4.1)
Diarrhea	1 (0.8)	0	0.8 (-4.6, 4.1)
Dyspepsia	1 (0.8)	0	0.8 (-4.6, 4.1)
Nausea	1 (0.8)	0	0.8 (-4.6, 4.1)
Esophageal varices hemorrhage	1 (0.8)	0	0.8 (-4.6, 4.1)
Infections and infestations (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Pneumonia	1 (0.8)	0	0.8 (-4.6, 4.1)
Investigations (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Hepatic enzyme increased	1 (0.8)	0	0.8 (-4.6, 4.1)
Musculoskeletal and connective tissue disorders (SOC)	2 (1.5)	0	1.5 (-3.8, 5.3)
Arthralgia	1 (0.8)	0	0.8 (-4.6, 4.1)
Pain in extremity	1 (0.8)	0	0.8 (-4.6, 4.1)
Nervous system disorders (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Headache	1 (0.8)	0	0.8 (-4.6, 4.1)
Skin and subcutaneous tissue disorders (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Erythema nodosum	1 (0.8)	0	0.8 (-4.6, 4.1)

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Vascular disorders (SOC)	1 (0.8)	0	0.8 (-4.6, 4.1)
Peripheral embolism	1 (0.8)	0	0.8 (-4.6, 4.1)

Source: adae.xpt; Software: R; FDA reviewer analysis

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of participants in treatment arm; n, number of participants with adverse event; SOC, system organ class

Adverse event leading to dose interruption occurred in seven (5%) participants who received rilzabrutinib in the DB period and no participants in the placebo arm. Adverse events included periorbital hematoma, ear secretion, elevated platelet count, and diarrhea, each occurring in one participant; kidney abscess and urinary tract infection; COVID-19 infection and pneumonia; nausea and vomiting occurring in one participant each.

Open-Label and Long-Term Extension Periods

During the OL and LTE periods, TEAEs leading to permanent discontinuation or treatment interruption were rare and were most frequently related to underlying disease (low platelets or bleeding) or infection.

During the OL period, six (3.3%) participants experienced a TEAE that led to treatment discontinuation. TEAEs leading to permanent discontinuation during the OL period were: thrombocytopenia, urosepsis, Hepatitis B reactivation, and subdural hematoma, increasing nausea, vaginal bleeding, and interstitial pneumonia. During the LTE, one (2%) participant discontinued treatment due to pregnancy.

During the OL period, eight (4.4%) participants experienced a TEAE that led to treatment interruption. There were thrombocytosis, COVID-19, petechiae, suspected sepsis, diarrhea, nausea, vomiting, pulmonary *Aspergillosis*, CMV viremia, and thrombocytosis. During the LTE, four (8%) participants experienced a TEAE that led to treatment interruption. These were: stomach pain, nausea, vomiting, peripheral motor neuropathy, and COVID-19.

7.6.1.5. Treatment-Emergent Adverse Events, Double-Blind Treatment Period, LUNA 3

Frequency analysis for TEAEs, all grades during the DB period, based on OCMQ (narrow), are shown in [Table 25](#).

Adverse events, occurring in at least 10% of participants in the rilzabrutinib arm were diarrhea (32%), nausea (20%), headache (18%), abdominal pain (grouped term) (14%), and COVID-19 (14%), all of which were reported more frequently in the rilzabrutinib arm.

Frequency analysis of TEAS by SOC and PT is found in [Table 123](#).

Table 25. Participants With Adverse Events by OND Custom Medical Query (Narrow), Occurring at >5% Frequency Safety Population, LUNA 3

OCMQ (Narrow)	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Diarrhea	43 (32.3)	7 (10.1)	22.2 (10.5, 32.4)*
Nausea	27 (20.3)	4 (5.8)	14.5 (4.6, 23.2)*
Headache	24 (18.0)	5 (7.2)	10.8 (0.7, 19.6)*
Viral infection	22 (16.5)	5 (7.2)	9.3 (-0.7, 17.9)
Abdominal pain	19 (14.3)	1 (1.4)	12.8 (5.4, 20.1)*
Nasopharyngitis	16 (12.0)	6 (8.7)	3.3 (-6.7, 11.6)
Dyspepsia	14 (10.5)	0	10.5 (5.0, 16.9)*
Dizziness	12 (9.0)	1 (1.4)	7.6 (0.6, 14.0)*
Arthralgia	12 (9.0)	3 (4.3)	4.7 (-3.8, 11.6)
Fatigue	10 (7.5)	6 (8.7)	-1.2 (-10.9, 6.3)
Vomiting	9 (6.8)	2 (2.9)	3.9 (-3.8, 10.0)
Bacterial infection	8 (6.0)	3 (4.3)	1.7 (-6.5, 7.9)
Cough	7 (5.3)	0	5.3 (-0.1, 10.5)
Anemia	7 (5.3)	8 (11.6)	-6.3 (-16.5, 1.2)
Hemorrhage	6 (4.5)	6 (8.7)	-4.2 (-13.6, 2.6)

Source: adae.xpt; Software: R; FDA reviewer analysis

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each OCMQ asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; OCMQ, OND Custom Medical Query; OND, Office of New Drugs; N, number of participants in treatment arm; n, number of participants with adverse event; PT, preferred term; SOC, system organ class

7.6.1.6. Laboratory Findings, Double-Blind Treatment Period, LUNA 3

The protocol specified the routine monitoring of complete blood count, clinical chemistries, hepatic and renal evaluations. See Section [15.1.1](#).

Overall, there were no meaningful clinical changes in mean value for hemoglobin, chemistry, and kidney laboratory assessments over time (see Section [17.2.4.1](#)).

Outlier analysis for cytopenia is discussed in Section [7.6.3.4](#). Outlier analysis for liver analytes is discussed in Section [7.6.3.2](#).

General Chemistry

Outlier analysis for general chemistry laboratory assessments is found in [Table 125](#). Frequency of abnormalities in electrolyte and chemistries did not differ significantly between treatment groups, including those more commonly observed with BTK inhibitors, e.g., hyponatremia, hyperkalemia, hypophosphatemia.

Renal Function

Outlier analysis for laboratory assessments of renal function is shown in [Table 126](#). For eGFR⁹, 7 participants out of 127 for whom there were baseline and post values (5.5%) in the rilzabrutinib arm compared to no participants in the placebo arm had a 25% to <50% decrease.

⁹ Based on chronic kidney disease epidemiology collaboration (CKD-EPI) equation

However, outlier analysis of increased creatinine identified only two out of 131 participants (1.5%) with Level 1 ($\geq 1.5x$ and $< 2x$ ULN), compared to none in the placebo arm. In both participants, the increase in creatinine was transient, with values returning to baseline within reference range by the next assessment, with no change in rilzabrutinib dosing, and remained within reference range for several months of continued treatment with rilzabrutinib. Thus, the observed transient changes are unlikely to be related to rilzabrutinib.

7.6.1.7. Vital Signs Analyses, Double-Blind Treatment Period, LUNA 3

Analysis of vital signs for LUNA 3 during the DB period did not identify any clinically meaningful changes from baseline for values for body temperature, pulse or respiration rate, or blood pressure (see Section [17.2.4](#)) Outlier analysis of blood pressure is discussed more with hypertension in Section [7.6.3.7](#).

7.6.2. Subgroup Analyses, Double-Blind Treatment Period, LUNA 3

There were no significant differences among groups based on age, race, or ethnicity. [Table 26](#) summarizes subgroup analyses for SAEs reported in LUNA 3 during the DB treatment period.

Table 26. Overview of Serious Adverse Events by Demographic Subgroup, Double-Blind Treatment Period, LUNA 3

Characteristic	Rilzabrutinib N=133 n/N _s (%)	Placebo N=69 n/N _s (%)	Risk Difference % (95% CI)
Sex			
Female	6/78 (7.7)	6/49 (12.2)	-4.6 (-17.5, 5.9)
Male	6/55 (10.9)	2/20 (10.0)	0.9 (-20.4, 14.6)
Age group, years			
<65	6/112 (5.4)	6/54 (11.1)	-5.8 (-17.4, 2.5)
≥ 65	6/21 (28.6)	2/15 (13.3)	15.2 (-14.3, 40.4)
Age group ≥ 75 , years			
≥ 75	1/6 (16.7)	0/3 (0)	16.7 (-47.4, 58.5)
Race			
American Indian or Alaska Native	0/3 (0)	0/1 (0)	0.0 (-83.7, 63.1)
Asian	1/40 (2.5)	0/24 (0)	2.5 (-11.6, 13.0)
Black or African American	0/1 (0)	0/0 (NA)	NA
White	10/85 (11.8)	8/40 (20.0)	-8.2 (-24.2, 4.6)
Other	1/3 (33.3)	0/2 (0)	33.3 (-51.9, 82.0)
Not collected	0/1 (0)	0/2 (0)	0.0 (-74.2, 85.2)
Ethnicity			
Hispanic or Latino	3/28 (10.7)	1/13 (7.7)	3.0 (-24.4, 21.7)
Not Hispanic or Latino	9/103 (8.7)	6/53 (11.3)	-2.6 (-14.7, 6.8)
Not reported	0/2 (0)	1/3 (33.3)	-33.3 (-82.0, 51.9)

Characteristic	Rilzabrutinib N=133 n/N _s (%)	Placebo N=69 n/N _s (%)	Risk Difference % (95% CI)
Is in United States			
United States	1/12 (8.3)	0/3 (0)	8.3 (-51.2, 36.5)
Not United States	11/121 (9.1)	8/66 (12.1)	-3.0 (-13.9, 5.8)

Source: adae.xpt; Software: R; FDA reviewer analysis

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants with adverse event; NA, not applicable; N_s, total number of participants for each specific subgroup and were assigned to that specific arm

[Table 27](#) summarizes subgroup analyses for TEAEs reported in LUNA 3 during the DB treatment period by demographic subgroups. There were no significant differences in rates of TEAEs among subgroups based on age, race, or ethnicity. Any minor differences are likely due to small size of some subgroups.

Table 27. Overview of Adverse Events by Demographic Subgroup, Double-Blind Treatment Period, LUNA 3

Characteristic	Rilzabrutinib N=133 n/N _s (%)	Placebo N=69 n/N _s (%)	Risk Difference % (95% CI)
Sex			
Female	65/78 (83.3)	39/49 (79.6)	3.7 (-9.7, 18.8)
Male	46/55 (83.6)	13/20 (65.0)	18.6 (-2.2, 42.3)
Age group, years			
<65	92/112 (82.1)	39/54 (72.2)	9.9 (-3.2, 24.6)
≥65	19/21 (90.5)	13/15 (86.7)	3.8 (-18.8, 30.4)
Age group ≥75, years			
≥75	6/6 (100)	3/3 (100)	0.0 (-41.9, 59.0)
Race			
American Indian or Alaska Native	3/3 (100)	1/1 (100)	0.0 (-63.1, 83.7)
Asian	33/40 (82.5)	15/24 (62.5)	20.0 (-2.0, 42.6)
Black or African American	1/1 (100)	0/0 (NA)	NA
White	71/85 (83.5)	34/40 (85.0)	-1.5 (-14.0, 14.2)
Other	2/3 (66.7)	1/2 (50.0)	16.7 (-60.2, 78.7)
Not collected	1/1 (100)	1/2 (50.0)	50.0 (-64.2, 93.1)
Ethnicity			
Hispanic or Latino	26/28 (92.9)	10/13 (76.9)	15.9 (-5.6, 44.6)
Not Hispanic or Latino	83/103 (80.6)	40/53 (75.5)	5.1 (-8.0, 19.9)
Not reported	2/2 (100)	2/3 (66.7)	33.3 (-51.9, 82.0)
Is in United States			
United States	11/12 (91.7)	3/3 (100)	-8.3 (-36.5, 51.2)
Not United States	100/121 (82.6)	49/66 (74.2)	8.4 (-3.5, 21.6)

Source: adae.xpt; Software: R; FDA reviewer analysis

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants with adverse event; NA, not applicable; N_s, total number of participants for each specific subgroup and were assigned to that specific arm

7.6.3. Adverse Events of Special Interest and Adverse Events of Clinical Interest, LUNA 3

The Applicant identified the following AESIs in LUNA 3.

- Any Grade 4 or 5 infection where the patient is hospitalized ≥ 24 hours and/or requires emergency care and/or requires intravenous antibiotics
- Increase in ALT $> 3 \times \text{ULN}$ (Grade 2)
- Pregnancy of a female participant entered in a study and received at least one dose of the IMP as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP
- Symptomatic overdose with IMP

Based on nonclinical studies with rilzabrutinib, clinical experience with other BTKIs, and patient population, the Agency considered the following additional adverse events to be adverse events of clinical interest: cardiac toxicity (particularly arrhythmias), cytopenias, new malignancy, hemorrhage, and gastrointestinal disorders (including diarrhea, nausea, vomiting), and thromboembolic events. These, along with hepatotoxicity and infection, are discussed individually below. The Division did not consider increase in ALT $> 3 \times \text{ULN}$ as a sufficient criterion to evaluate possible hepatotoxicity and performed a more comprehensive evaluation of hepatotoxicity, subsuming the Applicant's criterion. The Division did not agree with the Applicant's definition of AESI of infection and analyzed and reported here infections by seriousness and grade.

7.6.3.1. Infections

Experience With Other BTKIs

Increased risk of infections¹⁰ with use of the drug is included in Warnings and Precautions of all four approved BTKIs and include report of fatal infections occurring with three of the BTKIs. The rates of Grade 3 or greater or serious infections range from 21% to 32%. This is an on-target effect due to inhibition of BTK, which is crucial for the function of various immune cells ([Wanget al. 2022](#)).

Experience With Rilzabrutinib

In the DB period of LUNA 3, the frequency of infection overall is higher in the rilzabrutinib arm (33%) compared to the placebo arm (20%). The frequency of serious adverse events in the Infection and Infestation SOC was 3% in the rilzabrutinib arm, including one fatal event (0.8%), compared to no serious or fatal infections in the placebo arm. There were no Grade 4 infections on either arm. There were four Grade 3 events (3%) in the rilzabrutinib arm compared to no Grade 3 events in the placebo arm.

Across all periods (DB, OLE, LTE) in LUNA 3, 101 (37%) of 198 participants had at least one TEAE in the Infection and Infestation SOC while receiving rilzabrutinib. There were no

¹⁰ For CTCAE grading of specific types of infection, in general, Grade 2 involves need for oral intervention e.g., antibiotic, antifungal, or antiviral; Grade 3 involves need for intravenous antimicrobial or invasive intervention, and Grade 4 involves life threatening consequence or need for urgent intervention.

additional fatal infections beyond the double-blind period, resulting in an overall frequency across periods of 0.3%. A total of six (3%) participants had a serious infection (i.e., serious adverse event under the SOC of Infections and Infestations) while receiving rilzabrutinib in any period on LUNA 3. There were no Grade 4 events. The frequency of Grade 3 infections across the three periods was 4.5% (9/198).

Frequency analysis of infections by preferred term is presented in [Table 124](#).

Conclusion

As with other BTKIs, rilzabrutinib is associated with an increased risk of infection. The overall rate is approximately 1.5 times the rate seen with placebo. While rare, fatal and serious adverse events occurred in participants who received rilzabrutinib and were not observed in participants who received placebo. The frequency of serious infections was similar across all periods in participants receiving rilzabrutinib.

Infections will be included in Warnings and Precautions as follows:

An increased risk of serious infections (including bacterial, viral, or fungal) can occur in patients treated with Bruton's tyrosine kinase (BTK) inhibitors, including WAYRILZ. In the LUNA-3 trial, fatal pneumonia occurred in one participant in the WAYRILZ group. Other serious infections [one each (0.8%)] included COVID-19 infection, wound infection, and one patient experienced urinary tract infection and kidney abscess. Monitor patients for signs and symptoms of infection and treat appropriately.

7.6.3.2. Hepatotoxicity and Assessment of Drug-Induced Liver Injury

Experience With Other BTKIs

Risk of hepatotoxicity, including severe, life-threatening, and potentially fatal cases of DILI, has occurred in patients treated with each of the approved BTKIs and is included in Warnings and Precautions of the United States Prescribing Information (USPI) for each of them. Specific number of cases/rates of hepatotoxicity or DILI are not included in Section 5 of the USPIs for these products. The mechanism by which the other BTKIs cause hepatotoxicity is not well understood but may include direct drug toxicity, off-target effects, and immune suppression resulting in reactivation of viral hepatitis, particularly hepatitis B virus .

Experience With Rilzabrutinib

Laboratory Assessments

Outlier analysis of liver analytes alkaline phosphatase (ALP), ALT, AST, and bilirubin is shown in [Table 28](#). Overall, elevation of any of these analytes is rare, and there are no significant differences between the two arms. No participant on either arm had Level 3 observed for any analyte. In the rilzabrutinib arm, three (2.3%) of participants had elevation $>3x$ and $\leq 5x$ ULN of ALT and one (0.8%) had elevation $>5x$ and $\leq 10x$ ULN. This is not significantly different from placebo arm.

In the OL period, one participant (0.6%) had at least one assessment of Grade 2 ALT increase. No participant had elevated AST or ALP. In the LTE, no participant had an abnormal liver assessment (AST, ALT, ALP, Bilirubin) $\geq$ Grade 1.

In LUNA 2, Part A, one participant had an abnormal ALT that went from within reference range at screening to 2.3xULN on Cycle 4, Day 1, which returned to within reference range during Cycle 5 but was mildly elevated during Cycle 6 (max 1.6xULN). The same participant had similar changes with AST.

Table 28. Participants With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Double-Blind Treatment Period, LUNA 3

Laboratory Parameter	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)	Rilzabrutinib vs. Placebo Risk Difference (%) (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	1/131 (0.8)	1/68 (1.5)	-0.7 (-7.2, 2.9)
Level 2 (>2X ULN)	1/131 (0.8)	1/68 (1.5)	-0.7 (-7.2, 2.9)
Level 3 (>3X ULN)	0/131 (0)	1/68 (1.5)	-1.5 (-7.9, 1.4)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	4/131 (3.1)	1/68 (1.5)	1.6 (-5.0, 6.4)
Level 2 (>5X ULN)	1/131 (0.8)	1/68 (1.5)	-0.7 (-7.2, 2.9)
Level 3 (>10X ULN)	1/131 (0.8)	0/68 (0)	0.8 (-4.6, 4.2)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	1/131 (0.8)	1/68 (1.5)	-0.7 (-7.2, 2.9)
Level 2 (>5X ULN)	1/131 (0.8)	0/68 (0)	0.8 (-4.6, 4.2)
Level 3 (>10X ULN)	0/131 (0)	0/68 (0)	0.0 (-5.4, 2.9)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	2/131 (1.5)	2/68 (2.9)	-1.4 (-8.7, 3.0)
Level 2 (>2X ULN)	1/131 (0.8)	1/68 (1.5)	-0.7 (-7.2, 2.9)
Level 3 (>3X ULN)	0/131 (0)	0/68 (0)	0.0 (-5.4, 2.9)

Source: adlb.xpt; Software: R; FDA reviewer analysis

Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide ([FDA 2021](#))

Duration is the 24-week double-blind treatment period.

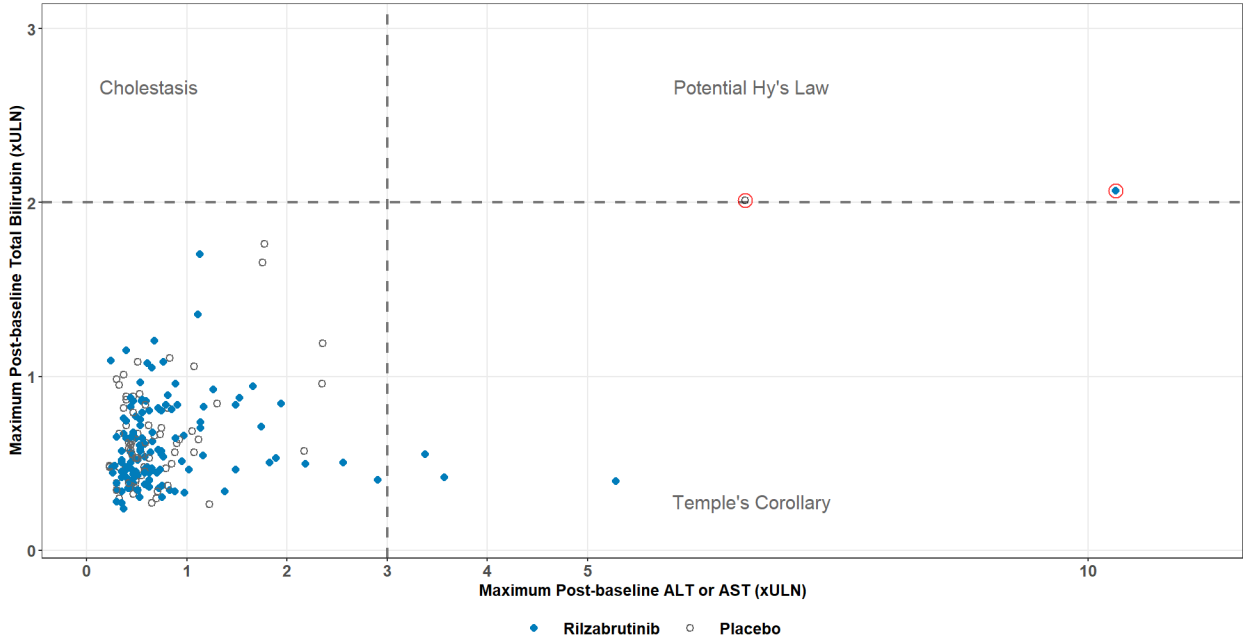
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal

FDA DILI screening analysis for potential cases of hepatocellular DILI is summarized in [Figure 8](#) and [Table 29](#). The analysis identified one case of potential Hy's Law in each arm as well as three cases of Temple's corollary, all in the rilzabrutinib arm. Brief narratives for each of these

cases are presented below. After review of the individual narratives, the review team concluded that none of the cases represent drug-induced hepatotoxicity.

Figure 8. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, LUNA 3



Source: adlb.xpt; Software: R; FDA reviewer analysis
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Quadrant	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)
Potential Hy's Law (right upper)	1/131 (0.8)	1/68 (1.5)
Cholestasis (left upper)	0/131 (0)	0/68 (0)
Temple's corollary (right lower)	3/131 (2.3)	0/68 (0)
Total	4/131 (3.1)	1/68 (1.5)

Source: adlb.xpt; Software: R; FDA reviewer analysis
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal

Potential DILI Cases

- **Participant** (b) (6) was identified based on laboratory values as a possible case of DILI. Full narrative for this participant who had a past medical history of hepatic cirrhosis and esophageal variceal hemorrhage and had recurrent esophageal variceal hemorrhage at the time of the liver transaminase elevation is presented in Section 7.6.1.3. The participant had AST, ALT, and total bilirubin values within reference range at baseline. Post baseline, on Day 49, the participant had an ALT increase >10xULN, AST >8xULN, with alkaline phosphatase above ULN and bilirubin within reference range. The participant discontinued rilzabrutinib. On Day 52, ALT remained elevated (>3xULN) along with elevated total bilirubin (>3xULN) and alkaline phosphatase above ULN. Given the past medical history and concurrent events of liver cirrhosis and esophageal variceal hemorrhage, the review team concludes this case does not meet criteria for DILI.

Temples Corollary Cases

- **Participant** (b) (6) is a 24-year-old Hispanic/Latino female with history of chronic ITP, epilepsy, increased gamma-glutamyl transferase (ongoing for 2 years), increased ALT, increased AST (both reported normal 30 days prior to study start), intermenstrual bleeding and anemia ongoing for 4.5 months prior to start of study, who was randomized to receive rilzabrutinib and continued concomitant eltrombopag and prednisone. On Day 10 and 11 of the study, intermenstrual bleeding, pelvic inflammatory disease, fever (Grade 3), and vaginal hemorrhage (Grade 3 SAE) were reported, and the participant was hospitalized and treated with ceftriaxone, clindamycin, IV hydrocortisone, oral ethinylestradiol/levonorgestrel, cimetidine, hyoscine butyl bromide, oral dexchlorpheniramine maleate, platelet transfusion, and red blood cell transfusion. Cyclosporine was started on Day 15 for platelet count rescue. On Day 20, the participant had increased ALT (Grade 2) of 113 IU/L (local lab, normal range: 10 to 37 IU/L), increased AST (Grade 1) at 55.5 IU/L (local lab, normal range: 10 to 37 IU/L). ALP and bilirubin values were not reported. On Day 27 the ALT increase improved to Grade 1. The participant experienced intermittent worsening of anemia to Grade 3, followed by gastroenteritis (Grade 2) and ALT increased to Grade 2 on Day 55. On No action was taken with the rilzabrutinib due to the elevated ALT.

During the open-label treatment period, on Day 165 of the study, an AE of increased ALT (Grade 3) was reported. No action was taken with the rilzabrutinib. The elevated ALT was attributed to cyclosporine given as rescue medication, carbamazepine and phenytoin. The increase in ALT was not attributed to rilzabrutinib by the Investigator. The review team agreed that the ALT increase was likely attributable to the medications administered for the anemia, seizure prophylaxis, and intercurrent illness, and rilzabrutinib is unlikely to have been the cause of these events. The team concludes the case does not meet criteria for DILI.

- **Participant** (b) (6) is a 19-year-old male with history of chronic ITP who was randomized to rilzabrutinib arm. On study day 57, he had an isolated elevation of AST to 3.4 ULN, AST to 1.1xULN, with normal (baseline) bilirubin. No action was taken with the rilzabrutinib. These events occurred just after an upper respiratory infection for which he received oseltamivir from Day 47 to Day 57. On day 85, all liver assessments had returned to baseline (within reference range). There were no subsequent abnormal liver assessments reported. The review team concludes given the transience of the abnormal liver laboratory

assessments and resolution without change to rilzabrutinib, the study drug did not cause the liver abnormalities. The case does not meet criteria for DILI.

- **Participant** (b) (6) is a 21-year-old Asian male with history of chronic ITP who was randomized to rilzabrutinib arm and continued oral prednisolone and eltrombopag. He experienced elevations of ALT and AST on Day 36 with an ALT of 121 IU/L (normal range: 10 to 42 IU/L, baseline value: 34 IU/L [normal range: 10 to 53 IU/L]), AST at 44 IU/L (normal range: 13 to 30 IU/L, baseline value: 18 IU/L [normal range: 14 to 43 IU/L]), with normal ALP and bilirubin. Interventions to improve transaminase levels included: discontinuation of eltrombopag, famotidine, IV cysteine/ glycine/ glycyrrhizic acid, oral dL-methionine/ glycine/ glycyrrhizic acid, oral ammonium salt, and glutathione. On Day 40 an AE of hepatic steatosis (Grade 1) was diagnosed by ultrasound and computed tomography of the abdomen and ALT peaked at 150 IU/L (normal range 10 to 42 IU/L) (Grade 2) and 130 IU/L (normal range: 10 to 53 IU/L) and AST 49 IU/L (normal range: 13 to 30 IU/L) and 44 IU/L (normal range: 14 to 43 IU/L). The participant recovered from abnormalities of liver analytes on Day 92. Hepatic steatosis did not resolve. No action was taken with the rilzabrutinib for the abnormal transaminases. The Investigator's assessment of causality for abnormal hepatic function was not related to rilzabrutinib. The review team agrees given the fluctuations of the abnormal transaminases with ultimate return to baseline despite no change to rilzabrutinib dosing. The case does not meet criteria for DILI.

Analysis of adverse event reporting identified 2 participants, both in the rilzabrutinib arm, with TEAEs in the AEHLGT Hepatic and hepatobiliary disorders during the DB period, participant (b) (6) and participant (b) (6). Full narratives for these patients are provided above. No additional TEAEs under the AEHLGT Hepatic and hepatobiliary disorders occurred during the OL or LTE periods.

In LUNA 2 Study, no additional TEAEs under the AEHLGT Hepatic and hepatobiliary disorders were reported.

Conclusion

Hepatotoxicity and DILI has been reported with use of other BTKIs in clinical trials and is included in Warnings and Precautions for all of them. No cases of DILI were identified in participants who received rilzabrutinib on LUNA 3 or LUNA 2. There does not appear to be a significant signal of hepatotoxicity in participants who received rilzabrutinib on LUNA 3 or LUNA 2. Increases in liver analytes during the DB period of LUNA 3 are rare, with equal frequency between arms. Because hepatotoxicity is identified in all other BTKIs, is potentially an on-target effect, and the safety population for rilzabrutinib is small, hepatotoxicity will be included in Warnings and Precautions class labeling as follows:

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of DILI, can occur in patients treated with BTK inhibitors. In the clinical trials of WAYRILZ in patients with ITP, elevations of liver transaminases occurred and were generally mild to moderate in severity. Evaluate bilirubin and transaminases at baseline and as clinically indicated during treatment with WAYRILZ. For patients who develop abnormal liver tests after WAYRILZ, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold WAYRILZ. Upon confirmation of DILI, discontinue WAYRILZ.

7.6.3.3. Cardiac Arrhythmias

Experience With Other BTKIs

Risk of cardiac arrhythmias occurring with the use of the drug is included in Warnings and Precautions for all approved BTKIs. The rate of Grade 3 or 4 atrial arrhythmia (atrial fibrillation or flutter) ranged from 1.5% to 3.7% (all grades reported in some USPIs ranged from 3.2% to 7%). The rate of Grade 3 or 4 ventricular arrhythmias reported in some USPIs ranged from 0.2% to 0.6%. Deaths or sudden deaths was reported in Warnings and Precautions for one BTKI and was 1% with Grade ≥ 3 cardiac failure of 1.2%. However, cardiac deaths and failures were not included in the USPI for 3 of the 4 approved BTKIs. Cardiac arrhythmias are a primarily an off-target effect ([McMullen et al. 2014](#)). They are not a known complication of conditions associated with absence or non-functional BTK ([Kanegane et al. 2025](#)).

Experience With Rilzabrutinib

Thorough QT Study

The Interdisciplinary Review Team for Cardiac Safety Studies reviewed the Applicant's QT evaluation report¹¹. Based on the report, there were no cardiac related serious AEs or AEs that resulted in rilzabrutinib discontinuation. None of the events identified to be of clinical importance per the International Council for Harmonisation (ICH) E14 guidelines ([May 2024](#)) (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study. The thorough QT (TQT) study demonstrated that rilzabrutinib was observed to shorten the QTc interval without changes in PR or QRS. This pattern of electrocardiogram (ECG) changes is consistent with mexiletine, a Vaughan-Williams IB sodium channel blocker. If rilzabrutinib is a sodium channel blocker, then it could be associated with an increased proarrhythmic risk in patients with structural heart disease. Because the Applicant has not conducted experiments to elucidate the mechanism of the observed QTc shortening, it is not possible to rule out that rilzabrutinib is a sodium channel blocker.

Final labeling to Section 12.2 Cardiac Electrophysiology states:

In a Thorough QT study, concentration dependent shortening in the QTc interval was observed. Following a single dose of rilzabrutinib 400 mg, the mean maximum QTcF decrease of -7 msec (90% confidence interval: -9 msec to -5 msec) was observed at 2 hours post-dose. The mean maximum QTcF decrease at exposures 4-fold the highest recommended dose, i.e., 400 mg BID, was -10 msec (90% confidence interval: -12 msec to -8 msec) at 2 hours post-dose.

Clinical Experience With Rilzabrutinib

During the DB period of LUNA 3, two participants in the rilzabrutinib arm (1.5%) and two participants in the placebo arm (2.8%) had at a TEAE with the AEHLGT Cardiac arrhythmias or cardiac disorders, signs and symptoms NEC. TEAEs in the rilzabrutinib arm were cardiac arrhythmias (PT Arrhythmia (Grade 1) in one participant and PTs extrasystoles [Grade 1] and

¹¹ Report included the previous integrated review under investigational new drug (IND) 132668 dated 04/05/2018, study report PR1008-014, study protocol PR1008-014, cardiac safety report – last appendix in SAP (NDA 210695), the Applicant's Proposed Label (NDA 219685) and highlights of clinical pharmacology and cardiac safety.

tachycardia [Grade 2] in the other). In the placebo arm, one participant had PT of bundle branch block right (Grade 1) and another had PT of palpitations (Grade 1).

During LUNA 2 Part A, there was one (2.2%) participant in the 400 mg BID group who had a TEAE of heart rate irregular (Grade 1). During LUNA 2 Part B, there was one (3.8%) participant in the 400 m BID group who had TEAE of palpitations during the main treatment group (Grade 1).

The Applicant reported in the ITP rilzabrutinib pool (N=284), which included LUNA 2 and LUNA 3 (across all treatment periods), there was one case of syncope (Grade 3) and there were no cases of Torsade des pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, or seizure. Our review of the AE data confirmed this.

Per the Applicant, two (0.7%) participants had abnormal clinically significant ECG results. One participant had atrial fibrillation (during the LTE period of LUNA 2 Part B).

Conclusion

Cardiac arrhythmias are reported in Warnings and Precautions for all approved BTKIs with a frequency of Grade 3 or 4 events ranging from 1.5% to 3.7%. No Grade 3 or 4 events were reported in LUNA 2 or LUNA 3. The low-grade events of arrhythmias reported in the DB part of LUNA 3 occurred more frequently in the placebo arm (2.8%) compared to the rilzabrutinib arm (1.5%). Cardiac arrhythmias associated with approved BTKIs are an off-target effect and may be related to the approved populations (older patients with B-cell malignancies) or the non-selectivity of those BTKIs. Given the differences in patient populations and the higher degree of selectivity of rilzabrutinib, the review team does not recommend inclusion of increased risk of cardiac arrhythmias in Warnings and Precautions for rilzabrutinib in ITP. Given the lower frequency of events in the rilzabrutinib arm compared to placebo, inclusion in Section 6 is also not recommended.

7.6.3.4. Cytopenias

Experience With Other BTKIs

Cytopenias are included in Warnings and Precautions for all four of the approved BTKIs. Grade 3 or 4 neutropenia and thrombocytopenia is noted in all 4 of the BTKIs. Anemia is noted in 3 of them. The rate of Grade 3 or 4 neutropenia ranged from 21% to 26% with frequency of Grade 4 neutropenia of 14% noted in one USPI. The rate of Grade 3 or 4 anemia (hemoglobin decreased) ranged from 8% to 12%. The mechanism by which the approved BTKIs can cause neutropenia is not fully understood and may include both on-target effect on BTK in myeloid-cells and off-target kinase inhibition ([Fiedler et al. 2011](#)). The mechanism by which the approved BTKIs can cause anemia is not clear.

Clinical Experience With Rilzabrutinib

Outlier analysis for key hematology analytes for DB period of LUNA 3 is shown in [Table 127](#). For all analysis of all hematology and coagulation laboratory findings, see [Table 127](#).

Overall, the frequency of low white count (Level 1, $<3.5 \times 10^3$ cells/ μ l) is higher in the rilzabrutinib arm compared to the placebo arm, 7.6% compared to 4.4%, respectively. This is all

due to higher frequency of Level 2, WBC $<3 \times 10^3$ cells/ μ L rilzabrutinib (4.5%) in the rilzabrutinib arm compared to 0% in the placebo arm. The frequency of low lymphocytes is similar between the arms for levels 1 and 2, but a slightly higher percentage of participants in the rilzabrutinib arm with Level 3 ($<0.5 \times 10^3$ cells/ μ L).

The frequency of low neutrophils ($<2 \times 10^3$ cells/ μ L) is greater in the rilzabrutinib arm (11%) compared to placebo (4.4%); however, there are no significant differences between the arms at more severe levels of neutropenia. These differences in frequency of neutropenia are small and may be due to chance given the small sample size.

There are no significant differences in frequency of anemia between the two arms.

Table 30. Outlier Analysis Key Hematology Analyte Values, Double-Blind Treatment Period, LUNA 3

Laboratory Parameter	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)	Rilzabrutinib vs. Placebo Risk Difference (%) (95% CI)
WBC, low (10^3 cells/ μ L)			
Level 1 (<3.5)	10/132 (7.6)	3/68 (4.4)	3.2 (-5.3, 9.9)
Level 2 (<3)	6/132 (4.5)	0/68 (0)	4.5 (-0.9, 9.6)
Level 3 (<1)	0/132 (0)	0/68 (0)	0.0 (-5.4, 2.8)
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	13/131 (9.9)	7/68 (10.3)	-0.4 (-10.7, 8.0)
Level 3 (>2 g/dL dec. from baseline)	6/131 (4.6)	4/68 (5.9)	-1.3 (-10.0, 5.0)
Lymphocytes, low (10^3 cells/ μ L)			
Level 1 (<1)	27/132 (20.5)	13/68 (19.1)	1.3 (-11.2, 12.3)
Level 2 (<0.75)	18/132 (13.6)	8/68 (11.8)	1.9 (-9.1, 11.0)
Level 3 (<0.5)	5/132 (3.8)	1/68 (1.5)	2.3 (-4.4, 7.4)
Neutrophils, low (10^3 cells/ μ L)			
Level 1 (<2)	15/132 (11.4)	3/68 (4.4)	7.0 (-1.8, 14.4)
Level 2 (<1)	1/132 (0.8)	1/68 (1.5)	-0.7 (-7.2, 2.9)
Level 3 (<0.5)	1/132 (0.8)	0/68 (0)	0.8 (-4.6, 4.2)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide ([FDA 2021](#)).

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants meeting criteria; NA, not available; N_w, number of participants with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, White blood cells

Conclusion

Based on laboratory data from the DB period of LUNA 3, there does not appear to be a safety signal for anemia associated with rilzabrutinib. There does appear to be a safety signal for mild neutropenia associated with rilzabrutinib; however, the 95% CI for the risk difference for Level 1 does cross 0, indicating the observed difference may be due to chance. Although cytopenias, specifically anemia and neutropenia, are noted in Warnings and Precautions of other BTKIs, the risk varies with more favorable profiles in the more selective BTKIs. The risk of cytopenias with these approved BTKIs may also be related in part to the approved populations.

Because the risk of anemia was not observed in clinical trials in ITP with rilzabrutinib and frequency observed with the approved BTKIs appears related to selectivity of the BTKI, the review team recommends against including anemia as a class Warnings and Precautions.

Similarly, the review team concluded that neutropenia should not be included as a class warning in Section 5 of the USPI; however, because there was a signal of mild neutropenia with a higher rate observed in the rilzabrutinib arm, the review team recommends inclusion of the rate of neutropenia in Section 6 of the USPI.

7.6.3.5. New Malignancy

Experience With Other BTKIs

Malignancies (second primary) are reported in Warnings and Precautions for all 4 approved BTKIs. Frequency ranges from 9% to 18%, including nonskin and skin cancers. The mechanism by which BTKIs increases risk of new malignancy includes on and off-target effects specifically and include on-target immunomodulatory effects and off-target inhibition of other kinases ([Wang et al. 2022](#)).

Clinical Experience With Rilzabrutinib

In the ITP rilzabrutinib pool (N=284), which includes LUNA 2 (all doses) and LUNA 3 (all treatment periods), six participants had a report of a primary neoplasm specified as malignant or not specified (2%). They are summarized in [Table 31](#). Half were of these were skin neoplasms. Several were either unspecified as malignancy and/or could be associated with benign conditions.

Table 31. New Primary Malignancies in Participants Receiving Rilzabrutinib¹

Participant ID	Age	Study	Dosage, BID	Malignancy	Day of Rilzabrutinib
(b) (6)	68	LUNA 3	400 mg	IgG lambda paraproteinemia	394
	29	LUNA 3	400 mg	Clear cell carcinoma Ovary	129
	29	LUNA 3	400 mg	Lung adenocarcinoma ²	635
	45	-010	400 mg	Skin neoplasms malignant and unspecified	74
	54	-010		Intraepidermal squamous cell carcinoma (Bowen's disease)	54
	59	-010		Metastatic melanoma	400

Source: FDA reviewer analysis

¹ Includes LUNA 2 (all doses) and LUNA 3 (all treatment periods)² Reported in 120-day safety update.

Abbreviation: BID, twice daily

The Exposure-Adjusted Incidence Rate (EAIR) per 100 participant-years for treatment-emergent malignancy was 1.64 overall¹² in the ITP rilzabrutinib pool.

Conclusion

New malignancies were rare in participants receiving rilzabrutinib on clinical trials.

In the 6-month study in mice and 2-year carcinogenicity study, rilzabrutinib was not carcinogenic. The frequency of new (primary) malignancy associated with approved BTKIs is reported in Warnings and Precautions of the USPIs is much higher than observed with

¹² Applicant Submission, NDA 219685, SDN 1, Summary of Clinical Safety, Section 3.1.5.4.4.4

rilzabrutinib in participants with ITP. This likely reflects the treated population, including age and prior therapies, as well as the effect of the earlier BTKI's on T-cell and NK-function, impairing tumor surveillance. Because rilzabrutinib is more selective and does not impact T-cell and NK-function and the EAIR for new malignancy in the rilzabrutinib pool is consistent with that reported in the literature in the ITP population of 1.8 per 100 patient-years ([Ekstrand et al. 2020](#)), the review team does not recommend inclusion of an increased risk of malignancy in the USPI for rilzabrutinib as a Warnings and Precautions or in Section 6.

7.6.3.6. Hemorrhage

Experience With Other BTKIs

The risk of hemorrhage is included Warnings and Precautions of all 4 approved BTKIs and includes fatal and serious or Grade ≥ 3 events. The rate of major (serious or Grade 3 or higher and any central nervous system (CNS) bleeding) ranged from 3% to 4.4%. The rate of fatal hemorrhage was 0.2 to 0.4%. Bleeding of any grade excluding bruising and petechiae ranged from 17% to 40%. The underlying mechanism of action of the hemorrhage observed with BTKIs is impaired platelet function, including platelet aggregation and thrombus formation.

Clinical Experience With Rilzabrutinib

Based on OCMQ (Narrow) analysis of TEAE reporting during the DB period of LUNA 3, the frequency of hemorrhage was 5% in the rilzabrutinib arm compared to 9% in the placebo arm. The frequency of SAE of hemorrhage was 3% in the rilzabrutinib arm compared to 6% in the placebo arm.

Conclusion

In LUNA 3, there rate of hemorrhage TEAEs and SAEs was higher in the placebo arm compared to the rilzabrutinib arm. Analysis of hemorrhage related to a drug treating ITP is confounded by the underlying disease, which would predispose to bleeding related to low platelets, and to treatment effect of the drug under investigation, which would potentially decrease bleeding in participants who have a response. The review team recommends not including hemorrhage as a risk associated with rilzabrutinib.

7.6.3.7. Hypertension

Experience With Other BTKIs

Hypertension is included in the Warnings and Precautions for only one of the approved BTKIs (nonreversible). The rate of Grade ≥ 3 HTN was 8% with mean onset of 5.9 months. The mechanism for the increased risk of hypertension observed with the approved BTKIs is not clear but is likely due to off-target effects.

Clinical Experience With Rilzabrutinib

Based on TEAE reporting and OCMQ (narrow) analysis, there were no cases of systemic hypertension in participants in the rilzabrutinib arm, compared to 3 participants (4%) in the placebo arm during the DB period of LUNA 3.

In the ITP rilzabrutinib pool, 6 participants (2%) had a TEAE with the preferred term of hypertension. Three of these participants (1%) had Grade 3 hypertension.

Conclusion

Only one of the approved BTKIs includes hypertension in Warnings and Precautions, indicating it is not a class effect. Hypertension was rarely reported in participants receiving rilzabrutinib on clinical trials, and in the DB of LUNA 3, the frequency was not greater in the rilzabrutinib arm. The review team recommends not including hypertension in Warnings and Precautions or Section 6 (Adverse Reactions) of the USPI for rilzabrutinib.

7.6.3.8. Thromboembolic Events

Experience With Other BTKIs

Thrombosis/thromboembolic events are not included in Warnings and Precautions of other BTKIs

Clinical Experience With Rilzabrutinib

Thromboembolic events are identified by the Applicant as a significant adverse event of interest. Thromboembolic events can be seen in patients with ITP. During the DB period in LUNA 3, one participant in the rilzabrutinib arm had a thromboembolic event of Grade 3 peripheral embolism. The event was serious and was assessed based on narrative (see Section [7.6.1.3](#)) as not related to rilzabrutinib. No participant in the placebo arm had thromboembolic TEAE.

During the OL period of LUNA 3, one participant had SAEs of pulmonary embolism and deep vein thrombosis. Narrative for this participant (b) (6) is presented in Section [7.6.1.3](#). These events were also considered unlikely to be related to rilzabrutinib.

One participant in the LTE of LUNA 2, Part A, experienced a thromboembolic event of pulmonary embolism. Based on narrative (see below), the event was considered at least possibly related to rilzabrutinib by the review team. No participant experienced thrombosis during PRN 1008-010 Part B.

- Participant (b) (6) is a 46-year-old female with chronic ITP, depression, gastroesophageal reflux disease, migraine and thyroiditis randomized to receive rilzabrutinib. On Day 434 of rilzabrutinib, the participant developed a severe migraine. On Day 435 thrombocytosis ($1099 \times 10^9/L$) was reported. On Day 441, SAEs of **pulmonary embolism (Grade 3) and pneumonia (Grade 3)** were reported and required hospitalization. The participant was treated with apixaban and broad-spectrum antimicrobials. Rilzabrutinib was permanently discontinued and last received on Day 434. Thrombocytosis had improved by Day 449 ($567 \times 10^9/L$). Platelet count had further decreased to $27 \times 10^9/L$ by Day 463.

Prior to Day 435, platelet evaluations (n=50) after initiation of rilzabrutinib on day 1 ranged from $2 \times 10^9/L$ to $282 \times 10^9/L$. The maximum platelet count recorded in the 100 days prior to day 419 was $59 \times 10^9/L$. The last platelet evaluation before thrombocytosis was observed on day 434 was a platelet count of $6 \times 10^9/L$ recorded on Day 419.

Review of concomitant medications indicates the participant received rescue medication with prednisone from day 406 to day 442 and avatrombopag from day 422 to day 434.

The Investigator's and Sponsor's assessments of attribution for the events of migraine, thrombocytosis, pulmonary embolism, and pneumonia were not related to rilzabrutinib. The Division assessed the SAE of pneumonia as at least possibly related to rilzabrutinib given the known increased risk of infection associated with BTKIs, including rilzabrutinib; however, assessed the pulmonary embolism as not related. Although rilzabrutinib does increase platelet count, the mechanism is through decreased destruction rather than increased production, and therefore it is unlikely rilzabrutinib would lead to thrombocytosis. In contrast, thrombocytosis is a known risk of oral thrombopoietin receptor agonists, including avatrombopag. Steroids can also increase production of platelets. Based on rilzabrutinib's mechanism of action, the participant's historic response to rilzabrutinib, and concomitant use of avatrombopag and steroid just prior to the thrombocytosis and pulmonary embolism, the review team assessed the SAE of pulmonary embolism as not related to rilzabrutinib.

Conclusion

Thromboembolic events were rare in participants receiving rilzabrutinib, and those observed were considered unlikely or not related to rilzabrutinib. The review team does not recommend inclusion of thromboembolic events in the USPI.

7.6.3.9. Gastrointestinal Toxicity

Experience With Other BTKIs

Gastrointestinal toxicities are not included in Warnings and Precautions of any of the approved BTKIs, however, are included in Section 6 of the USPI for all approved BTKIs. The gastrointestinal disorders of diarrhea, vomiting, nausea, vomiting, abdominal pain, and constipation occurred at a rate of $\geq 10\%$ in at least one clinical trial reported in the USPI for each of the approved BTKIs. The mechanism by which BTKIs cause gastrointestinal disorders is due to on-target and off-target effects.

Clinical Experience With Rilzabrutinib

Gastrointestinal disorders were the most common TEAE by SOC occurring in 53% of participants in the rilzabrutinib arm compared to 23% in the placebo arm during the DB period of LUNA 3. TEAS for all of the most frequent ($\geq 10\%$) specific gastrointestinal disorders (Based on OCMQ (Narrow) during the DB period occurred more frequently in the rilzabrutinib arm: diarrhea (32% rilzabrutinib, 9% placebo), nausea (20% rilzabrutinib, 6% placebo), abdominal pain (14% rilzabrutinib, 3.5% placebo), and dyspepsia (11% rilzabrutinib, 0.9% placebo). All events were Grade 1 or 2. Of those who experienced GI adverse reactions, 2 participants discontinued due to GI adverse reactions. Recovery or resolution with supportive treatment allowed continuation of treatment with rilzabrutinib occurred in 91% of patients with diarrhea, 85% with nausea and 79% with abdominal pain.

Conclusion

Gastrointestinal disorders were common and consistent with those observed with other BTKIs. The specific gastrointestinal disorders are included in the table of common adverse reactions in Section 6 of the USPI. While frequent, they rarely resulted in permanent discontinuation and

could be managed with supportive care. Thus, inclusion in Warnings and Precautions is not warranted.

7.6.4. Integrated Safety Population Assessment

To identify rare but potentially serious AEs that may be detectable only in a larger dataset, an analysis of the ISP was performed, (see Section 17.1). The analysis did not identify any new or more severe safety signal not identified in the analysis of the DB period of LUNA 2. There were no reported cases of anaphylaxis, Stevens Johnson Syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), toxic epidermal necrolysis, allergic edema, toxic skin eruption, or rhabdomyolysis. The frequency analysis based on PT and using OND Custom Medical Query (Narrow) did not identify any new, more frequent, or more serious safety signals not identified with the analysis of LUNA 3 DB period.

7.6.5. Adverse Reactions

TEAEs were considered adverse reactions if they occurred in ≥ 5 of participants and occurred in at least 3% more in the rilzabrutinib arm than the placebo arm. Most common adverse reactions are shown in Table 32.

An additional rare adverse reaction identified through analysis of AESIs and adverse events of clinical interest (see Section 7.6.3) is neutropenia.

Table 32. Common Adverse Reactions Occurring at $\geq 5\%$ and at Least 3% More in the Rilzabrutinib Arm, Double-Blind Treatment Period, LUNA 3

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Diarrhea	43 (32.3)	7 (10.1)	22.2 (10.5, 32.4)*
Nausea	27 (20.3)	4 (5.8)	14.5 (4.6, 23.2)*
Headache	24 (18.0)	5 (7.2)	10.8 (0.7, 19.6)*
COVID-19	18 (13.5)	3 (4.3)	9.2 (0.4, 16.9)*
Arthralgia	12 (9.0)	3 (4.3)	4.7 (-3.8, 11.6)
Dizziness	11 (8.3)	1 (1.4)	6.8 (-0.1, 13.1)
Abdominal pain	10 (7.5)	1 (1.4)	6.1 (-0.8, 12.1)
Nasopharyngitis	9 (6.8)	2 (2.9)	3.9 (-3.8, 10.0)
Vomiting	9 (6.8)	1 (1.4)	5.3 (-1.5, 11.2)
Abdominal pain upper	7 (5.3)	0	5.3 (-0.1, 10.5)
Dyspepsia	7 (5.3)	0	5.3 (-0.1, 10.5)
Cough	6 (4.5)	0	4.5 (-0.9, 9.5)

Source: adae.xpt; Software: R; FDA reviewer analysis

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease of 2019; N, number of participants in treatment arm; n, number of participants with adverse event

7.7. Key Safety Review Issues

None.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Hepatic Impairment

A dedicated hepatic impairment study was conducted where participants with normal hepatic function, mild hepatic impairment (Child-Pugh Class A) and moderate hepatic impairment (Child-Pugh Class B) were given a single 400-mg dose of rilzabrutinib (Study PRN1008-020). Results ([Table 33](#)) show that moderate hepatic impairment (HI) significantly increased systemic exposure of rilzabrutinib. The mean $C_{\max}$ and AUC_{last} values of total rilzabrutinib in the moderate hepatic impairment group were approximately 4.2- to 4.8-fold higher than those of the normal group. Rilzabrutinib was highly bound to plasma proteins across all cohorts. The mean $C_{\max}$ and AUC of unbound rilzabrutinib were similar in subjects with mild HI compared to healthy-matched control subjects, and approximately 4.8- to 5.5-fold higher in subjects with moderate HI compared to healthy-matched control subjects, consistent with the observations for total rilzabrutinib. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of rilzabrutinib was not evaluated.

Table 33. Summary of Statistical Comparisons of Plasma Total Rilzabrutinib PK Parameters Following Administration of 400 mg Rilzabrutinib in Participants With HI vs. Healthy-Matched Control Participants (PK Analysis Population)

HI Group				Healthy-Matched Control		Comparison			
Parameter	Severity	n	Geo. LSM	n	Geo. LSM	Severity Comparison	GMR (%)	90% CI	IntraSubject CV%
AUC _{0-t} (ng*hr/mL)	mild	8	683.4	8	445.9	Mild vs. Normal	153.25	76.25-308.02	93.52
	moderate	7	1997	8	412.6	Moderate vs. Normal	484.00	265.22-883.25	65.14
AUC _{0-inf} (ng*hr/mL)	mild	8	693.6	7	513.6	Mild vs. Normal	135.04	66.41-274.61	90.64
	moderate	7	2040	7	455.4	Moderate vs. Normal	447.98	219.11-915.93	73.77
C _{max} (ng/mL)	mild	8	217.1	8	141.8	Mild vs. Normal	153.15	75.88-309.10	94.27
	moderate	7	482.6	8	114.1	Moderate vs. Normal	423.06	224.43-797.51	70.39

Source: Reviewer summary

Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo, geometric; GMR, geometric mean ratio; HI, hepatic impairment; LSM, least-squares mean; n, number of participants with condition; PK, pharmacokinetic

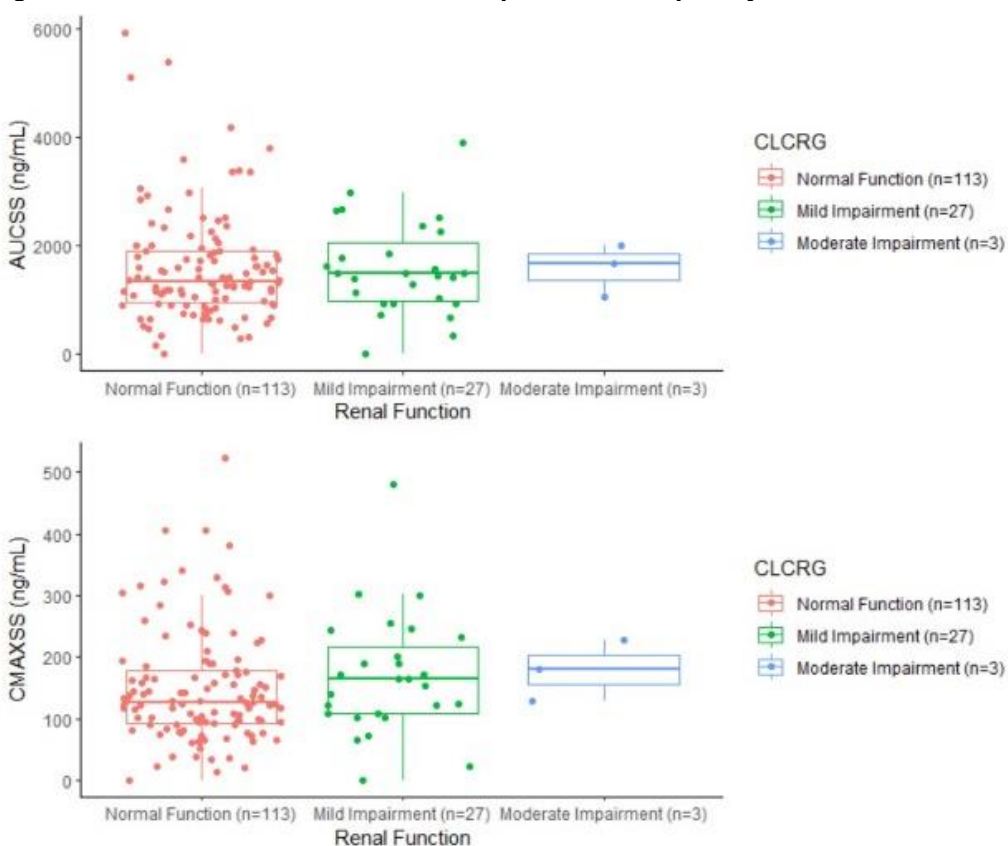
Based on the results observed, the impact of moderate hepatic impairment on the PK of rilzabrutinib is significant. The review team agrees with the Applicant's proposal that rilzabrutinib should not be administered in patients with moderate and severe hepatic impairment.

8.1.2. Renal Impairment

A dedicated renal impairment (RI) study was not conducted. Urinary excretion of rilzabrutinib as unchanged drug is low (fractional excretion =0.03%). Therefore, population PK (PopPK) and physiologically based pharmacokinetic (PBPK) modeling were used to assess the effect of renal impairment. Mild to moderate renal function was assessed as a covariate in PopPK analysis, while the impact of moderate to severe renal impairment was assessed via PBPK. Based on Agency's review, the renal impairment model used in the submitted PBPK analyses is not adequately validated to predict the effects of renal impairment on rilzabrutinib exposure. In the model validation, for drugs whose exposure increased more than 50%, the effects of renal impairment on their exposure tended to be underpredicted (see detail in Section [14.5.3.4.4](#)).

PopPK analysis confirmed that mild to moderate renal function had no effect on the pharmacokinetics of rilzabrutinib (Study POH01157). Normal renal function (creatinine clearance (CLCr) ≥ 90 mL/min) represented 76.7% of subjects in the dataset, with mild (CLCr between 60 to <90 mL/min) and moderate (CLCr 30 to <60 mL/min) renal impairment representing 19.7% and 3.5% of subjects, respectively, in the dataset. The lowest CLCr was 46 mL/min in the moderate renal impairment group. Based on pharmacometrics review, CLCr is not a significant covariate that would affect rilzabrutinib exposure ([Figure 9](#)).

Figure 9. Box Plot of Rilzabrutinib PK Exposures Grouped by Renal Function



Source: Reviewer analysis

Abbreviations: AUC_{ss}, area under the concentration-time curve from 0 to 24 hours on the last day of exposure; CLCRG, creatinine clearance group; C_{MAXSS}, maximum plasma concentration at steady state, n, number of subjects within renal function group; PK, pharmacokinetic

The lack of exposure changes in mild and moderate renal impairment groups is also corroborated by the mass balance study (PRN1008-015) results which show only 5% of the administered dose excreted in urine, with unchanged rilzabrutinib only in trace amounts. However, no definitive conclusions about the impact of severe renal impairment can be drawn. It is known that inhibition of hepatic function by uremic toxins is a plausible mechanism to increase exposure in severe renal impairment. For rilzabrutinib, hepatic metabolism plays a significant role, as exposures in moderate hepatic impairment increases by 4-to-5 fold.

The review team agrees with the Applicant's proposal that a dose adjustment is not needed for patients with mild or moderate RI. Patients with severe renal impairment have not been studied. As the potential for increased exposures cannot be ruled out in subjects with severe renal impairment; the review team recommends avoiding the use of rilzabrutinib in such patients. Further, a PMR will be issued for a study to evaluate the effect of severe renal impairment on rilzabrutinib pharmacokinetics.

8.1.3. Other Intrinsic Factors

The covariate effect analyses in the PopPK model indicated that weight, age, race, and sex did not have a significant effect on the pharmacokinetics of rilzabrutinib. Hence, dose adjustment is not needed for these intrinsic factors.

8.2. Extrinsic Factors

8.2.1. Drug Interactions

8.2.1.1. Metabolic Pathway

Rilzabrutinib is predominantly metabolized by cytochrome P450 (CYP)3A4, with minor contributions from CYP2D6, in vitro. Drugs that are inhibitors or inducers of CYP3A have the potential to affect rilzabrutinib exposures. The Applicant conducted clinical drug-drug interaction (DDI) studies to evaluate the impact of a strong CYP3A inhibitor and a strong CYP3A inducer on the pharmacokinetics of rilzabrutinib. The effects of strong, moderate, and weak CYP3A inhibitors as well as strong, moderate, and weak CYP3A inducers were evaluated by PBPK modeling and simulations.

8.2.1.2. Effects of Other Drugs on Rilzabrutinib

8.2.1.2.1. Effects of CYP3A4 Inhibitors on Rilzabrutinib

Ritonavir, a strong CYP3A inhibitor, was dosed (100 mg, 2 doses) and its effect was evaluated on single doses of 100 mg and 400 mg rilzabrutinib. Ritonavir increased the AUC and C_{max} of 100 mg rilzabrutinib by approximately 18- and 8-fold, whereas increased the AUC and C_{max} of 400 mg rilzabrutinib by approximately 8- and 5-fold. The effects of ritonavir, three moderate CYP3A inhibitors, fluconazole, verapamil, and diltiazem, and one weak CYP3A inhibitor, cimetidine, were also evaluated using PBPK modeling and simulations (see Section [14.5.3.4.3](#) for details).

PBPK simulations showed that ritonavir increased rilzabrutinib AUC and C_{max} by 7.3- and 6.3-fold, respectively, following a single rilzabrutinib dose of 400 mg. Fluconazole increased rilzabrutinib AUC and C_{max} by 3.1- and 3.3-fold, respectively, following a single rilzabrutinib dose of 400 mg. Verapamil increased rilzabrutinib AUC and C_{max} by 2.8- and 3-fold, respectively, following a single rilzabrutinib dose of 400 mg. Diltiazem increased both rilzabrutinib AUC and C_{max} by 1.5-fold, following a single rilzabrutinib dose of 400 mg. Cimetidine increased rilzabrutinib AUC and C_{max} by 1.4- and 1.6-fold, respectively, following a single rilzabrutinib dose of 400 mg.

The review team agrees with the Applicant that the use of rilzabrutinib with strong and moderate CYP3A inhibitors should be avoided due to the large increase in rilzabrutinib exposure. For use with weak CYP3A inhibitors, the team does not propose any dose adjustment.

8.2.1.2.2. Effects of CYP3A4 Inducers on Rilzabrutinib

Rifampin, a strong CYP3A inducer, was dosed (600 mg QD for 11 days) and its effect was evaluated on single dose of 400 mg rilzabrutinib. Rifampin decreased the AUC and C_{max} of rilzabrutinib by 77% and 80%, respectively, similar to the simulated results from using PBPK modeling. The effects of a strong CYP3A inducer, carbamazepine, two moderate CYP3A inducers, efavirenz and rifabutin, and one weak CYP3A inducer, dexamethasone, were also evaluated using PBPK modeling and simulations (see Section [14.5.3.4.3](#) for details).

Based on the PBPK simulations, carbamazepine decreased rilzabrutinib AUC and C_{max} by approximately 75% and 81%, respectively, following a single rilzabrutinib dosage of 400 mg. Efavirenz, a moderate CYP3A inducer, decreased both rilzabrutinib AUC and C_{max} by approximately 70%, following a single rilzabrutinib dosage of 400 mg. Rifabutin decreased rilzabrutinib AUC and C_{max} by approximately 60% and 66%, respectively, following a single rilzabrutinib dosage of 400 mg. Dexamethasone, a weak CYP3A inducer, decreased both rilzabrutinib AUC and C_{max} by approximately 30%, following a single rilzabrutinib dosage of 400 mg.

Based on E-R analysis, 30% rilzabrutinib exposure decrease would lead to a reduction in platelet count response by approximately 15%, compared to no change in rilzabrutinib exposure. This degree of change is not likely clinically significant.

The review team agrees with the Applicant that the use of rilzabrutinib with strong and moderate CYP3A inducers should be avoided due to the large decrease in rilzabrutinib exposure. The team agrees with the Applicant that the use of rilzabrutinib with weak CYP3A inducers are allowed without additional instructions or dose-adjustment (see Section [14.2.11](#) for details).

8.2.1.2.3. Effect of Acid Reducing Agents on Rilzabrutinib

Rilzabrutinib has pH-dependent solubility in the relevant physiological pH range. The solubility of rilzabrutinib is >120 mg/mL at pH values less than 4, however, decreases significantly to 0.35 mg/mL at pH 4.5. Thus, rilzabrutinib is likely to have interactions with acid reducing agents (ARAs).

Esomeprazole, a proton pump inhibitor (PPI), was dosed (40 mg QD, 5 doses) and its effect was evaluated on single dose of 300 mg rilzabrutinib. Administering esomeprazole two hours before rilzabrutinib decreased both its AUC and C_{max} by approximately 50%. Famotidine, an H₂ receptor antagonist (H₂RA), was dosed (20 mg QD, 3 evening doses) and its effect was evaluated on the administration of 400 mg rilzabrutinib on Day 3 (10 hours after the famotidine dose on Day 2), as well as on the administration of evening dose of 400 mg rilzabrutinib on Day 3 (2 hours before the famotidine dose on Day 3). Dosing rilzabrutinib in the morning following administration of 20 mg famotidine the previous evening, resulted in a reduction in the rilzabrutinib AUC_{inf} and C_{max} by 35.3% and 27.7%, respectively. However, when rilzabrutinib was administered in the evening, two hours prior to the evening famotidine dose, AUC and C_{max} were reduced by only 2.4% and 9.5%, respectively.

The review team agrees with the Applicant that the use of rilzabrutinib with PPIs should be avoided due to the large decrease in rilzabrutinib exposure. The team agrees with the Applicant

that the use of rilzabrutinib with H2RAs are allowed, however rilzabrutinib should be administered 2 hours prior to the use of H2RAs.

8.2.1.2.4. Effect of P-Gp Inhibitor on Rilzabrutinib

In vitro studies indicated that rilzabrutinib is a P-glycoprotein (P-gp) substrate. Quinidine, a P-gp inhibitor, was dosed (300 mg Q8h, 5 days) and its effect was evaluated on single dose of 400 mg rilzabrutinib. Quinidine increased the AUC of rilzabrutinib by 13% and decreased C_{max} of rilzabrutinib by 14%. These changes in rilzabrutinib exposures are not clinically significant.

The review team agrees with the Applicant that the use of rilzabrutinib with P-gp inhibitors are allowed.

8.2.1.3. Effect of Rilzabrutinib on Other Drugs

In vitro studies indicated that rilzabrutinib is an inhibitor and a weak inducer of CYP3A4. Rilzabrutinib is also an inhibitor of transporters P-gp, breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B3, and bile salt export pump (BSEP).

Refer to Section [14.1](#) for details of the in vitro studies of rilzabrutinib.

Effect of rilzabrutinib towards substrates of CYP3A was evaluated using midazolam in a dedicated study, and also evaluated using PBPK modeling and simulations.

PBPK modeling and simulations were conducted for rilzabrutinib to test its inhibition potential on P-gp, BCRP, and OATP1B3 substrates.

8.2.1.3.1. Effect of Rilzabrutinib on CYP3A Substrates

Rilzabrutinib is an inhibitor and a weak inducer of CYP3A. Administration of a single dose of 400 mg rilzabrutinib increased midazolam exposure by approximately 1.7- to 2.2-fold. Based on PBPK simulation, 5-day administration of 400 mg rilzabrutinib (QD, BID, TID) increased midazolam exposure by approximately 2-fold. Further, testing only the induction potential of rilzabrutinib, 14-day administration of 400 mg rilzabrutinib (QD, BID, TID) decreased midazolam exposure by 20%. Analysis of the net effect of CYP3A inhibition and induction predicted an increase in midazolam exposure by approximately 2-fold indicating that CYP3A inhibition was the major driver of the interaction of rilzabrutinib with midazolam.

The review team conducted PBPK simulations and midazolam AUC is predicted to increase up to 3.5-fold in patients with immune thrombocytopenia following coadministration with 400 mg rilzabrutinib twice daily (see Section [14.5.3.4.2](#) for details). (b) (4)

8.2.1.3.2. Effect of Rilzabrutinib on P-Gp, BCRP, and OATP1B3 Substrates

In vitro studies showed that rilzabrutinib is an inhibitor of P-gp ($IC_{50} < 10 \mu M$), BCRP ($IC_{50} < 10 \mu M$), and OATP1B3 ($IC_{50} = 0.18 \mu M$). Based on the static model, the intestinal luminal

concentration of the interacting drug (I_{gut})/ IC_{50} for both P-gp and BCRP is greater than 10, and the R value for OATP1B3 is close to the threshold of 1.1.

PBPK modeling and simulation were conducted to evaluate the potential interactions between rilzabrutinib and P-gp, BCRP, and OATP1B substrates. The inhibition was assessed using digoxin, pravastatin, and rosuvastatin as model substrates for P-gp, OATP1B1, and OATP1B3, respectively. Rilzabrutinib was predicted to not result in clinically significant changes in transporter substrates exposure, according to the Applicant.

Based on the risk assessment using the PBPK approach, the potential interaction of rilzabrutinib with substrates of these transporters cannot be ruled out. The potential inhibitory effects of rilzabrutinib may increase plasma concentrations of substrate drugs that are used in this patient population, which may increase the incidence and severity of adverse reactions due to drug toxicity of the substrate drugs. A dedicated DDI study to evaluate the interaction potential between rilzabrutinib and P-gp, BCRP and OATP1B substrates will be issued as a PMR.

8.3. Plans for Pediatric Drug Development

Rilzabrutinib received orphan drug designation for the treatment of ITP (Designation request # DRU-2017-6057, dated 15 October 2018); therefore, rilzabrutinib is exempt from the Pediatric Research Equity Act requirements for the indication.

Rilzabrutinib is currently being evaluated in (b) (4) patients age ≥ 12 and < 18 years with primary ITP > 6 months duration who were unresponsive to available therapies in a separate cohort as part of LUNA 3. The study design for the pediatric cohort is the same as for adults but with differences in randomization algorithms and stratification.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Animal Data

The following nonclinical data in [Table 34](#) is used to support the label. Additional detailed information is available in Section [13](#).

Table 34. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	Risk Summary Based on animal data, rilzabrutinib may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of rilzabrutinib to pregnant rats and rabbits during organogenesis at exposures 4 to 10 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 400 mg twice daily did not cause adverse developmental effects. However, adverse visceral and skeletal findings occurred in rat fetuses at a maternally toxic dose at exposures 22 times the human exposure (based on AUC) at the MRHD (<i>see Animal Data</i>). Animal Data Rilzabrutinib given to pregnant rats by oral gavage at 50, 150, or 300 mg/kg/day during the period of organogenesis (gestation day 7 to 17) did not cause adverse effects on embryo-fetal development at exposures approximately 10 times the clinical exposure at the MRHD, based on AUC. Increased incidence of postimplantation loss (25%), delayed ossification associated with a markedly lower (24%) mean fetal weight and increased skeletal (scoliosis) and visceral malformations (abnormalities of major vessels, urogenital tract, and kidney) occurred in a preliminary study in rats at a maternally toxic dose of 500 mg/kg/day that resulted in exposures 22 times the clinical exposure at the MRHD, based on AUC. Rilzabrutinib given to pregnant rabbits by oral gavage at 10, 30, or 100 mg/kg/day during the period of organogenesis (gestation day 7 to 19) did not cause adverse effects on embryo-fetal development at exposures approximately 4 times the clinical exposures at the MRHD, based on AUC. Renal visceral malformations occurred in a single fetus in a preliminary study in rabbits at 150 mg/kg/day that resulted in exposures 5.6 times the clinical exposure at the MRHD, based on AUC. In a pre- and postnatal developmental toxicity study, pregnant rats were given rilzabrutinib by oral gavage at doses of 50, 150, or 300 mg/kg/day during the periods of gestation, parturition, and lactation (gestation day 7 to lactation day 21). Decreased body weight was observed in pups in the presence of maternal toxicity at 300 mg/kg/day, at exposures approximately 18 times the MRHD based on AUC. There were no effects of rilzabrutinib on the ability of F1 offspring to reproduce or on subsequent F2 development at any dose.
8.2 Lactation	There are no data on the presence of rilzabrutinib or its metabolites in either human or animal milk, the effects on the breastfed child, or the effects on milk production. Due to the potential for adverse reactions in a breastfed child from rilzabrutinib, advise lactating women not to breastfeed while taking rilzabrutinib and for at least 1 week after the final dose.

Source: PI labeling and FDA reviewer

Abbreviations: AUC, area under the concentration-time curve; MRHD, maximum recommended human dose; PI, prescribing information; F1, first filial

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed NDA 219685 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

LUNA 3 and LUNA 2 clinical studies were conducted under International Council on Harmonisation Good Clinical Practice guidelines. A signed written Informed Consent Form was required to enroll in any of the trials. The studies were reviewed and monitored by an Institutional Review Board, Research Ethics Board, or any Independent Ethics Committee depending on the country in which the trial site was located.

The results of the clinical site inspections conducted by the Office of Scientific Investigations is summarized below in Section [22](#) and Applicant inspection support the conclusion that the trials were conducted adequately, and the data generated support the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section [22](#) for a summary of inspection findings and Section [25](#) for financial disclosures for LUNA 3.

11. Advisory Committee Summary

The application did not raise efficacy or safety issues requiring external expert advice. Therefore, an Advisory Committee meeting was not convened to discuss this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

On October 17, 2016, the Sponsor submitted a Type B pre-investigational new drug application (PIND) 132668 meeting request to discuss the development of PRN1008 (also known as rilzabrutinib), the design of the proposed study in patients with ITP, and the overall clinical development plan. On December 14, 2016, FDA provided written responses to Sponsor questions in lieu of a Type B PIND meeting under PIND 132668. The Agency agreed the proposed tests for drug substance specifications were appropriate for the stage development. The Agency recommended the Sponsor request an end of Phase 1 (EOP1) meeting at the completion of Phase 2 to discuss dose selection for future clinical trials based on available pharmacokinetic, pharmacodynamic, safety, and activity data and to discuss their proposed clinical pharmacology development plan.

On April 12, 2017, the Sponsor submitted an investigational new drug (IND 132668) application under Section 505(i) of the Federal Food, Drug, and Cosmetic Act (IND 132668) from Principia Biopharma titled “an Adaptive, Open-Label, Dose-Finding, Phase 1/2 Study Investing the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of PRN1008, an Oral BTK Inhibitor, in Patients with Relapsed Immune Thrombocytopenic Purpura.”

On May 10, 2017, the IND was placed on full clinical hold due to unreasonable and significant risk of illness or injury to human subjects [21 CFR 312.42(b)(1)(i)] and due to insufficient information to assess risks to human subjects [21 CFR 312.42(b)(1)(iv)]. Deficiencies included findings of neurotoxicity in animal models based on influx of neutrophils into meninges and neuropil and the unknown long-term clinical effects when considering the potential for chronic use in ITP.

On July 5, 2017, a Type B meeting was held to discuss the clinical hold deficiencies [21 CFR 312.42(b)(1)(i) and 21 CFR 312.42(b)(1)(iv)] and responses to the nonclinical hold comments identified in the clinical hold letter dated May 10, 2017. The Sponsor submitted a complete response to clinical hold on July 7, 2017. The full clinical hold was removed on August 1, 2017.

On June 1, 2018, a request for Special Protocol Assessment (SPA) was submitted for a 2-year animal carcinogenicity protocol. On June 26, 2018, the Executive Carcinogenicity Assessment Committee (ECAC) held a meeting to discuss conducting a carcinogenicity study to support the registration of rilzabrutinib for the treatment of various autoimmune and inflammatory diseases. An ECAC report with recommendations and conclusions on the 2-year animal carcinogenicity protocol was provided to the Sponsor, on June 28, 2018.

Rilzabrutinib was granted ODD on October 15, 2018, for the treatment of ITP.

On June 10, 2019, a request for SPA was submitted for a 26-week animal carcinogenicity protocol. The ECAC held a meeting on July 9, 2019, to discuss the proposed 6-month carcinogenicity study for rilzabrutinib for the treatment of various autoimmune and inflammatory diseases. An ECAC report with recommendations and conclusions was provided to the Sponsor on July 19, 2019.

On March 19, 2020, a request for SPA was submitted for 26-week animal carcinogenicity study. The ECAC held a meeting on April 21, 2020, to discuss major metabolite concentrations in the transgenic mice in the proposed 26-week carcinogenicity study. An ECAC report with recommendations and conclusions was provided to the Sponsor on April 29, 2020.

On May 27, 2020, an end of Phase 2 (EOP2) Type B guidance meeting was held to discuss the clinical development plan for rilzabrutinib, including LUNA 2 Part B with historical cross study comparison and a proposed randomized placebo-controlled trial in support of a marketing application. In the meeting, the Agency identified concerns regarding early crossover of participants at 12 weeks, which would complicate the analysis and interpretation of study results. Specifically, participants who cross over will be ‘missing’ from the analysis of the primary efficacy endpoint because they will not have completed the 24-week treatment period, even though they will be counted early as failures. These participants will reflect a selected subpopulation of the enrolled participants, and there likely will be imbalances in the numbers of these less effected participants between the two treatment arms. The Agency also recommended to include age, severity of platelet count, and prior splenectomy as stratification factors and to include an increase in doses of concomitant ITP medication e.g., corticosteroids, as use of rescue medication. Participants who take rescue therapy or who are withdrawn due to an adverse event should be censored as having a loss of platelet response at the time of the event occurring.

During the meeting, the Sponsor’s proposed clinical outcome assessments were discussed. The topics of whether the instruments intended for measurement were fit for purpose (b) (4) were addressed as “premature to comment on”. FDA recommendations for any COA (b) (4) and the importance of use of patient input were provided to the Sponsor.

On July 17, 2020, the Sponsor submitted the Phase 3 clinical study protocol for PRN1008-018 (LUNA 3). FDA comments were received on August 19, 2020. On September 18, 2020, the Sponsor submitted their responses to these FDA comments, including the following (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Fast Track designation for rilzabrutinib for the treatment of ITP was granted on October 15, 2020.

On March 16, 2021, the Sponsor submitted General Correspondence – Pediatric Study Plan, stating that since rilzabrutinib for ITP has ODD, it is exempt from Pediatric Research Equity Act requirement, and thus, they do not intend to submit an agreed iPSP.

On December 12, 2021, the Sponsor submitted Protocol PRN1008-018 Amendment 03, which included moving the Idiopathic Thrombocytopenic Purpura Bleeding Scale (IBLS) assessment

from a secondary to an exploratory endpoint and to introduce fatigue assessment using the Fatigue component of the ITP-PAQ, as a key secondary endpoint.

On February 10, 2022, clinical responses/information requests were provided to the Sponsor via Advice/Information Request email communication and included the following comments from the Division of Clinical Outcome Assessments.

1. The ITP-PAQ uses only one item (item 10) to assess physical fatigue over the past 4 weeks. A single item cannot sufficiently measure fatigue, which is multidimensional (physical fatigue, mental fatigue). Item 10 measures both disease and treatment-related symptoms that may overlap. FDA stated concerns regarding recall error due to the 4-week recall period. (b) (4) [REDACTED] FDA recommended using a multi-item fatigue assessment measuring the most important and relevant fatigue dimensions of the target population.
2. PGIS and PGIC anchor scales to assess the threshold for meaningful within-patient score change in the ITP-PAQ Fatigue domain score may limit the interpretability of the anchor-based analyses. The PGIS and PGIS-Fatigue assess “past week” while ITP-PAQ item 10 assesses “past 4 weeks” and ITP-PAQ item 10 measures symptom frequency, while PGIS scales measure symptom severity. Due to the limitations of the anchor scales, FDA recommended the Sponsor consider exploring other methods to assess the threshold for meaningful within-patient change.

On June 30, 2022, the Sponsor responded to the February 10, 2022, FDA feedback regarding PRN1008-018 draft protocol Amendment 03 PRO strategy. In the Sponsor response, they stated they recognized that “the Agency has questions about whether item 10 from the ITP-PAQ instrument is a well-defined and reliable measure of fatigue” and acknowledged “the limitations of the anchor scales in PRN1008-018 highlighted by the Agency.”

On September 30, 2022 FDA provided an email communication reiterating that, “We continue to have concern regarding the use of a single item to measure a multidimensional concept like fatigue, particularly over a lengthy time frame (i.e., 4 weeks), but will review the completed qualitative and quantitative data to evaluate content validity and other measurement properties for item 10 of the Immune Thrombocytopenia Patient Assessment Questionnaire (ITP-PAQ) at the time of NDA submission.”

On October 13, 2022, comments via email were provided to the Sponsor in reference to PRN1008-018 draft protocol Amendment 03, specifically highlighting continued concerns regarding the use of a single item to measure a multidimensional concept like fatigue over a lengthy timeframe (4 weeks). Additional questions regarding the “meaningful change assessment of ITP-PAQ item 10” were the subject of other information requests. FDA reiterated it will review the data and other measurement properties for item 10 of the ITP-PAQ at the time of NDA submission.

On January 10, 2024, the Agency provided Written Responses for a Type C meeting request. The purpose of the meeting was to discuss the assessment of clinical efficacy, assessment of clinical safety and Integrated Summary of Safety, SAP, study data standardization plan, and “covered studies” for the Bioresearch Monitoring package. The Applicant was strongly encouraged to request a meeting to discuss topline efficacy and safety results from PRN1008-018 and plans for providing confirmatory evidence prior to the NDA submission. In addition, FDA requested justification for the Sponsor’s proposed data cutoff for financial disclosure (approximately 6 months prior to the planned NDA submission).

NDA 219685
WAYRILZ (rilzabrutinib)

On June 27, 2024, the Sponsor requested Breakthrough Therapy Designation for rilzabrutinib for the treatment of ITP. The request was denied on August 26, 2024. Reasons for denial included:

(b) (4)

A Type B pre-NDA meeting was held on July 15, 2024. The purpose of the meeting was to seek the Agency's concurrence regarding the Sponsor's plan to submit an NDA for rilzabrutinib for the treatment of ITP and to discuss the adequacy of the efficacy and safety data package to support the filing and review of the NDA for the proposed indication, Drug Abuse Liability Assessment strategy, proposed plan for the 120-day safety update, proposed NDA table of contents, proposed study data standardization plan, regulatory milestones including application orientation meeting and advisory committee meeting. The FDA disagreed with the Applicant's proposal to submit the Day 120-Safety Update one month late (end of February 2025) to allow for all participants to complete the open-label period of LUNA 3, requesting instead that it be submitted Day 120 (end of January 2025). In addition, the FDA stated concerns regarding the high number of participants in both treatment arms who did not complete the 24-week double-blind treatment period and noted this may impact interpretability of the safety and efficacy results. FDA reiterated its continued concerns regarding the use of a single item to measure a multidimensional concept like fatigue, particularly over a lengthy time frame (i.e., 4 weeks) for the PRO endpoint, but noted, it would review the completed qualitative and quantitative data to evaluate content validity and other measurement properties for item 10 of ITP-PAQ at the time of NDA submission. Additional nonclinical studies were requested to be included with the dossier.

On August 29, 2024, Genzyme Corporation submitted an NDA under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR Section 314.50 (NDA 219685) for rilzabrutinib, a new molecular entity, for the treatment of adult patients with persistent or chronic immune thrombocytopenia who have had an insufficient response (b) (4) to a previous treatment. The Applicant requested priority review. The application was accepted with no filing review issues. The application was set to be reviewed under a standard review timeline.

On May 13, 2025, the ECAC met to discuss the carcinogenicity potential of rilzabrutinib in a 6-month study in transgenic RasH2 (Tg-RasH2) mice and a 2-year study in Wistar Han rats. The ECAC provided concurrence on study protocols in mice and rats and provided recommendations and conclusions to the Sponsor on June 2, 2025.

On December 9, 2024, the proposed proprietary name WAYRILZ was conditionally approved for rilzabrutinib.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Primary Pharmacology

Data from a series of in vitro and in vivo nonclinical pharmacology studies ([Table 35](#)) were completed with rilzabrutinib, a new molecular entity BTK inhibitor, to support the mechanism of action and potential benefits of rilzabrutinib for the treatment in patients with ITP.

Primary pharmacology studies established:

- Rilzabrutinib is a reversible, covalent BTK inhibitor with an IC_{50} of 1.3nM for BTK enzymatic activity as demonstrated in a biochemical assay using glutathione S-transferase-tagged full-length recombinant BTK and fluorescent peptide substrate.
 - In vitro, rilzabrutinib demonstrates extended target occupancy with 85% BTK occupancy maintained at 24 hours after initial binding.
- Rilzabrutinib exhibits inhibition of key BTK-dependent immune pathways with IC_{50} values in the low nM to ~100nM range for B cell proliferation, IgG-mediated monocyte activation, and B cell receptor-mediated B cell activation in human whole blood.
 - Rilzabrutinib does not affect platelet aggregation in normal healthy volunteers or participants with ITP despite BTK expression in platelets.
 - In a proof-of-concept ITP mouse model, rilzabrutinib demonstrated dose-dependent prevention of platelet loss compared to vehicle-treated controls.

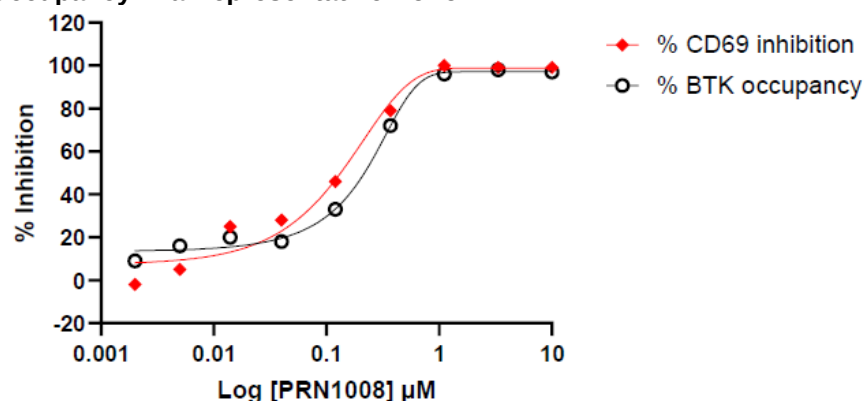
Table 35. Summary of Primary Pharmacology Studies

Study No./ Study Title	Key Study Findings
Study DVR0102/ Biochemical characterization of PRN1008* GLP compliance: No	In Vitro Rilzabrutinib inhibited BTK with an IC₅₀ of 1.3nM in a biochemical kinase assay using glutathione S-transferase (GST)-tagged, full-length recombinant BTK enzyme and a fluorescent peptide substrate (FAM-GEEPLYWSFPAKKK-NH₂) with detection via electrophoretic separation on the LabChip 3000 platform.
Study DVR0070/ The in vitro cell pharmacology of PRN1008* GLP compliance: No	Rilzabrutinib inhibition in human whole blood: - Decreased B cell activation, mean IC₅₀ of 123±38nM. (Inhibition of CD69 expression on stimulated CD20 plus B cells by flow cytometry). - BTK target occupancy in PBMCs, IC₅₀ of 233±75nM. (BTK target occupancy IC₅₀ is the concentration of rilzabrutinib needed to block 50% of BTK binding sites, measured by adding fluorescent probes that can only bind to unoccupied BTK sites and then detecting how much probe binding is prevented.) - Decreased basophil activation IC₅₀ of 490±130nM. (Inhibition of CD63 expression by rilzabrutinib measured using flow cytometry). Inhibition of rilzabrutinib in human Ramos B cells: - BTK target occupancy, IC₅₀ of 8±2nM (BTK target occupancy in Ramos B cells was measured by treating cells with a biotinylated probe (PRN299-001) that binds to unoccupied BTK sites and detecting the probe binding using Alphascreen technology.) - Durable BTK binding, 76±8% occupancy 4 hours after washout and 60±13% at 18 hours after washout (occupancy in Ramos B cells over time). Activity of rilzabrutinib in off-target cellular cross screens: - Minimal activity (IC₅₀>5 µM) in non-BTK pathways, as determined measuring IL-4-induced STAT6 (signal transducer and activator of transcription 6) activation in Ramos B cells, nuclear factor of activated T cells (NFAT) activation in Jurkat T cells (stimulated with anti-CD3/anti-CD28 or thapsigargin), AP-1 (activator protein 1) activation in ME-180 (human cervical carcinoma) cells (stimulated with epidermal growth factor), and cytotoxicity testing in HCT-116 (human colon carcinoma) cells. Overall, the potency of rilzabrutinib in the B cell activation assay mirrored BTK target occupancy (Figure 10).

Study No./ Study Title

Key Study Findings

Figure 10. Dose-Dependent Inhibition of Human Whole Blood CD69 Expression and BTK Occupancy in a Representative Donor



Source: Applicant study data

Overlay of % CD69 expression inhibition versus % BTK occupancy in 1 individual blood donor; representative plot selected from n=4 donors.

Abbreviations: BTK, Bruton's tyrosine kinase; CD69, cluster of differentiation 69; HWB, human whole blood

Study DVR0167/ Inhibitory Effect of 4 compounds on anti-IgM induced human B cell proliferation	Rilzabrutinib showed inhibitory effects on anti-IgM-induced human B cell proliferation with an IC_{50} value of 5.03 ± 2.44 nM. This inhibitory effect at nM levels supported rilzabrutinib-related inhibition of B cell proliferation induced by anti-IgM, which mimics B cell receptor signaling, which is considered a key mechanism in B cell-mediated autoimmune diseases like ITP.

GLP compliance: No.

Study DVR0286/ PRN1008* antibody mediated in vitro cellular pharmacology	Rilzabrutinib inhibited IgG-mediated $TNF\alpha$ production (IC_{50} of 55.7 ± 45.0 nM) in human monocytes. This inhibitory effect at nM levels demonstrated that rilzabrutinib can potently inhibit IgG-mediated $TNF\alpha$ production in human monocytes. This is important because it shows a potent effect of rilzabrutinib on Fc receptor signaling, considered another key pathway in autoimmune diseases like ITP, in addition to its effects on B cells.

GLP compliance: No

Study No./ Study Title	Key Study Findings
Study DVR0307/ Assessing in vitro effects of PRN1008* and ibrutinib on agonist-induced platelet aggregation GLP compliance: No	The study tested rilzabrutinib's effects on platelet aggregation using platelet-rich plasma isolated from whole blood collected from healthy volunteers and participants with ITP induced by multiple agonists: 5 μM (7.14 μg/ml) thrombin receptor activating peptide, 10 μM (4.27 μg/ml) adenosine diphosphate (ADP), 1,500 μg/ml ristocetin, 5 μg/ml collagen, 2.5 μg/ml collagen, and 5 μM (1.76 μg/ml) U46619 (a thromboxane receptor agonist). Rilzabrutinib at concentrations of 0.3 μM (0.197 μg/ml) and 1 μM (0.666 μg/ml) had no significant effect on platelet aggregation induced by any of the agonists tested in either healthy volunteers or participants with ITP. Rilzabrutinib did not induce spontaneous platelet aggregation when tested with saline. However, the positive control roxifiban (an integrin αIIbβ3 antagonist) substantially inhibited platelet aggregation, as expected, confirming the validity of the assay.
Study DVR0106/ Murine in vivo BTK PK/PD occupancy durability PO study Female Lewis and Sprague Dawley rats, female C57BL/6 mice; oral (ROA in rats: oral gavage; in mice: in diet) GLP compliance: no	In Vivo At 14 hours postdoses of 10, 20, and 40 mg/kg rilzabrutinib to Lewis rats, BTK occupancy was 60.9%, 63.6%, and 74.6%, respectively. In addition, at 24 hours, BTK occupancy remained 49.9-65.3%, despite rilzabrutinib plasma levels being below the quantification limit. BTK occupancy at 14 hours where rilzabrutinib was present at 1.3 ng/mL in plasma was 61.5% at 20 mg/kg in Sprague Dawley rats. BTK occupancy was 84.6% and 91.4% when rilzabrutinib was given at 1.67 and 3.33 g/kg/day for 14 days in medicated feed, respectively, to C57Bl/6 mice.

Study No./ Study Title

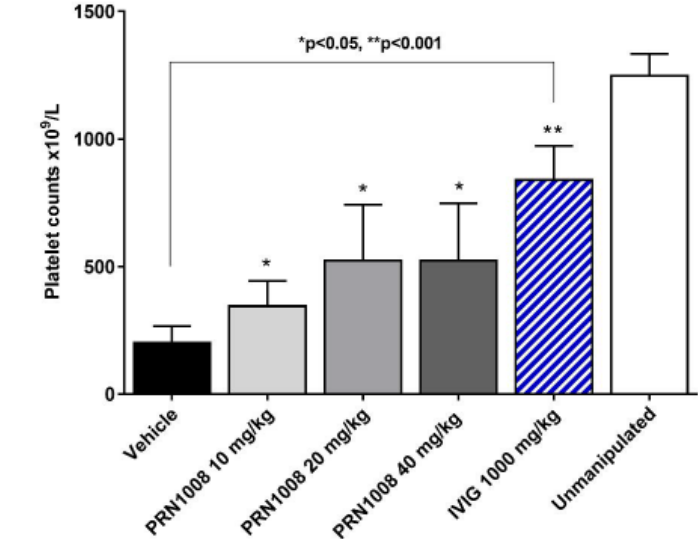
Study DVR0288/ Evaluation of PRN1008* in a mouse model of immune thrombocytopenia. Male BALB/c mice; oral (gavage)

Key Study Findings

In vivo proof-of-concept was established using an ITP mouse model, with induction of ITP via anti-CD41 injection (which causes platelet destruction/removal leading to dramatically reduced platelet counts). Administration of rilzabrutinib caused a dose-dependent prevention of platelet loss at 6 hours after anti-CD41 injection in comparison to vehicle control-treated ITP mice ([Figure 11](#)).

GLP compliance: no

Figure 11. Effect of Rilzabrutinib on Platelet Counts in the Mouse ITP Model



Source: Study report DVR0288
Platelet counts in mice (n=5/group) at 6 hours following induction of ITP via anti-CD41 injection
Abbreviations: ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin injection for infusion

Source: Applicant's submission
*PRN1008 denotes rilzabrutinib
Abbreviations: BTK, Bruton's tyrosine kinase; CD41, integrin alpha IIb; CD69, cluster of differentiation 69; GLP, good laboratory practice; IgG, Immunoglobulin G; ITP, immune thrombocytopenia; PBMC, peripheral blood mononuclear cell; PO, by mouth; ROA, rat optimization algorithm; TNF- α , tumor necrosis factor alpha

13.1.2. Secondary Pharmacology

Table 36. Summary of Secondary Pharmacology Studies

Study No./ Study Title

Study DVR0102/ Biochemical Characterization of PRN1008*

GLP compliance: no

Key Study Findings

In Vitro

In a screen of 251 kinases, only 6 kinases (including BTK) showed >90% inhibition at 1 μ M rilzabrutinib. BTK is the primary target for treating ITP, as it plays a crucial role in B cell receptor and Fc receptor signaling, which are important in the pathogenesis of ITP.

The most potently inhibited kinases besides BTK were tyrosine kinase expressed in hepatocellular carcinoma (TEC), bone marrow tyrosine kinase in chromosome X (BMX), T cell X chromosome kinase (TXK), and B-cell lymphocyte kinase (BLK), with IC₅₀ values <10nM. The IC₅₀ for BTK was 1.3nM. Rilzabrutinib shows similar potency against TEC, BMX, TXK, and BTK, while BLK is about 5-fold less potent ([Table 37](#)) than BTK inhibition and the relevance of inhibition of these additional targets is unclear. However, toxicology studies in two species (rats and dogs) did not reveal any adverse effects associated with this additional kinase inhibition.

Table 37. In Vitro Potency of Rilzabrutinib Against BTK and Related Kinases

Kinase	IC ₅₀ (nM)
BTK	1.3
TEC	0.8
BMX	1.0
TXK	1.2
BLK	6.3

Source: Reviewer's generated table

Abbreviations: BLK, B-cell lymphocyte kinase; BMX, bone marrow tyrosine kinase in chromosome X; BTK, Bruton's tyrosine kinase; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TXK, T cell X chromosome kinase

Binding to BTK was reversible, in contrast to the irreversible inhibitor ibrutinib (data not shown).

Rilzabrutinib maintained 85% occupancy on BTK after 24 hours, while percent occupancy for other kinases were 6%-59% at 24 hours ([Table 38](#)).

Table 38. Durability of Rilzabrutinib Occupancy on BTK and Other Cross-Reacting Kinases

Kinase	Compound	Percent Occupancy ^a at 1 hour	Percent Occupancy ^a at 6 hours	Percent Occupancy ^a at 24 hours
BTK	PRN35 ^b	98 ±1	97 ±2	98 ±3
BTK	rilzabrutinib	95 ±1	91 ±1	85 ±2
BLK	rilzabrutinib	49 ±5	12 ±6	6 ±8
BMX	rilzabrutinib	88 ±2	70 ±1	36 ±1
TEC	rilzabrutinib	87 ±2	73 ±3	59 ±16
TXK	rilzabrutinib	85 ±1	73 ±3	58 ±5

^a Results reported as mean ± standard deviation; n = 4 for all results

^b Durability of PRN35 to these 4 other off-target kinases was assessed separately from this study and showed that PRN35 was durable with high (>90%) levels of occupancy maintained at 24 hours (data not shown).

Abbreviations: BLK: B-cell lymphocyte kinase; BMX: Bone marrow tyrosine kinase in chromosome X; BTK: Bruton's tyrosine kinase; TEC: Tyrosine kinase expressed in hepatocellular carcinoma; TXK: T cell X chromosome kinase

Source: Applicant's study data

Study DVR0095/ In Vitro Pharmacology: Binding Assay Study of PRN1008*

GLP compliance: no

Rilzabrutinib was tested at a concentration of 10 µM (6657.7 ng/mL) against a panel of over 50 different receptors, ion channels, and transporters. Rilzabrutinib showed significant inhibition (>50% inhibition of positive control-specific binding) for the following targets:

- M2 (muscarinic) receptor: 50.7% inhibition
- NK2 receptor: 50.2% inhibition
- Na⁺ channel (site 2): 59.3% inhibition
- Dopamine transporter: 81.8% inhibition.

Moderate inhibition (25-50% inhibition) was observed for:

- H2 (histamine) receptor: 43.9% inhibition
- 5-HT1A receptor: 46.1% inhibition
- 5-HT transporter: 34.0% inhibition

For other targets tested, rilzabrutinib showed low inhibition (<25%) or no significant effect.

Study DVR0159/ Excretion Mass Balance and Tissue Distribution by Quantitative Whole-Body Autoradiography in Rats Following a Single Oral Dose (40 mg/kg) of [¹⁴C]PRN1008*

In Vivo

Quantitative whole-body autoradiography (QWBA) evaluated the tissue distribution of [¹⁴C]rilzabrutinib following a single 40 mg/kg oral dose in male rats. The analysis detected radioactivity concentrations below the limit of

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GLP compliance: no

quantification (BQL) in all examined central nervous system tissues, including the cerebrum, cerebellum, medulla, and spinal cord.

These findings demonstrate that rilzabrutinib exhibits minimal CNS penetration and does not readily cross the blood-brain barrier at the tested dose level.

Study DVR0212/ Cerebral Spinal Fluid Concentrations of PRN1008* in Female Wistar Han Rats Following an Oral Dose

GLP compliance: no

The blood-brain barrier penetration study demonstrated that rilzabrutinib does not cross into the central nervous system when administered orally at 50 mg/kg in female Wistar Han rats. All rilzabrutinib concentrations in cerebrospinal fluid remained below the lower limit of quantitation (LLOQ =1.25 ng/mL) at all timepoints, indicating no detectable CNS penetration. Plasma concentrations validated adequate systemic exposure, with rilzabrutinib levels at 1 hour (894 ng/mL), 4 hours (320 ng/mL), and 24 hours (0.6 ng/mL) consistent with those observed in the 13-week repeat dose toxicology study (1010 ng/mL, 142 ng/mL, and 1.5 ng/mL, respectively). Despite achieving equivalent plasma exposures, rilzabrutinib was undetectable in cerebrospinal fluid, establishing limited central nervous system penetration.

Study DVR0223/ Pharmacokinetic/Pharmacodynamic (PK/PD) Study With Daily PO Dosing of PRN1008*, PRN35, PRN2296 and PRN1669 for 3 Days and Daily IV Dosing of PRN1008 for 3 Days

GLP compliance: no

A 3-day rat study assessed CNS effects of rilzabrutinib and other three orally administered BTK inhibitors and intravenous rilzabrutinib, examining neuroinflammation and microglial activation in brain tissue.

Rilzabrutinib:

- At 500 mg/kg oral dose: Caused minimal to moderate neutrophilic inflammation in meninges and neuropil (4/5 animals), and increased IBA-1 positivity in periventricular areas and neuropil.
- At 10 mg/kg intravenous dose: No significant microscopic changes or increased IBA-1 positivity observed.

Other BTK inhibitors (oral dosing only):

- Ibrutinib (PRN35) at 175 mg/kg: Caused minimal inflammation (1/5 animals) and increased IBA-1 positivity in periventricular areas and neuropil.
- PRN2296 (Structural analog/chemical structure variant of rilzabrutinib within the same company's pipeline) at 300 mg/kg: No inflammation, but increased IBA-1 positivity in periventricular areas and neuropil.
- PRN1669 (Alternative BTK inhibitor, a backup compound or alternative development candidate) at 300 mg/kg: No significant microscopic changes or increased IBA-1 positivity observed.

The study revealed that oral administration of rilzabrutinib at high doses (AUC at 500 mg/kg is 32,600 ng*hr/mL) can result minimal to moderate neuroinflammation and microglial activation in rats, while intravenous

	administration of rilzabrutinib at a lower dose (AUC at 10 mg/kg, 7,280 ng*hr/mL) resulting in a 5-fold lower plasma exposure did not produce CNS effects. These results suggested the study may have used insufficient intravenous dose(s) of rilzabrutinib to assess any difference in impact of the intravenous route on the CNS.
Study DVR0219/ Study DVR0224/ Pharmacokinetic-Pharmacodynamic Study With Daily Intrajejunal Dosing of PRN1008* up to 100 mg/kg for 3 Days in Female Wistar Hans Rats GLP compliance: no	A previous study (DVR0223) with oral administration caused minimal to moderate neutrophilic inflammation in meninges and neuropil (4/5 animals), and increased IBA-1 positivity in periventricular areas and neuropil. These findings raised questions about potential CNS toxicity. In the current study, administration of rilzabrutinib at 100 mg/kg for 3 days by the intrajejunal route (bypassing the stomach), resulted in a minimal increase in IBA-1 positivity in the periventricular region surrounding the lateral ventricles in one of four rats. IBA-1 is a relatively specific immunohistochemical marker for microglial cells. Increased IBA-1 positivity suggests an increase in the number and/or size of microglial cells in the brain. While this could suggest potential neuroinflammation, H&E staining revealed no evidence of neurodegeneration or inflammation. This study suggested that avoiding upper GI exposure decreased the CNS effect compared to oral gavage administration at similar plasma exposures. The implications of this effect are unclear.
Study DVR0225/ Pharmacokinetic-Pharmacodynamic Study With Daily PO Dosing of PRN1008* at 500 mg/kg and PRN35 (Ibrutinib) at 175 mg/kg for 3 Days in Female Wistar Hans Rats GLP compliance: no	Rilzabrutinib administered orally at 500 mg/kg caused minimal to mild neutrophilic inflammation in the meninges and neuropil and increased IBA-1 positivity (indicating microglial activation) in all treated animals (5 out of 5). Despite these observations, no detectable evidence of neurodegeneration was found in brain sections by H&E staining, and the significance of the increased IBA-1 positivity remains unclear.
Study DVR0226/ Crossover Canine Gut Hormones' Study of PRN1008* Through PO Administration to Male Beagle Dogs GLP compliance: no	A single oral dose of 30 mg/kg rilzabrutinib increased plasma levels of both peptide YY and leptin in male beagle dogs. In this acute, single dose study with a limited 6-hour food intake observation period, no reduction in food consumption was observed. These findings demonstrate that rilzabrutinib can influence gut hormone pathways, though acute hormonal changes did not translate to immediate effects on appetite regulation in this short-term study.
Study DVR0235/ Effect of PRN1008* and Cinnamaldehyde on Gastric Emptying Through Oral or Intrajejunal Administration to Wistar Hans Female Rats	Delayed gastric emptying was observed at 1, 3, 5, and 7-hours postdose following repeated oral dosing of rilzabrutinib at 500 mg/kg for 4 days, while no

GLP compliance: no	effect on gastric emptying was observed up to 7 hours postdose following repeated intrajejunal dosing of rilzabrutinib at 100 mg/kg for 3 days. These results suggest local action in the stomach may influence the gastric effects rather than rilzabrutinib direct systemic effects after absorption. Oral administration of rilzabrutinib showed that the stomach weights and sizes were increased compared to vehicle control, whereas intrajejunal administration did not affect stomach weight or size.
Study DVR0301/ Twelve-Week Oral Capsule Bridging Study of PRN1008* in Beagle Dogs (n=16; 4/sex/Group; Doses 30 or 50 mg/kg/day) GLP compliance: no	The study demonstrated that the capsule formulation was well-tolerated with no mortality and all animals surviving to scheduled termination. Dose-related emesis (males at 50 mg/kg; females at both doses), abnormal fecal quality at both dose levels, and body weight loss in females at the high dose (two animals lost 15%-18% body weight, requiring supplemental feeding for one animal). Systemic exposure was confirmed in all animals with $T_{max} < 2$ hours and less than 2-fold accumulation over the dosing period. Overall, this capsule formulation demonstrated improved tolerability compared to the 13-week gavage study (study # 1281-14256 discussed under general toxicology section) using liquid citric acid formulation, showing significant reductions in stool changes and emesis, absence of deaths from severe weight loss, while maintaining similar drug exposure levels. The 30 mg/kg dose represents a well-tolerated dose level with minimal adverse findings, while 50 mg/kg represents a maximum tolerated dose with reversible findings.

Source: Applicant's submission

*PRN1008 denotes rilzabrutinib

Rilzabrutinib (and its major metabolites) showed minimal to no brain penetration in rats, indicating it does not readily cross the blood-brain-barrier. Studies comparing intrajejunal (IJ) to PO dosing in rats showed that brain findings were less frequent and severe with IJ administration despite achieving similar plasma drug concentrations by PO dosing. While these results did not determine the mechanism of action causing brain findings with rilzabrutinib in rats, they do suggest involvement of the gut-brain axis and indicate that the lesions were unlikely to represent a direct effect of rilzabrutinib in the brain.

Abbreviations: AUC, area under the concentration-time curve; BTK, Bruton's tyrosine kinase; CNS, central nervous system; GI, gastrointestinal; GLP, good laboratory practice; H&E, hematoxylin and eosin; IBA-1, ionized calcium binding adapter protein 1; ITP, immune thrombocytopenia; IV, intravenous; PO, by mouth; T_{max} , time to maximum concentration

13.1.3. Safety Pharmacology

A core battery of safety pharmacology studies evaluated the potential effects of rilzabrutinib on cardiovascular, respiratory, and neurologic endpoints. These studies included an in vitro human ether-à-go-go related gene (hERG) assay, an in vivo assessment of the cardiovascular system in dogs, and in vivo assessments of the CNS and respiratory system in Sprague Dawley rats. The hERG assay showed significant inhibition only at irrelevantly high plasma concentrations (based on free drug). The in vivo studies were conducted at doses up to 500 mg/kg, which did not show any adverse rilzabrutinib-related effects in the CNS, respiratory or cardiovascular systems (including QTc).

Table 39. Summary of Safety Pharmacology Studies

Study No./ Study Title	Key Study Findings
Study DVR0111/ Effects of PRN1008 ¹ on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (HEK293)	Rilzabrutinib caused mean human ether-à-go-go related gene (hERG) inhibition of 0.3 and 33.8% of cell current at 1 and 10 µM, respectively. Positive control (E-4031) inhibited 98% of cell current at 0.5 µM

GLP compliance: no

Concentration: 1 or 10 µM

Study PAT0302/ Effect of SAR444671² on Cloned hERG

Potassium Channels Expressed in Human Embryonic Kidney Cells

Table 40. hERG Current Inhibition by Rilzabrutinib

Concentration (µM)	hERG Current Inhibition (Mean ± SEM%)
Control (0)	3.1±0.8
0.3	2.8±1.3
1	19.4±0.8
3	47.9±1.0
10	74.2±0.9
Positive control Terfenadine (0.060)	80.1±8.1

GLP compliance: yes

Concentration: 0.3, 1, 3 and 10 µM

Source: Reviewer's generated table from Study PAT0302

Abbreviations: hERG, human ether-à-go-go-related gene; SEM, standard error of the mean

An IC₅₀ was determined at 3.5 µM (2330 ng/mL). The risk of QT prolongation in human is considered low due to rilzabrutinib's high protein binding (97.5%) in plasma. At a projected C_{max} of 150 ng/mL, corresponding to a 400 mg BID dose, the estimated maximum free drug concentration would be only 3.75 ng/mL (assuming a free fraction of 2.5%). This free drug concentration is approximately 621-fold below the hERG IC₅₀, providing an adequate safety margin.

Study No./ Study Title	Key Study Findings
Study DVR0176/ PRN1008 ¹ : Irwin Test Assessment Following Oral Administration to Rats.	A single oral (gavage) dose of rilzabrutinib to male Wistar Han rats at a dose of 50, 150, or 500 mg/kg did not affect the gross behavioral, physiological, or neurological state of the animals.
GLP compliance: yes Species/ Strain: rat, Han Wistar Number/Sex/Group: 6 males/group.	
Study DVR0177/ PRN1008 ¹ : Cardiovascular, Respiratory and Toxicokinetic Assessment Following Oral Administration to Conscious, Radiotelemetry Instrumented Dogs.	The NOAEL for cardiovascular toxicity was 500 mg/kg, the highest dose tested, based on the absence of rilzabrutinib-related effects on electrocardiogram (ECG) waveform morphology, ECG intervals, body temperature, or respiratory parameters (respiratory frequency, tidal volume, or minute volume). This dose corresponded to mean AUC _{last} , C _{max} , T _{max} , and t _{1/2} values of 20,200 ng*h/mL, 3,760 ng/mL, 3.0 h, and 2.4 h, respectively.
GLP compliance: yes Species/ Strain: beagle dog Number/Sex/Group: 4 males/group.	
Source: Applicant's submission ¹ . PRN1008 denotes rilzabrutinib ² . SAR444671 denotes rilzabrutinib Abbreviations: AUC _{last} , area under the concentration-time curve to the last measurable concentration; BID, twice daily; C _{max} , maximum plasma concentration; GLP, good laboratory practice; IC ₅₀ , half-maximal inhibitory concentration; NOAEL, no-observed-adverse-effect level; QT, QT interval; t _{1/2} , half-life; T _{max} , time to maximum concentration	

13.1.4. ADME/Pharmacokinetics

13.1.4.1. Nonclinical Pharmacokinetic Parameters of Rilzabrutinib

Rilzabrutinib is a small molecule combination of E (up to 90%) and Z isomers and R/S enantiomers (predominantly R). The Z isomer is mostly converted to E isomer following oral dosing in rats and humans. Both E and Z isomers have comparable pharmacological activity. The R enantiomer has greater durability of pharmacological potency, but there is negligible conversion of R to S in vivo. In addition, physiochemical properties of rilzabrutinib include high hydrophobicity and pH-dependent solubility, which appear to dictate its absorption, distribution, metabolism, and excretion (ADME) profile in both animals and humans, resulting in minimal renal clearance.

The pharmacokinetic and toxicokinetic properties of rilzabrutinib were addressed primarily in rats, dogs, mice, rabbits, and monkeys. Single oral/IV dose PK studies found rilzabrutinib to have a rapid rate of absorption, metabolism, and clearance rate and variable bioavailability in all test species. The half-life of rilzabrutinib in single dose studies ranged from 0.6 to 2.6 hrs. ([Table 41](#)). The shortest t_{1/2} in all test species occurred following IV and low oral doses and t_{1/2} appeared to be longer after larger oral doses. In single dose studies, a 5-fold increase in dose was associated with a 10-fold increase in exposure (20 mg/kg versus 100 mg/kg) in rats. In contrast, the increase in exposure was dose proportional in repeat dose studies. Rilzabrutinib bioavailability in rats increased from 12.5% at 20 mg/kg to 52.7% at 100 mg/kg in single dose

PK studies. Similar findings were also seen in dogs where the bioavailability increased from 7.5% at 20 mg/kg to 28.2% at 100 mg/kg ([Table 41](#)).

Table 41. Pharmacokinetic Parameters of Rilzabrutinib After Single Oral or Intravenous Administration of Rilzabrutinib in Rats, Dogs, and Monkeys

Species	Sex	Route	Dose, mg/kg	T _{max} , h	C _{max} , ng/mL	t _{1/2z} , h	AUC, ng*h/mL	V _z , L/kg	CL, L/h.kg	%F ¹
Rat study	F	IV	2	-	1608	0.6	505	0.33	66	-
DVR0077	F	PO	20	0.5	270	1.5	622			12.3
	F	PO	100	1.0	2795	2.6	13310			52.7
Dog study	M	IV	2	-	2066	0.7	827	13.31	40	-
DVR0078	M	PO	20	0.5	378	2.2	695			7.5
	M	PO	100	4.0	2050	2.0	11667			28.2
Monkey study	M	IV	2	-	2790	0.4	1464	2.62	23	-
DVR0080	M	PO	20	1.0	181	1.0	473			3.2
	M	PO	100	4.0	431	2.5	2772			3.8

Source: Applicant provided PK studies

¹: %F denotes bioavailability

Abbreviations: AUC, area under the plasma concentration time curve; CL, clearance; C_{max}, maximum plasma concentration; F, female; IV, intravenous; M, male; NA, not applicable; PK, pharmacokinetic; PO, by mouth; t_{1/2z}, terminal half-life; T_{max}, time to maximum concentration; V_z, apparent volume of distribution during the terminal phase

The variability observed in the t_{1/2}, plasma exposure, and bioavailability in single dose studies from small to large doses of rilzabrutinib (20 versus 100 mg/kg) is likely reflective of limited capacity of liver CYP enzymes to metabolize rilzabrutinib. Large doses of rilzabrutinib were likely exceed the metabolizing capacity, which is not seen with low doses. Repeated administration of rilzabrutinib resulted in adaptive hepatic increase in microsomal enzymes (liver hypertrophy) leading to increase in liver CYP capacity, preventing rilzabrutinib accumulation with large doses in repeat dose studies ([Gilbert and Goldberg 1965](#)). Whether greater absorption occurred at higher doses is not clear. When rilzabrutinib was delivered intrajejunal route bypassing the stomach, a significant increase in rilzabrutinib was observed at 50 mg/kg (2 to 3-fold) and 100 mg/kg (6 to 7-fold). Rilzabrutinib is an acidic compound, and it is possible that larger doses allowed faster transit from the stomach than small doses.

Rilzabrutinib was highly protein bound in all species tested. Rilzabrutinib plasma protein binding in rat, dog and human was ≥99%, 96% and 97.5%, respectively. As a small hydrophobic molecule with minimal solubility in water or basic environment, rilzabrutinib is not expected to readily enter red blood cells (RBCs). In vitro partitioning assays of rilzabrutinib to blood cells versus plasma ([Table 42](#)) found rilzabrutinib had limited ability to bind RBCs and the plasma concentration of rilzabrutinib was more than 2-fold greater than the concentration in RBCs. In vivo partitioning of [¹⁴C] rilzabrutinib found blood to plasma ratio nearly equal (up to 4 hrs. postdose). The blood to plasma ratio increased to 1.55 at 168 hrs. suggesting that slow release from blood cells was one of the last reservoirs for rilzabrutinib.

Table 42. Rilzabrutinib Partitioning to RBC Across Different Species

Compound	Red Blood Cells to Plasma Ratio ($K_{RBC/PI}$)		
	Human	Dog	Rat
Rilzabrutinib	0.47 ¹	0.40	0.27
Chloroquine (control)	5.07	8.19	7.01

Source: Applicant study DVR0083

¹: Red blood cell to plasma distribution ratio of 0.47, indicating limited RBC binding in human

Chloroquine was used as a comparator

Distribution of rilzabrutinib to different tissues and biological fluids in rats (Long Evans and Sprague Dawley rats) were evaluated using radiolabeled [¹⁴C] rilzabrutinib. Radiolabeled rilzabrutinib was distributed to most tissues in both strains of rats following oral administration with most of radioactivity detected in the gastrointestinal (GI) tract, from esophagus to large intestine. Rilzabrutinib metabolized in the liver was excreted into bile (67% of total radioactivity) and to feces (90%) in rats. Limited radioactivity was detected in the urine in rats (1-3%) highlighting that kidney played a minor role in clearance of rilzabrutinib, which is consistent with limited renal clearance in humans. Tissues with the lowest rilzabrutinib distribution were, fatty tissues such as mammary gland, adipose, bone marrow, spinal cord, and (unexpectedly) brain. Transfer of rilzabrutinib and metabolites across the blood brain barrier to cerebral spinal fluid, spinal cord and brain were below detection limits in Wistar rats. Rilzabrutinib concentrations in the pigmented tissues (eye uveal, skin) were higher than nonpigmented tissues suggesting rilzabrutinib may interact with melanin.

Rilzabrutinib underwent oxidation, dealkylation, hydrogenation, hydrolysis, and sulfation. Metabolic pathway among test species and humans were qualitatively similar. Hepatic CYP3A4 was identified as the primary CYP enzyme responsible for rapid metabolism of rilzabrutinib to the prominent thiocyanate metabolite, PRN4400 (M1), which comprised ~94% of total drug-related plasma radioactivity in rats. In humans, M1 was a major circulating metabolite (≥10% of total drug-related AUC). PRN834 (also known as M16 or hydrolyzed metabolite), representing ~6% of plasma radioactivity in rats and <10% in humans, was formed in all species by extrahepatic pathway and is not expected to compete with coadministered drugs that are metabolized by CYP3A4.

The M1 thiocyanate metabolite was identified in later stages of rilzabrutinib development during an in vivo human mass balance study. In vitro metabolism studies and in vivo animal metabolism studies failed to identify thiocyanate as a metabolite. It appears that earlier studies had failed due to coelution of thiocyanate with cyano acetic acid in high performance liquid chromatography (HPLC) analysis and the fact that thiocyanate is also formed endogenously from dietary sources in humans and animals, may have contributed to uncertainty. Thiocyanate concentrations in human serum have been reported to range from 3 to 15 mg/L (3 to 15 µg/mL) ([Exela°Pharma°Sciences 1988](#)). The mass balance study in humans conducted by the Applicant determined the C_{max} for thiocyanate in plasma between 2.4 and 6.6 µg/mL at maximum clinical dose of 400 mg BID. The identity of thiocyanate as rilzabrutinib's primary metabolite was confirmed in a 14-day bridging study in rats at 150 and 500 mg/kg/day. The T_{max} for M1 thiocyanate metabolite ranged from 0.5 to 24 hours on Day 1. There was no notable evidence of M1 accumulation at 150 mg/kg (<2-fold). However, larger 500 mg/kg dose resulted in greater than 2-fold in M1 thiocyanate metabolite in rats which is consistent with adaptive hepatic CYP enzyme to repeat large doses breaking down more rilzabrutinib discussed earlier ([Table 43](#)). The C_{max} for thiocyanate in rats at 150 mg/kg and 500 mg/kg rilzabrutinib approximated the clinical

thiocyanate exposure at maximum clinical dose of 400 mg BID rilzabrutinib. Thiocyanate has the potential to interfere with iodine uptake by inhibiting thyroid sodium-iodide symporter ([EPA 2006](#); [Darrouzet et al. 2014](#)), and be mildly neurotoxicant at very high concentration (60 µg/mL). However, since thiocyanate levels formed from rilzabrutinib were within the normal range reported in humans and similar thiocyanate levels were tested in rats, the overall safety risk is considered to be negligible.

Table 43. Rilzabrutinib and M1 Thiocyanate Metabolite (PRN4400) in Rats

Study# Duration	Dose, mg/kg/Day	Rilzabrutinib (Parent)		PRN4400 (Thiocyanate, M1)		M1/Parent	
		C _{max} F/M	AUC F/M	C _{max} F/M	AUC F/M	C _{max} F/M	AUC F/M
1281-21219	150	1730/801	13200/5250	3170/4860	58100/96200	13/42	30/125
14-day ^a	500	4070/1720	37300/18200	7160/8020 ^b	149000/184000	12/32	27/69

Source: Derived from Study#1281-21219

^a 14-day bridging study conducted in rats to determine the thiocyanate metabolite exposure (PRN4400)

^b Thiocyanate exposure in rats at the highest dose level was comparable to clinical exposure at 400 mg BID

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; F, female; M, male

13.1.4.2. Toxicokinetic Parameters of Rilzabrutinib

The toxicokinetics of rilzabrutinib were evaluated following once daily oral administration in chronic toxicity studies conducted in Sprague Dawley rats ([Table 44](#)) and beagle dogs ([Table 45](#)). Plasma concentrations of rilzabrutinib and its metabolites were measured by validated HPLC tandem mass spectrometry. Oral administration of rilzabrutinib was associated with dose-proportional increases in AUC exposure with no evidence of accumulation (<2-fold) with repeated exposures in rats and dogs. The increases with repeated dosing were lower than normally anticipated at steady state. Low accumulation at steady-state was likely due to adaptive increases in hepatic microsomal CYP enzyme (seen as hepatic hypertrophy) in rats. Rilzabrutinib exposures in female rats was ~2-fold greater than in males. There was no notable sex-related difference (<2-fold) in rilzabrutinib exposures in dogs.

Table 44. Toxicokinetic Parameters of Rilzabrutinib in the Rat Study

		Dose, mg/kg/Day										NOAEL, mg/kg/Day	
Study#	C _{max} ,	15		50		150		300		500			
Duration	AUC	M	F	M	F	M	F	M	F	M	F	M	F
DVR0174	C _{max}	-	-	602	1650	1450	3460	-	-	2350	4270		
4-week	AUC	-	-	1540	3490	5420	13600	-	-	23200	39900	500	500
DVR0207	C _{max}	-	-	715	2690	1400	3220	-	-	2350	5730		
13-week	AUC	-	-	2170	3120	8450	17000	-	-	21300	34700	150	150
DVR0376	C _{max}	258	304	606	2010	1170	3440	2300	4950	-	-		
6-month	AUC	394	721	2060	5760	6860	14100	17800	27200	-	-	150	50

Source: Applicant study #DVR0174, DVR0207, and DVR0376

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; F, female; M, male; NOAEL, no-observed-adverse-effect level

Table 45. Toxicokinetic Parameters of Orally Administered Rilzabrutinib in Dogs

Table 10: Pharmacokinetic Parameters of orally administered riluzole in Dogs											
Dog Study#		Dose, mg/kg/Day									
		15		30		50		100		300	
Duration	Parameters	M	F	M	F	M	F	M	F	M	F
DVR0184	C _{max}	-	-	514	486	-	-	1500	1450	1440	1380
4-week	AUC	-	-	870	942	-	-	5040	3210	4550	7480
DVR0206	C _{max}	-	-	592	484	-	-	736	1670	*	1780
13-week	AUC	-	-	1070	1040	-	-	1980	4410	*	7350
DVR0377	C _{max}	65.7	202	257	339	593	940	-	-	-	-
9-month	AUC	248	377	689	751	2410	3250	-	-	-	-

Source: Applicant study #DVR0184, DVR0206, and DVR0377

* High-dose males were euthanized prior to Day 91 due to clinical signs of toxicity. Values shown here represent those measured on Day 25, Day 91/92, and Day 273 for studies DVR0184, DVR0206, and DVR0377, respectively.

NOAELs: in 4-week study 300 mg/kg/day for both, male and female dogs in 13-week study 30 mg/kg/day for male dogs (not determined in females) in 9-month study 30 mg/kg/day for both, male and female dogs

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; F, female; M, male; NOAEL, no-observed-adverse-effect level

13.1.5. General Toxicology

Study 1281-16101: Six-Month Oral GLP Toxicity Study of Rilzabrutinib in Rats

Key Study Findings

- Target organs of toxicity included brain and gastrointestinal tract.
- Rilzabrutinib-related mortality was noted in five females and 1 male at high dose (HD) but cause of death was not determined except for a HD female that was linked to brain inflammation at exposures 12x higher than the MRHD exposure.
- Microscopic findings included:
 - Brain: Minimal to moderate mixed cell inflammation in meninges, neutrophilic inflammation in neuropil, increased periventricular IBA-1 positivity (microgliosis) and GFAP positivity (astrocyte increase) indicative of neurotoxicity that were partially resolved at the end of recovery. Similar findings were observed in the 13-week toxicology study in rats.
 - Gastrointestinal system: Hemorrhage/inflammation in stomach, duodenum, and esophagus (inflammation only at HD in two females) occurred at exposures that were approximately 9 to 12 times higher than the MRHD exposure.
- Overall, administration of rilzabrutinib shows dose-dependent effects across multiple organ systems. Brain findings suggest neurotoxicity with partial recovery, consistent with previous 13-week study in rats. Inflammatory changes (neutrophil infiltration, microglial activation) in brains occurred without evidence of neuronal damage or degeneration. The occurrence of microgliosis in the absence a direct effect on neurons is consistent with the reported BTK expression pattern in the brain (higher microglial expression, lower neuronal expression).
 - Thyroid changes indicate potential endocrine disruption, with some sex-specific effects. Liver findings suggest adaptive responses even at lower doses. Gastrointestinal effects, observed at high exposures, imply potential for mucosal irritation and/or damage.

- The no observed adverse effect level (NOAEL) was defined at 50 mg/kg/day based on mortality, inflammation of meninges/neuropil and hemorrhage/inflammation of stomach at higher doses with corresponding AUC₀₋₂₄ 2060 and 5760 ng*h/mL in males and females. Exposures at the NOAEL approximated the clinical exposures at the MRHD of 400 mg BID, based on AUC.

Good Laboratory Practice Compliance

Yes.

Table 46. Methods of Six-Month Oral GLP Toxicity Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0, 15, 50, 150, or 300 mg/kg/day
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous, in purified water at concentrations of 0.72-4.32 mg/mL
Species/strain	CrI:WI(Han) Wistar Han rats
Age	7 weeks
Number/sex/group	20/sex/group (Toxicokinetics: 9/sex/group)
Satellite groups	Toxicokinetics: 3/sex/group (0 mg/kg/day rilzabrutinib) 9/sex/group (15, 50, 150, and 300 mg/kg/day)
Deviation from study protocol affecting the interpretation of results	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Applicant-provided report

Abbreviation: GLP, good laboratory practice

Table 47. Observations and Results of the 6-Month Oral (Gavage) Toxicity Study in Rats

Parameter	Major Findings
Mortality	Eight toxicology animals and five toxicokinetic animals did not survive to scheduled sacrifice. Six of eight early deaths in the toxicology groups (3 females at 150 mg/kg/day, 1 male at 300 mg/kg/day, and 2 females at 300 mg/kg/day) were considered rilzabrutinib-related but cause of death was not determined except for a HD female that was linked to brain inflammation.
Clinical signs	No rilzabrutinib-associated clinical signs except dyspnea, red staining around mouth, pallor, and decreased activity at 150 and 300 mg/kg/day. No clinical signs were noted during the recovery period.
Body weights	Group mean body weight was consistently lower in males and females at 300 mg/kg/day (up to -6%). No changes were noted during the recovery period.
Food consumptions ophthalmology, hematology, coagulation, clinical chemistry, urinalysis, or peripheral blood immunophenotyping.	There were no rilzabrutinib-related findings.
Gross pathology	Red and black foci in glandular stomach corresponding to hemorrhage findings in four terminal sacrifice male and females were noted at ≥150 mg/kg/day.

Parameter	Major Findings
Histopathology Adequate battery: yes	Histopathology findings were noted in the thyroid, brain, stomach, duodenum, esophagus, and liver. Rilzabrutinib-related minimal diffuse, follicular cell hypertrophy in females (4/15) at 300 mg/kg were observed in the thyroid. Follicular cell hypertrophy was not observed in males at any dose. The hypertrophy is likely linked to hepatic microsomal induction, as hepatocellular hypertrophy was also observed microscopically in females at the same dose. The transcriptomic data from rat liver spheroids confirmed that rilzabrutinib induces uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes involved in thyroid hormone metabolism, supporting the proposed mechanism (hepatic microsomal enzyme induction) regardless of the atypical sex distribution. In addition, a single male at 50 mg/kg (3M41) exhibited minimal, focal, follicular cell hyperplasia, while another male (5M96) at 300 mg/kg had minimal, focal, C-cell hyperplasia. The link between these findings and rilzabrutinib remains unclear. In the brain, mixed cell inflammation in the meninges was seen in 300 mg/kg/day males and 150 and 300 mg/kg/day females and neutrophilic inflammation in the neuropil was seen in 150 and 300 mg/kg/day females. These findings were not noted during the recovery period. In addition, increased periventricular ionized calcium binding adapter protein 1 (IBA-1) positivity, indicative of microgliosis, was observed in 150 and 300 mg/kg/day males and 50, 150, and 300 mg/kg/day females. Increased periventricular glial fibrillary acidic protein (GFAP) positivity, indicative of increase in astrocytes, was observed in 150 and 300 mg/kg/day males and females. At the recovery necropsy, partial recovery of IBA-1 and GFAP staining positivity was observed. Hemorrhage/inflammation in stomach was seen in two 300 mg/kg/day males, two 150 mg/kg/day females and three 300 mg/kg/day females. Hemorrhage/inflammation was also noted in duodenum (one 300 mg/kg/day female) and esophagus (inflammation only, one 1500 mg/kg/day female and one 300 mg/kg/day female). Minimal hepatocyte hypertrophy was mainly noted at 150 and 300 mg/kg/day in both sexes. The hypertrophy was observed in centrilobular location, which is characteristic of and consistent with microsomal enzyme induction, as this zone contains the highest concentration of cytochrome P450 enzymes and is the primary site where drug-metabolizing enzymes are induced. While the minimal severity may appear relatively mild compared to classical enzyme inducers, the centrilobular distribution pattern supports the enzyme induction mechanism. The histopathology findings in stomach, duodenum, esophagus, and liver were resolved during the recovery period.

Parameter	Major Findings
Toxicokinetics	TK results are shown in Table 48 below. Exposure was generally greater in females than in males. Exposure increased with dose, in a roughly greater than dose proportional manner. Slight drug accumulation was seen in males over repeat dosing.

Table 48. Toxicokinetic Parameters in Rats After Rilzabrutinib Treatment for 6 Months

Dose (mg/kg/day)	Study day	Gender	AUC ₀₋₂₄	C _{max}	t _{1/2}
15	1	Male	324	109	1.53
		Female	858	313	NA
	182	Male	481	258	2.28
		Female	779	304	1.43
50	1	Male	1520	458	2.05
		Female	4060	1520	2.04
	182	Male	2060	606	2.78
		Female	5760	2010	2.90
150	1	Male	3390	599	2.78
		Female	14000	3190	3.08
	182	Male	6860	1170	4.44
		Female	14100	3440	3.87
300	1	Male	9530	1040	3.48
		Female	25600	2690	NA
	182	Male	17800	2300	2.87
		Female	27200	4950	7.74

Source: Applicant study data

Abbreviations: AUC₀₋₂₄, area under the concentration-time curve from time 0 to 24 h; C_{max}, maximum plasma concentration; NA, Not available; t_{1/2}, half-life

Source: Applicant's provided reports

Abbreviations: HD, high dose; TK, toxicokinetic

Study 1281-14255: 13-Week Oral GLP Toxicity Study of Rilzabrutinib in Rats With One-Month Recovery Period

Key Study Findings

- The NOAEL was conservatively determined at 50 mg/kg/day in males and females (C_{max} = 715 and 2690 ng/mL; AUC_{last} = 2170 and 3120 ng*h/mL, respectively) based on rilzabrutinib-related increased IBA-1 and GFAP staining in brain at ≥150 mg/kg/day, which can indicate neuroinflammation, neurodegeneration, and injury, but adverse histopathological findings in the brain were absent.
- Exposures at the NOAEL dose approximated the clinical exposures at the MRHD of 400 mg BID, based on AUC.
- Nonadverse microscopic findings were observed across multiple organ systems in the 13-week rat toxicity study, including the brain, thyroid, liver, lung, and thymus, primarily characterized by their minimal severity and reversible nature.

Good Laboratory Practice Compliance

Yes.

Table 49. Methods of 13-Week Oral GLP Toxicity Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0, 50, 150, or 500 mg/kg/day
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous, in purified water at concentrations of 0.72-4.32 mg/mL
Species/strain	CrI:WI(Han) Wistar Han rats
Age	7 weeks
Number/sex/group	10/sex/group (Recovery: 5/sex/group)
Satellite groups	Toxicokinetics: 3/sex/group (0 mg/kg/day rilzabrutinib); 9/sex/group (50, 150, and 500 mg/kg/day)
Deviation from study protocol affecting the interpretation of results	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Applicant-provided report

Abbreviation: GLP, good laboratory practice

Table 50. Observations and Results of the 13-Week Oral (Gavage) Toxicity Study in Rats

Parameter	Major Findings
Mortality	No rilzabrutinib-related mortality except one toxicokinetic male (7M144) at 150 mg/kg/day found dead on Study Day 41.
Clinical signs	Dose-related clinical signs were wetness/staining around mouth and urogenital area noted mainly at 150, and 500 mg/kg/day. No clinical signs were noted during the recovery period.
Body weights	The administration of 500 mg/kg/day rilzabrutinib produced reduced body weight (14%) in males with transient reduction (23%) of food consumption (first two weeks). Lower dosages of rilzabrutinib did not significantly affect body weight or body weight change in either male or female rats throughout the study.
Hematology	There were no rilzabrutinib-related findings.
Coagulation	Rilzabrutinib-related reduced APTT (up to 21%) was noted at 150 mg/kg/day in males and 500 mg/kg/day in both males and females compared to vehicle controls. No group differences in coagulation parameters were observed at the end of the recovery period.
Clinical chemistry	While female rats administered rilzabrutinib showed elevated aspartate aminotransferase (AST) levels (up to 3.2X) across the dose groups, lacked corresponding increases in other liver enzymes, and had no histological correlates concluded that these AST elevations were not considered adverse. In addition, total bilirubin (TBIL) was decreased (1.75X) in females given 500 mg/kg/day rilzabrutinib at the end of dosing and this finding was resolved at the end of the recovery period.
Urinalysis, or flow cytometry parameters.	There were no rilzabrutinib-related findings.
Gross pathology	There were no rilzabrutinib-related findings.

Parameter	Major Findings
Organ weights	Rilzabrutinib-related increased absolute and relative weights (up to 33%) of liver were noted at 150 and 500 mg/kg/day in both males and females. Minimal microscopic centrilobular hypertrophy (1/10) observed at 500 mg/kg/day in males corresponds to the increased liver weight. Decreased absolute and relative weights (up to 22%) at 500 mg/kg/day were observed in the thymus both males and females. In females, this finding corresponds with minimal decreased lymphocytes in the thymic cortex and medulla at 500 mg/kg/day. The thymic weight decrease, and lymphocyte depletion are most likely secondary effects related to stress rather than a direct pharmacological effect of rilzabrutinib on thymic tissue. This is a common finding in toxicology studies when animals experience systemic stress from high drug doses.
Histopathology Adequate battery: yes	Histopathology findings were noted in the thyroid, liver, thymus, brain, and lung. Rilzabrutinib-related minimal diffuse follicular cell hypertrophy in the thyroid was observed in 7 out of 10 females in the 500 mg/kg/day group, characterized by reduced colloid in follicles and high-cuboidal to columnar follicular cells with vacuolated cytoplasm. This finding, likely an adaptive response to hepatic enzyme induction, was supported by increased liver weights in both sexes at 150 and 500 mg/kg/day doses. The female predominance likely reflects enhanced sensitivity in females to enzyme induction effects. In addition, females consistently showed ~1.5x higher systemic AUC exposures than males. The combination of higher exposure and enhanced sensitivity in females likely reached the threshold for detectable thyroid effects at 500 mg/kg/day, while males might require higher doses to achieve similar tissue-level enzyme induction effects. Minimal hepatocellular hypertrophy was noted in one high dose (500 mg/kg/day) male. One high dose (500 mg/kg/day) female showed decreased lymphocytes in cortex and medulla in thymus. Increased IBA-1 immunopositivity of microglial cells were noted in females ≥ 50 mg/kg/day and males ≥ 150 mg/kg/day. Increased GFAP staining (astrocytes) was seen in all treated rats. In addition, one high dose (500 mg/kg/day) female showed minimal numbers of neutrophils seen in the meninges and perivascularly in the neuropil. Increased alveolar macrophages with accumulations of mucus and mucosal papillary bronchiolar hyperplasia in 4/10 males and 9/10 females at 500 mg/kg/day were observed. Most findings were resolved or tend to be resolved at the end of the recovery periods except minimal IBA-1 staining in one high dose (500 mg/kg/day) male and one mid dose female (150 mg/kg/day). While these microscopic changes in the brain, thyroid, liver, lung, and thymus were rilzabrutinib-related, they were not considered adverse due to their minimal severity, adaptive nature, and evidence of reversibility during the recovery period.

Parameter	Major Findings
Toxicokinetics	TK results are shown in Table 51 below. Exposure was generally greater in females than in males. Exposure increased with dose proportional manner. Slight drug accumulation was seen in males over repeat dosing.

Table 51. Toxicokinetic Parameters in Rats of Rilzabrutinib for the 13-Week Study

Dose (mg/kg/Day)	Study Day	Gender	AUC _{last}	C _{max}	T _{max}
50	1	Male	970	553	0.5
		Female	3580	1150	0.5
	91/92	Male	2170	715	0.5
		Female	3120	2690	0.5
150	1	Male	4030	707	0.25
		Female	9270	2310	0.5
	91/92	Male	8450	1400	1.0
		Female	17000	3220	0.5
500	1	Male	9930	1010	1.0
		Female	23800	3100	0.5
	91/92	Male	21300	2350	0.5
		Female	34700	5730	0.5

Source: Applicant's provided report

Abbreviations: AUC_{last}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Source: Applicant-provided report

Abbreviations: APTT, activated partial thromboplastin time; AUC, area under the concentration-time curve; GFAP, glial fibrillary acidic protein; IBA-1, ionized calcium binding adapter protein 1; TK, toxicokinetic

Study 1281-16100: Nine-Month Oral GLP Toxicity Study of Rilzabrutinib in Beagle Dogs

Key Study Findings

- Target organ of toxicity included liver and stomach.
- Microscopic findings included:
 - Liver: minimal to mild Kupffer cell hypertrophy and increased Kupffer cell pigment at HD in both males and females suggestive of an adaptive immune response to injury and stress rather than acute injury (necrosis) observed in 13-week study.
 - Stomach: mild increased intraepithelial lymphocytes with mucosal atrophy at HD in males indicating injury to the stomach's lining or inflammation and an immune response potentially associated with gastritis.
- The NOAEL was determined at 30 mg/kg/day in both males and females ($C_{\max}$ =257 and 339 ng/mL; AUC_{last} =747 and 812 ng*h/mL, respectively) based on rilzabrutinib-related adverse findings of body weight loss with decreased food consumption and subsequent mortality at 50 mg/kg/day. Exposures at the NOAEL dose approximated the clinical exposures at the MRHD of 400 mg BID in both males and females.

Good Laboratory Practice Compliance

Yes.

Table 52. Methods of Nine-Month Oral GLP Toxicity Study in Dogs

Parameter	Method Details
Dose and frequency of dosing	0, 15, 30, and 50 mg/kg/day
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous, in purified water at concentrations of 18.1-31.1 mg/mL in rilzabrutinib-treated groups and 31.1 mg/mL in control group.
Species/strain	Beagle dog
Age	7-8 months
Number/sex/group	8/sex/group (Terminal: 5/sex/group, Recovery: 3/sex/group)
Satellite groups	Toxicokinetic
Deviation from study protocol affecting the interpretation of results	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Applicant-provided report

Abbreviation: GLP, good laboratory practice

Table 53. Observations and Results of the Nine-Month Oral (Gavage) Toxicity Study in Dogs

Parameter	Major Findings
Mortality	A high dose (50 mg/kg/day) male dog (4M30) in the recovery group was euthanized on Day 53 due to rilzabrutinib-related weight loss ($\downarrow$ 26%), lack of food consumption, and poor health conditions.
Clinical signs	Across all dose groups, rilzabrutinib administration produced dose-dependent gastrointestinal effects (e.g., stool changes and emesis) and localized skin reactions (e.g., erythema in males, eyelid swelling in females).

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WAYRILZ (rilzabrutinib)

Parameter	Major Findings
Body weights	At the high dose (50 mg/kg/day), mean body weights were decreased in male (↓9%) and females (↓18%) compared to control on Day 273. This weight loss was consistent with significantly reduced food consumption throughout the dosing period.
ECG, Hematology, Coagulation, Urinalysis, Gross pathology, and Immunophenotyping (flow cytometry)	There were no rilzabrutinib-related findings.
Clinical chemistry	Male and female dogs showed significant increases in liver enzymes (ALT, AST, ALP) on Days 85/86 and 268/269. These changes were corresponded with minimal to mild microscopic hepatic changes of increased Kupffer cell pigment and Kupffer cell hypertrophy at ≥30 mg/kg/day, without evidence of hepatocellular injury or necrosis that would typically account for the elevated liver function tests. The elevated transaminases (ALT, AST) in the absence of hepatocyte damage suggests a non-hepatocellular mechanism for the enzyme elevation, possibly related to the observed Kupffer cell activation and inflammatory response. These findings were resolved at the end of the recovery periods.
Organ weights	Increased brain (↑16%) to body weight ratio was noted in females at 50 mg/kg/day, likely due to lower body weights in this group.
Histopathology Adequate battery: yes	Rilzabrutinib-related minimal to mild Kupffer cell hypertrophy and increased Kupffer cell pigment in the liver at 50 mg/kg/day, without evidence of hepatocellular injury or necrosis. These findings were resolved at the end of the recovery periods. Mildly increased intraepithelial lymphocytes with mucosal atrophy of the stomach at 50 mg/kg/day in male dogs. IBA-1 staining showed no significant findings in the brain.

Parameter	Major Findings
Toxicokinetics	TK results are shown in Table 54 below. Exposure was generally greater in females than in males. Exposure increased with dose proportional manner. No drug accumulation was seen in both males and females over repeat dosing.

Table 54. Toxicokinetic Parameters in Dogs After Rilzabrutinib Treatment for 9 Months

Dose (mg/kg/Day)	Study Day	Gender	AUC ₀₋₂₄	C _{max}	T _{max}
15	1	Male	501	257	0.88
		Female	1090	559	1.0
	273	Male	280	66	2.9
		Female	401	202	0.94
30	1	Male	920	360	1.3
		Female	1400	558	0.84
	273	Male	747	257	1.8
		Female	812	339	1.3
50	1	Male	2480	806	1.4
		Female	2540	817	1.0
	273	Male	2760	593	2.7
		Female	3640	940	2.5

Source: Applicant-provided report

Abbreviations: area under the concentration-time curve from time 0 to 24 h; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Source: Applicant-provided report

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; IBA-1, ionized calcium binding adapter protein 1; TK, toxicokinetic; AUC, area under the concentration-time curve

Study 1281-14256: 13-Week Oral GLP Toxicity Study of Rilzabrutinib in Beagle Dogs

Key Study Findings

- Target organs of toxicity included liver and lymphoid tissues.
- Microscopic findings included:
 - Liver: Minimal increased single cell necrosis, centrilobular hepatocyte vacuolation, and brown pigment in Kupffer cells (both sexes, most pronounced in females at HD; correlated with elevated ALT (↑7-14X) and total bilirubin (↑2-3X) at mid dose (MD) and HD in females. These findings suggest potential hepatocellular injury, with a more pronounced effect in females at higher doses.
 - Lymphoid tissues: Minimal to moderate decreased lymphocyte numbers in mesenteric lymph nodes (reduced lymphocytes in germinal centers at MD and HD in both males and females, cervical lymph nodes (less consistently affected), and Peyer's patches (decreased lymphocytes across all dose levels, both sexes, affecting B and T lymphocyte compartments; small, poorly formed, or absent germinal centers; reduced cell numbers in T lymphocyte zones).
 - These findings indicate a significant impact of rilzabrutinib on the immune system, particularly on lymphocyte populations. The widespread effect across different lymphoid tissues suggests a systemic immunomodulatory action.
- The NOAEL was determined at 30 mg/kg/day in both males and females (C_{max} = 592 and 484 ng/mL; AUC_{last} = 1070 and 1040 ng*h/mL, respectively) based on rilzabrutinib-related

adverse findings of body weight loss with decreased food consumption and subsequent mortality at ≥ 100 mg/kg/day. Exposures at the NOAEL dose approximated the clinical exposures at the MRHD of 400 mg BID, based on AUC.

Good Laboratory Practice Compliance

Yes.

Table 55. Methods of 13-Week Oral GLP Toxicity Study in Dogs

Parameter	Method Details
Dose and frequency of dosing	0, 30, 100, or 300 mg/kg/day
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous, in purified water at concentrations of 18.1-31.1 mg/mL in rilzabrutinib-treated groups and 31.1 mg/mL in control group.
Species/strain	Beagle dog
Age	9-10 months
Number/sex/group	5/sex/group (Terminal: 3/sex/group, Recovery: 2/sex/group)
Satellite groups	Toxicokinetic
Deviation from study protocol affecting the interpretation of results	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Applicant-provided report
Abbreviation: GLP, good laboratory practice

Table 56. Observations and Results of the 13-Week Oral (Gavage) Toxicity Study in Dogs

Parameter	Major Findings
Mortality	Early terminations were noted at 100 mg/kg/day (2/10, 1 male and 1 female) and at 300 mg/kg/day (7/10, 4 males, 3 females) due to reduced food consumption (also anorexia and/or inappetence) and body weight reduction (~20% of Predose). Mortality was first observed on Day 27 of the study period.
Clinical signs	Frequent observations of abnormal fecal quality (e.g., diarrhea) and emesis at ≥ 100 mg/kg/day.
Body weights	Rilzabrutinib-related significant weight loss was observed in male dogs at ≥ 100 mg/kg/day, leading to early euthanasia and necessitating food supplementation. Statistically significant decreases in food consumption observed in males administered 300 mg/kg. Female dogs showed statistically significant weight reductions at Week 4 (≥ 300 mg/kg) and Week 6 (≥ 100 mg/kg), with a 10% decrease from control at ≥ 100 mg/kg/day on Day 91. Statistically significant decreases in food consumption were observed at ≥ 100 mg/kg.
Ophthalmology, ECG, Hematology, Coagulation, Urinalysis, Gross pathology, and Immunophenotyping (flow cytometry)	There were no rilzabrutinib-related findings.
Clinical chemistry	Rilzabrutinib-related increased ALT ($\uparrow 7$ -14X) and TBIL ($\uparrow 2$ -3X) were noted in female dogs at ≥ 100 mg/kg/day. There was no supportive histopathological evidence for changes of ALT and total bilirubin levels. These findings were resolved at the end of the recovery periods.

Parameter	Major Findings
Organ weights	Rilzabrutinib-related decreased liver weight was noted in female dogs at ≥ 100 mg/kg/day, which corresponded with the increasing ALT and TBIL and histopathological findings of single cell necrosis, centrilobular hepatocyte vacuolation, and brown pigment accumulation in Kupffer cells in liver. Decreased spleen, thyroid, ovary, uterus, and thymus weights (absolute and relative) were noted at ≥ 100 mg/kg/day.
Histopathology Adequate battery: yes	Histopathology findings were noted in the liver and lymphoid tissues. Rilzabrutinib-related minimal increased single cell necrosis, centrilobular hepatocyte vacuolation, and brown pigment in Kupffer cells were noted in both males and females. However, these findings were most pronounced in females at 300 mg/kg/day, which correlated with elevated ALT and total bilirubin levels at ≥ 100 mg/kg/day in females. These findings were resolved or tended to resolve by the end of the recovery period, except for minimal hepatocyte vacuolation in one female at 100 mg/kg/day. Rilzabrutinib treatment resulted in decreased lymphocyte numbers in various lymphoid tissues. The mesenteric lymph nodes were more consistently affected than cervical lymph nodes, with reduced lymphocytes in germinal centers in both males and females at ≥ 100 mg/kg/day. Peyer's patches showed decreased lymphocytes across all rilzabrutinib dose levels in both males and females, affecting both B and T lymphocyte compartments. Germinal centers were small, poorly formed, or absent, and T lymphocyte zones showed reduced cell numbers. These findings were resolved at the end of the recovery period.
Toxicokinetics	TK results are shown in the Table 57 below. Exposure was generally greater in females than in males. Exposure increased with dose proportional manner. No drug accumulation was seen in both males and females over repeat dosing.

Table 57. Toxicokinetic Parameters in Dogs After Rilzabrutinib Treatment for 13 Weeks

Dose (mg/kg/Day)	Study Day	Gender	AUC _{last}	C _{max}	T _{max}
30	1	Male	985	575	0.3
		Female	821	365	0.4
	91/92	Male	1070	592	0.5
		Female	1040	484	0.7
100	1	Male	1500	441	1.4
		Female	5530	1280	1.9
	91/92	Male	1980	736	0.3
		Female	4410	1670	0.5
300	1	Male	2190	718	0.30
		Female	12100	1730	4.9
	91/92	Male	NA	NA	NA
		Female	7350	1780	0.25

Source: Applicant-provided report
Abbreviations: AUC_{last}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; NA, not available; T_{max}, time to maximum concentration

Source: Applicant-provided report
Abbreviations: ALT, alanine aminotransferase; ECG, electrocardiogram; TBIL, total bilirubin; TK, toxicokinetic

13.1.6. Phototoxicity

Table 58. Rilzabrutinib Determined To be Nonphototoxic in In Vitro Studies

Study No /Study Type GLP Status	Key Findings
Study DVR0374/ In Vitro Assessment of Phototoxicity in BALB/C3T3 Cells GLP: no	No phototoxicity PIF =1.93.
Study PHV0082/ Neutral Red Uptake Phototoxicity Assay of SAR444671* in BALB/c 3T3 Mouse Fibroblasts GLP: yes	No phototoxicity PIF =1.11.

Source: Applicant's submission

*SAR444671 denotes rilzabrutinib

The criterion for "phototoxic" is PIF $\geq$ 5.0

Abbreviations: GLP, good laboratory practice; PIF, photo irritation factor

13.1.7. Genotoxicity Studies

Rilzabrutinib is considered not genotoxic under the test conditions used in in vitro and in vivo assessments.

Table 59. Summary of Genetic Toxicology Studies

Study No./ Study Title	Key Study Findings
Study DVR0169/ In Vitro Reverse Mutation Assay in Bacterial Cells. GLP compliance: yes Study is valid: yes	Mutagenicity assessment used rilzabrutinib concentrations up to 5000 µg/plate in <i>Salmonella typhimurium</i> (Strains TA98, TA100, TA1535, and TA1537) with and without S-9 metabolic activation. Rilzabrutinib did not present any evidence of a mutagenic potential.
Study DVR0169/ In Vitro Mammalian Chromosome Aberration Assay in Human Peripheral Blood Lymphocytes. GLP compliance: yes Study is valid: yes	Human peripheral blood lymphocytes were treated with rilzabrutinib up to 45 µg/mL with and without S-9 metabolic activation. There was no increase in structural chromosome aberrations in rilzabrutinib treated cells and rilzabrutinib was considered negative for clastogenicity.
Study DVR0185/ In Vivo Micronucleus Assay in Rats. GLP compliance: yes Study is valid: yes	Rilzabrutinib dose levels were 375, 750, or 1500 mg/kg in female rats and 500, 1000, or 2000 mg/kg in male rats. No mortality occurred at any dose level. No statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the rilzabrutinib-treated groups was observed compared to the negative control group. The positive control (cyclophosphamide) induced a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes. Rilzabrutinib was considered negative for clastogenicity/aneugenicity in the rat (up to 2000 mg/kg in males and 1500 mg/kg in females) bone marrow micronucleus assay.

Source: Applicant's submission

Abbreviations: GLP, good laboratory practice; S-9, mammalian liver postmitochondrial fraction

13.1.8. Carcinogenicity Studies

Study 1281-20014: Twenty-Six Week Oral GLP Carcinogenicity Study of Rilzabrutinib in Tg-RasH2 Mice

Key Study Findings

- Tg-RasH2 mice (25/sex/group) were administered rilzabrutinib at 0, 30, 100, or 300 mg/kg/day by oral gavage in 0.5% aqueous methylcellulose (400 cps) in deionized water for up to 6 months.
- There was no rilzabrutinib-related statistically significant dose response in mortality or increased incidence of neoplastic lesions in male and female Tg-RasH2 mice at doses up to 300 mg/kg/day.
- FDA statistical analysis did not identify imbalances in tumor incidence that were statistically significant by both trend and pairwise comparison.
- The positive control of urethane produced expected increases in tumors.

Good Laboratory Practice Compliance

Yes.

Executive Carcinogenicity Assessment Committee Conclusions

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that there was no evidence of drug-related neoplasms in male and female mice in the 6-month study in Tg-rasH2 mice.

Table 60. Methods for Carcinogenicity Study in RasH2 Mice With Rilzabrutinib Treatment for 26 Weeks

Parameter	Method Details
Dose and frequency of dosing	0 [0.5% methylcellulose (400 cps)], 30, 100, or 300 mg/kg (males and females), Urethane (positive control) - 1000 mg/kg intraperitoneal (IP) (Days 1, 3, 5) Once daily (rilzabrutinib), Once on Days 1, 3, and 5 (Urethane)
Route of administration	Oral gavage (rilzabrutinib), IP injection (Urethane)
Formulation/vehicle	Vehicle for rilzabrutinib: 0.5% aqueous methylcellulose (MC) – 400 cps Vehicle for positive control (Urethane): 0.9% Sodium Chloride (NaCl, saline)
Species/strain	Mouse/ CB6F1-TgN (RasH2)
Age	6 weeks
Number/sex/group	25/sex/group, 10/sex/group (positive control)
Satellite groups	TK group: 6 or 39/Sex/TK Group control or rilzabrutinib groups, respectively.
Deviation from study protocol affecting the interpretation of results	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Applicant-provided report
Abbreviation: TK, toxicokinetic

Study 1281-18051: Twenty-Four Month Oral GLP Carcinogenicity Study of Rilzabrutinib in Rats

Key Study Findings

- Wistar Han rats (60/sex/group) were administered rilzabrutinib at doses of 0, 10, 30, or 100 mg/kg/day and 0, 5, 15, or 50 mg/kg/day in males and females, respectively, by oral gavage in citric acid anhydrous USP (0.29 to 2.89%) in deionized water for up to 2 years.
- There were no rilzabrutinib-related statistically significant effects on mortality, survival, body weight, and increase in incidence of any tumor type in both sexes at doses up to 100 mg/kg/day and 50 mg/kg/day in males and females, respectively.
- The FDA statistical analysis showed no tumor type with a statistically significant positive dose response relationships and/or pairwise comparison relative to vehicle control.

Good Laboratory Practice Compliance

Yes.

Executive Carcinogenicity Assessment Committee Conclusions

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that there was no evidence of drug-related neoplasms in male and female rats in the 2-year study in Wistar rats.

Table 61. Methods for Carcinogenicity Study in Wistar Rats With Rilzabrutinib Treatment for 24 Months

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle control), 10, 30, or 100 mg/kg/day for males; 0 (vehicle control), 5, 15, or 50 mg/kg/day for females. Once daily for 24 months.
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous USP 0, 2, 6, and 20 mg rilzabrutinib in citric acid (0.29%-2.89%) solution.
Species/strain	Rat/ Wistar Han
Age	7 weeks
Number/sex/group	60/sex/group
Satellite groups	TK group: 5 or 10/Sex/TK Group control or rilzabrutinib groups, respectively.
Deviation from study protocol affecting the interpretation of results	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Applicant-provided report

Abbreviations: TK, toxicokinetic; USP, United States Pharmacopeia

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Reproductive Toxicology

Study 20131082: Study of Fertility and Early Embryonic Development to Implantation of Rilzabrutinib Administered by Oral Gavage in Rats

Key Study Findings

- Mean body weights were significantly reduced in both male (↓4-7%) and female (↓2-4%) at 300 mg/kg/day with no effects on reproductive competence. In addition, a reduction in body weight gain was noted in both males (↓27%) and females (↓33%) at 300 mg/kg/day with corresponding reduction in food consumption in both males (↓7%) and females (↓8%) during the pre-mating period, compared to control. In addition, the reduction in body weight gain was ↓28% in males during the entire dosing period.
- There were no rilzabrutinib-related effects on any reproductive parameters, including estrous cycling, mating, fertility, sperm parameters, or any ovarian and uterine parameters.
- The NOAEL for general toxicity was identified as 150 mg/kg/day, for both males and females, based on adverse effects on body weight in males and body weight gain in females noted at 300 mg/kg/day.
- The NOAEL for fertility and reproductive performance in males and the early embryonic development in females was identified as the high dose, 300 mg/kg/day, based on the absence of any adverse effects at the highest dose with exposures approximately 12x and 18x the human AUC exposure at the MRHD of 400 mg BID in male and females, respectively.
- Exposure multiples were based on AUC from 6-month rat study (#1281-16101) since PK data were not assessed in this study.

Good Laboratory Practice Compliance

Yes.

Table 62. Methods of Fertility and Early Embryonic Developmental Study in Rats

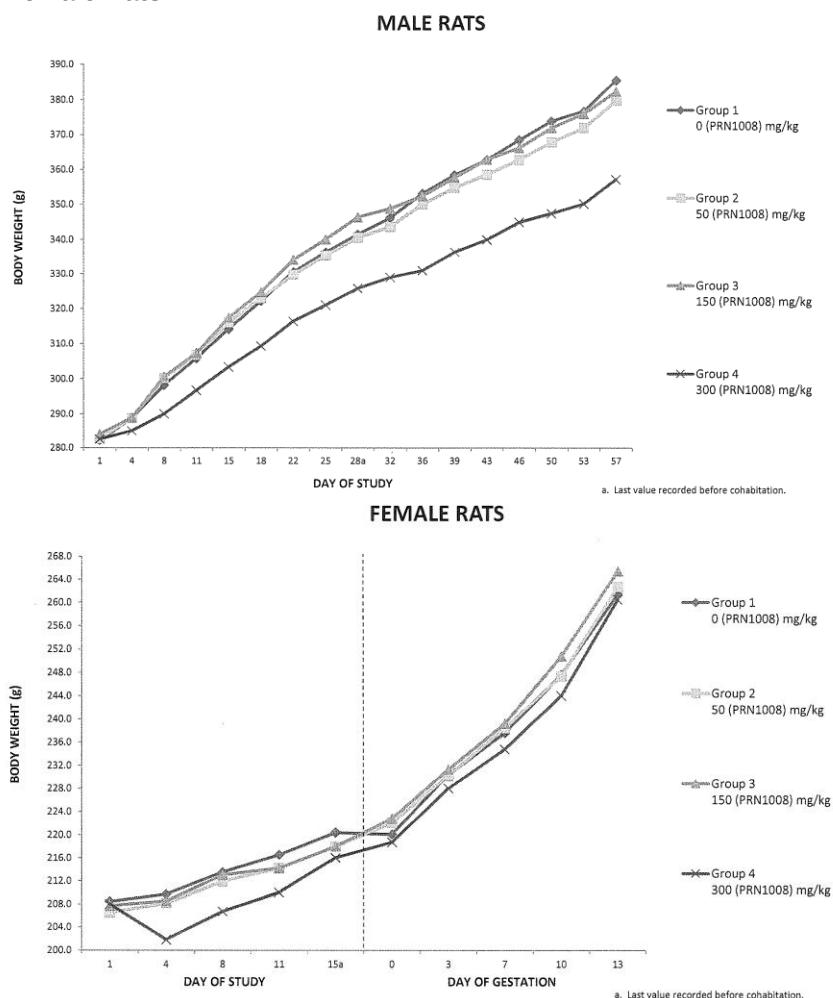
Parameter	Method Details
Dose and frequency of dosing	0, 50, 150, or 300 mg/kg/day
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous, in reverse osmosis deionized water at concentrations of 0.72, 2.16, and 4.32 mg/mL
Species/strain	Wistar Hans male and female rats (CrI: WI(Han))
Number/sex/group	22/sex/group
Satellite groups	No
Study design	Once daily by oral gavage beginning 28 days before cohabitation, during cohabitation and continuing through the day before euthanasia. Males were given a 56 to 59 doses of the test article or the vehicle control article formulations. Females were given the test article or the vehicle control article formulations once daily by oral gavage beginning 15 days before cohabitation, during cohabitation and continuing until GD 7. Animals were euthanized by carbon dioxide inhalation. The study did not include a TK group.
Deviation from study protocol affecting the interpretation of results	None of the deviations impacted the overall integrity of the study or interpretation of study results
Source: Applicant-provided report Abbreviations: GD, gestation day; TK, toxicokinetic	

Table 63. Observations and Results of Fertility and Early Embryonic Developmental Study in Rats

Parameter	Major Findings
Mortality	No rilzabrutinib-related death except one male at 50 mg/kg/day group euthanized on Day 6 due to adverse clinical signs and one female (9484) at 300 mg/kg/day on Day 11, whose deaths were not dose-dependent and were attributed to a dosing error.
Clinical signs	No rilzabrutinib-associated clinical signs except an increased incidence of rales in the 300 mg/kg/day dose group in males (5 animals on 1 or 2 days of the dose period beginning on Day 6).
Body weights	Mean body weights were significantly reduced in both male (↓4%-7%) and female (↓2%-4%) at 300 mg/kg/day (Figure 12). Mean body weight gains at the 300 mg/kg/day dose group were significantly reduced on Day 1-28 and Day 1-57 (up to 28%) in males (Figure 12 and Table 64). Rilzabrutinib-related reduced pre-mating body weight gain on Day 1-15 (33%) was noted with statistical significance at 300 mg/kg/day (Figure 12 and Table 64). No rilzabrutinib-related effects on maternal body weights or maternal mean body weight gains at any dose level during the gestation period. Corresponding decrease in food consumption (9-28%) were observed during pre-mating period (Day 1-4 and Day 4-8) and GD 0-7 in female rats.

Parameter	Major Findings

Figure 12. Rilzabrutinib-Related Effects on Body Weight in Male and Female Rats



Source: Applicant's submission
Broken vertical line separates pre-mating and gestation day in female rats.

Table 64. Percent Changes of Body Weight Gain in Male and Female Rats Compared to Controls After Administration of Rilzabrutinib

Study Day	Dose (mg/kg/Day)		
	50	150	300
Male			
1-28 ^a	-3	+5	-27**
1-57	-7	-5	-28**
Female			
1-15 ^a	-4	-15	-33*
0-13	-2	+3	+1.2

Source: Reviewer generated table
^a Last value recorded before cohabitation.
 +/- denotes increase/decrease.
 ** Significantly different from control (p≤0.01)
 * Significantly different from control (p≤0.05)

Parameter	Major Findings
Spermatogenic evaluation	No rilzabrutinib-related effect on spermatogenesis endpoints, includes mean cauda epididymal sperm numbers, sperm motility, or epididymal weight. However, the caudal epididymal sperm density was significantly increased (20%-25%) in the 50 and 300 mg/kg/day dose groups, which was not considered adverse as this finding has no impact on sperm numbers and motility.
Estrous cycling, mating, and fertility	There were no rilzabrutinib-related effects on the number of days cohabitated prior to mating (2.1 to 2.4 days), the number of rats that mated (100%), or the fertility index (90.5% to 100%). In addition, there were no rilzabrutinib-related effects on any reproductive parameters, including estrous cycling, mating, fertility, or any ovarian and uterine parameters.
Necropsy findings/ cesarean section data	There were no rilzabrutinib-related necropsy findings in female rats.

Source: Applicant's study data
Abbreviation: GD, gestation day

Study AB20877-D: Rilzabrutinib Free Base, Dose Range-Finding Study by the Oral Route (Gavage) in the Pregnant Rat

Key Study Findings

- Rilzabrutinib-related maternal toxicity in rats was associated with dose-related reductions in mean body weight gain (68%) corresponding to reduced food consumption (36%) during the dosing period (gestation day (GD) 6-18), with clinical changes (hypersalivation, abnormal foraging, decreased activity, and piloerection) observed at 500 mg/kg/day.
- There were no rilzabrutinib-related macroscopic findings noted at maternal necropsy examinations.
- The maternal NOAEL for rilzabrutinib is defined at 150 mg/kg/day (mean AUC_{inf} of 15,300 ng*h/mL on GD 17) based on decreased body weight gain, food consumption, with clinical changes (hypersalivation, abnormal foraging, decreased activity, and piloerection) observed at 500 mg/kg/day, with exposures approximately 10-times the clinical AUC exposure at 400 mg BID.
- The NOAEL for fetal developmental and fetal external, visceral, or skeletal malformation or variations was 150 mg/kg/day (mean AUC_{inf} of 15,300 ng*h/mL on GD 17), based on the increased incidence of postimplantation loss (25%), delayed ossification associated with a markedly lower (24%) mean fetal weight, and increased skeletal (scoliosis) and visceral malformations (abnormalities of major vessels, urogenital tract, and kidney) at 500 mg/kg/day, with exposures approximately 10-times the clinical AUC exposure at 400 mg BID.

Good Laboratory Practice Compliance

No.

NDA 219685
WAYRILZ (rilzabrutinib)

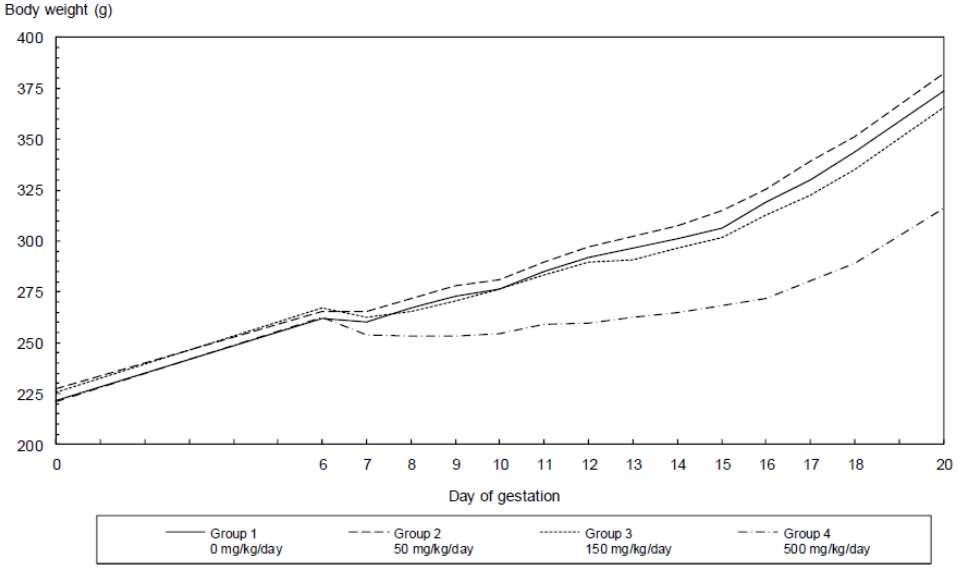
Table 65. Methods of Oral DRF Embryo-Fetal Developmental Study in Rats

Parameter	Details
Dose and frequency of dosing mg/kg/day	0, 50, 150, or 500
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous USP in purified water at concentrations of 2.16 mg/mL and 7.2 mg/mL
Species/strain	Sprague-Dawley rats: Crl:CD(SD)
Number/sex/group	Main study: 10 females/group; satellite study: 4-8 females/group
Study design	Premated female rats treated daily from GD 6 to 17

Source: Applicant's study (Study #AB20877-D)

Abbreviations: DRF, developmental reproductive toxicity; GD, gestation day; SD, Sprague-Dawley

Table 66. Observations and Results of Oral DRF Embryo-Fetal Developmental Study in Rats

Parameters	Major Findings
Mortality	All survived
Clinical signs	Rilzabrutinib-related clinical signs included moderate to marked hypersalivation, abnormal foraging, decreased activity, and piloerection in all animals at 500 mg/kg/day. In addition, hypersalivation with or without abnormal foraging were noted in all females at 150 mg/kg/day.
Body weight and food consumption	Administration of rilzabrutinib resulted in dose-related marked reduction in body weight (up to 15%) (Figure 13) and body weight gain (68%) during dosing period (GD 6-18) at 500 mg/kg/day. In addition, reduction in body weight gain (16%) during dosing period was noted at 150 mg/kg/day. Rilzabrutinib-related marked food consumption reduction (36%) throughout dosing period, most pronounced during first 3 days (GD 6-9) (47%) were observed at 500 mg/kg/day. There were no rilzabrutinib-related effects on lower mean maternal body weights, mean maternal body weight gains in the 50 mg/kg/day dose groups, and on lower mean maternal food consumption in the 50 and 150 mg/kg/day dose groups. Figure 13. Administration of Rilzabrutinib at the High Dose (500 mg/Kg/Day) Resulted in Maternal Toxicity of Lower Mean Body Weights  Source: Applicant's submission
Necropsy findings/ cesarean section data	No rilzabrutinib-related macroscopic findings at maternal necropsy. Gravid uterus weight was reduced (35%) in the 500 mg/kg/day group compared to control due to decreased mean live litter size and fetal weight (24%), while the 50 and 150 mg/kg/day groups showed no rilzabrutinib-related effects on gravid uterus weight. All groups achieved 100% pregnancy rates with viable fetuses at cesarean section, and pre-implantation data were comparable across groups. However, the 500 mg/kg/day group demonstrated higher postimplantation loss (25%) compared to concurrent control, resulting in reduced mean live litter size.

Parameters	Major Findings
Necropsy findings/offspring	Delayed ossification associated with a markedly lower (24%) mean fetal weight and increased skeletal (scoliosis) and visceral malformations (abnormalities of major vessels, urogenital tract, and kidney) occurred at a maternally toxic dose of 500 mg/kg/day.

Source: Applicant's study (Study #AB20877-D)

Abbreviations: DRF, developmental reproductive toxicity; GD, gestation day

Toxicokinetics

- AUC exposure increased with increasing dose in a more than dose-proportional manner between 50 and 150 mg/kg/day and in a less than dose-proportional manner between 150 and 500 mg/kg/day on both GD 6 and GD 17. Specifically, AUC_{inf} increased approximately 4.3-fold when dose increased 3-fold (from 50 to 150 mg/kg/day) and only 1.5-fold when dose increased 3.3-fold (from 150 to 500 mg/kg/day) on GD 6. There were no signs of rilzabrutinib accumulation after repeated dosing.
- T_{max} was consistently rapid, with maximum plasma concentrations observed between 0.25 and 0.5 hours after dosing across most treatment groups, except for females treated at 500 mg/kg/day on GD 6 (T_{max} = 1 hour).

Table 67. Mean Toxicokinetic Parameters in Female Rats After Administration of Rilzabrutinib

Parameter	Dose (mg/kg/Day)		
	50	150	500
	GD 6		
AUC _{inf} (ng*h/mL)	3700	15800	24300
C _{max} (ng/mL)	1280	2600	3010
T _{max} (h)	0.5	0.5	1
	GD 17		
AUC _{inf} (ng*h/mL)	4100	15300	33500
C _{max} (ng/mL)	1080	2200	2760
T _{max} (h)	0.25	0.5	0.25
Accumulation ratio	1.1	0.97	1.3

Source: Applicant's study (Study #AB20877-D)

Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Study 20131080: An Embryo-Fetal Development Study of Rilzabrutinib by Oral Gavage in Rats

Key Study Findings

- Rilzabrutinib-related maternal toxicity in rats was associated with lower mean maternal body weights (4%) and lower mean maternal food consumption (16%) at 300 mg/kg/day from the GD 7 to GD 21 but did not induce fetal developmental or toxic effects.
- There were no rilzabrutinib-related macroscopic findings noted at maternal necropsy examinations, and there were no rilzabrutinib-related effects on any ovarian and uterine parameters. In addition, there were no rilzabrutinib-related external, visceral, or skeletal fetal malformations or variations.
- The maternal NOAEL for rilzabrutinib is defined at 150 mg/kg/day (C_{max} of 3470 and 2970 ng/mL and AUC_(0-t) of 10600 and 18200 ng*h/mL on GD 7 and 17, respectively) based

on the lower mean maternal body weights, lower mean maternal body weight gains, and lower mean maternal food consumption at 300 mg/kg/day. Exposures at the maternal NOAEL were approximately 12-times the clinical AUC exposure at 400 mg BID.

- The NOAEL for fetal developmental and fetal external, visceral, or skeletal malformation or variations was 300 mg/kg/day (C_{max} of 3390 and 3260 ng/mL and $AUC_{(0-t)}$ of 31200 and 15800 ng*h/mL on GD 7 and 17, respectively), based on the absence of any adverse effects at the highest dose with exposures approximately 10-times the clinical AUC exposure at 400 mg BID.

Good Laboratory Practice Compliance

Yes.

Table 68. Methods of Oral Embryo-Fetal Developmental Study in Rats

Parameter	Details
Dose and frequency of dosing mg/kg/day	0, 50, 150, or 300
Route of administration	Oral gavage
Formulation/vehicle	0.05 M HCl in sterile water, pH of 1.35 to 1.80
Species/strain	Wistar Han [CrI:Wi(Han)] rats
Number/sex/group	20/sex/group*
Study design	Premated female rats treated daily from GD 7 to 17.
Deviation from study protocol	Protocol deviations neither affected the overall interpretation of study affecting interpretation of results findings nor compromised the integrity of the study.

Source: Applicant study

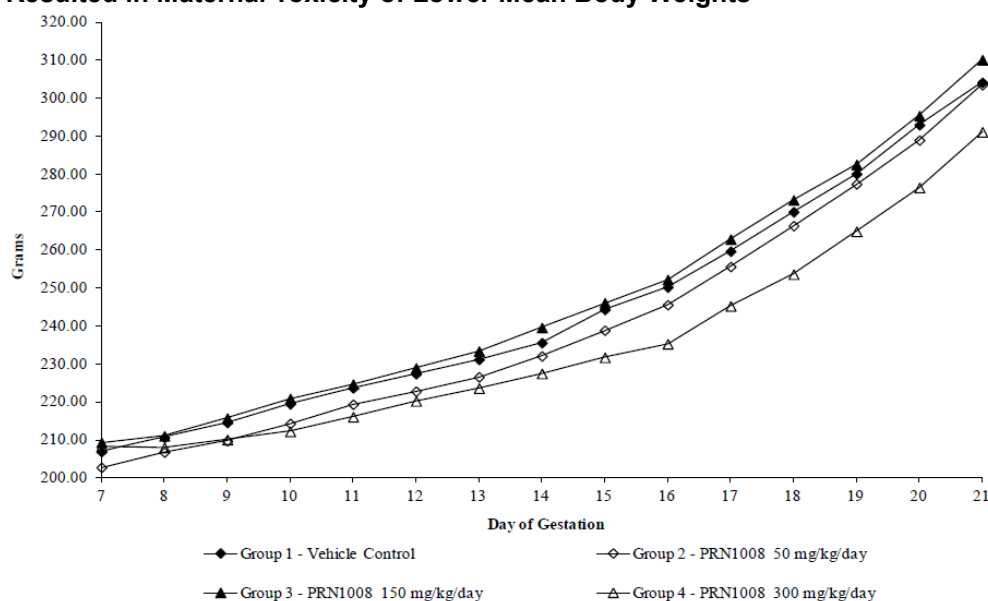
*For toxicokinetic group 6/sex/group

Abbreviation: GD, gestation day

Table 69. Observations and Results of Oral Embryo-Fetal Developmental Study in Rats

Parameters	Major Findings
Mortality	All survived
Clinical signs	No rilzabrutinib-related clinical signs
Body weight	Administration of rilzabrutinib resulted in lower mean maternal body weights (4.28%) (Figure 14), lower mean maternal body weight gains (15%), and lower mean maternal food consumption (16%) at 300 mg/kg/day for the GD 7 to GD 21. There were no rilzabrutinib-related effects on mean maternal body weights (Figure 14), mean maternal body weight gains, and lower mean maternal food consumption in the 50 and 150 mg/kg/day dose groups.

Figure 14. Administration of Rilzabrutinib at the High Dose (300 mg/Kg/Day) Resulted in Maternal Toxicity of Lower Mean Body Weights



Source: Applicant's submission

Necropsy findings/ cesarean section data	There were no rilzabrutinib-related effects on any ovarian or uterine parameter in dams at any dose level and falls within the historical control ranges.
Necropsy findings/ offspring	There were no rilzabrutinib-related fetal body weight changes or external, visceral, or skeletal fetal malformations or variations observed. There was a statistically significant reduction ($p < 0.05$) in the number of litters that had fetuses with an incompletely ossified squamosal bone. This finding was unrelated to rilzabrutinib because it reflected an overall increase in this observation in the control group. In addition, there was a statistically significant increase ($p < 0.01$) in the incidence of supernumerary thoracic rib pairs with associated statistically significant increases and decreases ($p < 0.01$) in the mean numbers of thoracic and lumbar vertebrae at 300 mg/kg/day. This finding was considered unrelated to rilzabrutinib because there was no effect on the total number of presacral vertebrae, indicating a homeotic transformation rather than a true malformation.

Source: Applicant's submission
Abbreviation: GD, gestation day

Toxicokinetics

- AUC exposure increased with increasing dose in an approximately dose proportional manner on GD 7 and in a less than dose proportional manner (4-fold across a 6-fold dose increase from 50 to 300 mg/kg/day) on GD 17. C_{max} exposure increased in a less than dose proportional manner (approximately 1-fold increase across a 6-fold dose increase from 50 to 300 mg/kg/day) on both GD 7 and GD 17 days ([Table 70](#)). There were no signs of rilzabrutinib accumulation after repeated dosing.
- T_{1/2} ranged from 2.67 to 7.07 hours.

Table 70. Mean Toxicokinetic Parameters in Female Rats After Administration of Rilzabrutinib

Parameter	Dose (mg/kg/Day)		
	50	150	300
GD 7			
AUC _(0-t) (ng*h/mL)	4280	10600	31200
C _{max} (ng/mL)	2590	3470	3390
T _{max} (h)	0.5	0.5	0.5
t _{1/2} (h)	2.71	3.42	NR
GD 17			
AUC _(0-t) (ng*h/mL)	3940	18200	15800
C _{max} (ng/mL)	2300	2970	3260
T _{max} (h)	0.5	1	0.5
t _{1/2} (h)	2.67	3.7	7.07
Accumulation ratio	0.9	1.7	0.5

Source: Applicant's submission

NR = Not reportable due to values not meeting acceptance criteria

Abbreviations: AUC_(0-t), area under the concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum plasma concentration; GD, gestation day; T_{max}, time to maximum concentration; t_{1/2}, half-life

Study AB20878: Rilzabrutinib Free Base, Dose Range-Finding Study by the Oral Route (Gavage) in the Pregnant Rabbit

A non-GLP dose range-finding study was conducted in pregnant New Zealand White rabbits to evaluate the embryo-fetal development effects of rilzabrutinib administered orally at 50, 100, and 150 mg/kg/day during organogenesis (Days 6 to 19 of gestation).

Malformations observed in the rabbit dose range-finding study were considered equivocal and not rilzabrutinib-related due to the lack of dose-response relationship and occurrence as isolated findings in single fetuses from individual litters. Given the absence of clear rilzabrutinib-related developmental effects, no further detailed discussion of malformation findings from this dose range-finding study is included in this developmental toxicity assessment.

Study 20131081: An Embryo-Fetal Development Study of Rilzabrutinib by Oral Gavage in Rabbits

Key Study Findings

- Rilzabrutinib-related maternal toxicity in rabbits was associated with lower mean maternal body weight gains (29%) and lower mean maternal food consumption (11%) compared to concurrent control at 100 mg/kg/day.

- There were no macroscopic findings noted at maternal necropsy examinations, and there were no rilzabrutinib-related effects on any ovarian and uterine parameters. In addition, there were no rilzabrutinib-related effects on embryo-fetal viability, fetal body weights, or fetal external, visceral, or skeletal morphology at any dose level.
- The maternal NOAEL for rilzabrutinib is defined at 30 mg/kg/day ($C_{\max}$ of 232 and 340 ng/mL and $AUC_{(0-t)}$ of 175 and 313 ng*h/mL on GD 7 and 19, respectively) based on lower body weight gain and food consumption at 100 mg/kg/day, which is approximately 0.2-times the clinical AUC exposure at 400 mg BID.
- The NOAEL for fetal developmental and fetal external, visceral, or skeletal malformation or variations in rabbit was defined at 100 mg/kg/day ($C_{\max}$ of 2240 and 5110 ng/mL and $AUC_{(0-t)}$ of 3980 and 6920 ng*h/mL on GD 7 and 19, respectively), based on the absence of any adverse effects at the highest dose, which is approximately 4.5-times the clinical AUC exposure at 400 mg BID.

Good Laboratory Practice Compliance

Yes.

Table 71. Methods of Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing	0, 10, 30, or 100 mg/kg/day
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous in sterile water, at concentrations of 0.72, 2.16, and 7.2 mg/mL
Species/strain	New Zealand white rabbits
Number/sex/group	20/group
Satellite groups	No
Study design	Pregnant rabbits were treated from GD7 to GD19
Deviation from study protocol affecting interpretation of results	No notable deviation

Source: Applicant's submission
Abbreviation: GD, gestation day

Table 72. Observations and Results of Oral Embryo-Fetal Developmental Study in Rabbits

Parameters	Major Findings
Mortality	All survived
Clinical signs	No rilzabrutinib-related clinical signs occurred
Body weight	Administration of rilzabrutinib resulted in lower mean maternal body weight gains (29%), and lower mean maternal food consumption (11%) at 100 mg/kg/day for the GD 7 to GD 20. There were no rilzabrutinib-related effects on mean maternal body weights, mean maternal body weight gains, and lower mean maternal food consumption in the 10 and 30 mg/kg/day dose groups.
Necropsy findings/cesarean section data	There were no rilzabrutinib-related effects on any ovarian or uterine parameter in dams at any dose level and falls within the historical control ranges.
Necropsy findings/offsprings	There were no rilzabrutinib-related fetal body weight changes or external, visceral, or skeletal fetal malformations or variations observed. There were statistically significant increases and decreases ($p \leq 0.05$) in the mean numbers of thoracic and lumbar vertebrae, respectively at 100 mg/kg/day. This finding was considered unrelated to rilzabrutinib because there was no effect on the total number of presacral vertebrae, indicating a homeotic transformation rather than a true malformation. A similar homeotic transformation was also observed in the rat embryo-fetal development study at 300 mg/kg/day.

Source: Applicant's submission
Abbreviation: GD, gestation day

Toxicokinetics

- Accumulation ratios were 2.9, 1.8, and 1.76 at the 10, 30 and 100 mg/kg/day dose levels, respectively for the rilzabrutinib from GD 7 to GD 19. Accumulation ratio appeared to decrease with increasing dose.
- $T_{1/2}$ ranged from 0.6 to 0.8 hours.

Table 73. Mean Toxicokinetic Parameters in Female Rabbits After the Administration of Rilzabrutinib

Parameter	Dose (mg/kg/Day)		
	10	30	100
GD 7			
AUC _(0-t) (ng*h/mL)	9.56	175	3980
C _{max} (ng/mL)	10.7	232	2240
T _{max} (h)	0.5	0.5	0.8
T _{1/2} (h)	NC	NC	0.6 ¹
GD 19			
AUC _(0-t) (ng*h/mL)	27.3	313	6920
C _{max} (ng/mL)	35.1	340	5110
T _{max} (h)	0.5	0.5	0.5
T _{1/2} (h)	NC	0.7 ¹	0.6
Accumulation ratio	2.9	1.8	1.76

Source: Applicant's submission

¹ denotes a value determined by N=1

Abbreviations: AUC_(0-t), area under the concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum plasma concentration; GD, gestation day; NC, not calculable; T_{max}, time to maximum concentration; t_{1/2}, half-life

Study 00958013: An Oral (Gavage) Study of the Effects of Rilzabrutinib on Pre- and Postnatal Development, Including Maternal Function in Rats

Key Study Findings

- Rilzabrutinib-related maternal toxicity in rats was associated with lower mean body weights, body weight gains, and food consumption during gestation compared to concurrent control at 150 and 300 mg/kg/day.
- Decreased mean body weight gain corresponds to the clinical observations includes increased occurrence of small stature in 22 pups from 12 litters in first filial (F1) male and female pups at 300 mg/kg/day during the preweaning period.
- There were no rilzabrutinib-related effects on F1 males and females at any dose.
- The NOAEL for the maternal (F0) toxicity was 50 mg/kg/day based on lower mean body weight gain, and food consumption during gestation compared to concurrent control at 150 and 300 mg/kg/day, which provides approximately 3.7-times the clinical AUC exposure at 400 mg BID.
- There were no direct rilzabrutinib-related F1 neonatal/developmental effects observed. The increased occurrence of small stature at 300 mg/kg/day was considered secondary to maternal toxicity (decreased body weight gains and food consumption) rather than direct developmental toxicity.
- The NOAELs for F1 parental toxicity, F1 reproductive toxicity, and F2 embryonic toxicity were 300 mg/kg/day, based on the absence of any adverse effects at the highest dose, which is approximately 18-times the clinical AUC exposure at 400 mg BID.
- Exposure multiples were based on AUC from 6-month rat study (#1281-16101) since PK data were not assessed in this study.

Good Laboratory Practice Compliance

Yes.

Table 74. Methods of Oral Pre- and Postnatal Development, Including Maternal Function in Rats

Parameters	Method Details
Dose and frequency of dosing	0, 50, 150, or 300 mg/kg/day
Route of administration	Oral gavage
Formulation/vehicle	Citric acid anhydrous in reverse osmosis deionized water at concentrations of 0.72, 2.16, and 4.32 mg/mL.
Species/strain	SD Rats
Number/sex/group	25/group
Satellite groups	No
Study design	Standard pre- and postnatal developmental study; pre-mated rats (F0) were orally administered rilzabrutinib from gestation Day 6 through lactation Day 20. The F1 animals were not directly exposed to the rilzabrutinib at any time during the study; the offspring of the F0 parental generation were potentially exposed to the test article in utero and while nursing.
Deviation from study protocol affecting interpretation of results	All the deviations were accidental with no meaningful/consequential impact.

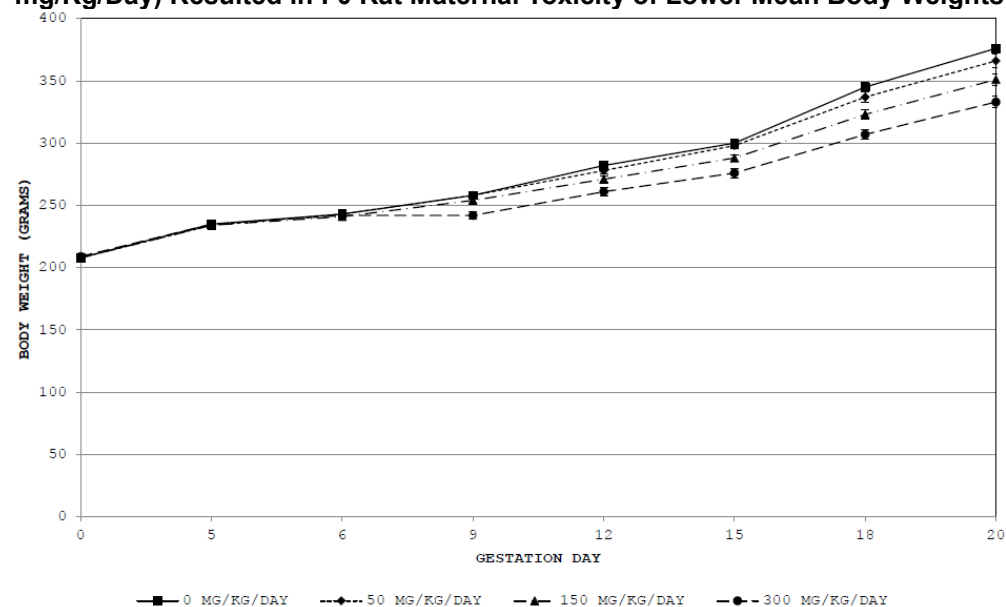
Source: Applicant's submission

Abbreviation: SD, Sprague Dawley; F1, first filial

Table 75. Observations and Results of Oral Pre- and Postnatal Development, Including Maternal Function in Rats

Parameters	Major Findings
	F0 Generation
Mortality	There were no rilzabrutinib-related effects on F0 maternal rat's survival, except two females in the 150 mg/kg/day group and one female in the 300 mg/kg/day group, whose deaths were attributed to dosing errors.
Clinical signs	No rilzabrutinib-related clinical signs occurred.
Body weight	Administration of rilzabrutinib produced lower mean body weights, body weight gains, and food consumption during gestation compared to concurrent control at 150 and 300 mg/kg/day (Figure 15 and Table 76). Mean absolute body weights in the 300 mg/kg/day group were up to 10.5% lower than the control group during Lactation Days 1–17 (Figure 16). Slightly lower food consumption was noted in the 300 mg/kg/day group females throughout lactation (Figure 15 and Table 76).
Food consumption	

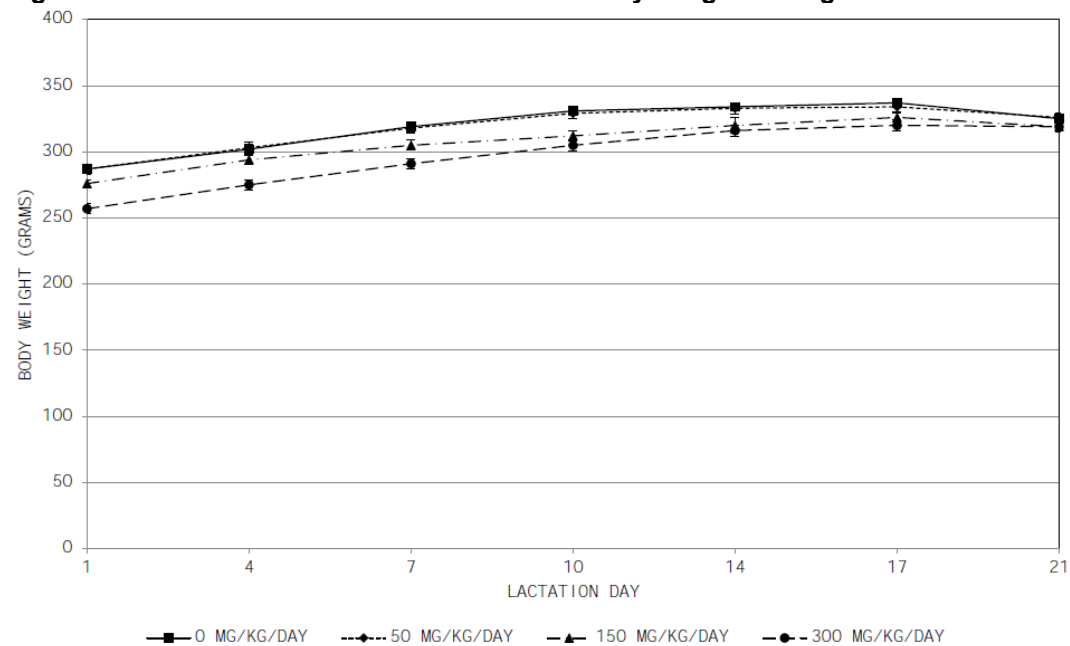
Figure 15. Administration of Rilzabrutinib at the Mid Dose (150 mg/Kg/Day) and High Dose (300 mg/Kg/Day) Resulted in F0 Rat Maternal Toxicity of Lower Mean Body Weights



Source: Applicant's submission

Parameters	Major Findings

Figure 16. Effect of Rilzabrutinib on Maternal Body Weight During Lactation Period



Source: Applicant's submission

Parameters	Major Findings

Table 76. F0 Rat Maternal Toxicity of Lower Mean Body Weights at the Mid Dose (150 mg/Kg/Day), High Dose (300 mg/Kg/Day) and Lower Mean Food Consumption at the High Dose (300 mg/Kg/Day), After the Administration of Rilzabrutinib

Daily Dose (mg/kg)	0 (Control)	50	150	300
F₀ Females:				
Gestation Body Weight Changes, g				
G 6-9	15	16	13	0**
G 9-12	24	20	17**	19
G 15-18	45	40	35**	31**
G 6-20	133	123	110**	91**
Lactation Body Weight g (%) ^a				
L 1	287	287 (0.0)	276 (-3.8)	257 (-10.5)**
L 4	302	303 (0.3)	294 (-2.6)	275 (-8.9)**
L 7	319	318 (-0.3)	305 (-4.4)*	291 (-8.8)**
L 10	331	329 (-0.6)	312 (-5.7)**	305 (-7.9)**
L 14	334	333 (-0.3)	320 (-4.2)	316 (-5.4)*
L 17	337	334 (-0.9)	326 (-3.3)	320 (-5.0)**
Gestation Food Consumption g/animal/day				
G 6-9	19	18	18	13**
G 9-12	20	20	19*	17**
G 12-15	22	22	21	19**
G 15-18	25	23	22*	20**
G 18-20	26	25	24	21**
Lactation Food Consumption g/animal/day				
L 1-4	37	36	37	35
L 4-7	43	42	40	38**
L 7-10	51	51	50	47

- No noteworthy findings; G= Gestation day; L= Lactation day

* p<0.05 ** p<0.01 when compared to the control group using Dunnett's test

^a= For all groups, means are shown. For test article-treated groups, percent differences from control are shown in parentheses. Statistical significance is based on actual data (not on the percent differences).

Source: Applicant's submission

Gestation length and parturition	No rilzabrutinib-related findings were noted on mean gestation lengths or the process of parturition.
Macroscopic findings	No rilzabrutinib-related macroscopic findings were observed.
F1 Generation (Prewaning)	
Litter data and postnatal survival	No rilzabrutinib-related findings were noted. The mean number of F1 pups born, live litter size, percentage of males per litter at birth, and postnatal survival between birth and postnatal days were unaffected by the F0 maternal with the rilzabrutinib exposure across the dose groups.

Parameters	Major Findings
Pup observations	Total 4 pups from 4 litters, 5 pups from 4 litters, and 7 pups from 5 litters were found dead or euthanized in the control, 50, and 150 mg/kg/day groups, respectively (Table 77). In the 300 mg/kg/day group, 22 pups from 12 litters were noted with a small stature during the preweaning period compared to 3 pups from 3 litters in the control group (Table 77). The increased occurrence of small stature in this group corresponded with the lower mean absolute body weights noted for the F0 maternal animals during gestation and lactation.

Table 77. Administration of Rilzabrutinib at the High Dose (300 mg/Kg/Day) Resulting in Rat Pups Toxicity of Deaths and Increased Occurrence of Small Stature

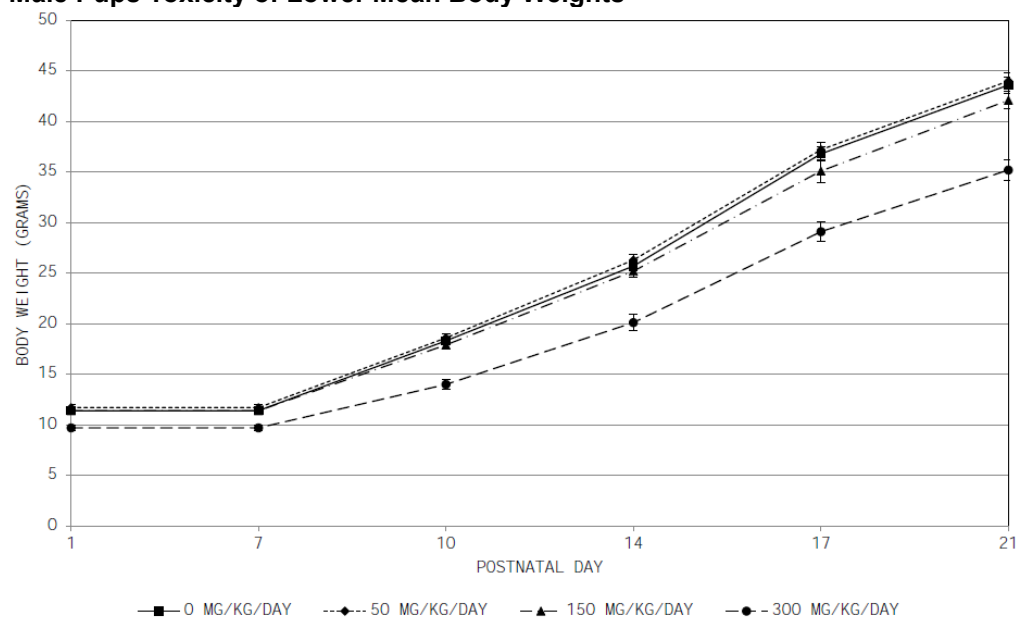
CATEGORY FINDING	GROUP:	1	2	3	4
NORMAL					
NO SIGNIFICANT CLINICAL OBSERVATIONS		1639/325	1483/287	1454/291	1460/304
	LITTERS:	25	24	25	25
DISPOSITION					
FOUND DEAD; PARTIALLY CANNIBALIZED		0/ 0	0/ 0	0/ 0	1/ 1
	LITTERS:	0	0	0	1
FOUND DEAD; MECHANICAL INJURY		0/ 0	1/ 1	0/ 0	0/ 0
	LITTERS:	0	1	0	0
FOUND DEAD		3/ 3	4/ 4	6/ 6	6/ 6
	LITTERS:	3	3	5	4
EUTHANIZED IN EXTREMIS		1/ 1	0/ 0	1/ 1	0/ 0
	LITTERS:	1	0	1	0
EUTHANIZED; DEATH OF DAM		0/ 0	0/ 0	19/ 19	8/ 8
	LITTERS:	0	0	2	1
BODY/INTEGUMENT					
SUBCUTANEOUS HEMORRHAGE FACIAL AREA		0/ 0	1/ 1	0/ 0	2/ 1
	LITTERS:	0	1	0	1
SMALL STATURE		8/ 3	6/ 3	17/ 6	61/ 22
	LITTERS:	3	3	6	12

1- 0 MG/KG/DAY 2- 50 MG/KG/DAY 3- 150 MG/KG/DAY 4- 300 MG/KG/DAY					

Source: Applicant's submission

Parameters	Major Findings
Body weight	Rilzabrutinib-related effects were observed in both male and female F1 pups (Figure 17 and Figure 18) at 300 mg/kg/day, provided evidence of significantly lower (9-9.3%) body weights in F1 pups compared to concurrent control. This trend persisted through postnatal day 1-21, with reductions of 14.9-23.5% in males and 12.8%-20.6% in females.

Figure 17. Administration of Rilzabrutinib at the High Dose (300 mg/Kg/Day) Resulted in Rat F1 Male Pups Toxicity of Lower Mean Body Weights



Source: Applicant's submission
Abbreviation: F1, first filial

Parameters	Major Findings																																			
	Figure 18. Administration of Rilzabrutinib at the High Dose (300 mg/Kg/Day) Resulted in Rat F1 Female Pups Toxicity of Lower Mean Body Weights <table><caption>Estimated data from Figure 18: Rat F1 Female Pups Body Weight (Grams) vs Postnatal Day</caption><thead><tr><th>Postnatal Day</th><th>0 MG/KG/DAY</th><th>50 MG/KG/DAY</th><th>150 MG/KG/DAY</th><th>300 MG/KG/DAY</th></tr></thead><tbody><tr><td>1</td><td>10.5</td><td>10.5</td><td>10.5</td><td>10.5</td></tr><tr><td>7</td><td>10.5</td><td>10.5</td><td>10.5</td><td>10.5</td></tr><tr><td>10</td><td>17.5</td><td>17.5</td><td>17.5</td><td>14.0</td></tr><tr><td>14</td><td>25.0</td><td>25.0</td><td>25.0</td><td>20.0</td></tr><tr><td>17</td><td>36.0</td><td>36.0</td><td>36.0</td><td>29.0</td></tr><tr><td>21</td><td>43.0</td><td>43.0</td><td>43.0</td><td>35.0</td></tr></tbody></table> Source: Applicant's submission Abbreviation: F1, first filial	Postnatal Day	0 MG/KG/DAY	50 MG/KG/DAY	150 MG/KG/DAY	300 MG/KG/DAY	1	10.5	10.5	10.5	10.5	7	10.5	10.5	10.5	10.5	10	17.5	17.5	17.5	14.0	14	25.0	25.0	25.0	20.0	17	36.0	36.0	36.0	29.0	21	43.0	43.0	43.0	35.0
Postnatal Day	0 MG/KG/DAY	50 MG/KG/DAY	150 MG/KG/DAY	300 MG/KG/DAY																																
1	10.5	10.5	10.5	10.5																																
7	10.5	10.5	10.5	10.5																																
10	17.5	17.5	17.5	14.0																																
14	25.0	25.0	25.0	20.0																																
17	36.0	36.0	36.0	29.0																																
21	43.0	43.0	43.0	35.0																																
F1 developmental landmark data	Rilzabrutinib-related effects were observed in both male and female F1 pups at 300 mg/kg/day, provided evidence that the mean age of balanopreputial separation (44.8 days) was comparable to the control (44.0 days), however body weight at separation was 8.2% lower, though not statistically significant. Vaginal patency occurred at a similar age (34.0 vs. 34.4 days in controls); however, body weight was significantly lower (12.3%).																																			
F1 neurobehavioral data	No rilzabrutinib-related effects on locomotor activity, prepulse inhibition of the acoustic startle response, or on spatial learning and memory in the Morris water maze in either sex.																																			

NDA 219685
WAYRILZ (rilzabrutinib)

Parameters	Major Findings
	F1 Generation (Postweaning)
Mortality and clinical observations	No rilzabrutinib-related findings observed except for one male was found dead on postnatal day 64 in the 300 mg/kg/day group, with no clinical observations, necropsy findings, or body weight effects corresponding with the death.
Body weight	Rilzabrutinib-related lower body weight (6.5%-15.4% in male and 6.3%-12.4% in female) were observed through Postnatal Day 28-70 at 300 mg/kg/day. This finding was corresponded to F0 maternal administration of rilzabrutinib but not considered adverse based on the lack of effects on mean body weight gain following weaning.
Gestation	No rilzabrutinib-related findings observed.
Reproductive performance	No rilzabrutinib-related findings observed.
Necropsy findings	There were no rilzabrutinib-related necropsy findings.
	F2 Generation
Necropsy findings/ cesarean section data	There were no rilzabrutinib-related effects on mean numbers of corpora lutea, implantation sites, and intrauterine survival of the F2 embryos at any dose groups.
Source: Applicant's submission Abbreviations: F1, first filial	

14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding

The plasma protein binding of rilzabrutinib at 1 μ M, determined in human plasma by using equilibrium dialysis method, averaged 97.5%. Similar high plasma protein binding, with unbound fractions ranging from 3.67% to 3.81%, was observed using rilzabrutinib at concentrations of 0.1, 1, 5 and 10 μ M.

14.1.2. Distribution in Red Blood Cells

Rilzabrutinib was not preferentially partitioned into red blood cells (RBCs), with blood-to-plasma ratio of 0.47 at 5 μ M.

14.1.3. Metabolism Studies

14.1.3.1. Rilzabrutinib as Substrate

The metabolism of rilzabrutinib was studied in human liver fractions and recombinant microsomes.

Biotransformation of rilzabrutinib via oxidation, dealkylation, and/or hydrogenation was noted using human liver S9 fractions.

Incubation of rilzabrutinib with recombinant CYP enzymes suggested that rilzabrutinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP2D6.

14.1.3.2. Potential for CYP Enzyme Inhibition

Rilzabrutinib was evaluated as a direct inhibitor of CYP3A4 over the concentration range of 0.1 to 50 μ M in human liver microsomes (HLM).

Rilzabrutinib exhibited direct inhibition of CYP3A4/5 (IC_{50} 1.09 μ M; midazolam). The IC_{50} , k_{inact} , and K_I values were normalized with protein binding of rilzabrutinib to HLM. Estimated R_1 and R_{1gut} values suggest the potential for rilzabrutinib to cause DDIs resulting from inhibition of CYP3A4/5, but not other CYP enzymes.

The ability of rilzabrutinib to inhibit human liver uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1 and sulfotransferase 1E1 enzymes was evaluated over the concentration range of 3 to 200 μ M in HLM. Rilzabrutinib exhibited inhibition of UGT1A1 and sulfotransferase 1E1, with an IC_{50} value of 6.46 μ M (alamethicin) and 28.9 μ M (estradiol), respectively. These results show the poor inhibitory potential of rilzabrutinib in comparison to measured clinical exposure, with a margin of more than 800-fold above the clinical C_{max} of unbound rilzabrutinib ($\sim$ 5 ng/mL).

14.1.3.3. Potential for CYP Enzyme Induction

Rilzabrutinib was evaluated as an inducer of CYP1A2, CYP2B6 and CYP3A4 expression in human hepatocytes. Treatment of cultured human hepatocytes with up to 30 μ M rilzabrutinib caused increase in mRNA expression of CYP3A in one of the three donors. Calculated maximum drug-induced effect ($E_{\max}$) was 4.4-fold, and concentration of drug that achieved half-maximal effect values for induction of CYP3A enzyme mRNA expression was 1.49 μ M. Based on these in vitro data, rilzabrutinib has a calculated R3 value of 1.12, thus is a potential inducer of CYP3A.

14.1.4. Transporter Characterization

14.1.4.1. Rilzabrutinib as Substrate

To determine if rilzabrutinib is a substrate of P-gp, the bidirectional permeability of rilzabrutinib at 1 μ M across Caco-2 cells was measured (Study DVR0501). Rilzabrutinib (1 μ M) had moderate permeability (apparent permeability [P_{app}], $A \rightarrow B = 1.713 \times 10^{-6}$ cm/sec and P_{app} , $B \rightarrow A = 5.299 \times 10^{-6}$ cm/sec) in Caco-2 cells and a concomitant moderate net flux ratio of 3.1 in the absence of a P-gp inhibitor. Overall, rilzabrutinib exhibited a flux ratio greater than 2 in this experiment, suggesting that it may be a potential substrate of P-gp efflux transporter expressed in Caco-2 cells.

Madin-Darby canine kidney (MDCK)- multidrug resistance mutation (MDR1) cells were also used to determine whether rilzabrutinib is a P-gp substrate at the concentration of 1 μ M (Study DVR0091). Rilzabrutinib (1 μ M) had moderate permeability in MDCK-MDR1 cells and a concomitant moderate net flux ratio of 4.3 in the absence of the P-gp inhibitor. The addition of the P-gp inhibitor reduced the net flux ratio by more than 50% to 0.8. These results indicate that rilzabrutinib may be a potential P-gp substrate.

To determine if rilzabrutinib is a substrate of P-gp and BCRP, the bidirectional transport of rilzabrutinib (1 to 100 μ M) across Caco-2/TC7 cells was measured in the presence and absence of P-gp and BCRP inhibitors, PSC833 and fumitremorgin C (FTC), respectively (Study TRS0024). The efflux ratio decreased from 12.3 in the absence of inhibitor to 0.387 in the presence of PSC833 and to 3.51 in the presence of FTC. The suppression of transport asymmetry in the presence of PSC833 and the reduction of transport symmetry in the presence of FTC indicated that efflux transporters (P-gp and BCRP) are involved in rilzabrutinib transport.

Rilzabrutinib was investigated for its potential to be a substrate for organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, OATP1B1, OATP1B3 (in MDCK-II cells), BCRP (in Caco-2 cells), P-gp (in MDCK-MDR1), or BSEP (in Sf9 cell vesicles) (Study DVR0158). Results show that rilzabrutinib was not a substrate for OAT1, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, or BCRP. At 10 μ M rilzabrutinib, uptake was 13.8% higher in OAT3-transfected cells than in control cells, however, this difference was less than 2-fold, therefore rilzabrutinib was not considered to be a substrate of OAT3. The efflux ratios for P-gp were approximately 20 and 15 for rilzabrutinib at 1 and 10 μ M, respectively, and the efflux ratio dropped to 1 upon the addition of the P-gp inhibitor verapamil. Therefore, these findings indicate that rilzabrutinib is a P-gp substrate.

Based on the above, rilzabrutinib is a substrate of P-gp.

14.1.4.2. Potential Transporter Inhibition

The ability of rilzabrutinib to inhibit human ABC efflux transporters P-gp (ABCB1/MDR1), BCRP (ABCG2/MXR), and BSEP (ABCB11/SPGP) was evaluated (Study DVR0157). The ability of rilzabrutinib (3 μ M) to inhibit the transport of reference substrates was assessed using MDCK-MDR1 cells expressing P-gp (digoxin), Caco-2 cells expressing BCRP (genistein), or Sf9 membrane vesicles containing human BSEP (taurocholate). The results indicate that rilzabrutinib did not inhibit P-gp or BCRP at 3 μ M.

The ability of rilzabrutinib to inhibit human uptake transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3 was evaluated indirectly by assessing accumulation of probe substrates in MDCK-II cells overexpressing individual uptake transporters (Study DVR0157). The results indicate that rilzabrutinib did not inhibit OAT3, OCT1, OCT2, or OATP1B3 at 3 μ M.

Rilzabrutinib (0.008 to 26 μ M) was evaluated as an inhibitor of the solute carrier transporters OAT1, OAT3, OCT1, OCT2, multidrug and toxin extrusion protein (MATE)1, MATE2-K, OATP1B1, and OATP1B3 by measuring the inhibition of substrate uptake after incubation with HEK293 cells (Study TRI0053). The results suggest that rilzabrutinib is an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2-K, OCT1, OCT2, OAT1, OAT3, and OCT2 with IC₅₀ values of 0.705 μ M, 0.180 μ M, 2.9 μ M, 6.71 μ M, 2.93 μ M, 5.36 μ M, 22.2 μ M, and 36.4 μ M, respectively. Inhibitory potential of rilzabrutinib of efflux transporters (BCRP and BSEP) was also assessed in this study. Results show that rilzabrutinib has the ability to inhibit BCRP and BSEP with IC₅₀ values of 7.61 μ M and 1.42 μ M, respectively.

P-gp was found to be inhibited by rilzabrutinib with IC₅₀<10 μ M in study report 0055.

Based on the comparison of calculated I_{gut}/IC₅₀ values, R values with the current FDA recommended thresholds, there is potential for DDIs with P-gp, BCRP, and OATP1B3 substrates. Rilzabrutinib is also an inhibitor of BSEP.

The clinically relevant effect of rilzabrutinib on the systemic exposures of transporter substrates was investigated via PBPK modeling and simulations (Study PBS0017).

14.2. In Vivo Studies

14.2.1. Study PRN1008-001: a Phase 1, Randomized, Double-Blind, Placebo-Controlled Ascending-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Orally Administered Rilzabrutinib

Study Design

This was a two-part study. Part A contained a total of 40 healthy participants, 8 participants per cohort (6 active/2 placebo) were treated with single dose of rilzabrutinib oral liquid formulation (50, 150, 300, 600, and 1200 mg) or placebo. Blood samples were collected at predose and up to

24 hours postdose for the measurement of plasma concentrations of rilzabrutinib. Blood samples were also drawn at 4, 12 and 24 hours postdose to measure BTK occupancy in peripheral blood mononuclear cells (PBMCs). Part B contained a total of 40 healthy participants, 10 participants per cohort (8 active/2 placebo) were treated with repeat doses of rilzabrutinib oral liquid formulation (300 mg QD, 300 mg BID, 600 mg QD and 450 mg BID) or matching placebo QD for 10 days. Blood samples were collected at predose and up to 24 hours postdose on dosing Day -1, 1 and 10 for the measurement of plasma concentrations of rilzabrutinib. Blood samples were also drawn at 4, 12, 24 and 36 hours postdose on Day 1 and Day 10 to measure BTK occupancy in PBMCs. All doses were administered orally after a 10-hour fast, and participants continued to fast until 4 hours postdose.

Results

In Part A, following single oral doses of a liquid formulation of rilzabrutinib, the mean plasma C_{max} and $AUC_{0-\infty}$ increased close to or more than dose-proportionally from 50 mg to 600 mg. Increasing the dose from 600 mg to 1200 mg did not result in further increases in C_{max} or $AUC_{0-\infty}$, suggesting a plateau in absorption with doses greater than 600 mg with the liquid formulation administered in this study. The median T_{max} of rilzabrutinib increased from 0.5 to 2.5 hours as doses increased from 50 mg to 1200 mg. The mean apparent terminal elimination half-life of rilzabrutinib was approximately 3 to 4 hours. Measurement of BTK occupancy showed a dose-dependent increase of BTK occupancy. The maximum observed response was at 4 hours postdose and a plateau of response was reached with the 600 mg dose (mean of 92%).

In Part B, following multiple oral doses of rilzabrutinib on Day 10, the mean plasma $AUC_{0-\infty}$ of rilzabrutinib in plasma increased in a dose-proportional fashion over a dose range of 300 mg to 600 mg. The mean apparent terminal elimination half-life ranged from 3.8 to 4.5 hours for all cohorts on Day 10 and did not appear to change with the different dosing regimen. Minimal accumulation (<2-fold) was observed after multiple oral dose administration. Following multiple oral doses of rilzabrutinib, mean BTK occupancy in PBMCs of 91% was observed 4 hours after the final dose for all but the 300 mg QD regimen, and approximately 55-60% was observed 24 hours later.

Table 78. Summary of Exposures After Single Dose of Rilzabrutinib as an Oral Liquid Formulation in Part A, Study PRN1008-001

	Mean (CV)				
Dose (mg)	50	150	300	600	1200
C_{max} (ng/mL)	15.1 (37%)	45.9 (54.6%)	103 (64.6%)	302 (51.5%)	263 (53.0%)
AUC_{inf} (ng.h/mL)	15.3 (19.6%)	98.9 (86%)	240 (45.6%)	1060 (57.6%)	1070 (54.3%)

Source: Applicant's analysis PRN1008-001 report

Abbreviations: AUC_{inf} , area under the concentration-time curve estimated to infinity; C_{max} , maximum plasma concentration; CV, coefficient of variation

Table 79. Summary of Multiple Dose Rilzabrutinib Pharmacokinetic Parameters Following the Last Dose as an Oral Liquid Formulation in Part B, Study PRN1008-001

Cohort	Day	Dose (mg)		t _{max} (h)	C _{max} (ng/mL)	AUC _{tau} (h.ng/mL)	t _{1/2} (h)	AR
B1	11	300 QD	N	8	8	8	8	8
			Mean	1.50	172	434	4.01	0.90
			Median	1.50	172	391	4.09	0.84
			CV%	25.2	51.8	51.7	48.6	35.8
B2	10	300 BID	N	8	8	8	8	8
			Mean	1.25	223	477	4.02	1.82
			Median	1.00	209	442	4.45	1.60
			CV%	42.8	41.5	46.9	35.1	39.6
B3	10	600 QD	N	8	8	8	8	8
			Mean	1.63	313	936	3.82	1.52
			Median	1.50	281	755	3.83	1.36
			CV%	45.8	34.6	39.1	12.9	56.8
B4	10	450 BID	N	8	8	8	8	8
			Mean	1.38	251	680	4.5	1.53
			Median	1.25	213	544	5.13	1.44
			CV%	32.2	53.7	65.1	36.3	32.1

Source: Applicant's analysis PRN1008-001 report. Table 11 on page 58

Abbreviations: AR, accumulation ratio; AUC_{tau}, area under the concentration-time curve over the dosing interval; BID, twice daily; C_{max}, maximum plasma concentration; CV, coefficient of variation; QD, once daily; N, number of participants in cohort; t_{1/2}, half-life; t_{max}, time to maximum concentration

Table 80. Occupancy of BTK Following 10 Days of Dosing

	PRN1008 BTK Occupancy (%) ^a			
	Day 10 Pre dose	Day 10 4 h ^b	Day 10 12 h	Day 10 24 h
300 mg QD	29 ± 24.6	84 ± 4.4	62 ± 12.7	27 ± 19.4
300 mg BID	74 ± 4.2	91 ± 2.3	77 ± 6.7	60 ± 8.3
600 mg QD	58 ± 11.4	93 ± 2.0	80 ± 5.6	59 ± 11.1
450 mg BID	76 ± 7.4	91 ± 4.6	75 ± 8.4	54 ± 15.1

Source: Applicant's analysis PRN1008-101 report. Table 15 on page 63

Abbreviations: BID, twice daily; BTK, Bruton tyrosine kinase; h, hour; QD, once daily

Summary

Using the liquid formulation, rilzabrutinib exposure increased in a near dose proportional manner (50 to 600 mg). No additional increase in exposure was observed when doses were increased beyond 600 mg. Rilzabrutinib mean plasma half-life ranged from approximately 3 to 4.5 hrs. and showed modest accumulation between 50 to 80% when dosed twice daily over 10 days.

Maximum BTK occupancy (approximately 90%) was achieved with daily doses of 600 mg and above.

14.2.2. Study PRN1008-015: a Two Part-Phase 1, Open-Label Study of the Absorption, Metabolism, Excretion and Absolute Bioavailability of [¹⁴C]-PRN1008 in Healthy Male Participants

Study Design

This was a two-part study. In Part A, 8 participants received a single oral dose of 400 mg rilzabrutinib immediate release tablet followed 2 hours later by an intravenous (IV) administration of 100 µg [¹⁴C]-rilzabrutinib (containing about 1 µCi), as an IV push over 2 minutes. Blood samples were collected predose and up to 72 hours postdose for determination of plasma concentrations of rilzabrutinib and [¹⁴C]-rilzabrutinib. In Part B, 10 participants received a single oral dose of 300 mg [¹⁴C]-rilzabrutinib as a liquid formulation (containing about 1000 µCi). All participants had blood, urine, and feces collection. Two of the 10 participants also had bile sample collected. All administrations were given after a 10-hour fast, and participants continued to fast until 4 hours postdose.

Results

In Part A, after a 400 mg oral dose followed by an IV injection of 100 µg [¹⁴C]-rilzabrutinib, rilzabrutinib clearance was estimated to be 58.1 L/h. Volume of distribution at terminal phase after IV administration was estimated to be 149 L. Oral bioavailability of rilzabrutinib was estimated to be 4.73%. The median t_{max} was approximately 2.0 hours and geometric mean $t_{1/2}$ was 3.2 h.

In Part B, following oral administration of [¹⁴C]-rilzabrutinib, rapid absorption of rilzabrutinib was observed with a median t_{max} value of 1.0 hour in plasma, while maximal levels of total radioactivity in plasma and blood were reached with a median t_{max} of 3.5 hours postdose. After reaching C_{max} , plasma concentrations of rilzabrutinib declined in a biphasic manner, with a geometric mean $t_{1/2}$ of 2.5 hours (range: 1.2 to 9.0 hours). In contrast, for total radioactivity, the terminal $t_{1/2}$ in plasma and blood was 182 hours and 176 hours, respectively. The mean AUC_{last} of rilzabrutinib in plasma was approximately 0.3% of that of the total radioactivity in plasma. Data of this study demonstrated that rilzabrutinib undergoes extensive metabolism, mediated primarily by dealkylation, oxidative N-dealkylation, and oxidation. The metabolism produced a total of 46 radiolabeled components, of which, 25 metabolites were identified or characterized. Rilzabrutinib was a trace radiolabeled component in plasma and accounted for 0.760% of total radioactivity. PRN4400 (thiocyanate, M1) was identified as the primary circulating metabolite representing 94.2% of total radioactivity exposure in plasma. PRN834 (M45), a previously characterized metabolite, accounted for 1.09% of total plasma radioactivity exposure. The other metabolites were identified as trace amount (<1%) metabolites in plasma. The overall mean recoveries of radioactivity in urine, bile (as applicable), feces, and vomitus samples were 92.9% (non-bile collection participants) and 87.6% (bile collection participants). [¹⁴C]-Rilzabrutinib-derived radioactivity was predominantly excreted in feces (approximately 86% of dose) and to a lesser extent in urine (approximately 5% of dose, total radioactivity) and bile (approximately 6%

of dose). Rilzabrutinib was the most abundant radiolabeled component in feces, accounting for a mean of 9.02% of the dose in non-bile collection participants. Approximately 0.03% of dose was recovered as unchanged drug in urine. Rilzabrutinib metabolites accounted for approximately 3.8% of the dose in urine, approximately 4.2% of the dose in bile, and approximately 63.0% of the dose in feces. The prevalence of metabolites in feces indicates that metabolism is the major mechanism of elimination of rilzabrutinib in humans.

Summary

The mass balance data indicate that rilzabrutinib is rapidly absorbed and undergoes extensive metabolism. Renal excretion is not the major elimination pathway for rilzabrutinib.

14.2.3. Study PRN1008-020: an Open-Label, Phase 1 Study To Evaluate the Effect of Mild to Moderate Hepatic Impairment on the Single-Dose Pharmacokinetics of Rilzabrutinib

Study Design

The primary objective of this study was to evaluate the PK profile of rilzabrutinib following a single oral tablet dose of 400 mg rilzabrutinib in participants with mild and moderate HI relative to control participants with normal hepatic function. The study population consisted of male and female participants who were ≥ 18 to ≤ 75 years, with mild HI (Group 1; 8 participants, Child-Pugh Class A, score of 5 to 6), moderate HI (Group 2; 8 participants; Child-Pugh Class B, score of 7 to 9) and normal hepatic function (Group 3; 13 participants). Participants with normal hepatic function were to be matched by age (± 10 years), sex and body mass index (BMI; $\pm 15\%$) to participants with HI. Rilzabrutinib tablet of 400 mg under fasted condition was administered after a 10-hour fast, and participants continued to fast until 4 hours postdose. Blood samples for analysis of rilzabrutinib in plasma were collected predose and up to 30 hours postdose. Blood samples to determine unbound fraction of rilzabrutinib were collected predose and up to 24 hours postdose.

Results

Following treatment with rilzabrutinib, the geometric least squares means (LSM) and the ratios of HI/control group for the primary PK parameters, plasma AUC and $C_{\max}$, of total rilzabrutinib are presented in [Table 81](#). The geometric mean ratios (90% CI) expressed as percentages in mild and moderate HI groups compared to control for $C_{\max}$ were 153% (76%, 309%) and 423% (224%, 798%); for $AUC_{(0-t)}$ were 153% (76%, 308%) and 484% (265%, 883%), and for $AUC_{(0-inf)}$ were 135% (66%, 275%) and 448% (219%, 916%), respectively. Following a single oral dose of 400 mg rilzabrutinib, $C_{\max}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ were modestly higher in the mild HI group compared to the normal hepatic function group and significantly higher (>4 -fold) in the moderate HI group compared to the normal hepatic function group.

Rilzabrutinib was highly bound to plasma proteins across all cohorts, with mean percent unbound (%fu) of $<3\%$ across the cohorts and did not increase significantly in participants with HI ([Table 82](#)). Changes in rilzabrutinib exposure based on unbound rilzabrutinib is similar to what was observed with total rilzabrutinib.

Table 81. Statistical Comparison of Total Rilzabrutinib Pharmacokinetic Parameters

HI	Parameter	C _{max} (ng/mL)	AUC _{0-t} (ng*h/mL)	AUC _{0-inf} (ng*h/mL)
Mild HI	Geometric LSM	64.38	513.0	548.7
Control for mild HI	Geometric LSM	49.57	424.0	450.1
	GMR (%)	129.90	120.99	121.90
	90% CI	79.16-213.14	72.21-202.71	72.54-204.85
	Intrasubject CV%	60.99	64.01	64.45
Moderate HI	Geometric LSM	482.6	1997	2040
Control for moderate HI	Geometric LSM	114.1	412.6	455.4
	GMR (%)	423.06	484.00	447.98
	90% CI	224.43-797.51	265.22-883.25	219.11-915.93
	Intrasubject CV%	70.39	65.14	73.77

Source: Reviewer summary from Study PRM1008-020

Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GMR, geometric mean ratio; HI, hepatic impairment; LSM, least square mean

Table 82. Summary of Statistical Comparisons of Plasma Unbound Rilzabrutinib Pharmacokinetic Parameters Following Administration of 400 mg Rilzabrutinib in Participants With Moderate HI vs. Healthy-Matched Control Participants (PK Analysis Population)

Parameter	Moderate HI (Test)		Healthy-Matched Control to Moderate HI (Reference)				
	Geometric LSM	n	Geometric LSM	n	Geometric Mean Ratio (%)	90% Confidence Interval	*Intra-subject CV%
AUC _{0-t,u} (ng*hr/mL)	55.57	7	10.16	8	547.07	294.42 - 1016.50	67.26
AUC _{0-inf,u} (ng*hr/mL)	56.56	7	10.77	7	525.35	243.34 - 1134.17	77.17
C _{max,u} (ng/mL)	13.39	7	2.809	8	476.88	252.13 - 901.95	70.14

Source: Clinical study report PRN1008-020. Table 11-7 on Page 54

Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; C_{max}, maximum plasma concentration; CV, coefficient of variation; HI, hepatic impairment; LSM, least square mean; n, number of participants tested; PK, pharmacokinetic

Summary

Variability was relatively higher in the measurement of rilzabrutinib unbound concentrations. Nevertheless, the changes in exposure of unbound rilzabrutinib was similar as seen with total rilzabrutinib across the HI groups relative to control. There is no clinically significant impact of mild HI on rilzabrutinib pharmacokinetics. Moderate HI had a significant impact with >4-fold increase in rilzabrutinib exposure.

14.2.4. Study PRN1008-025: a Randomized, Open-Label Phase I Study, To Assess the Effects of Food and Formulation on the Pharmacokinetics of a Single Dose of Rilzabrutinib in Healthy Male and Female Participants

Study Design

This was a two-part study. Only Part A, the food effect study, is under review. A total of 24 participants participated in a 2-period crossover study in which participants received a single 400 mg dose of the immediate release (IR) tablet formulation of rilzabrutinib in the fed and fasted states. Treatment A: fasted treatment, participants received rilzabrutinib with 240 mL of water following an overnight fast of 10 hours, food was also restricted until 4 hours after dosing. Treatment B: fed treatment, participants fasted overnight for approximately 10 hours, then ate a high-fat breakfast 30 minutes prior to study drug administration. Administration of each treatment were separated by a washout period of 4 days. Blood samples for analysis of rilzabrutinib in plasma were collected predose and up to 24 hours postdose on Day 1 and Day 6.

Results

Following coadministration of 400 mg IR tablet formulation with a high-fat meal or rilzabrutinib, the ratio of geometric LSM (Fed/Fasted [B/A]) and 90% CI were 81.75% (69.40% to 96.29%), 78.70% (67.27% to 92.06%) and 69.04% (55.36% to 86.11%) for AUC_{0-last}, AUC_{0-inf}, and C_{max}, respectively. The intraparticipant variability (coefficient of variation (CV)%) were 34.0%, 31.6%, and 46.9% for AUC_{0-last}, AUC_{0-inf}, and C_{max}, respectively.

Table 83. Statistical Comparisons Between Treatments B and A in the Pharmacokinetic Population
Analyte: Rilzabrutinib (PRN1008)

Comparison	Parameter (unit)	Geometric LSM		Ratio ¹ (%)	90% Geometric C.I. ²		Intra-participant CV ³ (%)
		Treatment B	Treatment A		Lower (%)	Upper (%)	
B vs. A	AUC _{0-last} (h*ng/mL)	359.896	440.248	81.75	69.40	96.29	34.0
	AUC _{0-inf} (h*ng/mL)	359.779	457.163	78.70	67.27	92.06	31.6
	C _{max} (ng/mL)	102.77	148.85	69.04	55.36	86.11	46.9

Source: Applicant's analysis PRN1008-025 report. Table 20 on page 97

Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation

Summary

The design of this food effect study is acceptable with a standard high-fat meal and sufficiently long washout period. The tablet formulation used in this food effect study is the same as used in the pivotal Phase 3 study and to-be-marketed product. Rilzabrutinib total exposure was lower by about 20%, and C_{max} was lower by approximately 30%, compared to the fasting conditions. The food effect was minimal and considered not clinically significant. This study guided instructions

for administering rilzabrutinib in relation to meals for study participants (taken with or without food).

14.2.5. Study PRN1008-022: a Phase 1, Single-Center, Open-Label Study, To Evaluate the Pharmacokinetics, Safety and Tolerability of Rilzabrutinib in Chinese Healthy Male and Female Participants

Study Design

Ten healthy Chinese male and female participants, aged between 18 to 45 years, enrolled in this open-label study to investigate the PK, safety, and tolerability of a single dose of 400 mg rilzabrutinib in the IR tablet formulation. Rilzabrutinib was given after an overnight fast. Blood samples were collected at predose and 24 hours postdose for plasma quantitation of rilzabrutinib.

Results

Following a single oral administration of 400 mg rilzabrutinib, rilzabrutinib was absorbed with a median $t_{\max}$ of 1.5 hours and eliminated with a mean $t_{1/2}$ of 3.1 hours. The mean systemic exposure parameters for rilzabrutinib, $C_{\max}$ and AUC_{last} , were 221 ng/mL and 614 h*ng/mL, respectively. Note that the half-life in Chinese participants is shorter compared with participants of other races.

Table 84. Summary of Studies To Evaluate Effects of Race

Study (Country)	Study Objective	Study Design	Study participants (M/F) Type Age Mean (Range)	Dose, Form, Route [Product ID]	Population Type	Pharmacokinetic Parameters					Study Report Location
						Mean (SD) [Geometric mean ratio, CV]			Median (min, max)	Mean (SD)	
						$C_{\max}$ (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{inf} (ng.h/mL)	$t_{\max}$ (h)	$t_{1/2z}$ (h)	
PRN1008-023 (Japan)	PK in Japanese	Single-center, open-label parallel group study	11 (Japanese) (8/3)	100 mg QD,	Japanese						Sec. 5.3.3.3
			45.5 (25, 62)	200 mg QD,	100 mg	34.9 (34.8)	55.2 (46.4)	56.4 (48.9)	0.500 (0.50, 3.00)	2.12 (0.65)	
			12 (Caucasian) (5/7)	400 mg BID tablet, p.o. (fasted)	200 mg	[NA]	[NA]	[NA]			
			43.4 (26,58)	[PRN1008]	400 mg	67.63 (56.2)	152.4 (130.7)	164.5 (138.1)	1.500 (0.50, 2.50)	3.46 (1.9)	
						[NA]	[NA]	[NA]			
						228.8 (213.2)	545.1 (512.7)	551.6 (516.4)	2.020 (1.00, 4.00)	8.4202 (1.53)	
						1.6 [1.22, 2.1]	1.74 [1.35, 2.24]	[NA]			
					Caucasian						
					400 mg	175.1 (129.2)	494.5 (369.8)	535.15 (376.0)	2.260 (1.05, 6.00)	8.24 (5.32)	
						2.28 [1.73, 3.02]	2.17 [1.65, 2.85]	[NA]			
PRN1008-022 (China)	PK in Chinese	Single-center, open label, parallel group study	10 (Chinese) (8/2) 31.4 (22, 40)	400 mg tablets, p.o [PRN1008]	Chinese, healthy volunteers	221 (143) [NA]	613 (388) [NA]	746 (321) [NA]	1.50 (1.00, 3.00)	3.10 (1.07)	Sec. 5.3.3.3

Source: Summary from Study PRN1008-022 and Study PRN1008-023

Abbreviations: AUC_{inf} , area under the concentration-time curve estimated to infinity; AUC_{last} , area under the concentration-time curve to the last measurable concentration; $C_{\max}$, maximum plasma concentration; F, female; h, hour; ID, identification; M, male; max, maximum; min, minimum; NA, not available; PK, pharmacokinetic; SD, standard deviation; $t_{\max}$, time to maximum concentration; $t_{1/2z}$, terminal half-life

Summary

Exposure in Chinese participants demonstrated similar exposure to the Caucasian population from Study PRN1008-023 ([Table 84](#)).

14.2.6. Study PRN1008-023: a Phase 1, Single-Center, Open-Label Study To Evaluate the Pharmacokinetics and Tolerability of Rilzabrutinib in Japanese and Caucasian Healthy Male and Female Participants

Study Design

Eleven healthy Japanese male and female participants and 12 healthy Caucasian male and female participants, aged between 18 to 45 years, enrolled in this open-label study to evaluate the PK of rilzabrutinib following single and multiple doses. Japanese participants had three sequential treatment periods separated by 4-day washout periods: 100 mg single dose on Day 1, 200 mg single dose on Day 5 and 400 mg BID from Day 9 to 13, and Caucasian participants had one treatment period (400 mg BID from Day 1 to 5). All doses were administered as IR tablets after an overnight fast. Blood samples were collected at predose and for up to 24 hours postdose (for 100 mg and 200 mg) or up to 48 hours postdose (for 400 mg BID, on Day 13 in Japanese group and Day 5 in Caucasian group) for plasma quantitation of rilzabrutinib. Additional blood samples were collected predose and postdose after single dose and multiple doses, to assess the BTK occupancy in PBMCs.

Results

Following administration of the first dose of 400 mg rilzabrutinib to Japanese and Caucasian participants, slightly higher (16%) C_{max} of rilzabrutinib was observed for Japanese participants, while AUC_{last} and AUC_{tau} was slightly lower (6.5%) in Japanese participants versus Caucasian participants ([Table 85](#)). Following multiple dose administration of 400 mg BID, Japanese participants had lower C_{max} and AUC values (16% and 25%) of rilzabrutinib compared to Caucasian participants.

Table 85. Summary of PK Parameters for Japanese and Caucasian Groups on the First and Last Day of 400 mg BID Rilzabrutinib Treatment

Parameter	Visit	Japanese (400 mg BID)	Caucasian (400 mg BID)
C_{max} (mean, CV%, ng/mL)	First Dose	228.8 (129.2%)	175.1 (96.3%)
	Last (5 th) Dose	319.8 (89.1%)	373.5 (81.8%)
t_{max} (median, h)	First Dose	2.0	2.0
	Last (5 th) Dose	1.5	2.3
AUC_{0-last} (mean, CV%, h*ng/mL)	First Dose	545.1 (136.1%)	494.5 (84.6%)
	Last (5 th) Dose	848.8 (90.1%)	1173 (68.3%)

Source: Reviewer summary from Study PRN1008-023

Abbreviations: AUC_{0-last} , area under the concentration-time curve to the last measurable concentration; BID, twice daily; C_{max} , maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; t_{max} , time to maximum concentration

At 400 mg BID, the mean BTK occupancies at steady state were comparable between the Japanese and Caucasian participants.

Summary

Total variability for PK measurements was relatively high in both race groups, with CV% generally >70%. Variability for PD measurements was also high for Japanese participants.

14.2.7. Study PRN1008-002: a Phase 1, Single-Center, Open-Label, Fixed-Sequence Study To Assess the Effects of Rilzabrutinib on the Pharmacokinetics of Midazolam, a CYP3A4 Substrate, in Healthy Adults

Study Design

This is a Phase 1, open-label study to evaluate DDI of rilzabrutinib with midazolam (a CYP3A4 substrate) in 12 healthy adult participants aged 18 to 55.

The primary objective was to assess the effect of a single oral dose of rilzabrutinib (600 mg, liquid formulation) on the pharmacokinetics of a single oral dose of midazolam (2 mg). A single 2-mg oral dose of midazolam solution was administered alone on Day 1 under fasting condition, and again following a three-day washout period, on Day 4, one hour after a single oral dose of 600 mg rilzabrutinib as a liquid formulation. Blood samples were obtained over a period of 24 hours post-midazolam dosing to characterize the PK profile of midazolam and α -hydroxymidazolam and rilzabrutinib.

Results

Systemic exposure of midazolam was increased when coadministered with rilzabrutinib. Statistical analysis comparing the effect of rilzabrutinib 600 mg on C_{max} and AUC values of midazolam are shown in [Table 86](#). The geometric mean ratios for midazolam AUC_(0-inf), AUC_(0-last), and C_{max} when coadministered with rilzabrutinib compared to midazolam administered alone were 314%, 360%, and 241%, respectively.

Table 86. Statistical Analysis Summary, Effect of Rilzabrutinib on Midazolam Pharmacokinetic Parameters

Parameter	Midazolam Alone	w/ PRN1008	Ratio (%)	90% CI Lower	90% CI Upper
AUC _{0-∞} (ng*h/ml)	23.7	74.3	314	271	364
AUC _{0-last} (ng*h/ml)	19.3	69.5	360	302	428
C _{max} (ng/ml)	8.41	20.2	241	204	284
Ratio (%) = Midazolam w/ PRN1008 (day 4)/Midazolam Alone (day 1)					

Source: Applicant's PRN1008-002 PK report. Table 2 on page 63
Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; w/, with; PK, pharmacokinetic

Summary

Rilzabrutinib was not dosed to reach steady state in this study. However, the oral liquid formulation of rilzabrutinib has higher bioavailability compared with the tablet formulation, and

rilzabrutinib is dosed at 600 mg in this study. It is also noted that accumulation of rilzabrutinib when dose twice daily at 400 mg is only about 50%. Taken together, the results from this study indicate that rilzabrutinib is a moderate CYP3A inhibitor following clinically relevant doses.

14.2.8. Study PRN1008-006: Relative Bioavailability and Effect of Food Esomeprazole on the Pharmacokinetics of Rilzabrutinib in Healthy Volunteers

Study Design

This is a Phase 1, open-label, four-period, crossover study to evaluate the relative bioavailability of a single oral dose of rilzabrutinib when administered as a liquid formulation compared to a tablet formulation in the fasted state, to compare the impact of food on the pharmacokinetics of a tablet formulation of rilzabrutinib, and to evaluate the effect of a PPI (esomeprazole) on the pharmacokinetics of rilzabrutinib tablet formulation. The food effect part of this study is not under review since the tablet formulation used is not the commercial formulation.

Twelve healthy adult participants received 300 mg doses of two formulations under fasted (liquid and IR tablet) or fed (IR tablet only) conditions as the first 3 treatments in a randomized manner. The final treatment involved the administration of esomeprazole (40 mg QD) for 4 days and coadministration with a single dose of rilzabrutinib (300 mg IR tablet) on the fifth day after an overnight fast. Esomeprazole was administered 2 hours before the administration of rilzabrutinib. Blood samples were collected at predose and over 24 hours following rilzabrutinib dose to determine plasma concentrations of rilzabrutinib.

Results

Bioavailability of rilzabrutinib from the tablet formulation was lower relative to the liquid formulation. The geometric mean ratios for $AUC_{0-\infty}$, AUC_{0-last} and C_{max} were 70.8%, 70.5%, and 69.6% for the tablet formulation relative to the liquid formulation, respectively, under fasted conditions.

The geometric mean ratios for rilzabrutinib AUC_{inf} , AUC_{last} , and C_{max} were 49.1%, 47.9%, and 45.4%, respectively, for rilzabrutinib administered with esomeprazole compared to rilzabrutinib administered alone.

Table 87. Statistical Analysis Summary, Effect of Esomeprazole on Rilzabrutinib Pharmacokinetic Parameters

Parameter	Units	Reference	Test	Reference	Test	% Ratio	90% CI Lower	90% CI Upper
$AUC_{0-\infty}$	h*ng/ml	Tablet fasted	Tablet fasted with Esomeprazole	163	80.2	49.1	36.8	65.6
AUC_{0-last}	h*ng/ml	Tablet fasted	Tablet fasted with Esomeprazole	162	77.4	47.9	35.8	64.1
C_{max}	ng/ml	Tablet fasted	Tablet fasted with Esomeprazole	54.1	24.6	45.4	30.8	67.0
Analyte = PRN1008								
Geometric means are presented in table								

Source: Applicant's PRN1008-006 PK report. Table 4 on page 899

Abbreviations: AUC_{0-last} , area under the concentration-time curve to the last measurable concentration; $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max} , maximum plasma concentration; PK, pharmacokinetic

Summary

Rilzabrutinib exposure decreased by about 50% in the presence of a PPI (esomeprazole).

14.2.9. Study PRN1008-011: a Phase 1 Study of the Relative Bioavailability of Two Rilzabrutinib Tablet Formulations, Effect of Rilzabrutinib on Midazolam Pharmacokinetics, and Impact of Famotidine on Rilzabrutinib Pharmacokinetics in Healthy Participants

Study Design

This is a single-center, 4-period, open-label, randomized, crossover study to evaluate the potential DDI of rilzabrutinib with a H₂-receptor antagonist (famotidine) as a precipitant drug, and with a CYP3A substrate (midazolam) as a substrate drug. The relative bioavailability part of this study is not under review.

14 healthy adult male and female participants received a single 2 mg oral dose of midazolam (1 mg/mL solution) on Day -1. Rilzabrutinib treatment administration occurred as per the assigned sequence on Days 1, 3, 5 and 7 involving administration of one of the following treatments:

- Treatment 1: Single 400 mg oral dose of rilzabrutinib (reference IR tablet) with simultaneous administration of a single 2 mg oral dose of midazolam.
- Treatment 2: Single 400 mg oral dose of rilzabrutinib (Test Formulation #1) with simultaneous administration of a single 2 mg oral dose of midazolam.
- Treatment 3: Single 400 mg oral dose of rilzabrutinib (Test Formulation #2) followed by a single 2 mg oral dose of midazolam 2 hours later.
- Treatment 4: Participants received single 20 mg oral doses of famotidine in the evening of Days 5, 6, and 7. On Day 7, participants received two 400 mg oral doses of rilzabrutinib (IR tablet), one in the morning (after an overnight fast) and a second in the evening (approximately 12 hours after the morning dose). Participants then received a final famotidine dose 2 hours after the evening rilzabrutinib dose.

Blood samples were collected over 12 hours postdosing for determination of rilzabrutinib and midazolam PK.

Note that Test Formulation # 2 is most relevant to the commercial formulation.

Results

When administered simultaneously with single dose 400 mg rilzabrutinib IR tablet formulation (treatment 1), the midazolam geometric mean ratio for AUC_{0-inf} was 168% (90% CI: 144 to 195%) and for C_{max} was 141% (90% CI: 118 to 168%). Similar results were observed when midazolam was administered simultaneously with Test Formulation #1, with the geometric mean ratio for AUC_{0-inf} 172% (90% CI: 148 to 200%) and C_{max} 140% (90% CI: 117 to 168%). When

midazolam was administered 2 hours post-rilzabrutinib dosing, the geometric mean ratios of midazolam exposure for AUC_{0-inf} and C_{max} were 217% (90% CI: 187 to 252%) and 223% (90% CI: 187 to 267%), respectively, compared to midazolam alone.

Dosing rilzabrutinib in the morning following 20 mg famotidine administered the previous evening resulted in a reduction in the rilzabrutinib AUC_{inf} and C_{max} by 33.2% and 25.8%, respectively. When rilzabrutinib was administered in the evening, two hours prior to the evening famotidine dose, AUC_{inf} and C_{max} were reduced by only 2.5% and 8.1%, respectively ([Table 88](#)).

Table 88. Statistical Analysis Summary, Effect of Famotidine on Rilzabrutinib Pharmacokinetic Parameters

Treatment	C _{max} (ng/mL)	AUC _{0-inf} (h*ng/mL)	AUC _{0-last} (h*ng/mL)	C _{max} %Ratio	AUC _{0-inf} %Ratio	AUC _{0-last} %Ratio
Rilzabrutinib alone	64.4	199	196			
Morning dose with famotidine	47.8	133	131	74.2	66.8	66.8
Evening dose with famotidine	59.2	194	197	91.9	97.5	101

Source: Reviewer assessment

Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration

Summary

Rilzabrutinib was not dosed to steady state in this study. Even then, based on the result from this study and study PRN1008-002, rilzabrutinib increases the exposure of midazolam. Administration of famotidine two hours after the administration of evening dose rilzabrutinib did not significantly impact the exposure of the next evening dose, however, could decrease rilzabrutinib morning dose exposure by roughly 35%.

14.2.10. Study PRN1008-014: a Two-Part Study To Assess the Effect of Ritonavir on Rilzabrutinib Pharmacokinetics, and the Effects of Rilzabrutinib on QTc Interval Compared to Placebo and Moxifloxacin in Healthy Participants

Study Design

This is a single center, 2-part study in healthy participants. Part A was an open-label, 3-period crossover study in 12 adult participants to assess the safety and pharmacokinetics of single oral doses of rilzabrutinib when given alone (100 mg and 1200 mg, as 4x300 mg tablets) and when coadministered with ritonavir (100 mg rilzabrutinib with concomitant 100 mg ritonavir, with second dose of 100 mg ritonavir 12 hours later). Part B was a double-blind, placebo-controlled, 4-way crossover study with a 7-day washout between treatments. Thirty-nine participants received the first 3 treatments in a blinded manner (placebo, rilzabrutinib 400 mg single dose, and rilzabrutinib 400 mg single dose with two doses of 100 mg concomitant ritonavir 12 hours apart), followed by the 4th treatment in an open-label manner (moxifloxacin 400 mg single dose). Blood samples were collected for pharmacokinetics at predose and over 24 hours postdose for the determination of rilzabrutinib and moxifloxacin (open-label treatment only) concentrations.

The QT portion of this study is under review by the integrate review team, and report will be uploaded accordingly.

Results

Part A: Coadministration with ritonavir with 100 mg rilzabrutinib increased rilzabrutinib plasma AUC by approximately 18-fold, and $C_{\max}$ by approximately 8-fold ([Table 89](#)). When rilzabrutinib was administered alone at 1200 mg, three of the first four participants demonstrated significant gastrointestinal adverse events, and further dosing was stopped. Therefore, the 1200 mg dose of rilzabrutinib was considered insufficient to obtain adequate supratherapeutic exposures and coadministration of a lower dose of rilzabrutinib (400 mg) with ritonavir was chosen for ECG assessments in Part B.

Table 89. Statistical Analysis Summary, Effect of Ritonavir Coadministration on Rilzabrutinib (100 mg) Pharmacokinetic Parameters, Part A

Parameter	Reference GLSM	Test GLSM	% Ratio of GLSM	90% CI
AUC _{0-∞} (ng·h/mL)	47.46	838.15	1765.26	1309.94 - 2378.83
AUC _{0-last} (ng·h/mL)	46.78	827.71	1769.33	1308.93 - 2391.67
AUC ₀₋₂₄ (ng·h/mL)	47.46	827.65	1743.91	1291.77 - 2354.31
C _{max} (ng/mL)	24.12	180.57	748.60	526.160 - 1065.09

Source: Applicant's PRN1008-014 report. Table 14 on page 119

Abbreviations: AUC₀₋₂₄, area under the concentration-time curve from time 0 to 24 h; AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean

Part B: Coadministration of the therapeutic 400 mg rilzabrutinib dose with ritonavir increased rilzabrutinib AUC by approximately 8-fold and $C_{\max}$ by approximately 5-fold ([Table 90](#)). Results showed that the mean rilzabrutinib exposure following 1200 mg dose was lower than the exposure obtained following interaction with ritonavir (400 mg with 100 mg BID ritonavir), further supporting the dosing strategy for the QT prolongation analysis.

Table 90. Statistical Analysis Summary, Effect of Ritonavir Coadministration on Rilzabrutinib (400 mg) Pharmacokinetic Parameters, Part B

Parameter	Reference GLSM	Test GLSM	% Ratio of GLSM	90% CI
AUC _{0-∞} (ng·h/mL)	345.62	2880.63	833.47	686.65 – 1011.68
AUC _{0-last} (ng·h/mL)	342.49	2819.63	823.27	675.29 – 1003.67
AUC ₀₋₂₄ (ng·h/mL)	343.07	2818.87	821.65	673.98 – 1001.68
C _{max} (ng/mL)	105.97	551.49	520.44	409.12 – 662.05

Source: Applicant's PRN1008-014 report. Table 15 on page 120

Abbreviations: AUC₀₋₂₄, area under the concentration-time curve from time 0 to 24 h; AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean

Summary

Study results confirmed rilzabrutinib is a substrate for CYP3A4 and/or P-gp. The study results also demonstrated that the effect of ritonavir on rilzabrutinib pharmacokinetics was dependent on the dose of the substrate, as the magnitude of the drug interaction decreased with the increase in rilzabrutinib dose from 100 mg in Part A to 400 mg in Part B.

14.2.11. Study PRN1008-024: an Open-Label, Phase 1, Two-Part Drug-Drug Interaction Study To Evaluate the Effects of Quinidine and Rifampin on the Single-Dose Pharmacokinetics and Safety of Rilzabrutinib in Healthy Male and Female Volunteers

Study Design

This is an open-label, two-period, fixed-sequence study to evaluate the effect of a P-gp inhibitor, quinidine (Part A), and a CYP3A inducer, rifampin (Part B), on the pharmacokinetics of rilzabrutinib. Thirty-two healthy adult participants participated in two parts (16 participants per part).

Part A evaluated the effect of quinidine on single dose rilzabrutinib pharmacokinetics. On Period 1 Day 1 morning, participants received a single oral dose of 400 mg rilzabrutinib following an overnight fast. In Period 2, 300 mg quinidine once every 8 hours (Q8h) was administered for 5 days from Day 7 through Day 11. On Day 10 morning (following an overnight fast), a single oral dose of 400 mg rilzabrutinib was administered approximately 1 hour after the first 300 mg quinidine dose.

Part B evaluated the effect rifampin on single dose rilzabrutinib pharmacokinetics. On Period 1 Day 1 morning, participants received a single oral dose of 400 mg rilzabrutinib following an overnight fast. In Period 2, 600 mg rifampin QD was administered for 11 days from Day 7 through Day 17. On Day 16 morning (following an overnight fast), a single oral dose of 400 mg rilzabrutinib was coadministered with 600 mg rifampin.

For both parts, blood samples were collected at predose and over 48 hours in each period for the determination of plasma concentrations of rilzabrutinib and PRN834 (M45).

Results

Part A: After coadministration of rilzabrutinib with quinidine, a strong P-gp inhibitor, a modest increase in exposure of rilzabrutinib was observed by 12.7% and 6.9% for AUC_{inf} and AUC_{last} , respectively, relative to rilzabrutinib alone. The C_{max} of rilzabrutinib was decreased by 13.6% after coadministration of rilzabrutinib and quinidine, compared to rilzabrutinib only.

Table 91. Statistical Analysis Summary, Effect of Quinidine on Rilzabrutinib Pharmacokinetic Parameters

Parameters				
Parameter	n	Geometric LSMean ^a	Ratio [(Rilzabrutinib + Quinidine)/ Rilzabrutinib Only]	
			Geometric LSMean Ratio ^a	90% CI ^a
C _{max} (ng/mL)				
Rilzabrutinib + Quinidine	9	92.2949	0.864	0.647, 1.154
Rilzabrutinib Only	9	106.7823		
AUC _{0-last} (hr*ng/mL)				
Rilzabrutinib + Quinidine	9	384.5	1.069	0.803, 1.423
Rilzabrutinib Only	9	359.7		
AUC _{0-∞} (hr*ng/mL)				
Rilzabrutinib + Quinidine	6	340.6	1.127	0.919, 1.382
Rilzabrutinib Only	6	302.3		

Source: Applicant's PRN1008-024 report. Table 25 on page 95

Abbreviations: AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; LS, least squares; n, number of participants treated

Part B: Coadministration of rifampin, a strong CYP3A inducer, significantly decreased rilzabrutinib exposure compared to rilzabrutinib alone, with ratio of the geometric means for AUC_{last}, AUC_{inf}, and C_{max} of 19.9%, 20.5%, and 19.5%, respectively. There was a 69.7% and 72.4% decrease in C_{max} and AUC_{inf}, respectively, of PRN834 (M45), similar to that observed with the parent drug, rilzabrutinib.

Table 92. Statistical Analysis Summary, Effect of Rifampin on Rilzabrutinib Pharmacokinetic Parameters

Parameter	n	Geometric LSMean ^a	Ratio [(Rilzabrutinib + Rifampin)/ Rilzabrutinib Only]	
			Geometric LSMean Ratio ^a	90% CI ^a
C _{max} (ng/mL)				
Rilzabrutinib + Rifampin	16	25.8616	0.195	0.165, 0.231
Rilzabrutinib Only	16	132.4346		
AUC _{0-last} (hr*ng/mL)				
Rilzabrutinib + Rifampin	16	86.63	0.199	0.166, 0.239
Rilzabrutinib Only	16	434.6		
AUC _{0-∞} (hr*ng/mL)				
Rilzabrutinib + Rifampin	14	101.6	0.205	0.167, 0.251
Rilzabrutinib Only	14	496.7		

Source: Applicant's PRN1008-024 report. Table 26 on page 96

AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; LS, least squares; n, number of participants treated

Summary

The effect of P-gp inhibitor, quinidine, on rilzabrutinib pharmacokinetics was modest and not clinically significant. Rifampin, a strong CYP3A inducer, significantly decreased the exposure of rilzabrutinib, confirming the involvement of CYP3A in the metabolism of rilzabrutinib. The

substantial decreases seen in PRN834 (M45) exposure with rifampin treatment, suggests that its formation from rilzabrutinib is not mainly mediated by CYP3A. Unfortunately, the measurement of PRN4400 (M1), the major metabolite, was not available for all participants.

14.3. Bioanalytical Method Validation and Performance

Table 93. Bioanalytical Method Life Cycle Information of PK Assay Used To Measure Rilzabrutinib and PRN834 (M45) in Plasma

	Method Validation #1	Method Validation #2	Method Validation #3	Clinical study PRN1008-001, PRN1008-004, PRN1008-006, PRN1008-008, PRN1008-010, PRN1008-011, PRN1008-015, PRN1008-018, PRN1008-020 ^a	Clinical study PRN1008-010 ^b , PRN1008- 020, PRN1008-023, PRN1008-024, PRN1008-025	Clinical study PRN1008-018 ^c , PRN1008-022
Analyte	rilzabrutinib	rilzabrutinib, PRN834	rilzabrutinib, PRN834	rilzabrutinib	rilzabrutinib, PRN834	rilzabrutinib, PRN834
Validation type	Full validation	Full validation	Full validation and cross-validation	In-study	In-study	In-study
eCTD reference number	5.3.1.4	5.3.1.4	5.3.1.4	Module 5.3	Module 5.3	Module 5.3
Method ID	AV14-PRN1008-01	AV21-PRN1008-01	PDV0143	AV14-PRN1008-01	AV21-PRN1008-01	PDV0143
Duration of time method is in use	3/2014 - 6/2014	12/2020 - 10/2021	7/2021 - 7/2023	6/2014 - present	7/2018 - present	4/2023 - present
Bioanalytical site	(b) (4)					
Matrix	K ₂ EDTA Human Plasma					
Platform	liquid chromatography/tandem mass spectrometry (HPLC/MS/MS)					
Format	Validated assay using protein precipitation procedure followed by HPLC/MS/MS analysis					
Stock reference, lot number, expiration date	rilzabrutinib: 1334-NC-090-4 (27 May 2014) 03-STD-079 (31 Jan 2018)	rilzabrutinib: PS-8ER-102-180001-1 (11 Aug 2021) 0020002856 (07 Sep 2024) PRN834: PS-8FJ-102-180001-1 (09 Aug 2020) PS-8FJ-102-180001-2 (11 Jul 2011)	rilzabrutinib: PS-8ER-102-180001-1 (11 Aug 2021) 0020002856 (29 Apr 2023, 09 Jul 2024) PRN834: PS-8FJ-102-180001-2 (11 Jul 2021) PS-202467-101-00001-1 (11 Jan 2023, 17 Jul 2024)	rilzabrutinib: 1334-NC-090-4 (27 May 2014) 03-STD-079 (Apr 2015, Mar 2016, Feb 2017) 17CP08M.HQ00002 (31 Aug 2019) PS-8ER-102-180001-1 (11 Aug 2021) 0020002856 (29 Apr 2023)	rilzabrutinib: PS-8ER-102-180001-1 (11 Aug 2021) PRN834: PS-8FJ-102-180001-2 (11 Jul 2021) PS-202467-101-00001-1 (11 Jan 2023) PS-8FJ-102-180001-1 (09 Aug 2020)	rilzabrutinib: 0020002856 (29 Apr 2023, 09 Jul 2024) PRN834: PS-202467-101-00001-1 (11 Jan 2023, 17 Jul 2024)
Calibration range from the lower limit of quantitation (LLOQ) to the upper limit of quantitation (ULOQ)	0.1-100 ng/mL					
Matrix study population	Normal	Normal	Normal	Normal and diseased	Normal and diseased	Normal and diseased

Source: Applicant's summary of biopharmaceutical studies and associated analytical methods report. Table 13 on page 46
Abbreviations: eCTD, electronic common technical document; HPLC/MS/MS, high-performance liquid chromatography/tandem mass spectrometry; ID, identification; K₂EDTA, dipotassium ethylenediaminetetraacetic acid; LLOQ, lower limit of quantitation; PK, pharmacokinetic; ULOQ, upper limit of quantitation

NDA 219685
WAYRILZ (rilzabrutinib)

Table 94. Bioanalytical Method Life Cycle Information of PK Assay Used To Measure Rilzabrutinib in Urine

	Method Validation #1	Clinical study PRN1008-015
Analyte	rilzabrutinib	rilzabrutinib
Validation type	Full validation	In- study
eCTD reference number	5.3.1.4	Module 5.3
Method ID	DVR0523	DVR0523
Duration of time method is in use	12/2019 - 3/2020	2/2020 - 3/2020
Bioanalytical site	(b) (4)	
Matrix	Human urine	
Platform	liquid chromatography/tandem mass spectrometry (HPLC/MS/MS)	
Format	Validated assay using protein precipitation procedure followed by HPLC/MS/MS analysis	
Stock reference, lot number, expiration date	rilzabrutinib PS-8ER-102-180001-1, 11 Aug 2021	rilzabrutinib PS-8ER-102-180001-1, 11 Aug 2021
Calibration range from the lower limit of quantitation (LLOQ) to the upper limit of quantitation (ULOQ)	1-1000 ng/mL	
Matrix study population	Normal	Normal

Source: Applicant's summary of biopharmaceutical studies and associated analytical methods report. Table 14 on page 49
Abbreviations: eCTD, electronic common technical document; HPLC/MS/MS, high-performance liquid chromatography/tandem mass spectrometry; ID, identification; LLOQ, lower limit of quantitation; PK, pharmacokinetic; ULOQ, upper limit of quantitation

Table 95. Bioanalytical Method Life Cycle Information of PK Assay Used To Measure PRN4400 (M1) in Plasma

	Method Validation #1	Method Validation #2	Clinical study PRN1008-010, PRN1008-020, PRN1008-023, PRN1008-024, PRN1008-025	Clinical study PRN1008-022
Analyte	PRN4400	PRN4400	PRN4400	PRN4400
Validation type	Full validation	Full validation and cross-validation	In-study	In-study
eCTD reference number	5.3.1.4	5.3.1.4	Module 5.3	Module 5.3
Method ID	DVR0529	PDV0143- Thiocyanate	DVR0529	PDV0143- Thiocyanate
Duration of time method is in use	12/2020 - 5/2021	10/2021 - 7/2023	12/2020 - 6/2021	4/2023 - 4/2023
Bioanalytical site	(b) (4)			
Matrix	K ₂ EDTA Human Plasma			
Platform	liquid chromatography/tandem mass spectrometry (HPLC/MS/MS)			
Format	Validated assay using protein precipitation, derivatization procedure followed by HPLC/MS/MS analysis			
Stock reference, lot number, expiration date	Sodium Thiocyanate: MKCF0885 (09Nov 2021) MKCS7703 (07Feb 2024) MKCM6189 (07Jul 2024)	Potassium Thiocyanate: MKCM2710 (31Mar-2023, 31Mar-2026)	Sodium Thiocyanate: MKCF0885 (09Nov 2021) MKCQ3401 (29Dec 2022) MKCS7703 (07Feb 2024)	Potassium Thiocyanate: MKCM2710 (31-Mar-2026)
Calibration range from the lower limit of quantitation (LLOQ) to the upper limit of quantitation (ULOQ)	1000-50000 ng/mL			
Matrix study population	Normal	Normal	Normal and diseased	Normal and diseased

Source: Applicant's summary of biopharmaceutical studies and associated analytical methods report. Table 15 on page 50
Abbreviations: eCTD, electronic common technical document; HPLC/MS/MS, high-performance liquid chromatography/tandem mass spectrometry; ID, identification; K₂EDTA, dipotassium ethylenediaminetetraacetic acid; LLOQ, lower limit of quantitation; PK, pharmacokinetic; ULOQ, upper limit of quantitation

Four bioanalytical methods were used to quantify rilzabrutinib and/or PRN834 (M45) in human plasma or urine during drug development. [Table 93](#), [Table 94](#), and [Table 95](#) highlight the key features of these methods, as well as the two bioanalytical methods used to quantify PRN4400

(M1) in human plasma. The primary method used for quantification of rilzabrutinib in most clinical studies was AV14-PRN1008-01, except for DDI study PRN1008-025, ethnicity study PRN1008-024, and hepatic impairment study PRN1008-020 which used the assay AV21-PRN1008-01, along with ethnicity study PRN1008-022 which used the assay PDV0143. Table 16, 17, and 20 from the Applicant's summary of biopharmaceutic studies and associated analytical methods report list the validation and performance results of methods AV14-PRN1008-01, AV21-PRN1008-01, and PDV0143, respectively. Table 18 from the Applicant's summary of biopharmaceutic studies and associated analytical methods report lists the validation and performance results of method DVR0523 for rilzabrutinib quantification in urine. Table 22 from the Applicant's summary of biopharmaceutic studies and associated analytical methods report lists the performance results of BTK occupancy assessment. Methods used to quantify PRN4400 (M1) were reviewed and found acceptable.

All bioanalytical methods satisfied the method validation criteria in accordance with the FDA guidance. The performances of the assays are considered acceptable for sample analysis.

14.4. Immunogenicity Assessment—Impact of Pharmacokinetics/Pharmacodynamics, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Summary of Applicant's Population Pharmacokinetics and Pharmacokinetic Modeling Analyses

Population pharmacokinetic analysis was conducted to support the dose selection of rilzabrutinib for adult participants in ITP. The objectives of Applicant's modeling analyses were:

- To characterize rilzabrutinib pharmacokinetics using pooled data from healthy and ITP participants.
- To assess the influence of selected intrinsic and extrinsic factors on rilzabrutinib pharmacokinetics, in healthy volunteer and ITP population.
- Generate individual rilzabrutinib post hoc PK exposures in ITP participants that can be used to quantify exposure-response relationships with efficacy and safety endpoints.

Method

Pooled data from Phase 1-3 studies in adult participants with ITP after subcutaneous administration of rilzabrutinib were included in the analysis. NONMEM version 7.5.1 was used for all model estimations. The covariate analysis was performed using a stepwise selection procedure (stepwise covariate model building within the PsN tool ([Lindbom et al. 2025](#)))

including forward selection and backwards exclusion procedure. The sensitivity analysis was performed to assess the robustness of selected covariates through a set of model evaluations, such as visual predictive checks and bootstrap. After model validation, the final PopPK model was used to generate individual PK parameters and post hoc exposures in participants with ITP from 2 clinical studies (LUNA 2 and EFC17093). Simulations were conducted to assess the impact of statistically significant covariates on rilzabrutinib exposure in participants with ITP.

Results

A total of 7076 rilzabrutinib concentration records from 545 adult participants (255 healthy participants and 290 participants ITP) were included in the dataset from 10 clinical studies in healthy participants and two clinical studies with participants with ITP. [Table 96](#) summarizes the clinical studies included for this analysis. A two-compartment model with linear elimination and first order absorption with identical interindividual variability between clearance and central volume of distribution and including an interindividual variability on the residual error was confirmed as the final PopPK model. Among the tested covariates, disease, body weight, gender, formulation, and dose were identified as statistically significant covariates on rilzabrutinib pharmacokinetics in healthy participants and participants with ITP. The PK parameter estimates and associated standard errors for the final PopPK model in participants with ITP are provided in [Table 97](#). The goodness-of-fit plots for the final PopPK base model is presented in [Figure 19](#). No important systematic deviations or major bias in any of the goodness of fit plots were observed, which demonstrated a reasonable model performance. The predictive performance of the model was acceptable based on bootstrap evaluation and visual predictive checks ([Figure 20](#)), indicating stability and predictive performance of the final PopPK model in participants with ITP. The final PopPK model was used to conduct the simulations for the PK exposures (e.g., AUC and C_{max}) and to evaluate the impact of selected statistically significant covariates on these PK parameters. The impact of significant covariates was acceptable for the overall PK variability observed in participants with ITP, which indicated no clinically relevant effect of these covariates on rilzabrutinib pharmacokinetics in participants with ITP ([Figure 21](#)).

NDA 219685
WAYRILZ (rilzabrutinib)

Table 96. Summary of Clinical Studies Included in Rilzabrutinib PopPK Analysis

Phase	Study	Dose and Regimen ^a	Population	N ^b	PK Sampling	Current Status
1	PRN1008-001 ^c	Single and Multiple Ascending Dose Study to assess safety, tolerability and PK in healthy volunteers SAD: 50 mg, 150 mg, 300 mg, 600 mg single dose; MAD: 300 mg, 600 mg QD x 10 days; 300 mg, 450 mg BID x 10 days	Healthy subjects	62	Dense sampling	Completed
1	PRN1008-004 ^d	Relative bioavailability study between liquid and capsule formulation 300 mg, single dose	Healthy subjects	11	Dense sampling	Completed
1	PRN1008-006	Study for the effect of relative bioavailability, food and Esomeprazole on the PK of PRN1008 300 mg, single dose	Healthy subjects	12	Dense sampling	Completed
1	PRN1008-008 ^c	Evaluation of relative bioavailability between IR and DR tablet formulation and food effect. 200 mg, 400 mg, single dose	Healthy subjects	14	Dense sampling	Completed
1	PRN1008-014 ^d	Effect of Ritonavir on PRN1008 PK and impact of supratherapeutic levels of PNR1008 on QTc interval 100 mg and 1200 mg single dose	Healthy subjects	44	Dense sampling	Completed
1	PRN1008-020	Study to compare PK between participants with healthy and impaired livers 400 mg single dose	Healthy subjects	29	Dense sampling	Completed
1	PRN1008-022	Study to evaluate PK in healthy Chinese subjects 400 mg single dose	Healthy subjects	10	Dense sampling	Completed
1	PRN1008-023	Study to evaluate PK in healthy Japanese and Caucasian subjects 100 mg and 200 mg single dose, 400 mg BID doses	Healthy subjects	23	Dense sampling	Completed
1	PRN1008-024	Evaluating impact of Quinidine and Rifampin on Rilzabrutinib PK 400 mg single dose	Healthy subjects	32	Dense sampling	Completed
1	PRN1008-025	Evaluating the impact of food and formulation on Rilzabrutinib PK. 400 mg single dose	Healthy subjects	24	Dense sampling	Completed
1/2	PRN1008-010	Exploring the PK and clinical activity of PRN1008 in ITP patients 200 mg QD, 400 mg QD, 300 mg BID, 400 mg BID	ITP patients	86	Sparse sampling	Ongoing
3	PRN1008-018 (EFC17093)	Examining the efficacy of Rilzabrutinib in patients with refractory/relapsed ITP Placebo, 400 mg BID	ITP patients	215	Sparse sampling	Ongoing

Source: Applicant's Population Pharmacokinetics Study Report, Table I, Page 10

^a D: once daily; BID: twice daily.

^b Number exposed to rilzabrutinib in each study.

^c PK data with DR tablet will not be included.

^d PK data with 1200 mg from three participants will not be included.

Abbreviations: ITP, immune thrombocytopenia; MAD, multiple ascending dose; N, number of participants in the study; PK, pharmacokinetic; QD, once daily; SAD, single ascending dose; PopPK, population PK

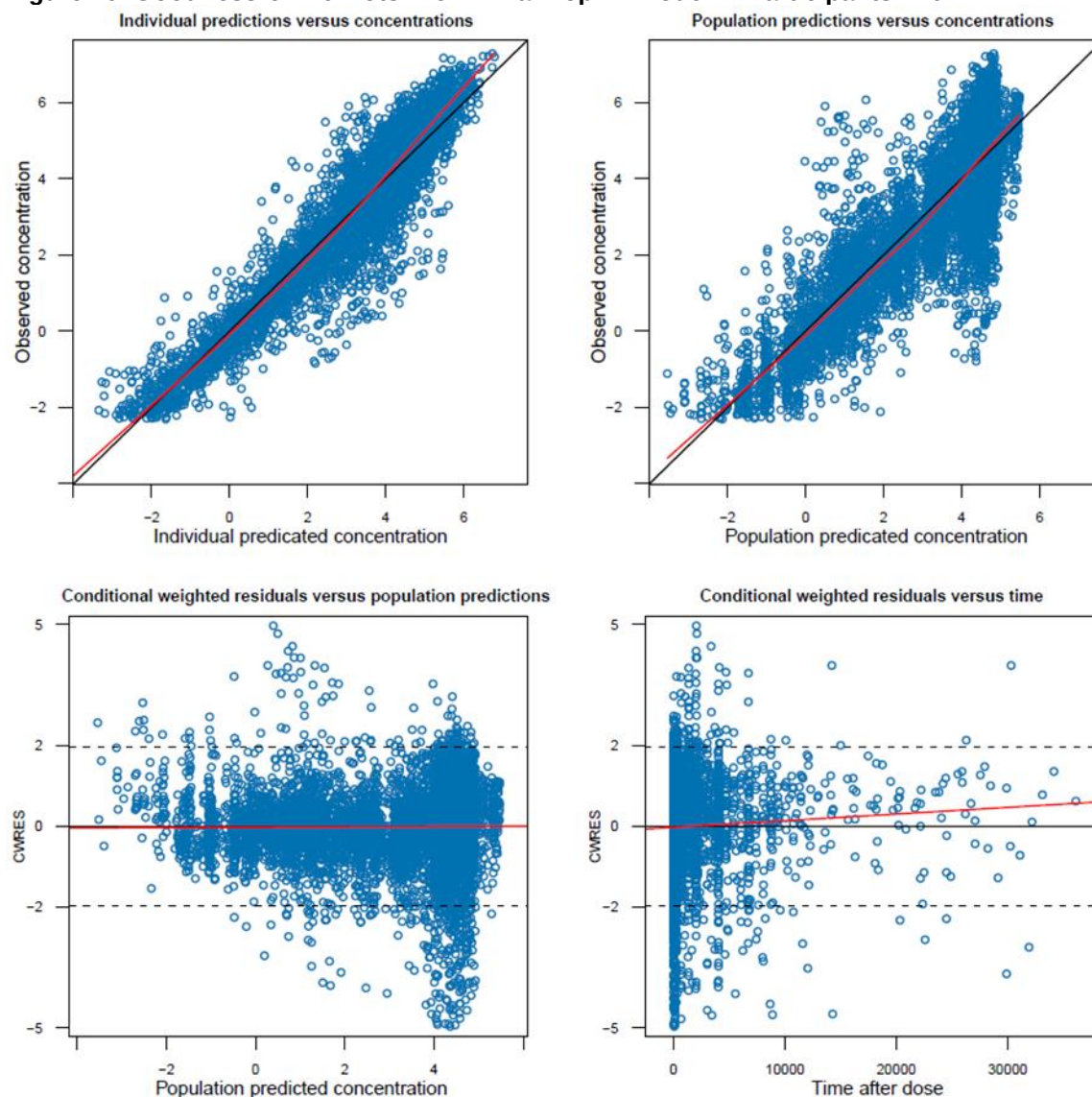
Table 97. Parameter Estimates for Final PopPK Model

Parameter	Estimate (% RSE)	[95%CI]	Bootstrap Median [2.5 th , 97.5 th]
CL/F (L/hour)	673 (5.46)	[600, 747]	672 [598, 749]
V ₂ /F (L)	1390 (5.64)	[1230, 1540]	1380 [1220, 1580]
K _a (1/hour)	0.725 (6.12)	[0.637, 0.814]	0.725 [0.661, 0.795]
Q/F (L/hour)	42.2 (5.49)	[37.5, 46.8]	41.5 [34.4, 49.7]
V ₃ /F (L)	463 (6.62)	[402, 525]	465 [383, 555]
Coefficient of ITP disease on CL/F	-0.082 (44.7)	[-0.155, -0.009]	-0.081 [-0.150, -0.015]
Coefficient of FORM=2 on CL/F	0.203 (21.9)	[0.114, 0.292]	0.203 [0.122, 0.288]
Coefficient of FORM=0 on CL/F	0.153 (33.6)	[0.050, 0.256]	0.150 [0.076, 0.232]
Coefficient of SEX on CL/F	0.325 (26.5)	[0.153, 0.497]	0.321 [0.168, 0.501]
Coefficient of DOSE on F1	0.00213 (3.01)	[0.00200, 0.00225]	0.00210 [0.00187, 0.00232]
Coefficient of FORM=0 on F1	0.280 (23.6)	[0.148, 0.412]	0.275 [0.047, 0.531]
Coefficient of DOSE on K _a	-0.00319 (10.5)	[-0.00386, -0.00252]	-0.00319 [-0.00396, -0.0025]
Coefficient of FORM=0 on K _a	0.599 (27.2)	[0.274, 0.925]	0.606 [0.322, 0.936]
Coefficient of SEX on V ₂ /F	0.222 (40.1)	[0.044, 0.401]	0.222 [0.040, 0.432]
Coefficient of WT on V ₂ /F	0.00375 (34.8)	[0.00114, 0.00637]	0.00366 [0.00158, 0.00589]
Inter-individual variability (IIV)			Bootstrap Median [2.5th, 97.5th]
	CV% (RSE%) [shrinkage%]	[95%CI]	
IIV on CL/F and V ₂ /F	66.4 (7.15) [9.04]	[61.5, 71.0]	66.1 [60.9, 720.]
IIV on K _a	72.0 (9.65) [26.4]	[64.7, 78.7]	71.9 [63.4, 81.9]
IIV on V ₃ /F	55.5 (23.4) [55.5]	[40.4, 67.3]	55.0 [44.7, 66.6]
Residual variability (RV)			
	Estimate (% RSE)	[95%CI]	
Proportion term (mg/L)	72.3%(0.330)	[72.0, 73.0]	72.3% [68.1, 76.2]

Source: Applicant's Population Pharmacokinetics Study Report, Table IV, Page 15

Abbreviations: CI, confidence interval; CL/F, apparent clearance at steady-state; CV, coefficient of variation; IIV: interindividual variability; ITP, immune thrombocytopenia; K_a, absorption rate constant; PopPK, population pharmacokinetic; Q/F, apparent intercompartmental clearance; RSE, percentage of relative standard error; RV, residual variability; SE, standard error; V₂/F, apparent peripheral volume of distribution at steady-state; V₃/F, apparent volume of distribution at steady-state; WT, body weight

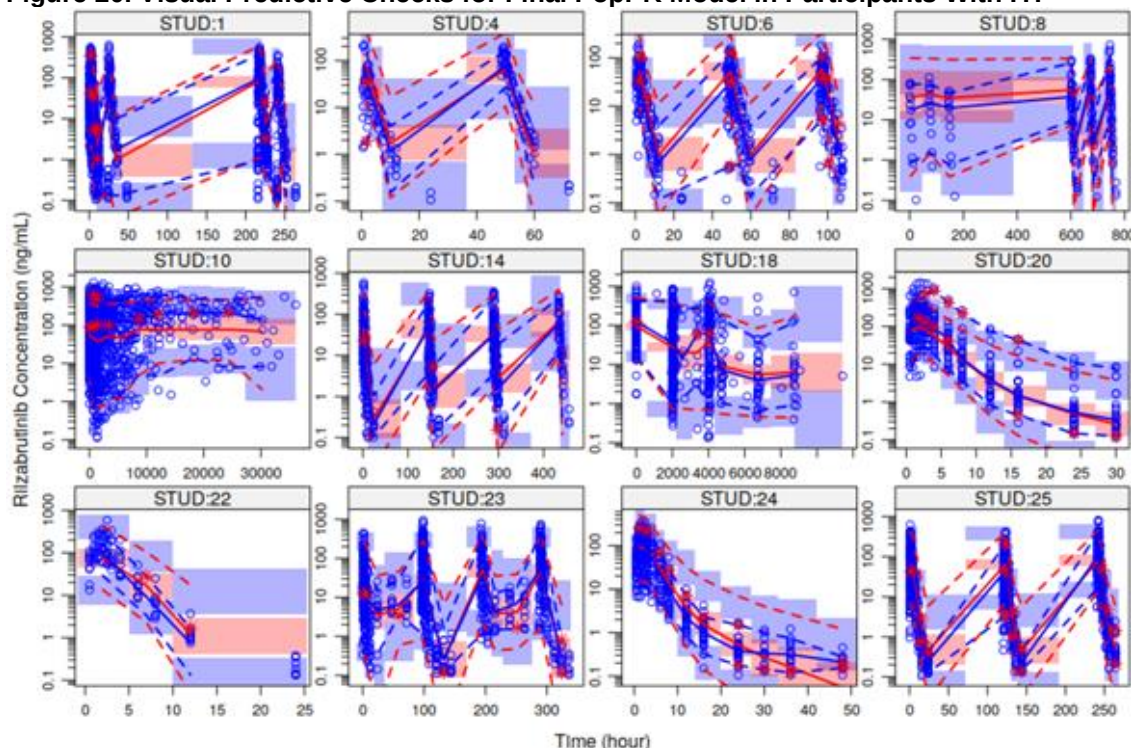
Figure 19. Goodness-of-Fit Plots From Final PopPK Model in Participants With ITP



Source: Reviewer's analysis

Note: The black solid line is the line of identity, and the red solid line is the trend line. The blue open circles are the observation
Abbreviations: CWRES, conditional weighted residuals; ITP, immune thrombocytopenia; PopPK, population pharmacokinetic

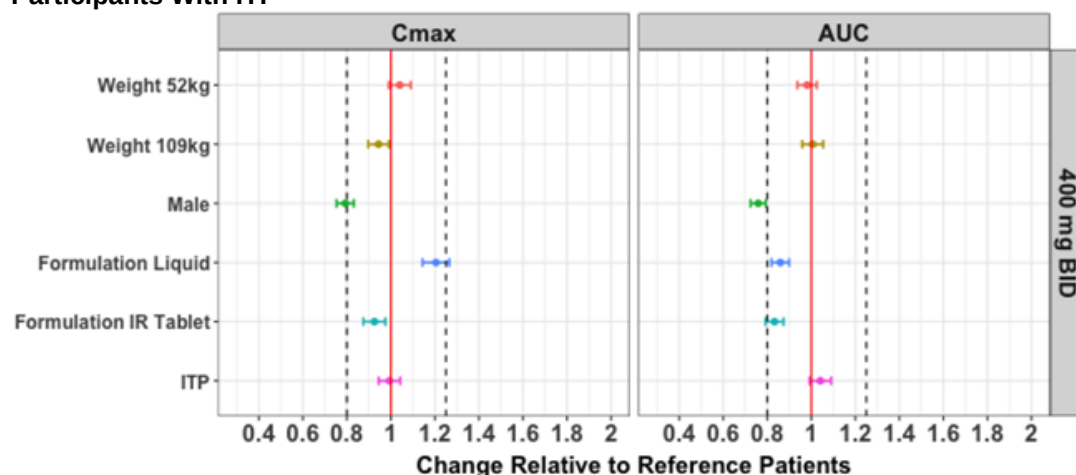
Figure 20. Visual Predictive Checks for Final PopPK Model in Participants With ITP



Source: Applicant's Population Pharmacokinetics Study Report, Figure II, Page 17

Legend: light blue dots: observations; blue solid and dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin. Red asterisks for time points where observations were outside simulated shaded areas. Abbreviations: ITP, immune thrombocytopenia; PopPK, population pharmacokinetic

Figure 21. Impact of Statistically Significant Covariates on Rilzabrutinib PK Exposure in Participants With ITP



Source: Applicant's Population Pharmacokinetics Study Report, Figure III, Page 19

Notes: Typical participants are typical female healthy participants with median values of body weight of 76 kg. The covariate values for simulation (n=1000) represented 5% and 95% percentile of the baseline weight distribution of PopPK population. Rilzabrutinib mean exposures (e.g., AUC and C_{max}) for the simulated typical participants were represented by the red solid vertical line. The black dashed vertical lines represented 80 and 125% of the typical mean steady-state exposures for simulated participants. The solid square and error bars represented the mean and 90% confidence interval (calculated based on standard errors) for the fold change of rilzabrutinib steady-state exposures in simulated participants relative to typical participants.

Abbreviations: AUC: area under the concentration-time curve at steady state; BID, twice daily; C_{max} : maximum concentration at steady state; IR, immediate-release; ITP, immune thrombocytopenia; PK, pharmacokinetic; PopPK, population PK

Summary

- Applicant's PopPK model appears to describe the rilzabrutinib serum concentration-time profiles in the observed range following the administration of rilzabrutinib in participants with ITP from all clinical studies adequately. Therefore, the PopPK model is acceptable for simulating post hoc exposure metrics, e.g., C_{max} and AUC of rilzabrutinib for E-R analyses of efficacy or safety measurements.
- Covariate analysis identified disease, body weight, gender, formulation and dose as statistically significant covariates on rilzabrutinib pharmacokinetics, which did not indicate clinically relevant effect of these covariates on rilzabrutinib pharmacokinetics in participants with ITP.

14.5.2. Exposure-Response Analysis of Efficacy and Safety

The Applicant conducted the E-R analysis of efficacy to characterize the relationship between rilzabrutinib exposures and efficacy and safety endpoints in participants with immune thrombocytopenia. The objective of Applicant's E-R analysis was to confirm the adequacy of the 400 mg BID regimen of rilzabrutinib for the treatment of ITP.

Method

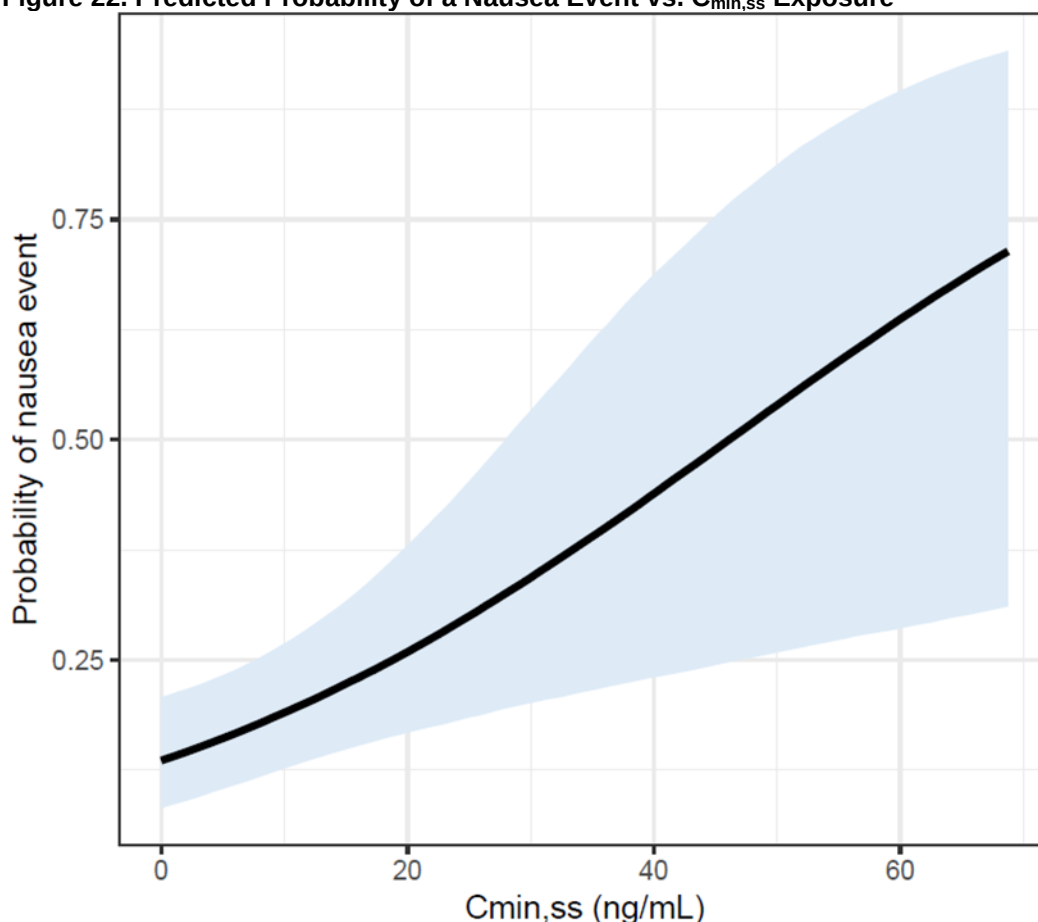
Participants from studies LUNA 2 and LUNA 3 who had at least one platelet count observation and evaluable PK data, if on active treatment were included in the analyses dataset for efficacy and safety. Data manipulation, visualization, and simulations was conducted using R (version 4.1.3 or later). The longitudinal platelet counts were selected as the primary efficacy endpoint which was based on key aspects of the ITP disease etiology and the presumed mechanisms of action of rilzabrutinib. E-R analyses of efficacy was conducted based on the repeated-measures endpoints (longitudinal platelet counts) and the exposure metrics. In addition, the exploratory analyses were performed to characterize the E-R for three adverse events (AEs) (nausea, diarrhea, and anemia). Three exposure metrics, maximum concentration in the dosing interval at steady state ($C_{max,ss}$), minimum concentration in the dosing interval at steady state ($C_{min,ss}$), and area under the concentration-time curve at steady state (AUC_{ss}) were selected as the exposure metrics. Logistic regression model fitting was carried out in a Bayesian full-model framework to build the final model. Participants in Study PRN1008-018 were included in the dataset of time for first rescue therapy and dropout analysis.

Results

The analysis population consisted of 86 participants from Studies LUNA 2 and 219 participants from PRN1008-018, which included 10,652 weekly platelet counts with no missing data or data that were below limit of quantification. An indirect exposure-response model adequately characterized platelet counts, including the magnitude of persistent and sometimes large fluctuations in platelet counts. The model indicated that response to prior corticosteroid therapy and concomitant use of corticosteroids were associated with higher response rates. In addition, baseline platelet counts below the median were associated with lower response rates while

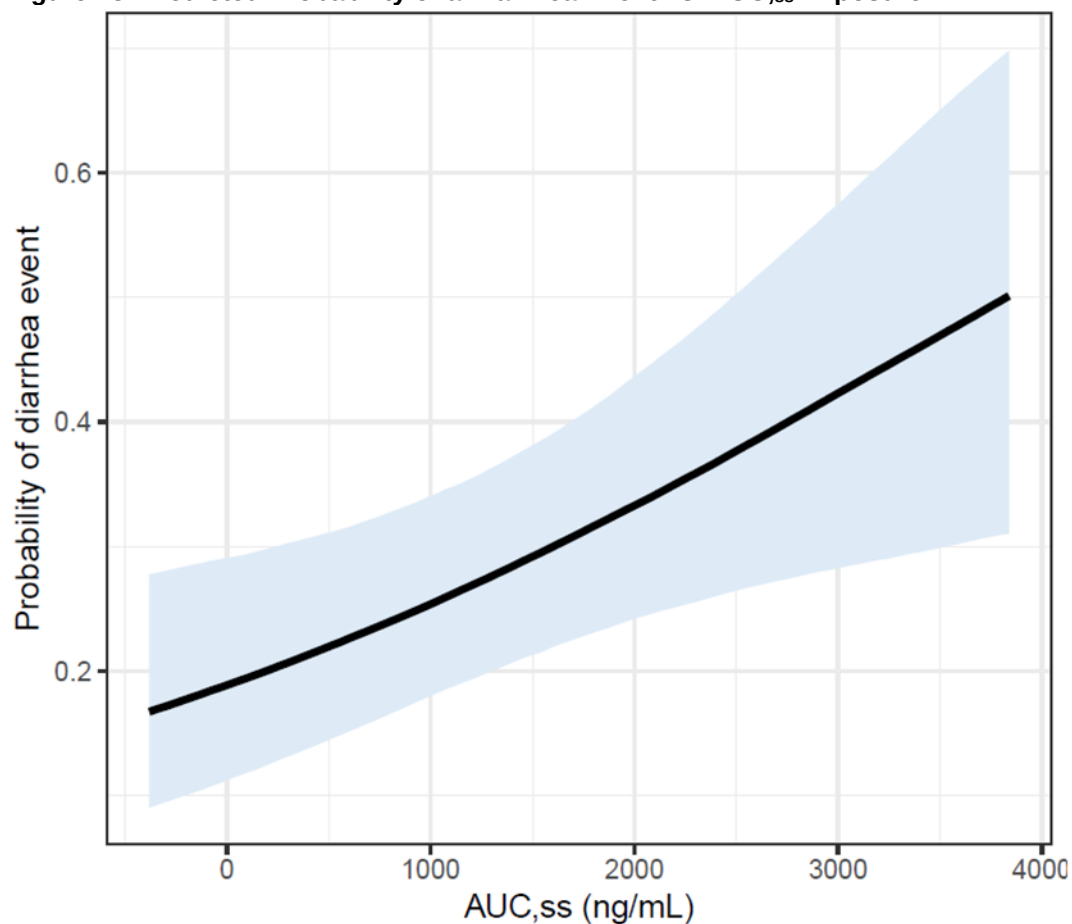
baseline counts above the median were associated with higher response rates. The reviewer explored the E-R relationships for both efficacy and safety between the PK exposures (e.g., AUC_{ss} or $C_{min,ss}$) and the primary endpoints using the logistics regression. [Figure 3](#) showed that participants with higher rilzabrutinib exposure (AUC_{ss}) were predicted to have more platelet counts increase from the baseline. However, response rate as defined by the primary endpoint of LUNA 3, did not appear to depend on exposure over the range at 400 mg BID (i.e., flat exposure-response) (see [Table 10](#) in Section 6.1.1.1). In terms of the safety analyses, participants with higher rilzabrutinib exposures (AUC_{ss} and $C_{min,ss}$) generally had higher rates of diarrhea and nausea ([Figure 4](#) and [Figure 5](#)). The Applicant's analyses results were basically similar as reviewer's findings ([Figure 22](#) and [Figure 23](#)). Anemia was not considered for further model development because events were rare overall, with less than 5% of participants experiencing an anemia event. The analysis of time to rescue therapy and dropout showed that rilzabrutinib exposure was not found to be predictive of time to first rescue therapy or time to dropout ([Figure 24](#)).

Figure 22. Predicted Probability of a Nausea Event vs. $C_{min,ss}$ Exposure



Source: Applicant's report of exposure-response analyses to characterize relationship between rilzabrutinib exposures and efficacy and safety endpoints in patients with immune thrombocytopenia, Figure SYN3, Page 28
The black line indicates the mean E-R relationship, and the shaded blue area indicates the 95% CrI.
Abbreviations: $C_{min,ss}$, minimum concentration in the dosing interval at steady state; CrI, credible interval; E-R, exposure-response

Figure 23. Predicted Probability of a Diarrhea Event vs. AUC_{ss} Exposure

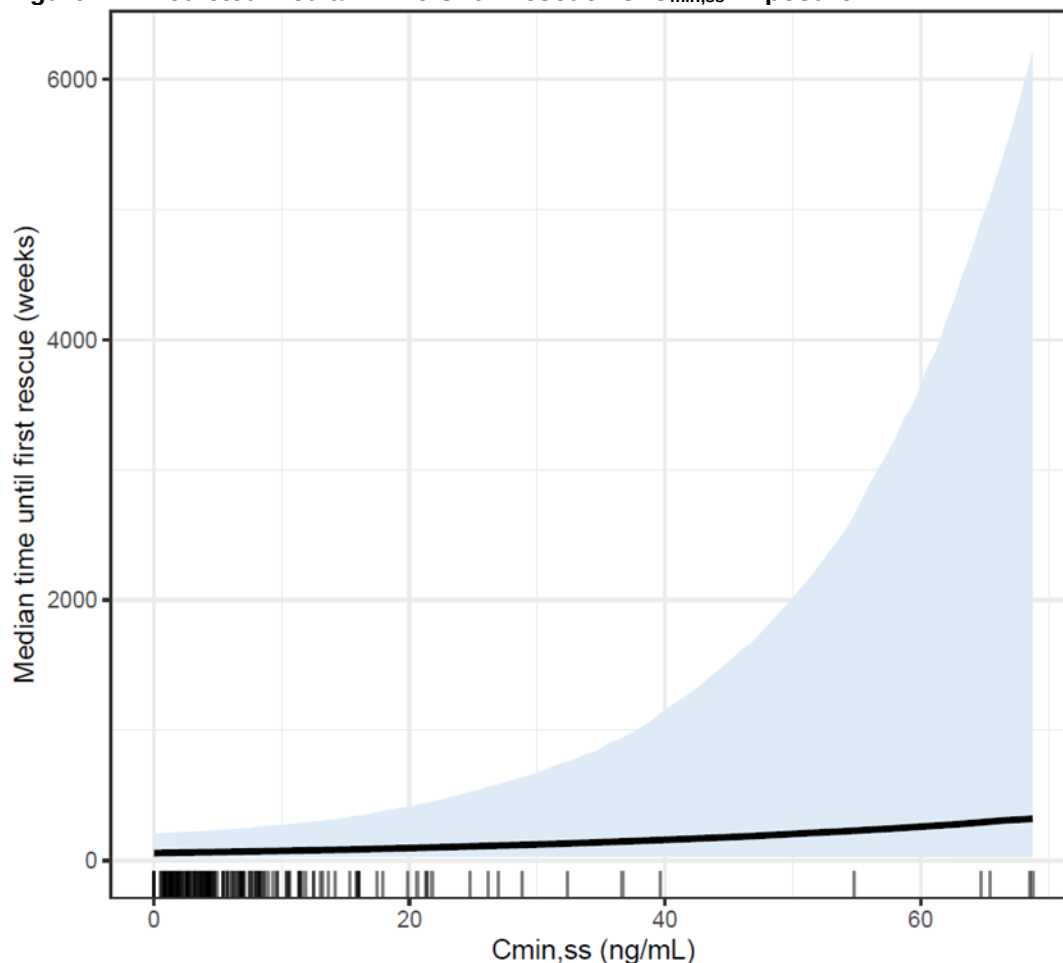


Source: Applicant's report of exposure-response analyses to characterize relationship between rilzabrutinib exposures and efficacy and safety endpoints in patients with immune thrombocytopenia, Figure SYN4, Page 29

Note: The black line indicates the mean E-R relationship, and the shaded blue area indicates the 95% CrI.

Abbreviations: AUC_{ss} , area under the concentration-time curve; CrI, credible interval; E-R, exposure-response

Figure 24. Predicted Median Time Until Rescue vs. $C_{min,ss}$ Exposure



Source: Applicant's report of exposure-response analyses to characterize relationship between rilzabrutinib exposures and efficacy and safety endpoints in patients with immune thrombocytopenia, Figure SYN5, Page 30

The black line indicates the mean time-to-event, and the shaded blue area indicates the 95% CrI. Black tick marks along the x-axis indicate observed exposure values in the data set.

Abbreviations: $C_{min,ss}$, minimum concentration in the dosing interval at steady state; CrI, credible interval

Summary

The results of the E-R analyses show a trend for greater increase in platelet count from baseline with higher rilzabrutinib exposure (AUC_{ss}). However, response rate as defined by the primary endpoint of LUNA 3, does not appear to depend on exposure over the range at 400 mg BID (i.e., flat exposure-response). In addition, participants with higher rilzabrutinib exposures (AUC_{ss} and $C_{min,ss}$) had relatively higher rates of diarrhea and nausea events.

14.5.3. Physiologically Based Pharmacokinetic Modeling

14.5.3.1. Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK analyses to:

- evaluate the DDI potential of rilzabrutinib as a substrate of moderate and weak CYP3A inhibitors at the therapeutic dose (400 mg)
- evaluate the DDI potential of rilzabrutinib as a substrate of moderate and weak CYP3A inducers
- evaluate the DDI potential of rilzabrutinib as an inhibitor of CYP3A, P-gp, OATP1Bs and BCRP, and an inducer of CYP3A at the therapeutic dose (400 mg)

The Division of Pharmacometrics has reviewed the PBPK reports (PBS0017, PMB0130 and PBS020) and related model summary reports, responses to FDA Clinical Pharmacology PBPK information requests dated October 22, 2024 (seq0015) and February 10, 2025 (seq0023 and seq0025), and the modeling supporting files, and concluded that:

- The rilzabrutinib PBPK model could be used to predict the effects of inhibitors or inducers on rilzabrutinib exposure.
 - The moderate CYP3A inhibitors fluconazole, erythromycin and verapamil were predicted to increase rilzabrutinib exposure approximately 3-fold following twice daily administration of 400 mg rilzabrutinib.
 - The weak CYP3A inhibitor cimetidine was predicted to increase rilzabrutinib exposure approximately 2-fold following twice daily administration of 400 mg rilzabrutinib.
 - The strong CYP3A inducers were predicted to reduce rilzabrutinib exposure by approximately 80%.
 - The moderate CYP3A inducer efavirenz was predicted to reduce rilzabrutinib exposure by approximately 70%.
 - The weak CYP3A inducer modafinil was predicted to reduce rilzabrutinib exposure by approximately 20%.
- Rilzabrutinib was predicted to increase midazolam C_{max} and AUC up to 2.6- and 3.5-fold in ITP participants following oral administration of rilzabrutinib 400 mg twice daily.
- The predicted effects of rilzabrutinib on the exposure of transporter substrates are considered inadequate because there are uncertainties about the in vitro to in vivo extrapolation of transporter inhibition parameters and potential effects of the major metabolite PRN834 on the transporter substrates were not considered. The potential interaction of rilzabrutinib with substrates of P-gp, OATP1B and/or BCRP cannot be ruled out.
- The renal impairment model was insufficiently verified for predicting the effects of renal impairment on rilzabrutinib exposure, especially in participants with severe renal impairment.

14.5.3.2. Background

Rilzabrutinib (PRN1008/SAR444671) is a reversible, covalent, potent BTKI in development for the treatment of autoimmune and inflammatory diseases. The recommended dosing regimen of rilzabrutinib is 400 mg taken orally twice daily with or without food. The 400 mg tablet is the only dose strength available.

Following oral administration of single doses of rilzabrutinib (liquid formulation) in healthy participants, AUC_{inf} increased greater than dose proportionally up to 600 mg, but C_{max} appeared to increase proportionally to the dose up to 300 mg (PRN1008-001). Similar exposures were observed from 600 to 1200 mg, indicating absorption with this formulation was dose limited. Following oral administration of multiple doses of rilzabrutinib (liquid formulation), the mean plasma AUC of rilzabrutinib increased approximately dose proportionality from 300 to 600 mg (PRN1008-001). Steady state was achieved every 3rd and 4th dosing day each week with approximately 2-fold accumulation. Compared to the fasted state, coadministration of rilzabrutinib as a liquid formulation with a moderate fat meal reduced C_{max} and AUC_{inf} by approximately 40% to 51%, respectively (PRN1008-001). Steady state rilzabrutinib exposures are comparable between a typical healthy subject and ITP participants (Study POH1156).

Rilzabrutinib is primarily metabolized by CYP3A4 with minor contribution from CYP2D6 in vitro. Following coadministration of a single dose of 400 mg rilzabrutinib with two doses of 100 mg ritonavir 12h apart in healthy participants, rilzabrutinib AUC and C_{max} increased by 8- and 5-fold, respectively (PRN1008-014). The results from the human ADME study in healthy male participants (PRN1008-015), conducted with a single oral dose of 300 mg rilzabrutinib (liquid formulation), showed that approximately 92.9% of the dose administered orally was recovered, in which approximately 5% and 86% of the dose were recovered in the urine and the feces, respectively, and unchanged drug was not detected in the urine and feces. Rilzabrutinib and its metabolite PRN834 (M45) accounted for 0.76% and 1.09% of the total radioactivity exposure in plasma, respectively, and the AUC of PRN834 was approximately 130% of its parent AUC (PRN1008-015). The absolute bioavailability study, conducted with a single oral dose of 400 mg rilzabrutinib (immediate release tablet) with an intravenous (IV) microdose of rilzabrutinib (100 µg), showed that rilzabrutinib had an oral bioavailability of 4.73%, and total plasma clearance of 58.1 L/h. Following oral administration of 300 mg rilzabrutinib, it had a renal clearance of 0.243 L/h (PRN1008-015).

Based on in vitro drug interaction studies, rilzabrutinib was not an inhibitor of most CYP enzymes except CYP3A with IC_{50} of 1.09µM (ICH0140). The rilzabrutinib metabolite, PRN834, was not identified as a reversible inhibitor of human CYPs but may be a time-dependent inhibitor of CYP3A. Its K_i and k_{inact} values were not determined due to activation effect at low concentration (ICH0140). A midazolam DDI study was conducted in healthy participants following a single dose of 400 mg rilzabrutinib (PRN1008-011). Midazolam exposure was increased by 1.7-fold when midazolam was given simultaneously with rilzabrutinib immediately released tablet, and 2.2-fold when midazolam was given 2 hours after rilzabrutinib administration (PRN1008-011). Midazolam exposure increased 3.14-fold when midazolam was given 1 hour after a single dose of 600 mg rilzabrutinib (PRN1008-002, liquid formulation). In vitro, rilzabrutinib is a CYP3A inducer and PRN834 is an inducer of CYP3A and CYP2B6 (IHH0096). However, at 50 times of unbound C_{max} , rilzabrutinib and PRN834 induced CYP3A mRNA less than 2-fold.

Rilzabrutinib is a substrate of P-gp and BCRP (DVR0091 and TRS0024), but not a substrate of OATP1B1/1B3, OAT1, OCT1/OCT2, (DVR0158). Rilzabrutinib and PRN834 are inhibitors of various efflux, and efflux and uptake transporters listed in [Table 98](#). In addition, rilzabrutinib is a P-gp inhibitor with an IC₅₀ value of 9.53 µM when assessed using the Caco-2/TC7 model, or 2.17 µM when assessed using the transfected vesicle model (TRI0055). Refer to Section [14.1](#) for information on rilzabrutinib ADME properties, in vitro and clinical studies used in PBPK modeling.

Table 98. Inhibition Parameters of Rilzabrutinib and Its Metabolite for Various Transporters

Test system	Probe substrates	Incubation time	IC ₅₀ (CV%)	
			Rilzabrutinib	PRN834
TransportoCells™ OATP1B1	³ H-Estradiol-17-β-Glucuronide [1 µM]	10 min (with 60 min compound preincubation)	0.705 µM (CV=7.8%)	1.87 µM (CV= 12.0%)
TransportoCells™ OATP1B3	³ H-Cholecystokinin-8 [0.5 µM]	10 min (with 60 min compound preincubation)	0.180 µM (CV=18.9%)	3.97 µM (CV=10.8)
TransportoCells™ OCT1	¹⁴ C-TEA [25 µM]	15 min	2.93 µM (CV=8.4%)	11.4 µM (CV=10.0%)
Genomembrane OCT2	¹⁴ C-Metformin [25 µM]	5 min	5.36 µM (CV=11.8%)	1.34 µM (CV=14.2%)
Genomembrane OAT1	³ H-p-Aminohippuric acid [5 µM]	2 min	22.2 µM (CV=8.6%)	122 µM (CV=18.7%)
TransportoCells™ OAT3	³ H-Estrone-3-sulfate [1 µM]	3 min	36.4 µM (CV=12.8%)	7.94 µM (CV=12.8%)
TransportoCells™ MATE1	¹⁴ C-TEA [5 µM]	5 min	2.91 µM (CV=15.4%)	0.138 µM (CV=18.7%)
TransportoCells™ MATE2-K	¹⁴ C-TEA [3 µM]	5 min	6.71 µM (CV=18.1%)	7.78 µM (CV=19.4%)
Caco-2/TC7 –BCRP	³ H-estrone-3Sulfate [5 µM]	120 min	7.61 µM (CV=8.3%)	5.25 µM (CV=9.5%)
HEK-BSEP vesicles	Taurocholate [2 µM]	5 min	1.42 µM (CV=14.2%)	16.7 µM (CV=19.7%)
Caco-2/TC7-P-gp	Digoxin (5 µM)	120 min	9.53 µM (CV=11.8%)	50.0 µM (CV=7.6%)
HEK P-gp vesicles	N-methyl-quinidine (2 µM)	3 min	2.17 µM (CV=3.0%)	34.9 µM (CV=5.3%)

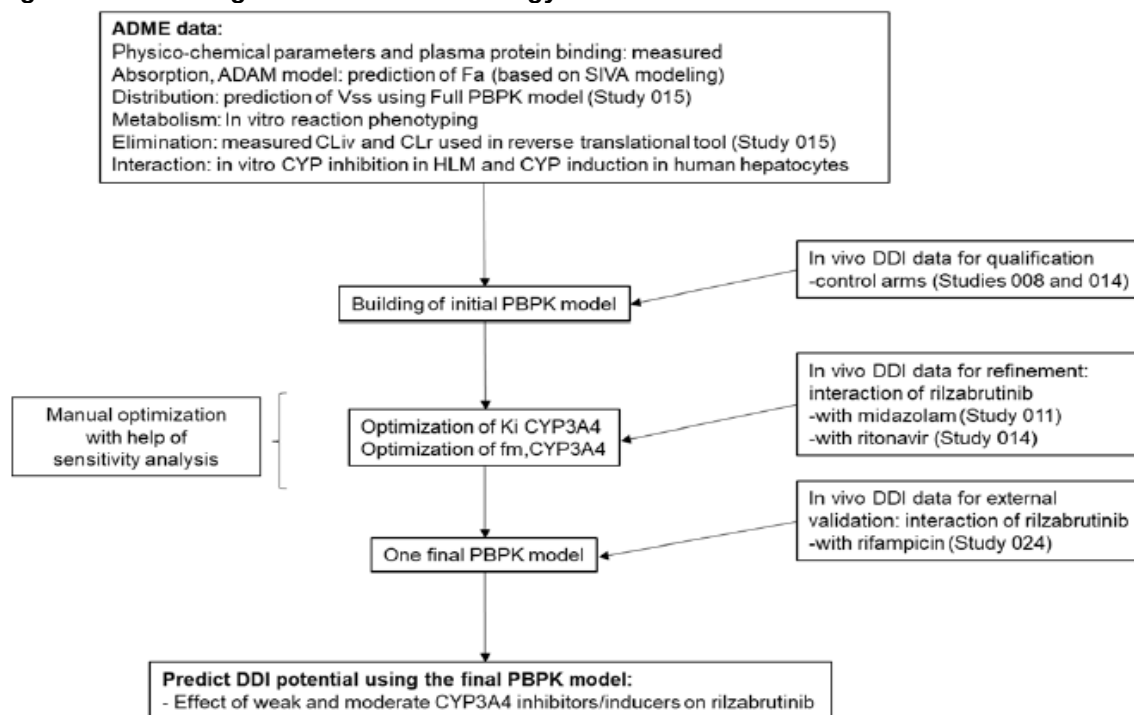
Source: transporter interaction study report TRI0053 and TRI0055

Abbreviations: IC₅₀, half maximal inhibitory concentration; CV, coefficient of variation

14.5.3.3. Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Versions 20, Certara, Sheffield, UK). Simulations were performed using healthy subject population (sim-Healthy Volunteers) model. Schemes of the PBPK modeling and simulation strategy are shown in [Figure 25](#), which summarizes the studies used for rilzabrutinib model development and verification, and model applications in predicting DDI of rilzabrutinib as a substrate of CYP3A4 induction or inhibition and as a precipitant of various transports and enzymes (not shown). The final model input parameters were summarized in [Table 99](#). The rilzabrutinib PBPK model consists of an Advanced Dissolution, Absorption and Metabolism (ADAM) model for describing drug absorption in each gut segment, a full PBPK model (method 3) for distribution, and an enzyme kinetics model and renal clearance for elimination. The Simcyp library files SV-ritonavir, erythromycin, verapamil, fluconazole, cimetidine, rifampin (SV-Rifampicin-MD), efavirenz, rifabutin, phenytoin, carbamazepine, midazolam, digoxin, pravastatin and rosuvastatin were used without any modification unless otherwise noted.

Figure 25. Modeling and Simulation Strategy



Source: Figure 1 in the PBPK report PBM0130

Abbreviations: ADAM, advance dissolution, absorption, and metabolism; CL_{iv}, in vivo clearance; CL_r, renal clearance; CYP, cytochrome P450; DDI, drug-drug interaction; HLM, human liver microsomes; PBPK, physiologically-based pharmacokinetic; SIVA, Simcyp in vitro data analysis; V_{ss}, volume of distribution at steady state

Table 99. Final Input Parameters in the Rilzabrutinib Model

Compound model	Parameter	Input	Comments	Compound model	Parameter	Input	Comments
Physical-chemical and blood binding parameters	Molecular weight	665.77		P-gp Substrate	J _{max} (pmol/min/cm ²)	1.75	
	LogP	3.5			K _m (μM)	0.184	TRS0024 (17)
	Compound type	Diprotic base			f _{u,ac}	1 (default)	
	pKa1	5.5	Investigator's Brochure (3)		RAF/REF	0.99 (default value)	
	pKa2	3.5		Distribution (full PBPK)	V _{ss} (L/kg)	1.59	Predicted V _{ss} using Method 3
	Fraction unbound in plasma (f _u)	0.025			K _p Scalar	0.6	
	Blood to plasma ratio	0.76	Calculated using E:P=0.47 Investigator's Brochure (3)	Elimination	CL _{int} CYP3A4 (μL/min/pmol)	16.597	
	Fraction unbound in gut (f _{u,gut})	0.4	Adjusted		Additional clearance HLM (pmol/min/mg protein)	235.175	Evaluated using reverse translational tool and fm CYP3A4 = 90%. After refinement with fm CYP3A4 = 80%, CL _{int} CYP3A4 = 14.753 μL/min/pmol and AddCL(liver) = 470.351 pmol/min/mg protein were the inputs in the final model.
	Papp (x 10 ⁻⁴ cm/s)	8.63	Modelled using SIVA and in vitro Caco2 data (pH7.4/7.4)		Additional clearance HLMs	NA	
	Peff, man (x 10 ⁻⁴ cm/s)	1	Predicted using Papp estimated above (no regional Peff)		Additional systemic CL (L/h)	4	
Absorption (ADAM model)	Intrinsic solubility (mg/mL)	0.037			CL _s (L/h)	0.268	Mean value from clinical study 015 (5)
	Solubility factor	2839		Interaction	K _i CYP3A4 (μM)	(b) (4)	Calibrated from ICH0140 (18), LPR1199 (19). After refinement by adjusting K _i CYP3A4 the value of K _i CYP3A4 : (b) (4) was the input in the final model.
	User logK _{m,w,neutral}	4.67	Modelled using SIVA and solubility pH profile data		K _i PgP (μM)	1.08	IC ₅₀ = 2.17 μM (TRS0024, (17)) K _i estimated as IC ₅₀ /2.
	User logK _{m,w,ion}	5.29			Ind _{max} CYP3A4	4.57	
	Precipitation kinetics	PRC 0.4 h ⁻¹ CSR 10	PRC adjusted using sensitivity analysis; Default value for CSR. (Modeling using SIVA cannot be performed due to the absence of enough data for evaluation)		IndC ₅₀ CYP3A4 (μM)	0.498745	IHH0096 (20) and calibrated using Simcyp calibrator for induction
	Particle Size Distribution	Batch CDNCW : (b) (4) Radius = (b) (4)	D ₅₀ of (b) (4)				
	Disintegration rate constant (h ⁻¹)	Batch CDNCW : (b) (4)	First order disintegration model. Modelled using SIVA and dissolution data at pH 2				
	Formulation Type	Immediate release tablet	-				

Source: Table 7 in the PBPK report PBM0130

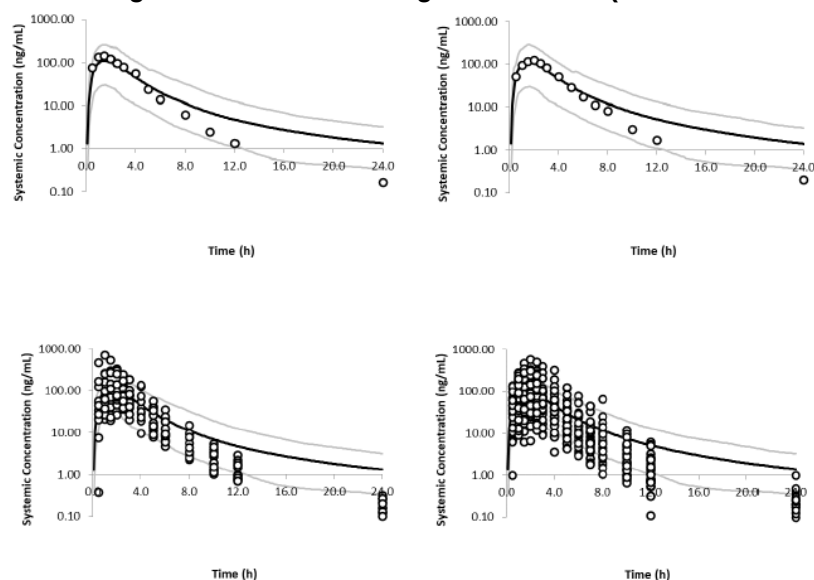
Abbreviations: CL, clearance; CL_r, renal clearance; CSR, critical supersaturation ratio; CYP, cytochrome P450; D₅₀, median particle size; log, logarithm; IC₅₀, half maximal inhibitory concentration; HLM, human liver microsome; Ind_{max}, maximum fold induction; IndC₅₀, concentration supporting half-maximal induction; K_i, inhibitory constant; K_m, Michaelis constant; K_p, partition coefficient; P-gp, P-glycoprotein; SIVA, Simcyp in vitro data analysis; PBPK, physiologically-based pharmacokinetic; PRC, precipitation rate constant; V_{ss}, volume of distribution at steady state; RAF, relative activity factor; REF, relative expression factor

14.5.3.4. Results

14.5.3.4.1. Can the PBPK Model Adequately Describe the PK Profiles of Rilzabrutinib?

Yes. Clinical PK data that had not been used in model development was used to verify the rilzabrutinib PBPK model. The model could reasonably describe the plasma concentration-time profiles of rilzabrutinib following single and multiple oral doses of rilzabrutinib in healthy participants (Figure 26 and Figure 27). The model-estimated AUC were mostly within 0.8- and 1.25-fold of the observed values, but the C_{max} values were mostly underpredicted (Table 100 and Table 101). However, the simulated steady-state C_{max} and AUC were 2-fold lower than that in ITP participants estimated from the PopPK analysis (Study POH1156, FDA-response-22Oct2024, Table 6).

Figure 26. Simulated and Observed Rilzabrutinib Plasma Concentrations in Healthy Participants After a Single Oral Dose of 400 mg Rilzabrutinib (PRN1008-008 and -014)

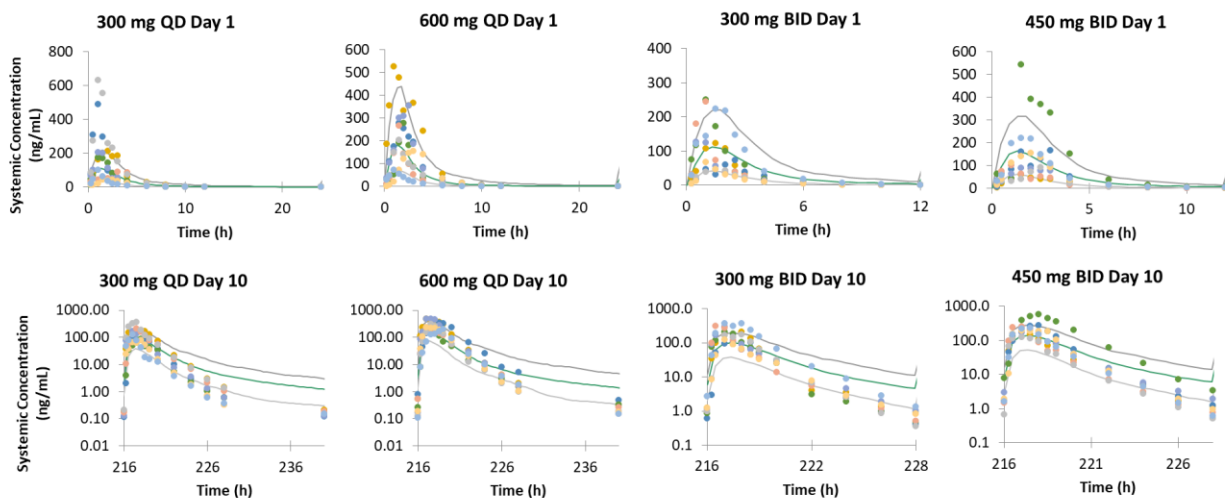


Source: Figure 7 in the PBPK report PBM0130

Opened circles are observed mean (top) or individual (bottom) plasma concentration-time profiles of rilzabrutinib (left: PRN1008-008 and right: PRN1008-014). The black line represents the simulated mean plasma concentration-time profiles of rilzabrutinib; gray lines represent the simulated 5th and 95th geometric percentiles of the simulations.

Abbreviations: PBPK, physiologically based PK

Figure 27. Simulated and Observed Rilzabrutinib Plasma Concentrations in Healthy Participants Following Multiple Doses of Rilzabrutinib Liquid Formulation (PRN1008-001)



Source: FDA response Oct 22, 2024 (seq0015)

Closed circles are observed individual plasma concentration-time profiles of rilzabrutinib (PNR1008-0001). The green line represents the simulated mean plasma concentration-time profile of rilzabrutinib; the gray lines represent the simulated 5th and 95th geometric percentiles of the simulations. The y-axis is in linear scale for Day 1, and in log-scale for Day 10.

Abbreviations: BID, twice daily; QD, once daily

Table 100. Simulated and Observed Rilzabrutinib Plasma Concentrations Geometric Mean With CV% for C_{max} and AUC in Healthy Participants After Single Dose Administration

Study		Population	t _{max} ^a (h)	C _{max} (ng/mL)	AUC _{last} (h.ng/mL)	AUC _{inf} (h.ng/mL)
Study-008 T4 400 mg	Observed	N = 14 18-58 years 29% female	2.00	133 (96.6%)	387 (70.6%)	388 (70.4%)
	Simulated	N = 100 (10x10) 18-58 years 29% female	1.55	89 (83%)	363 (77%)	386 (74%)
Ratio (Simulated/Observed)			NA	0.67	0.94	0.99
Study-014 PBT1 400 mg	Observed	N = 32 18-48 years 49% female	2.08	101 (115%)	328 (100%)	326 (99.8%)
	Simulated	N = 100 (10x10) 18-48 years 49% female	1.50	91 (85%)	369 (78%)	391 (76%)
Ratio (Simulated/Observed)			NA	0.90	1.12	1.20

^a Median for t_{max}.

Source: Table 11 in the PBPK report PBM0130

Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{last}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of participants in the study; NA, not available; PBPK, physiologically based PK; t_{max}, time to maximum concentration

Table 101. Simulated and Observed Rilzabrutinib Plasma Concentrations Geometric Mean With CV% for C_{max} and AUC in Healthy Participants After Multiple-Dose Administration of Rilzabrutinib as Liquid Formulation

Dose (mg)	Regimen	Day		C _{max} (ng/mL)	AUC _{tau} (h.ng/mL)	t _{max} (h)
300	QD	10	Obs (N=8)	172 (52%)	434 (52%)	1.50
			Pred (N=100)	105 (58%)	417 (58%)	1.35
			Ratio	0.61	0.96	0.90
			Ratio after exclusion ^a	0.72 ^a	1.11 ^a	0.90 ^a
300	BID	10	Obs (N=8)	223 (42%)	477 (47%)	1.00
			Pred (N=100)	101 (59%)	390 (59%)	1.35
			Ratio	0.45	0.82	1.35
			Ratio after exclusion ^b	0.50 ^b	0.97 ^b	1.35 ^b
600	QD	10	Obs (N=8)	313 (35%)	936 (39%)	1.50
			Pred (N=100)	204 (59%)	747 (59%)	1.25
			Ratio	0.65	0.80	0.83
450	BID	10	Obs (N=8)	251 (54%)	680 (65%)	1.25
			Pred (N=100)	143 (58%)	528 (58%)	1.30
			Ratio	0.57	0.78	1.04
			Ratio after exclusion ^c	0.69 ^c	1.00 ^c	1.30 ^c

Source: Table 1 in the FDA response, Oct 22, 2024 (seq0015)

PK parameters were rounded to 3 significant digits. Median t_{max} is given. The observed data are from PRN1008-001. AUC_{tau} is AUC_{0-24h} for QD dosing and AUC_{0-12h} for BID dosing.

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 h; AUC_{tau}, area under the concentration-time curve during the dosing interval; BID, twice daily; C_{max}, maximum plasma concentration; N, number of participants in treatment arm; PK, pharmacokinetic; QD, once daily; t_{max}, time to maximum concentration

14.5.3.4.2. Can PBPK Analyses Be Used To Estimate the Effects of Rilzabrutinib on Substrates of CYP3A, OATP1B, and BCRP?

Effects of Rilzabrutinib on Midazolam

Rilzabrutinib was predicted to increase midazolam AUC and C_{max} by 3.5- and 2.4-fold, respectively, following administration of 400 mg rilzabrutinib twice daily in ITP participants. Details are discussed as follows:

- In vitro, rilzabrutinib is an inhibitor and inducer of CYP3A. At 50 times of unbound C_{max} (0.3 to 0.6μM for rilzabrutinib and 0.66μM for PRN834), rilzabrutinib and its metabolite PRN834 induced CYP3A mRNA by less than 2-fold, indicating that these compounds are not considered as clinical inducers according to the ICH M12 guidelines.

- Clinical DDI studies of rilzabrutinib with midazolam in healthy participants showed that, following a single dose of 400 mg rilzabrutinib as tablet formulation (PRN1008-011), midazolam exposure was increased by 2.2-fold when midazolam was given 2 hours after rilzabrutinib administration (PRN1008-011). Midazolam exposure increased 3.14-fold when midazolam was given 1 hour after a single dose of 600 mg rilzabrutinib as liquid formulation (PRN1008-002). Simulation studies comparing predicted versus observed effects of rilzabrutinib on midazolam are presented in [Table 102](#). The effect of 400 mg rilzabrutinib tablet on midazolam was reasonably predicted, while the effect of the 600 mg liquid formulation was underpredicted. For the latter, the exposure of rilzabrutinib ([Table 103](#)) and midazolam in the absence of rilzabrutinib ([Table 102](#)) were well predicted, indicating that the underprediction may be caused by the CYP3A inhibition parameter K_i of rilzabrutinib. Reducing the K_i value from (b) (4) μM , used by the Applicant, to 0.003 μM , improved prediction accuracy for both 400 mg and 600 mg doses. Notably, the simulated exposure of rilzabrutinib following a single dose of 400 mg rilzabrutinib was (b) (4) higher than that observed in the midazolam study ([Table 103](#)), potentially explaining the reasonably prediction despite the suboptimal CYP3A K_i value.
- The effects of steady state rilzabrutinib on midazolam exposure, following administration of 400 mg rilzabrutinib twice daily in ITP participants, were simulated by both the Applicant and the reviewer. The results are shown in [Table 104](#). The effects predicted by the Applicant are likely underpredicted for two reasons: (1) the predicted steady-state rilzabrutinib following administration of 400 mg BID was approximately (b) (4) lower than that estimated in ITP participants by PopPK ([Table 105](#)), and (2) the suboptimal CYP3A K_i value were used in Applicant's simulations. To achieve the steady-state exposure of rilzabrutinib following administration of rilzabrutinib 400 mg BID in ITP participants, the simulations need to be performed at 700 mg BID. At the rilzabrutinib exposure achieved in ITP participants, rilzabrutinib was predicted to increase midazolam AUC and C_{max} by 3.5- and 2.4-fold, respectively. These results are similar to that observed in the midazolam study with a single 600 mg rilzabrutinib ([Table 104](#)), in which study rilzabrutinib exposure was similar to that in ITP participants and that simulated at rilzabrutinib 700 mg BID by the reviewer ([Table 105](#)).
- In Section 12.3 of the final product labeling, a 3-fold (b) (4) increase in midazolam AUC in patients with immune thrombocytopenia following coadministration with 400 mg rilzabrutinib twice daily was reported. This occurred because, during the labeling negotiation, the Applicant simulated this interaction using a CYP3A K_i value of 0.006 μM and Simcyp version 20.

Table 102. Simulated and Observed Effects of Rilzabrutinib on Midazolam Exposure Following Single Doses of Rilzabrutinib Administration

Dosing regimens	CYP3A4 Ki (μM)	Trials	Midazolam PK without rilzabrutinib			Midazolam PK with/without rilzabrutinib			Source
			C _{Max} (ng/mL)	AUC _{24h} (ng/mL.h)	AUC _{INF} (ng/mL.h)	C _{Max} Ratio	AUC _{24h} Ratio	AUC _{INF} ratio	
Rilzabrutinib 600 mg SD + Midazolam 2 mg 1 h after	(b) (4)	Observed	8.41	19.30	23.70	2.41	3.60	3.14	PRN1008-002
		Predicted	(b) (4)						Reviewer analyses
		Pred/obs							
	0.003	Predicted	7.25	21.47	21.95	2.61	3.26	3.27	
		Pred/obs	0.86	1.11	0.93	1.08	0.91	1.04	
Rilzabrutinib 400 mg SD + Midazolam 2 mg 2 h after	(b) (4)	Observed	6.86	16.20	17.30	2.23	2.18	2.18	
		Predicted	(b) (4)						PBPB report PBM0130
		Pred/obs							
	0.003	Predicted	7.75	23.5	23.93	2.17	2.45	2.45	Reviewer analyses
		Pred/obs	1.13	1.45	1.38	0.97	1.12	1.12	

Source: PRN1008-002, PRN1008-011, PBM0130 and reviewer's analyses

The Applicant's simulations were performed using Simcyp version 20, and the reviewer's simulations were performed using Simcyp version 22.

Abbreviations: AUC_{24h}, area under the concentration-time curve from time 0 to 24 h; AUC_{inf}, area under the concentration-time curve estimated to infinity; C_{max}, maximum plasma concentration; obs, observed; PK, pharmacokinetic; Pred, predicted; SD, single dose

Table 103. Comparison of Simulated and Observed Rilzabrutinib Exposure in the Midazolam Interaction Studies

Rilzabrutinib dose regimens	Population	Sources of observed data	Observed		Predicted		Predicted/Observed		Source of predicted data
			C _{Max} (ng/mL)	AUC _{INF} (ng/mL.h)	C _{Max} (ng/mL)	AUC _{INF} (ng/mL.h)	C _{max}	AUC _{INF}	
600 mg SD	Healthy	PRN1008-002	217	603	196	734	0.90	1.22	Reviewer
400 mg SD	Healthy	PRN1008-011	82	223	(b) (4)				PBM0130

Source: PBM0130 and reviewer's analyses

The Applicant's simulations were performed using Simcyp version 20, and the reviewer's simulations were performed using Simcyp version 22.

Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; C_{max}, maximum plasma concentration; SD, single dose

Table 104. Predicted Effects of Rilzabrutinib on Midazolam Exposure Following Administration of 400 mg Rilzabrutinib Twice Daily in ITP Participants

400 mg Rilzabrutinib Twice Daily in HIV-1 Participants				
Rilzabrutinib regimen	Midazolam regimen	C _{max} Ratio	AUC _{inf} Ratio	Source
400 mg BID for 14 days	comcomitant	(b) (4)		Applicant
	1h after			
	2h after			
700 mg BID for 5 days	comcomitant	2.41	3.5	Reviewer analysis
	1h after	2.61	3.54	
	2h after	2.4	3.03	

Source: PBM0130 and reviewer's analyses

Applicant's simulation was performed using the CYP3A K_i = (b) (4) μM and Simcyp version 20, and reviewer's simulation was performed using the CYP3A K_i = 0.003 μM and Simcyp version 22. 700 mg BID was used in the simulation to reproduce the exposure observed following 400 mg BID in ITP patients.

Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; BID, twice daily; C_{max}, maximum plasma concentration; CYP3A, cytochrome P450 3A, ITP, immune thrombocytopenia; K_i, inhibitory constant

Table 105. Comparison of Simulated Steady-State Rilzabrutinib Exposure With Steady State Rilzabrutinib Exposure in ITP Participants

Rilzabrutinib dose regimens	Population	Observed		Predicted		Predicted/Observed		Data Source
		C _{Max} (ng/mL)	AUC _{0-12h,ss} (ng/mL.h)	C _{Max} (ng/mL)	AUC _{0-12h,ss} (ng/mL.h)	C _{max}	AUC _{0-12h}	
400 mg BID	ITP patient	191	765					PRN1008-010
400 mg BID	ITP patient	151	770					EFC17093
400 mg BID	virtual Healthy			(b) (4)				FDA-response - 22Oct2024
700 mg BID	virtual Healthy			217	762	1.14	1.00	Reviewer*

Source: PRN1008-010, EFC17093, FDA-response-22Oct2024, and reviewer's analyses

700 mg BID was used in the simulation to reproduce the exposure observed following 400 mg BID in ITP patients. Median values are reported for observed and predicted steady state rilzabrutinib.

Abbreviations: AUC_{0-12h}, area under the concentration-time curve from time 0 to 12 h; AUC_{0-12h,ss}, area under the concentration-time curve from time 0 to 12 h at steady state; BID, twice daily; C_{max}, maximum plasma concentration; ITP, immune thrombocytopenia

Effects of Rilzabrutinib on OATP1B Substrate Pravastatin

Potential interaction between rilzabrutinib and the OATP1B1 substrate pravastatin cannot be ruled out. Details are discussed as follows:

- Drug interactions of pravastatin with OATP1B1/3 inhibitors were often not predicted using the pravastatin model in the Simcyp library even when the lowest in vitro transporter inhibition parameters of the inhibitors in the Certara DDI Database were applied in the simulations. The observed interactions with pravastatin could only be reproduced, within 0.8 -1.25 of clinical observations, when the lowest experimentally generated K_i or IC₅₀ values of OATP1B1/3 inhibitors were reduced approximately 10- to 100-fold ([ISSX 2024](#)). Rilzabrutinib predicted to increase pravastatin AUC and C_{max} by 1.4 and 1.8, respectively, when K_i values for both OATP1B1 and OATP1B3 were reduced by 100-fold ([Table 106](#)), when the rilzabrutinib exposure observed in ITP participants following administration of rilzabrutinib 400 mg BID was applied in the simulation. In addition to the uncertainty about the K_i value, it should be noted that this simulation didn't account for the potential inhibitory effects of the major circulating metabolite PRN834 on OATP1B1 and OATP1B3.
- PRN834 is the major metabolite of rilzabrutinib. Collectively, PRN834 and related metabolites account for approximately 26% of the total radioactive material recovered in the human ADME study and approximately 43% of total oxidative metabolites identified in the urine and feces (PRN1008-015-POP17292). PRN834 is one of the major circulating metabolites in human plasma. Following single and twice daily doses of 400 mg rilzabrutinib, the PRN834 to rilzabrutinib AUC ratio ranged from 1.6- to 2.1-fold in Japanese and Caucasian participants (PRN1008-023). Compared to rilzabrutinib, the in vitro IC₅₀ value of PRN834 for OATP1B1 was approximately 2.7-fold lower, Therefore, potential inhibitory effects of PRN834 on transporters cannot be ruled out.

Table 106. Predicted Effects of Rilzabrutinib on Statin Exposure Following Administration of 400 mg Rilzabrutinib Twice Daily in ITP Participants

OATP1B substrates	OATP1B1/3 IC ₅₀ (μM)	BCRP IC ₅₀ (μM)	P-gp IC ₅₀ (μM)	CYP3A K _i (μM)	AUC ratios	C _{max} ratios	Source
Pravastatin	(b) (4)						(b) (4) PBS0017; FDA-response-22Oct2024
	Ki/100				1.42	1.79	reviewer
Atorvastatin	Ki/100			0.003	2.77	3.83	
Rosuvastatin	(b) (4)						(b) (4) PBS0017; FDA-response-22Oct2024
	Ki/100	Ki/100			2.05	3.05	
	Ki/100	Ki/200			2.18	3.25	reviewer
Dabigatran			2.17		1.53	1.69	
			Ki/10		3.54	4.14	
			Ki/100		7.07	7.77	

Source: PBS0017, FDA-response-22Oct2024, and reviewer's analyses

Simulations conducted by the reviewed were performed at 700 mg rilzabrutinib BID using Simcyp version 22. Applicant's simulations were performed using Simcyp version 20.

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; CYP, cytochrome P450; IC₅₀, half maximal inhibitory concentration; K_i, inhibitory constant; OATP, organic anion transporting polypeptide

Effects of Rilzabrutinib on OATP1B and BCRP Substrate Rosuvastatin

Potential interaction between rilzabrutinib and the OATP1B/BCRP substrate rosuvastatin cannot be ruled out. Details are discussed as follows:

- The predicted effect of rilzabrutinib on rosuvastatin was likely inaccurate for two reasons: (1) the rosuvastatin model (V20) used to evaluate the effect of rilzabrutinib on both OATP1B and BCRP cannot capture the C_{max} of rosuvastatin and tends to underpredict its AUC in participants with OATP1B1 or BCRP genotypes ([Table 107](#)), and (2) the reviewer's analyses showed that drug interactions of rosuvastatin with OATP1B1/3 and BCRP inhibitors were either not predicted or significantly underpredicted even when the lowest in vitro transporter inhibition parameters of the inhibitors in the Certara DDI Database were applied in the simulations.
- For risk assessment, the reviewer performed simulations using the rosuvastatin model in Simcyp V22, which could reasonably predict its AUC in OATP1B1 and BCRP genotypes. However, the in vitro to in vivo extrapolation of BCRP inhibition parameter (K_i or IC₅₀) has not been established. Through the reviewer's independent analysis of OATP1B or/and BCRP inhibitors with clinical interaction data with both OATP1B1 endogenous biomarker CP-I and rosuvastatin, (b) (4)

When rilzabrutinib and rosuvastatin were administered simultaneously, (b) (4)

(b) (4) rilzabrutinib was predicted to increase rosuvastatin AUC and C_{max} by approximately (b) (4), respectively ([Table 106](#)). Additionally, the lowest IC₅₀ values of BCRP inhibitors in the DDI Database were mostly generated using the membrane vesicle system not the Caco-2 monolayer system used for rilzabrutinib. The BCRP IC₅₀ generated using the Caco-2 monolayer system was on average 11-fold less potent, ranging from 0.3 to 53-fold lower, compared to the HEK293 membrane vesicle system. Furthermore,

the major oxidative metabolite PRN834 is 50% more potent BCRP inhibitor compared to rilzabrutinib. Given that rilzabrutinib is extensively metabolized, potentially in part to PRN834, by CYP3A at the intestine, the potential effect of PRN834 on BCRP may not be ignored. Taken together, significant interaction between rilzabrutinib and rosuvastatin cannot be ruled out.

Table 107. Predictive Performance of the Rosuvastatin Model

Simcyp version	Observed		V19-21		V22		PMID		
PK parameters			Predicted/observed		Predicted/observed				
Phenotype or precipitants	C _{max} (ng/mL)	AUC (ng x h/mL)	C _{max}	AUC	C _{max}	AUC			
OATP1B1 phenotype			(b) (4)						
Extensive Transporter (ET)	4.21	33.7							17473846
Intermediate Transporter (IT)	6.38	53.1							
Poor Transporter (PT)	7.53	55.6							
BCRP phenotype			(b) (4)						
Extensive Transporter (ET)	7.06	62.3							19474787
Intermediate Transporter (IT)	7.85	76.2							
Poor Transporter (PT)	16.3	152.2							

Source: rosuvastatin summary reports assessed via Simcyp member area and reviewer's analysis

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; OATP, organic anion transporting polypeptide; PK, pharmacokinetic; PMID, PubMed ID; V, version

Effects of Rilzabrutinib on P-gp

Significant interaction between rilzabrutinib and the P-gp substrate dabigatran etexilate cannot be ruled out. Details are discussed as follows:

- The Applicant predicted the effect of rilzabrutinib on P-gp using the digoxin PBPK model, which is not fully verified. For risk assessment, the reviewer performed simulations using the PBPK models of dabigatran etexilate and dabigatran in Simcyp V22. Dabigatran etexilate is a P-gp substrate. Dabigatran is a metabolite of dabigatran etexilate and is not a P-gp substrate. The effects of P-gp inhibitors on dabigatran etexilate are assessed by changes in dabigatran plasma exposure. The ability of the PBPK models of dabigatran etexilate and dabigatran to predict P-gp interaction was assessed using clinical DDIs of dabigatran with verapamil, clarithromycin, quinidine, and ketoconazole (Dabigatran Simcyp summary report). In addition, the model could describe the dabigatran pharmacokinetics following administration of a microdose of dabigatran etexilate (0.375 mg, Simcyp V22 Dabigatran Etexilate and Dabigatran summary report). Of note, the ketoconazole DDI data were also used in the model development.
- Large range of IC₅₀ values of these inhibitors are reported in the Certara DDI Database. The difference in IC₅₀ between minimum and maximum values of each inhibitor ranges from 10- to 7450-fold if all the results were considered, and 1- to 42-fold if only experiments conducted in the condition similar to that of rilzabrutinib (e.g., P-gp expressing HEK membrane vesicles and N-methyl-quinidine as a probe substrate, study report TRI0055) were considered. Compared with the Ki values used in the models of the aforementioned inhibitors, the maximum IC₅₀ values generated using membrane vesicles were approximately 4 to 200-fold higher, and the minimum IC₅₀ values generated using membrane vesicles were approximately 2- to 15-fold higher. Given the large variability in P-gp IC₅₀, the predictability

of clinical DDI from in vitro data is of concern. For risk assessment, the reviewer conducted sensitivity analyses of Ki. Significant increase in dabigatran exposure was predicted when the Ki value was reduced only 10-fold (Table 106). Therefore, significant interaction between rilzabrutinib and the P-gp substrate dabigatran etexilate cannot be ruled out.

14.5.3.4.3. Can PBPK Analyses Predict the Effects of CYP3A Precipitants on the Pharmacokinetics of Rilzabrutinib?

Yes, the rilzabrutinib PBPK model could be used to predict the effects of CYP3A inhibitors or inducers. The moderate CYP3A inhibitors were predicted to increase rilzabrutinib exposure approximately 3-fold, and the weak CYP3A inhibitor cimetidine was predicted to increase rilzabrutinib exposure by approximately 2-fold (Table 108). The effect of rifampin on rilzabrutinib exposure was overpredicted, thus there may be some uncertainties about the predicted effects of other CYP3A inducers on rilzabrutinib exposure. See detailed discussion in the comments below.

Table 108. Predicted C_{max} and AUC Ratio of Drug-Drug Interactions With Rilzabrutinib as a Substrate in Healthy Participants, Fasted State

Categories	Precipitant	Rilzabrutinib 400 mg	C _{max} * Ratio	AUC* Ratio	Study Type
Strong CYP3A inhibitor	Ritonavir 100 mg Q12h, 2 doses	SD with 1st dose of ritonavir	5.8	9.6	Observed
			6.2	7.3	Simulated
			1.1	0.8	Simulated/Observed
Moderate CYP3A inhibitor	Fluconazole 200 mg QD 14d	SD	3.3	3.1	Simulated
		BID 10d	3.3	3.1	
	Erythromycin 500 mg TID 5d	SD	3.1	3.0	
		BID 10d	3.6	3.5	
	Verapamil 80 mg TID 10d	SD	2.8	2.6	
		BID 10d	3.6	3.3	
Weak CYP3A inhibitor	Cimetidine 400 mg TID 5d	400 mg BID	2.1	1.6	Simulated
Strong CYP3A inducer	Rifampicin 600 mg QD 11d	SD	0.20	0.23	Observed
			0.13	0.14	Simulated
			0.65	0.61	Simulated/Observed
	Phenytoin 300 mg QD 10d	SD	0.21	0.26	Simulated
		BID 10d	0.25	0.27	
Moderate CYP3A inducer	Carbamazepine 400 mg BID 15d	SD	0.19	0.25	Simulated
		BID 10d	0.21	0.24	
	Efavirenz 600 mg QD	SD	0.30	0.31	Simulated
		BID 10d	0.32	0.32	
Weak CYP3A inducer	Modafinil 200 mg QD 10d	BID 10d	0.81	0.80	Simulated

Source: FDA response Oct 22, 2024 (seq0015) and FDA response Feb 10, 2025 (seq0023)

* Single dose. For rilzabrutinib SD, ratio of AUC_{inf} is given; for rilzabrutinib BID, ratio of AUC₀₋₂₄ on day 10 is given.

Abbreviations: AUC, AUC, area under the concentration-time curve; AUC₀₋₂₄, area under the concentration-time curve from time 0 to 24 h; AUC_{inf}, area under the concentration-time curve estimated to infinity; BID, twice daily; C_{max}, maximum plasma concentration; CYP, cytochrome P450; d, days; Q12h, once every 12 hours; QD, once daily; SD, single dose; TID, three times daily

Summary

- To predict the effects of CYP3A inhibitors and inducers on rilzabrutinib pharmacokinetics, the fraction metabolized by CYP3A ($f_{m,CYP3A}$) is one of key parameters that need to be verified in the rilzabrutinib PBPK model. Based on the results from the study conducted using recombinant human CYP enzymes (DVR0108) and chemical inhibition study conducted in primary human hepatocytes (MIH0984), approximately 90% of rilzabrutinib metabolism was mediated by CYP3A4 with minor contribution from CYP2D6, approximately 8% on average. In the human ADME study (PRN1008-015-POP17292), although not all the radioactive components were identified, approximately 73% of the quantitated dose were identified as oxidative metabolites, indicating oxidative metabolism is the major elimination pathway of rilzabrutinib. The $f_{m,CYP3A}$ value in the rilzabrutinib model was optimized to be 80% based on its ability to reproduce the inhibitory effects of ritonavir on rilzabrutinib ([Table 108](#)).
- Ritonavir is an inhibitor of CYP3A and P-gp. Rilzabrutinib is a substrate of CYP3A and P-gp. rilzabrutinib had moderate permeability (DVR0091). Therefore, P-gp may play a role in rilzabrutinib absorption, and the observed effect of ritonavir on rilzabrutinib pharmacokinetics could be due to inhibition of both CYP3A and P-gp. Coadministration of rilzabrutinib with a P-gp inhibitor quinidine increased rilzabrutinib AUC only 12.7% (PRN1008-024). In addition, the human ADME study showed that approximately 90% of rilzabrutinib was absorbed. These data indicate that P-gp may not play a significant role in rilzabrutinib disposition. Therefore, the observed effect of ritonavir on rilzabrutinib pharmacokinetics is most likely due to CYP3A inhibition, and this rilzabrutinib model is suitable to predict the effects of CYP3A inhibitors that are also inhibitors of P-gp such as erythromycin and verapamil.
- Rifampin is known to decrease the exposure of P-gp substrates by P-gp induction. Even though P-gp may play an insignificant role in rilzabrutinib absorption, increase in P-gp expression by rifampin could potentially increase hepatic biliary clearance of rilzabrutinib. The PBPK simulation overpredicted the induction effects of rifampin on rilzabrutinib without incorporating P-gp induction in the rifampin model. The reason for this overprediction is unknown. Therefore, there may be some uncertainties in using the rilzabrutinib model to predict the effects of an inducer on its exposure.
- The Applicant also predicted the effect of a moderate CYP3A inducer using the rifabutin PBPK model. However, the results are not included in [Table 108](#) due to several limitations:

(b) (4)



(b) (4) Therefore, further verification is needed to establish the reliability of rifabutin's CYP3A induction capability.

- For the weak CYP3A inhibitor cimetidine, its PBPK model to predict inhibitory effects of cimetidine on CYP3A substrates was inadequately verified. As shown in (Table 109), the observed inhibitory effects of cimetidine on the exposure of CYP3A substrates were not predicted in >50-60% of the studies, even though predicted ratios of C_{max} and AUC were within 0.8- 1.25-fold of the observed values. For those that cimetidine was predicted to have inhibitory effects (>1.25 fold), its effects were generally underpredicted. The Applicant was requested to improve the prediction results by optimizing the CYP3A K_i parameter in the cimetidine model (FDA information request_10Jan2025). The Applicant reduced CYP3A K_i value (b) (4) to 11 μ M, which improved the predictions except for two studies (Table 109). This improved cimetidine model was used to predict the interaction of cimetidine with rilzabrutinib (Table 108).

Table 109. Verification of the Cimetidine PBPK Model To Predict Its Interactions With CYP3A Substrates

Cimetidine Dosing Regimens	Dosing Regimens of CYP3A Substrates	Observed		(b) (4)	Predicted (K_i = 11 μ M)	
		C_{max} R	AUCR		C_{max} R	AUCR
400 mg cimetidine BID (3 doses)	Midazolam 15 mg SD (D2) (30 min)	NA	1.35		1.63	1.82
400mg cimetidine SD	Midazolam 15mg SD (2 hrs after)	1.37	1.37		1.46	1.55
Cimetidine 200 mg TID with 400 mg pm on D1. 200 mg on D2	Midazolam 15 mg SD (D2) 2.5h after	2.38	2.02		1.21	1.24
Cimetidine 300 mg QID for 2 days	Triazolam 0.5 mg SD (D2)	1.39	1.32		1.34	1.43
Cimetidine 200 mg TID with 400 mg pm for 9 days	Triazolam 0.5 mg QD at night for 7 days	1.51	2.2		1.45	1.6
Cimetidine 300 mg QID (4 doses)	Triazolam 0.5mg SD (1 hr after 3rd cimetidine dose)	1.35	1.55		1.35	1.46
Cimetidine 200 mg TID with 400 mg pm for 9 days	Alprazolam 0.5mg TID for 7 days and morning dose on D8	1.82	1.64		1.13	1.17
Cimetidine 800 mg QD for 5 days	Nifedipine 10 mg TID for 4 Ds, 1 dose D5	2.3	2		1.55	2.04
Cimetidine 200 mg TID with 400 mg pm for 7 days	Nifedipine 10 mg QID for 6 Ds, 1 dose D7	2.02	1.6		1.28	1.53
Cimetidine 200 mg TID with 400mg pm for 3 days	Nifedipine 20 mg SD D2 (1 hr after first cimetidine dose)	NA	1.31		1.35	1.51
Cimetidine 300 mg QID for 7 days	Nifedipine 20 mg SD D7	1.4	1.52		1.43	1.72
Cimetidine 800 mg QD for 5 days	Nifedipine 20 mg SD D5 (1hr after cimetidine)	1.65	1.77		1.96	2.42
Cimetidine 300 mg QID for 7 days	Quinidine 330 mg (free base) SD on D6	1.2	1.57		1.13	1.32
Cimetidine 300mg QID for 3 days, a.m. dose day 4	Quinidine 330 mg (free base) SD on D4	1	1.27		1.13	1.2
Cimetidine 800 mg QD for 4 days	Sildenafil 50 mg SD D3 (2 hrs after)	1.54	1.56		1.65	1.78

Source: sv-cimetidinesummary-V21-kiupdated (NDA219685 seq0023)

Abbreviations: AUCR, area under the concentration-time curve ratio; BID, twice daily; CYP3A, cytochrome P450 3A; C_{max} R, maximum plasma concentration ratio; D, day; pm, at night; K_i , inhibitory constant; PBPK, population-based pharmacokinetic; QD, once daily; SD, single dose; TID, three times daily

- For the weak CYP3A inducer dexamethasone, its PBPK model has not been adequately verified to be used to simulate the effect of a weak CYP3A inducer on rilzabrutinib. The effects of dexamethasone on triazolam and aprepitant were too weak (AUC ratio (b) (4)) to be used to verify its induction effect on CYP3A (Table 4 in Simcyp V20 Dexamethasone summary report). The Applicant was requested to choose an alternative inducer whose induction effects result in AUC ratios of sensitive CYP3A substrates (e.g., midazolam, triazolam, etc.) <0.7 (FDA information request_10Jan2025). The Applicant selected modafinil as a weak CYP3A inducer. The modafinil PBPK model could adequately simulated its effects on CYP3A substrates (Table 110).

Table 110. Verification of the Modafinil PBPK Model To Predict Its Interactions With CYP3A Substrates

CYP3A substrate drugs	Observed		Predicted		Observed/predicted		PMID References
	C _{max} Ratio	AUC Ratio	C _{max} Ratio	AUC Ratio	C _{max} Ratio	AUC Ratio	
Midazolam	0.73	0.65	0.68(0.58 to 0.76)	0.63(0.53 to 0.72)	0.93	0.97	28082902
Ethinylestradiol	0.89	0.82	0.86(0.83 to 0.89)	0.82(0.78 to 0.85)	0.97	1.00	11823757
Triazolam	0.56	0.41	0.69(0.65 to 0.74)	0.56(0.52 to 0.63)	1.24	1.37	11823757
Omeprazole	1.22	1.36	1.37(1.23 to 1.53)	1.55(1.36 to 1.81)	1.12	1.14	28082902
Omeprazole	1.54	1.85	1.40(1.20 to 1.58)	1.58(1.29 to 1.88)	0.91	0.85	28082902

Source: Simcyp V20 modafinil summary report

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CYP3A, cytochrome P450 3A; PBPK, physiologically based pharmacokinetic; PMID, Pubmed ID

14.5.3.4.4. Can PBPK Analyses Predict the Effects of Renal Impairment on the Pharmacokinetics of Rilzabrutinib?

The renal impairment model may not be sufficiently verified for predicting the effects of renal impairment on rilzabrutinib exposure, especially in participants with severe renal impairment.

PBPK analyses were used to evaluate the effects of renal impairment on rilzabrutinib pharmacokinetics. The exposure of rilzabrutinib in participants with renal impairment were predicted to be no more than 1.5-fold higher compared to that in healthy participants (report PBS020). To verify the performance of renal impairment population models, the Applicant was requested to provide model verification documents that include the key parameters relating to the population models, the source of the values used, and, if any parameter optimization was done, list drugs and clinical studies used and describe the optimization process. In addition, the performance of each subpopulation needs to be demonstrated by comparing the observed and simulated pharmacokinetics of a set of drugs that have not been used in the parameter optimization to demonstrate the model performance. The drugs used in the model performance evaluation should have similar characteristics to rilzabrutinib that is predominantly (>80% preferred) metabolized by CYP3A with minimal renal elimination. [Table 111](#) summarizes the performance of the Applicant selected CYP3A substrates. Among the investigated drugs, metformin is mainly eliminated via renal excretion and the contribution of CYP3A in the model has not been verified. Nifedipine and sildenafil data were used to optimize the CYP3A abundance in these populations. In addition, renal impairment had limited impact on the exposure of most of the selected drugs. For drugs whose exposure increased more than 50%, the effects of renal impairment on their exposure tended to be underpredicted ([Table 111](#)). Therefore, the renal impairment model may not be sufficiently verified for predicting the effects of renal impairment on rilzabrutinib exposure, especially in participants with severe renal impairment.

Table 111. Simulated and Observed Difference in Exposure Ratios Between Renal Impairment and Healthy Control Ratios

Study	RI Classification	Substrates	Main Enzyme/ transporters	Administration Route	Observed RI/HC			Simulated/Observed RI/HC		
					f_u Ratio	C_{max} Ratio	AUC Ratio	f_u Ratio	C_{max} Ratio	AUC Ratio
2	Mild	Miazolam	CYP3A	PO	0.99	0.97	0.64	(b) (4)		
2	Moderate RI	Miazolam	CYP3A	PO	1.07	1.05	1.33			
2	Severe RI	Miazolam	CYP3A	PO	1.31	0.93	0.95			
5	Mild RI	Atorvastatin	CYP3A/OATP1B/BCRP/NTCP/P-gp	PO	1.12	1.48	1.13			
5	Moderate RI	Atorvastatin	CYP3A/OATP1B/BCRP/NTCP/P-gp	PO	1.19	2.55	1.75			
5	Severe RI	Atorvastatin	CYP3A/OATP1B/BCRP/NTCP/P-gp	PO	1.36	2.16	1.63			
8	Mild	Cinacalcet	CYP3A4	PO	1.00	1.51	1.51			
8	Moderate RI	Cinacalcet	CYP3A4	PO	1.38	0.56	0.68			
8	Severe RI	Cinacalcet	CYP3A4	PO	1.30	0.77	1.17			
9	Severe RI	Crizotinib	CYP3A4, P-gp	PO	0.93	1.34	1.80			
11	Mild	Drospiredone	CYP3A	PO	1.29	1.11	1.04			
11	Moderate RI	Drospiredone	CYP3A	PO	0.88	1.18	1.37			
15	Mild	Metformin	CYP3A4, OCT	PO	NA	1.41	1.58			
15	Moderate RI	Metformin	CYP3A4, OCT	PO	NA	3.27	4.72			
15	Severe RI	Metformin	CYP3A4, OCT	PO	NA	3.29	4.57			
17A	Mild	Nifedipine	CYP3A	IV	1.25	NA	1.16			
17A	Moderate RI	Nifedipine	CYP3A	IV	1.32	NA	1.02			
17A	Severe RI	Nifedipine	CYP3A	IV	1.62	NA	1.02			
17B	Mild	Nifedipine	CYP3A	PO	NA	0.91	NA			
17B	Moderate RI	Nifedipine	CYP3A	PO	NA	0.85	NA			
17B	Severe RI	Nifedipine	CYP3A	PO	NA	0.85	NA			
23	Mild	Sildenafil	CYP3A	PO	0.89	1.04	0.90			
23	Moderate RI	Sildenafil	CYP3A	PO	0.74	1.17	1.17			
23	Severe RI	Sildenafil	CYP3A	PO	0.81	1.89	2.01			

Source: ri-summary-v21 (seq 0023)

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; C_{max} , maximum plasma concentration; CYP3A, cytochrome P450 3A; f_u , free fraction of drug in plasma HC, healthy control; OATP1B, organic anion transporting polypeptide 1B; OCT, organic cation transporter; P-gp, P-glycoprotein; RI, renal impairment

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. LUNA 3

15.1.1. Clinical Protocol Synopsis for LUNA 3, (PRN1008-018), Version 4, July 24, 2023

PROTOCOL TITLE

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

PROTOCOL NUMBER

PRN1008-018 (EFC17093)

SPONSOR

Principia Biopharma Inc.

STUDY MEDICATION

The investigational drug product is rilzabrutinib (PRN1008/SAR444671).

PHASE

This is a Phase 3 pivotal study.

STUDY POPULATION

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

DURATION OF STUDY PARTICIPATION

For each participant, the study will last up to 60 weeks from the start of the screening period to the End of Study (EOS) visit. This includes screening (up to 4 weeks) through a 12 to 24-week blinded treatment period followed by a 28-week open-label period. Followed by a 4-week postdose follow-up. For adult participants, the maximum duration of the LTE period will be 12 months from the date of the last adult participant to enter the LTE.

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

NUMBER OF STUDY SITES

Approximately 150 sites worldwide.

OBJECTIVES

Primary Efficacy Objective (Blinded Treatment Period)

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

Key Secondary Efficacy Objectives (Blinded Treatment Period)

- To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet count $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and at least doubled from baseline, over the 24-week blinded treatment period in the absence of rescue therapy.
- To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet counts $\geq 30,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.
- To evaluate the effect of rilzabrutinib versus placebo on the time to first platelet count of $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and at least doubled from baseline.
- To evaluate the effect of rilzabrutinib versus placebo on the proportion of participants requiring rescue therapy.
- To evaluate the effect of rilzabrutinib versus placebo on the change from baseline on Item 10 of the ITP-PAQ (i.e., physical fatigue) in adult participants (≥ 18 years) at Week 13.

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

Other Secondary Objectives

Efficacy Objectives

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

Pharmacokinetic Objectives

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

Quality of Life Objectives

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

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

INVESTIGATIONAL PLAN

Study Design

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

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

Randomization will be carried out separately for the two age groups. For the adult group, stratified permuted block randomization will be implemented; for the pediatric group, dynamic randomization algorithm (minimization) will be implemented. The factors used for stratification (for adult participants) or balance (for pediatric participants) are splenectomy status (yes/no), and by severity of thrombocytopenia (Inclusion Criteria #3 platelet counts $<15,000/\mu\text{L}$ or $\geq 15,000/\mu\text{L}$).

After randomization, participants will start a blinded treatment period of up to 25 weeks followed by an open-label period of 28 weeks during which all participants will receive rilzabrutinib, and then a 4-week safety follow-up period or long-term extension.

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

- a. platelet count of $\geq 50,000/\mu\text{L}$ OR a platelet count between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and at least doubled from baseline at any time during the first 12 weeks and
- b. absence of rescue medication in the 4 weeks prior to the elevated platelet count that meets platelet response criteria.

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

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

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

The use of rescue medications (one of IVIg, high-dose CSs, platelet infusion, or anti-D immunoglobulin infusion) intended to increase platelet counts or prevent bleeding when platelet counts are less than $20,000/\mu\text{L}$, or for bleeding or wet purpura, will be allowed.

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

Participant(s) may continue in the LTE until:

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

Safety Measures Due to Coronavirus (COVID-19) Pandemic

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

STUDY DRUG AND DOSING REGIMEN

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

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

PLANNED NUMBER OF PARTICIPANTS

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

INDIVIDUAL PARTICIPANT STOPPING RULES

- Life-threatening or CTCAE Grade 4 rilzabrutinib-related TEAE except for adverse events (AEs) related to the disease under study or other underlying medical conditions
- Serious allergic reaction to rilzabrutinib or placebo, including anaphylactic reaction
- Pregnancy
- Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the participant to risk if the participant continues with rilzabrutinib or placebo or that prevents the participant's adherence to the protocol
- Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), viral hepatitis (B and C) infection occurring during the study
- Violation of protocol inclusion or exclusion criteria, that in the opinion of the Sponsor, would significantly compromise data interpretation
- Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Appendix 15 or in the presence of

abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

STUDY STOPPING RULES

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

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

INCLUSION CRITERIA

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

1. Participants will be male and female with primary ITP with duration of >6 months in pediatric participants aged 12 to <18 years (pediatric participants aged 10 to <12 years will be enrolled in the EU [EEA countries] only; refer to Appendix 10.2, Appendix 10.3, and Appendix 10.7 for country-specific requirements) and duration of >3 months in adults aged ≥ 18 years.
2. Participants who had a response (achievement of platelet count $\geq 50,000/\mu\text{L}$) to IVIg/anti-D or CSs that was not sustained and who have documented intolerance, insufficient response, or any contraindication to any appropriate courses of standard of care ITP therapy
3. An average of 2 platelet counts at least 5 days apart of $< 30,000/\mu\text{L}$ during the screening period, and no single platelet count $> 35,000/\mu\text{L}$, within 14 days prior to the first dose of study drug.
 - Pediatric participants must additionally be determined to need treatment for ITP as per clinical assessment by the Investigator (see Appendix 10.7 for EU [EEA countries] specific requirements).
4. Adequate hematologic, hepatic, and renal function (absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$, aspartate aminotransferase/alanine aminotransferase $\leq 1.5 \times \text{ULN}$, albumin $\geq 3 \text{ g/dL}$, total bilirubin $\leq 1.5 \times \text{ULN}$ [unless the participant has documented Gilbert syndrome], glomerular filtration rate > 50 [Cockcroft and Gault method]).
5. Hemoglobin $> 9 \text{ g/dL}$ within 1 week prior to Study Day 1.

6. All contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
 - a. Male participants

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

 - Refrain from donating or cryopreserving sperm plus either:
 - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
 - OR
 - Must agree to use contraception/barrier as detailed below.
 - A male condom: the participant should also be advised of the benefit for a female partner to use a highly effective method of contraception (as described in Appendix 13 Contraceptive and barrier guidance of the protocol) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.
 - b. Female participants

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

 - Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 13 of the protocol.
 - OR
 - Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 13 of the protocol, during the study intervention period (to be effective before starting the intervention) and for at least 4 weeks after the last administration of study intervention AND agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
 - A WOCBP must have a negative highly sensitive pregnancy test (serum) as required by local regulations) within 3 days before the first administration of study intervention.
 - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
7. Participants must be able to provide written informed consent or informed assent with corresponding informed consent obtained from the participant's guardian and agree to the schedule of assessments.

EXCLUSION CRITERIA

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

1. Participants with secondary ITP
2. Pregnant or lactating women
3. Electrocardiogram findings for participants:
 - Aged ≥ 10 and < 16 years: QTcF > 449 msec (males) or > 457 msec (females)
 - Aged ≥ 16 and < 18 years: QTcF > 450 msec (males) or > 460 msec (females)
 - Aged ≥ 18 years, of QTcF > 450 msec (males) or > 470 msec (females), poorly controlled atrial fibrillation (i.e., symptomatic participants or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities
4. History (within 5 years of Study Day 1) or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the study, with the exception of non-melanoma skin cancer
5. Transfusion with blood, blood products, plasmapheresis, or use of any other rescue medications with intent to increase platelet count within 14 days before Study Day 1
6. Change in CS and/or TPO-RA dose within 14 days prior to Study Day 1 (more than 10% variation from current doses)
7. Immunosuppressant drugs other than CSs within 5 times the elimination half-life of the drug or 14 days of Study Day 1, whichever is longer
8. Treatment with rituximab or splenectomy within the 3 months prior to Study Day 1
 - Participants treated with rituximab will have normal B-cell counts prior to enrollment.
9. Ongoing need for the use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change participant to histamine 2 receptor blocking drugs prior to Study Day 1)
10. Use of known strong-to-moderate inducers or inhibitors of cytochrome P450 (CYP) 3A within 14 days or 5 half-lives (whichever is longer) of Study Day 1 and until the end of the active treatment period
11. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin (except for low dose aspirin up to 100 mg per day), nonsteroidal anti-inflammatory drugs, and/or thienopyridines within 14 days of Study Day 1 and until the end of the active treatment period
12. Has received any investigational drug within the 30 days before receiving the first dose of study medication, or at least 5 times elimination half-life of the drug (whichever is longer); participant should not be using an investigational device at the time of dosing
 - Participants who previously received treatment with BTK inhibitors (except rilzabrutinib) within 30 days before the first dose of study drug are not eligible
 - Participants who previously received rilzabrutinib at any time are not eligible
13. Current drug or alcohol abuse
14. Refractory nausea and vomiting, malabsorption, external biliary shunt, significant bowel resection, or any other condition that would preclude adequate study drug absorption
15. History of solid organ transplant

16. Positive at Screening for HIV, hepatitis B virus (HBV) (surface and core antibodies unrelated to vaccination), or hepatitis C virus (anti-HCV antibody confirmed with Hep C RNA)

- Participants who are hepatitis B virus surface antigen (HBsAg) positive will not be eligible.
- Participants who are HBsAg negative and hepatitis B core antigen antibody (HBcAb) positive will be tested for HBV surface antibody (HBsAb) and HBV DNA. If HBV DNA is negative and HBsAb titer is ≥ 100 IU/L, participants may be enrolled. Monthly HBV DNA monitoring will be required while on treatment and for 6 months after the last dose of the study drug. Positive HBV DNA results will be managed appropriately as per local standard of care.
- Participants who are HBcAb positive and HBsAg negative with HBsAb titer < 100 IU/L or negative, are not eligible.

17. Positive QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus) at Screening unless all of the following 3 conditions are true:

- a. Chest X-ray does not show evidence suggestive of active tuberculosis (TB) disease
- b. There are no clinical signs and symptoms of pulmonary and/or extrapulmonary TB disease
- c. Documented receipt of one of the following prophylactic treatment regimens:
 - i. Oral daily Isoniazid for 6 months or
 - ii. Oral daily Rifampin for 4 months or
 - iii. Isoniazid and Rifapentine weekly for 3 months (3HP)

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

18. History of recurring (2 or more) serious infections requiring intravenous antibiotic, antivirals or antifungals therapy within the last 3 months before Study Day 1 or active serious or moderate infection ongoing on the day of randomization

19. Myelodysplastic syndrome

20. Live vaccine within 28 days prior to Study Day 1 or plan to receive one during the study

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

22. Any other clinically significant disease, condition, known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent (please see Section 6.1.1 for information on excipients), or medical history that, in the opinion of the Investigator or Sponsor's medical monitor, would interfere with participant safety, study evaluations, and/or study procedures

23. Positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) molecular test (if COVID-19 testing required per local guidelines to be determined for each site)

24. The COVID-19 vaccine within 14 days prior to Study Day 1 or planned during the last 12 weeks of the blinded treatment period

RANDOMIZATION PROCEDURE

Participants will be randomized in a 2:1 ratio to either active rilzabrutinib or placebo. The study is designed so that randomization will be carried out separately for the two age groups. For the adult group, stratified permuted block randomization will be implemented; for the pediatric group, dynamic randomization algorithm (minimization) will be implemented. The factors used for stratification or balance are splenectomy status (yes/no), and by severity of thrombocytopenia (Inclusion Criteria 3 platelet counts $<15,000/\mu\text{L}$ or $\geq 15,000/\mu\text{L}$).

STUDY ASSESSMENTS

Clinical Assessments Will Include:

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

Laboratory Assessments Will Include:

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

SAFETY AND TOLERABILITY ASSESSMENTS

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

Data Safety Monitoring Board

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

ENDPOINTS

Primary Efficacy Endpoint (Blinded Treatment Period)

- Durable platelet response defined as the proportion of participants able to achieve platelet counts at or above $50,000/\mu\text{L}$ for $\geq$ two-thirds of at least 8 nonmissing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 nonmissing weekly scheduled platelet measurements are at or above $50,000/\mu\text{L}$ during the last 6 weeks of the 24-week blinded treatment period; see Appendix 10.7 for country-specific definition of durable platelet response (EU [EEA countries] and UK).

Key Secondary Efficacy Endpoints (Blinded Treatment Period)

- Number of weeks with platelet count $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy
- Number of weeks with platelet counts $\geq 30,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy
- Time to first platelet count of $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and doubled from baseline
- Proportion of participants requiring rescue therapy during the 24-week blinded treatment period
- Change from baseline on Item 10 of the ITP-PAQ (i.e., physical fatigue) in adult participants (≥ 18 years) at Week 13

SAMPLE SIZE

The adult sample size chosen for this study was selected to achieve enrollment of 129 adult participants (≥ 18 years) on rilzabrutinib and 65 adult participants on placebo. The pediatric sample size of up to 30 participants (20 participants on rilzabrutinib and 10 participants on placebo) was determined based on clinical practice and is adequate to descriptively describe the safety and efficacy in pediatric participants. With a sample size of 20 pediatric participants on rilzabrutinib the maximum width of an exact 90% CI on response rate would be 40%.

A sample size of approximately 194 (129 versus 65 adult participants in the rilzabrutinib versus placebo arms, respectively) will provide 95% power to detect a 20% difference in response rates as defined in the primary endpoint (Section 3.2.1) between the 2 arms (25% versus 5%, in the rilzabrutinib versus placebo arms, respectively), using the Fisher's Exact test with a 0.05 two-sided significance level.

Table 112. Schedule of Assessments, Blinded Treatment Period

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

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

- a Participants may be re-screened once. The screening period can be up to -31 days of Study Day 1.
- b At the Week 13 visit review previous platelet counts for response during the first 12 weeks. If the participant met the criteria for response continue with the Week 13 visit assessments, the participant should continue in the blinded part. If the participant did not meet the criteria for response, complete the Week 25 visit assessments and the participant may start the open label period or discontinue from the study. Platelet response is defined as a) a platelet count of $\geq 50,000/\mu\text{L}$ OR a platelet count of between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and at least doubled from baseline at any time during the first 12 weeks and b) absence of rescue medication in the 4 weeks prior to the latest elevated platelet count that meets platelet response criteria.) Participants who receive rescue medication during the last 12 weeks also may join the open-label part or discontinue from the study. See [Figure 1](#) for decision tree for assessing response at Week 13 and for calculation of baseline platelet count.
- c For pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges) height is recorded at Screening, Week 13, Week 25, Week 37 and Week 53. For participants aged 18 years and older height is recorded at Screening only.
- d Full physical examination at Screening, 4-week follow-up and early termination; abbreviated physical examination at all other visits. Medical history should include vaccine history. See [Appendix 10.6](#) for Italy-specific requirements.
- e ECG for pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges) will be performed predose and 2 hours postdose (± 15 mins) at the Week 1 and Week 25 visits.
- f Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes.
- g Participants enrolled with positive HBV core antibody test result and HBsAb titer ≥ 100 IU/L will have HBV DNA monitored monthly while on treatment and for 6 months after treatment has ended.
- h For women of childbearing potential only. Serum pregnancy test must be performed at Screening; a urine pregnancy test must be performed at all other study timepoints.
- i To confirm postmenopausal status for women who are not surgically sterile and of reproductive potential.
- j Historical lab results may be used for ABO and Rh Blood Type.
- k Serum chemistry will include the following: aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin levels; alkaline phosphatase (ALP); albumin; creatinine; urea; total protein; sodium; chloride; calcium; phosphate; potassium; and glucose (random). Creatine phosphokinase (CPK) and estimated glomerular filtration rate (eGFR) is to be performed at Screening only.
- l Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), mean platelet volume, leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Local laboratories will be used for platelet analysis required at ALL visits (ie, Clinic Visits and Weekly Lab Visits in between Clinic Visits).
The central laboratory will be used for the analyses required at Clinic Visits including hematology, differential, and reticulocytes. The results of hematology, differential and reticulocytes obtained at local laboratories will be used only if the central lab results of Clinic Visits are missing due to any reason. Central platelet counts assessed at Clinic Visits will be used if local platelet results are missing for any reason.
- m Coagulation will include: PT/INR, thrombin time, activated partial thromboplastin time (aPTT), and fibrinogen level.
- n Hemolysis panel: consisting of Coombs test, haptoglobin levels.
- o PK samples for participants aged 18 years or older will be collected predose (within 1.5 hours predose) and 2 hours postdose (± 15 minutes) at the Week 1 visit. PK samples for pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (± 5 mins), 2 hours (± 5 mins) and 4 hours (± 15 mins), 6 hours (± 15 mins) at the Week 1 visit. At the Week 13 visit a sample will be taken Predose only. At these visits, participants will wait to take their morning dose until they complete the blood draw of pre-dose sample.
- p BTK Occupancy samples for participants aged 18 years or older will be collected Predose (within 1.5 hours predose) and 2 hours postdose (± 15 mins) at the Week 1 visit. BTK Occupancy samples for pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (± 5 mins), 2 hours (± 5 mins) and 4 hours (± 15 mins), 6 hours (± 15 mins) at the Week 1 visit. At the Week 13 visit a sample will be taken Predose only. At these visits, participants will wait to take their morning dose until they complete the blood draw of pre-dose sample.

- q* QOL Questionnaires include EQ-5D-5L, ITP-Patient Assessment Questionnaire (ITP-PAQ) or Kids' ITP Tools (ITP-KIT), and PGIS-Fatigue/PGIS/PGIC. ITP-PAQ, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC (in that order) will be administered for adults 18 years or older. ITP-KIT and EQ-5D-5L (in that order) will be administered for pediatric participants (see [Appendix 10.7](#) for EU (EEA countries) age ranges). **Questionnaires should be completed prior to all other study procedures and interactions with site staff.** Note: The PGIC will be collected starting after Day 1.
- r* See [Appendix 10](#) for country-specific requirements.
- s* Optional collection of 2 blood samples for vaccine-specific IgG in serum (See [Section 7.9.9](#) for a list of routine vaccines). The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine-specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded.
- t* Participants enrolled into the pediatric portion of the trial will still be considered as part of the pediatric group with all the planned assessments when they turn 18 years old, unless specified, and they should be re-consented with an adult consent. See [Appendix 10.7](#) for EU (EEA countries) age ranges.
- u* This visit is for platelet count assessment and can be conducted on-site or remotely. After the end of treatment (EOT) visit, weekly platelet count assessment is not required; however, it is up to the Investigator to decide whether to conduct weekly platelet assessments using unscheduled visits, if deemed necessary for participant safety.
- v* SARS-CoV-2 molecular test (if COVID-19 testing is required per local guidelines to be determined for each site).
- w* During the blinded treatment period (Week 13 to Week 24): Participants who discontinue from the blinded treatment period due to safety (or other) reasons and choose to join the open label period will attend the Week 25 assessments at their next scheduled visit.
- x* **All participants who discontinue treatment during the blinded or open-label period need to have an Early Termination visit as specified in Table 1 and an End of Study visit (4 weeks after last IMP intake) as specified in the End of Study visit in Table 2 (See End of Study [Table 2](#)).**

Source: Protocol RN1008-018, Version 04, July 24, 2023

Table 113. Schedule of Assessments, Open-Label Period

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

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

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- a For pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges) height is recorded at Screening, Week 13, Week 25, Week 37, and Week 53. For participants aged 18 and older height is recorded at Screening only.
- b Full physical examination at Screening, 4-week follow-up and early termination; abbreviated physical examination at all other visits. See [Appendix 10.6](#) for Italy-specific requirements.
- c ECG for pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges) will be performed predose and 2 hours postdose (± 15 minutes) at the Week 25 visit. Adult participants are also required to complete ECG at Week 25.
- d Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes.
- e For women of childbearing potential only. A urine pregnancy test must be performed at all study timepoints.
- f Serum chemistry will include the following: aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin levels; alkaline phosphatase (ALP); albumin; creatinine; urea; total protein; sodium; chloride; calcium; phosphate; potassium; and glucose (random).
- g Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), mean platelet volume, leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Local laboratories will be used for platelet analysis required at ALL visits (ie, Clinic Visits and Weekly Lab Visits in between Clinic Visits).
The central laboratory will to be used for the analyses required at Clinic Visits including hematology, differential, and reticulocytes. The results of hematology, differential and reticulocytes obtained at local laboratories will be used only if the central lab results of Clinic Visits are missing due to any reason. Central platelet counts assessed at Clinic Visits will be used if local platelet results are missing for any reason.
- h Coagulation will include: PT/INR, thrombin time, activated partial thromboplastin time (aPTT), and fibrinogen level.
- i Hemolysis panel: consisting of Coombs test, haptoglobin levels.
- j At Week 25 visit, PK samples for participants aged 18 years or older will be collected Predose (within 1.5 hours predose) and 2 hours postdose (± 15 minutes). At the Week 25 visit, PK samples for pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (± 5 minutes), 2 hours (± 5 minutes) and 4 hours (± 15 minutes), 6 hours (± 15 minutes). At these visits, participants will wait to take their morning dose until they complete the blood draw of pre-dose sample. At Week 53 and early termination visits, a random timepoint PK samples will be collected and the time of sample and time of the last dose of rilzabrutinib will be captured.
- k At Week 25 visit, BTK occupancy samples for participants aged 18 years or older will be collected Predose (within 1.5 hours predose) and 2 hours postdose (± 15 minutes). At Week 25 visit, BTK Occupancy samples for pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges) will be taken Predose (within 1.5 hours predose) and postdose at the following timepoints: 0.5 hours (± 5 minutes), 2 hours (± 5 minutes) and 4 hours (± 15 minutes), 6 hours (± 15 minutes). At these visits, participants will wait to take their morning dose until they complete the blood draw of pre-dose sample. At Week 53, a random timepoint BTK occupancy sample will be collected and the time of sample and time of the last dose of rilzabrutinib will be captured.
- l QOL Questionnaires include EQ-5D-5L, ITP-PAQ or ITP-KIT, and PGIS-Fatigue/PGIS/PGIC. ITP-PAQ, EQ-5D-5L and PGIS-Fatigue/PGIS/PGIC (in that order) will be administered for adults 18 years or older. ITP-KIT and EQ-5D-5L (in that order) will be administered for pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges). **Questionnaires should be completed prior to all other study procedures and interactions with site staff.**
- m See [Appendix 10](#) for country-specific requirements.
- n Optional collection of 2 blood samples for vaccine-specific IgG in serum (see [Section 7.9.9](#) for a list of routine vaccines). The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine-specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded.
- o Week 25/SD169 visit is the last visit of the blinded treatment period and may also serve as the start of the open label period.
- p For participants who will enter the open label period directly after 12 weeks of blinded treatment, they will attend the Week 13/SD85 visit which corresponds to the Week 25/SD169 visit (Table 2), this would be their last visit of the blinded treatment period and also the start of the open label period. They will follow the open label period schedule of assessments from Week 29 (Table 2) starting at their next scheduled visit for a total of 28 weeks.
- q For participants who will enter the open label period directly after 12 weeks of blinded treatment, they will follow the open label period schedule of assessments (**Week 25 to Week 53**) which means that they will be treated on the open-label part for a total of 28 weeks. After Week 53, the participants will follow the schedule of assessments according to their eligibility for the LTE period.
- r This visit is for platelet count assessment and can be conducted on-site or remotely. Lab visits will occur weekly from Week 25 to Week 53. The Investigator can request that the participant visits the clinic for additional platelet monitoring during unscheduled visits if needed. After the end of treatment (EOT) visit, weekly platelet count assessment is not required; however, it is up to the Investigator to decide whether to conduct weekly platelet assessments using unscheduled visits, if deemed necessary for participant safety.

Source: Protocol RN1008-018, Version 04, July 24, 2023

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Table 114. Schedule of Assessments, Long-Term Extension Period

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

- AE = adverse event; aPTT = activated partial thromboplastin time; CS = corticosteroids; ECG = electrocardiogram; EQ-5D-5L = EuroQOL-5 Dimension 5 Level; IBLS = ITP Bleeding Scale; IgG = immunoglobulin G; INR = international normalized level; ITP = Immune thrombocytopenia; ITP-PAQ = ITP-Patient Assessment Questionnaire; ITP-KIT = Kids' ITP Tools; PGIS = Patient Global Impression of Severity PGIS-Fatigue = Patient Global Impression of [Fatigue] Severity; QOL = Quality of Life; SD = study day; T/B/NK = T-lymphocytes/B-lymphocytes/natural killers; PGIC = Patient Global Impression of Change; PT = prothrombin time; TPO = Thrombopoietin; TPO-RA = thrombopoietin receptor agonist
- ^a Reductions in the doses or withdrawal of concomitant ITP medications will be permitted if the participant achieves platelet count of ≥50,000/μL in three scheduled visits (over 12 weeks). Retreatment with the same medication(s) and doses of ITP concomitant medication(s) used at baseline (an oral CS and/or a TPO-RA), changing the dose or initiation of new ITP medications (an oral CS and/or a TPO-RA) will also be allowed. Tapering of concomitant CS and/or TPO-RA should be performed in accordance with the schedule in Section 6.6.2.

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- b* Full physical exam at End of Study, abbreviated physical exam at all other visits. See [Appendix 10.6](#) for Italy-specific requirements.
- c* Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes.
- d* Urine pregnancy test for women of childbearing potential only.
- e* Serum chemistry will include the following: aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin levels; alkaline phosphatase (ALP); albumin; creatinine; urea; total protein; sodium; chloride; calcium; phosphate; potassium; and glucose (random).
- f* Hematology will include the following: hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), mean platelet volume, leukocyte count (white blood cell [WBC] count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, and monocytes). Local laboratories will be used for platelet analysis required at ALL visits (ie, Clinic Visits and Unscheduled Lab Visits in between Clinic Visits). The central laboratory will be used for the analyses required at Clinic Visits including hematology, differential, and reticulocytes. The results of hematology, differential and reticulocytes obtained at local laboratories will be used only if the central lab results of Clinic Visits are missing due to any reason. Central platelet counts assessed at Clinic Visits will be used if local platelet results are missing for any reason. After the end of treatment (EOT) visit, weekly platelet count assessment is not required; however, it is up to the Investigator to decide whether to conduct weekly platelet assessments using unscheduled visits, if deemed necessary for participant safety.
- g* T-lymphocytes/ B-lymphocytes/natural killers (T/B/NK) counts at Week 53, every 6 months during the long-term extension period and at End of Study.
- h* PT/INR, aPTT: only if needed to follow-up on bleeding adverse events.
- i* Hemolysis panel: consisting of Coombs test, haptoglobin levels.
- j* QOL Questionnaires include EQ-5D-5L, ITP-PAQ or ITP-KIT, and PGIS-Fatigue/PGIS/PGIC to be completed every 3 months. ITP-PAQ, EQ-5D-5L and PGIS-Fatigue/ PGIS/PGIC (in that order) will be administered for adults 18 years or older. ITP-KIT and EQ-5D-5L (in that order) will be administered for pediatric participants (see [Appendix 10.7](#) for EU [EEA countries] age ranges). Questionnaires should be completed prior to all other study procedures and interactions with site staff.
- k* See [Appendix 10](#) for country-specific requirements.
- l* Optional collection of 2 blood samples for vaccine-specific IgG in serum (see [Section 7.9.9](#) for a list of routine vaccines). The first blood sample should be collected within 6 weeks prior to each vaccine dose regimen and the second blood sample should be collected within approximately 3 to 6 weeks after the vaccine dose regimen is complete. Whenever possible, blood for vaccine- specific IgG should be collected at a scheduled visit; but may also be collected during an Unscheduled Visit. Dates of vaccination, disease, brand name of vaccine product and antigenic strain should be recorded.
- m* Early Termination Visit only.
- n* Assessments performed at the open label period Week 53 Visit will be used at the starting visit (Week 53) of the LTE.

Source: Protocol RN1008-018, Version 04, July 24, 2023

15.1.2. Summary of Protocol Amendments

Amended Clinical Trial Protocol 02 (February 19, 2021)

This was the first protocol amendment to Clinical Study Protocol PRN1008-018. Changes were primarily clarifications in nature.

Amended Clinical Trial Protocol 02 (July 21, 2021)

The following major clinical changes were included in the protocol amendment:

1. Stratification by age (i.e., 12 to <18 years and adult patients aged 18 years or older) during randomization was removed. Review comment: In study PRN1008-018, patients with primary ITP ages ≥ 12 will be enrolled. The Agency recommends that stratification should also include age (patients aged 12 to <18 years and adult patients aged 18 years or older) in addition to stratifying by splenectomy status (yes/no), and by severity of thrombocytopenia (platelet counts $< 15,000/\mu\text{L}$ or $\geq 15,000/\mu\text{L}$).
2. To continue on study treatment at the Week 13, the definitions of responder and nonresponder were revised to: At the end of 12 weeks of treatment, patients will be assessed for achieving a platelet response defined as platelet count of $\geq 50,000/\mu\text{L}$ or a platelet count between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and at least doubled from baseline at any time during the first 12 weeks and in the absence of rescue medication in the 4 weeks prior to the latest elevated platelet count that meets platelet response criteria. Baseline is defined as the average of all the patient's Predose platelet counts (Screening and Study Day 1).
 - Patients who respond will continue the blinded treatment period for a total of 24 weeks before entering the open-label Period.
 - Patients who do not respond (including patients who receive rescue medication after Week 8) will be allowed to discontinue from the study or may enter the 28-week open-label period at the end of Week 12, receiving treatment with 400 mg BID of rilzabrutinib. Initial study medication assignment will remain blinded. After completing the Open-Label Period, patients who demonstrate a platelet response defined as platelet counts $\geq 50,000/\mu\text{L}$ or $\geq 30,000/\mu\text{L}$ and at least doubled from baseline at $\geq 50\%$ of the visits without receiving rescue therapy during the last 8 weeks of the open-label period, will be allowed to enter the LTE.”
3. The planned number of adult participants was updated to 194 (from 153). Sample size was recalculated based on increasing the study power from 80% to 86% to detect a 20% difference in response rates between the 2 study arms.

Amended Clinical Trial Protocol 03 (August 11, 2022)

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

- To modify the primary endpoint and objective to specify participants having platelet counts at or above $50,000/\mu\text{L}$ for $\geq$ two-thirds of at least 8 nonmissing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 nonmissing weekly scheduled platelet

measurements are at or above 50,000/ μ L during the last 6 weeks of the 24-week blinded treatment period. This change does not apply to the EU (EEA countries) and the UK.

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

Amended Clinical Trial Protocol 04 (July 24, 2023)

Amendment 4 was implemented July 24, 2023. The primary reasons for this amendment and main changes to the protocol included the following:

- Update the 2-sided significance level from 0.01 to 0.05 for the hypothesis testing of the primary efficacy end point.
- Clarify distinct durations of participation in the LTE for the adult and pediatric populations.
- Updated the 2-sided significance level from 0.01 to 0.05 for the hypothesis testing (i.e., Cochran-Mantel-Haenszel test) of the primary efficacy end point.
- Updated the text on calculating baseline platelet count and added a footnote for calculating baseline platelet count based on availability of 3 platelet counts, or two platelet counts when the second qualifying count is collected on Study Day 1 prior to first dose.
- Exclusion of participants with known allergy to any of the study medication, their analogues, or excipients.
- The word “must” was added to the following sentence to ensure safety and comply with regulatory guidance. “Any female participant who becomes pregnant while participating in the study must discontinue study intervention or be withdrawn from the study.”

15.2. LUNA 2

15.2.1. Study Design

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

LUNA 2 was a global, 2-part, multicenter, open-label, dose-finding (Part A), with cohort expansion (Part B) safety, pharmacokinetics, and activity estimating study of rilzabrutinib in participants with primary or secondary ITP.

Part A enrolled participants with refractory or relapsed ITP with no available and approved therapeutic options and who had a platelet count $<30,000/\mu\text{L}$ and evaluated starting doses ranging from 200 mg to 400 mg po BID. Part B was an open-label study of rilzabrutinib in participants with ITP of at least 3 months duration who had had a response to IVIg/anti-D or corticosteroids that was not sustained and failed at least one other ITP therapy (that was not IVIg or corticosteroids) who had relapsed or had had an insufficient response to prior therapies and who had a platelet count $<30,000/\mu\text{L}$ and treated all participants at the selected dosage for cohort expansion of 400 mg orally twice daily. Efficacy was based on a 24-week treatment period.

In Part A, the primary efficacy endpoint was participants proportion of patients able to achieve two or more consecutive platelet counts, separated by at least 5 days, of $\geq 50,000/\mu\text{L}$ AND an increase of platelet count of $\geq 20,000/\mu\text{L}$ from baseline, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count.

In Part B, the primary efficacy endpoint was durable platelet response, defined as the proportion of patients who were able to achieve platelet counts $\geq 50,000/\mu\text{L}$ 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.

16. Efficacy

16.1. LUNA 3

16.1.1. Summary of Statistical Analysis Plan, Version 3

Analysis Population

The following analysis sets were defined for the statistical analysis:

- Intent-to-Treat (ITT) Population: the ITT population
- Modified ITT (mITT) Population: the mITT population included all participants from ITT population who are exposed. Participants were analyzed according to the intervention allocated by randomization. The mITT Population was used for sensitivity analysis.
- Safety Population: All randomized participants took at least 1 dose of study intervention, regardless of the amount of treatment administrated.

Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint was durable platelet response. The primary efficacy analysis was the Cochran-Mantel-Haenszel test adjusted by randomization stratification factors based on the ITT population. Stratification factors include the randomization strata of splenectomy status (yes, no) and severity of thrombocytopenia (platelet counts $<15,000/\mu\text{L}$, $\geq 15,000/\mu\text{L}$). The Mantel-Haenszel estimate of common risk difference in response rates and its associated 95% CI based on Mantel-Haenszel stratum weights and the Sato variance estimator were reported. The

observed response rate for each treatment group was presented along with its associated 95% asymptotic CI.

Analysis of the Key Secondary Efficacy Endpoints

The primary efficacy analysis was based on log-rank test adjusted by randomization stratification factors. Hazard ratio and its 95% CI were modeled using Cox regression model with treatment and randomization stratification factors as covariates. The fifth key secondary endpoint was the change from baseline on Item 10 of the ITP-PAQ (i.e., physical fatigue) in adult participants (≥ 18 years) at Week 13. The primary efficacy analysis was based on the ANCOVA model with the treatment group, randomization stratification factors, and geographic region as fixed effects and baseline Item 10 score as a covariate.

Number of Weeks With a Platelet Response

For the first and second key secondary endpoints, number of weeks with platelet response, the primary efficacy analyses were based on the MMRM approach was used to analyze the longitudinal binary platelet response data across visits in the ITT population. The analysis model included treatment, randomization stratification factors, week (Weeks 2 to 25), treatment-by-week interaction as categorical fix effects. Generalized estimating equations (GEE) was used to obtain statistical inference. A variance component working covariance matrix was used in the model to obtain unweighted proportions. Least squares (LS) mean number of weeks (% weeks) with platelet response across 24 weeks in each treatment group, difference in LS mean number of weeks (% weeks) with platelet response between treatment groups and its corresponding 95% CIs were provided along with the p-value. Number of weeks with platelet counts $\geq 30,000/\mu\text{L}$ and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy

Time to first platelet count of $\geq 50,000/\mu\text{L}$ OR between $\geq 30,000/\mu\text{L}$ and $< 50,000/\mu\text{L}$ and doubled from baseline

Time to First Platelet Response

The third key secondary endpoint was time to first platelet response. The primary efficacy analysis was based on log-rank test adjusted by randomization stratification factors. Hazard ratio and its 95% CI were modeled using Cox regression model with treatment and randomization stratification factors as covariates. Platelet counts were considered as no response during the use of rescue therapy and for 4 weeks after the rescue therapy ended.

Proportion of Participants Requiring Rescue Therapy During the 24-Week Blinded Treatment Period

The fourth key secondary endpoint was proportion of participants requiring rescue therapy. The primary efficacy analysis was based on log-rank test adjusted by randomization stratification factors. Hazard ratio and its 95% CI were modeled using Cox regression model with treatment and randomization stratification factors as covariates.

Change From Baseline on Item 10 of the ITP-PAQ (i.e., Physical Fatigue) in Adult Participants (≥18 Years) at Week 13

The fifth key secondary endpoint was the change from baseline on Item 10 of the ITP-PAQ (i.e., physical fatigue) in adult participants (≥18 years) at Week 13. The primary efficacy analysis was based on the ANCOVA model with the treatment group, randomization stratification factors, and geographic region as fixed effects and baseline Item 10 score as a covariate. Missing score at Week 13 was imputed via worst observation carried forward (WOCF) for the participants who were rescued after 8 weeks of double-blind treatment or discontinued before Week 13 due to lack of efficacy or related adverse events, or via multiple imputation otherwise. Each complete dataset was analyzed by fitting an ANCOVA model. Statistical inference obtained from all imputed data were combined using Rubin’s rule. LS mean score changes in each treatment group and that between treatment groups as well as their corresponding 95% CIs were provided along with the p-value.

Multiple Testing Strategy

To control the family-wise type I error, a fixed-sequence hierarchical testing procedure was applied to the primary endpoint and key secondary endpoints at 2-sided 5% significant level i.e., each hypothesis was formally tested only if the preceding one was statistically significant. The hierarchical testing order was prespecified and is presented in the Section [6.2.1.2](#).

Handling of Missing Data

The primary analysis for handling discontinuation of study intervention before Week 25 due to lack of response or related AE participants were considered as nonresponder.

Two sensitivity analyses (SA) were conducted to further address the impact of missing data not due to related Adverse Events or lack of response to demonstrate the robustness of the primary analysis for the primary endpoint ([Table 115](#)).

Table 115. Sensitivity Analyses for Primary Endpoint, LUNA 3

SA	Descriptive
SA 1	Tipping point analysis; missing considered due to missing data, or discontinuation not due to related adverse events or lack of response
SA 2	missing platelet count due to COVID-19 imputed using the participant’s median value of available weekly platelet counts

Source: FDA reviewer summary
Abbreviations: COVID-19, coronavirus disease of 2019; SA, sensitivity analysis

16.1.2. Sensitivity Analyses of Durable Platelet Response During 12-Week and 24-Week Double-Blind Period

Sensitivity analyses were conducted to handle all types of missing data, regardless of the reasons for missing data or dropouts, rather than for only treated lack of response or related AE as nonresponder. [Table 116](#) and [Table 117](#) present tipping point analyses for the 12-week and 24-week periods, respectively. In these analyses, participants with missing response data were imputed as responders at varying probabilities—denoted as p_0 for the placebo group and p_1 for

the rilzabrutinib group. The values of p_0 and p_1 were incrementally increased from 0% to 100% in 10% steps to evaluate the impact of different imputation assumptions on the treatment effect. [Table 116](#) and [Table 117](#) showed that the statistical significance of the treatment effect was lost when the assumed response rate among missing participants is relatively high in the placebo group (p_0 close to 0.2) and relatively low in the rilzabrutinib group (p_1 close to 0). For example, when $p_0=0.2$, the p-value is no longer significant if $p_1=0$ or 0.1. In this study, the placebo group had a durable response rate below 5%, indicating that assuming a higher p_0 is not consistent with the observed data. Overall, the tipping point results demonstrated that the primary analyses results for rilzabrutinib on durable platelet response during the 12-week and 24-week double-blind period remain robust (see Section [6.2.1.4.3](#))

Table 116. Sensitivity Analysis: Tipping Point Analysis of Durable Platelet Response During the Initial 12-Week Double-Blind Treatment Period, Adult ITT Population, LUNA 3

		Rilzabrutinib 400 mg BID (p_1)										
Placebo p_0	Nominal p-Value	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
	0	0.0005	0.0003	0.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
	0.1	0.0216	0.0096	0.0039	0.0016	0.0006	0.0002	<.0001	<.0001	<.0001	<.0001	<.0001
	0.2	0.1411	0.0766	0.0358	0.0164	0.0069	0.0029	0.0010	0.0004	0.0001	<.0001	<.0001
	0.3	0.3885	0.2555	0.1493	0.0777	0.0370	0.0168	0.0069	0.0029	0.0011	0.0004	0.0001
	0.4	0.6031	0.4833	0.3534	0.2337	0.1338	0.0694	0.0330	0.0153	0.0061	0.0025	0.0008
	0.5	0.5711	0.6119	0.5567	0.4390	0.3167	0.1990	0.1115	0.0581	0.0258	0.0113	0.0044
	0.6	0.3491	0.5095	0.6111	0.6103	0.5249	0.3995	0.2637	0.1596	0.0814	0.0393	0.0168
	0.7	0.1294	0.2714	0.4340	0.5853	0.6684	0.6215	0.4935	0.3515	0.2157	0.1171	0.0564
	0.8	0.0361	0.1012	0.2112	0.3741	0.5401	0.6634	0.6805	0.5833	0.4331	0.2712	0.1473
	0.9	0.0074	0.0263	0.0699	0.1565	0.2905	0.4635	0.6448	0.7342	0.6964	0.5324	0.3353
	1	0.0009	0.0048	0.0164	0.0459	0.1049	0.2140	0.3828	0.5882	0.7866	0.8259	0.6206

Source: Applicant's Response to Statistics Information Request dated 03 January 2025 and reviewer analyses
Given a set of (p_0 , p_1) where p_0 and p_1 are the response rate among those with missing durable response status in the placebo group and the rilzabrutinib group respectively, a participant with missing response will be randomly assigned as a responder or a nonresponder using binomial distribution to generate multiple imputed datasets. Each imputed complete dataset is analyzed using Cochran-Mantel-Haenszel test. The Chi-square statistic is then normalized via Wilson-Hilferty transformation. And the results across multiple complete datasets are combined using Rubin's rule
Abbreviations: BID, twice daily; ITT, intent-to-treat

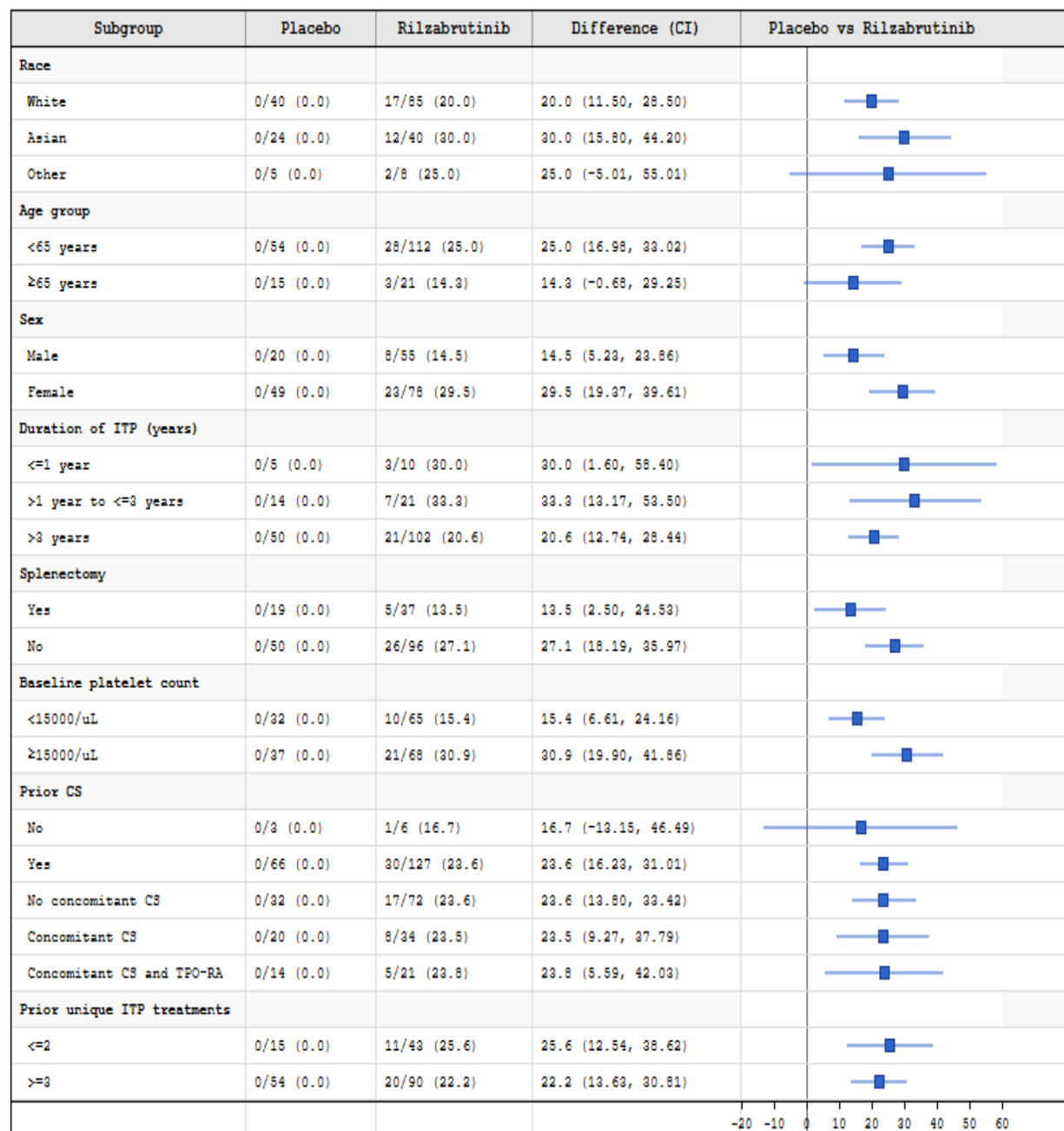
Table 117. Sensitivity Analysis: Tipping Point Analysis of Durable Platelet Response During the 24-Week Double-Blind Treatment Period, Adult ITT Population, LUNA 3

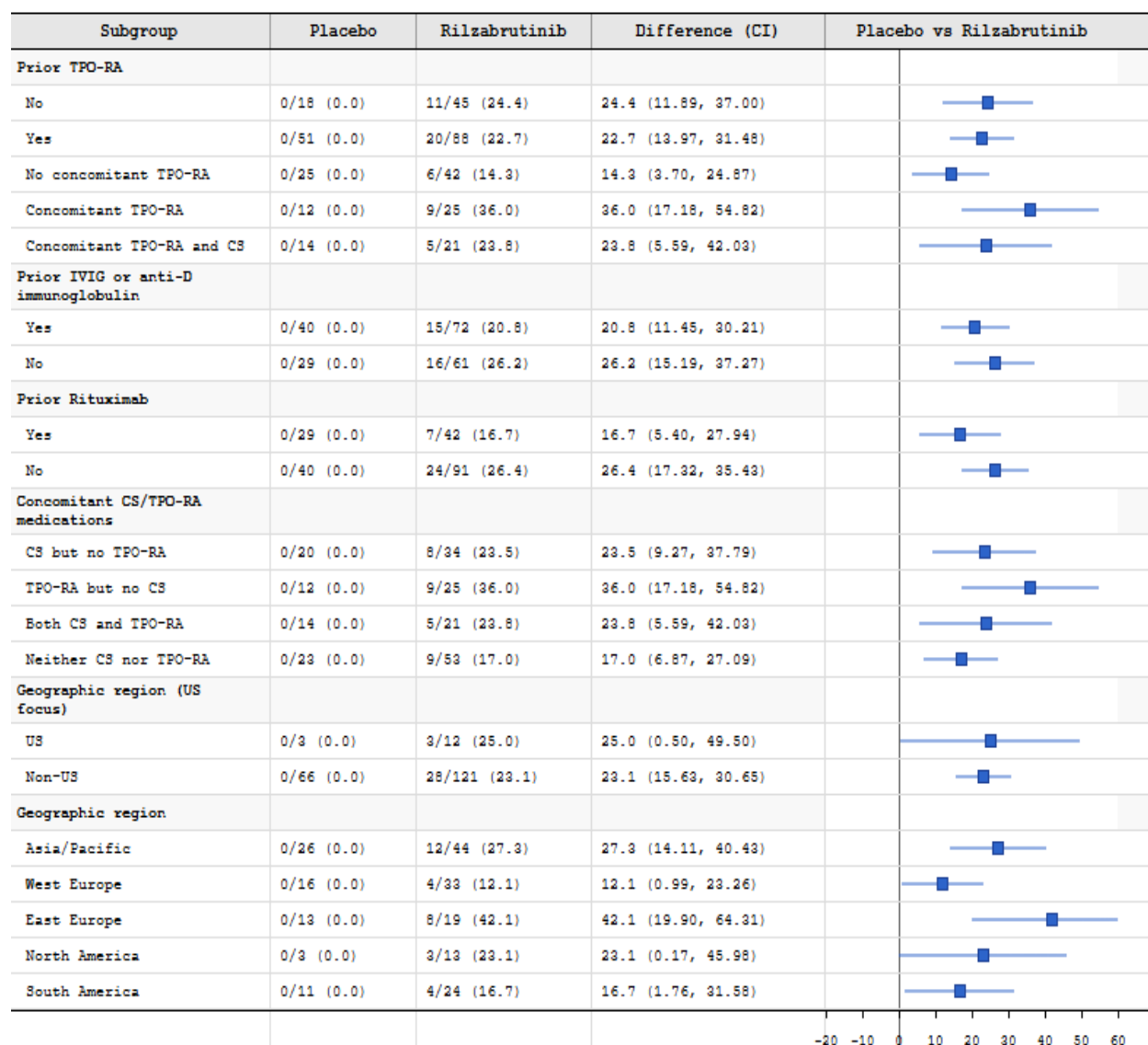
Rilzabrutinib 400 mg BID (p_1)												
Placebo p_0	Nominal p-Value	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
	0	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
	0.1	0.0304	0.0059	0.0011	0.0002	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
	0.2	0.3673	0.1638	0.0496	0.0118	0.0023	0.0003	<.0001	<.0001	<.0001	<.0001	<.0001
	0.3	0.5279	0.5109	0.3082	0.1313	0.0427	0.0103	0.0019	0.0002	<.0001	<.0001	<.0001
	0.4	0.1853	0.4083	0.5311	0.4401	0.2477	0.0946	0.0271	0.0049	0.0007	<.0001	<.0001
	0.5	0.021	0.1135	0.284	0.4748	0.5113	0.38	0.1945	0.0616	0.0135	0.0017	0.0001
	0.6	0.0009	0.0099	0.0607	0.1884	0.373	0.5321	0.4871	0.2988	0.1172	0.0244	0.0027
	0.7	<.0001	0.0004	0.004	0.0252	0.0976	0.2483	0.4589	0.5589	0.4181	0.192	0.0397
	0.8	<.0001	<.0001	0.0001	0.0012	0.0091	0.0412	0.1417	0.342	0.5438	0.5437	0.2831
	0.9	<.0001	<.0001	<.0001	<.0001	0.0002	0.0015	0.0101	0.0513	0.1749	0.4184	0.6668
	1	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0008	0.0051	0.0284	0.1387

Source: Applicant's Response to Statistics Information Request dated 03 January 2025 and reviewer analyses
Given a set of (p_0 , p_1) where p_0 and p_1 are the response rate among those with missing durable response status in the placebo group and the rilzabrutinib group respectively, a participant with missing response will be randomly assigned as a responder or a nonresponder using binomial distribution to generate multiple imputed datasets. Each imputed complete dataset is analyzed using Cochran-Mantel-Haenszel test. The Chi-square statistic is then normalized via Wilson-Hilferty transformation. And the results across multiple complete datasets are combined using Rubin's rule
Abbreviations: BID, twice daily; ITT, intent-to-treat

16.1.3. Subgroup Analyses of Durable Platelet Response During the 12- Week and 24-Week Double-Blind Period

Figure 28. Forest Plot of Risk Difference (95% CI) for Primary Endpoint by Subgroups, Adult ITT, LUNA 3





Source: Study LUNA 3 Clinical Study Report (CSR), Figure 7 (p.61) and FDA reviewer analysis
Abbreviations: anti-D, Rho(D) immune; CI, confidence interval; CS, corticosteroid; ITP, immune thrombocytopenia; ITT, intent-to-treat; IVIG, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist

17. Clinical Safety

17.1. Safety Analysis Populations, Definitions

The following pooled populations were used in one or more safety analyses.

Primary Safety Set: Used to establish primary safety profile of rilzabrutinib in ITP. Comprises 133 participants who received rilzabrutinib 400 mg BID and 65 participants who received placebo during the double-blind treatment period on LUNA 3.

Integrated Safety Population (ISP): Used to confirm the primary safety profile and to identify rare but serious events that might only be observed in a larger population. Comprises 276 participants with chronic ITP who received at least one dose of rilzabrutinib at the proposed dosage (400 mg BID) on LUNA 3 or LUNA 2. This includes 133 participants randomized to receive rilzabrutinib during the DB on LUNA 3, 65 participants who received placebo during the DB period and went on to receive rilzabrutinib during the OL period(s) and 52 participants from PRN1008-10 Part A and 26 from Part B. The analysis includes data from DB, OL, and LTE periods.

ITP Rilzabrutinib Pool: The Applicant defined pooled population comprising all ITP adult participants exposed to rilzabrutinib during the entire treatment period (Main/DB, OL, and LTE periods, cumulatively) (LUNA 3 and LUNA 2) (N=284 rilzabrutinib any dose). This pool is used when discussing adverse events of special interest and AEs of clinical interest in Section [7.6.3](#).

17.2. Supplemental Safety Analyses

17.2.1. Serious Adverse Events, LUNA 3

Table 118. Participants With Serious Adverse Events by System Organ Class and OND Custom Medical Query (Narrow), Double-Blind Treatment Period, LUNA 3

System Organ Class OCMQ (Narrow)	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)			
Thrombocytopenia	2 (1.5)	2 (2.9)	-1.4 (-8.6, 2.9)
Gastrointestinal disorders (SOC)			
Vomiting	0	1 (1.4)	-1.4 (-7.8, 1.4)
Hepatobiliary disorders (SOC)			
Hepatic injury	1 (0.8)	0	0.8 (-4.6, 4.1)
Infections and infestations (SOC)			
Bacterial infection	2 (1.5)	0	1.5 (-3.8, 5.3)
Pneumonia	1 (0.8)	0	0.8 (-4.6, 4.1)
Purulent material	1 (0.8)	0	0.8 (-4.6, 4.1)
Viral infection	1 (0.8)	0	0.8 (-4.6, 4.1)
Renal and urinary disorders (SOC)			
Renal & urinary tract infection	1 (0.8)	0	0.8 (-4.6, 4.1)
Reproductive system and breast disorders (SOC)			
Abnormal uterine bleeding	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Excessive menstrual bleeding	0	1 (1.4)	-1.4 (-7.8, 1.4)
Vascular disorders (SOC)			
Hemorrhage	4 (3.0)	4 (5.8)	-2.8 (-11.3, 2.9)

Source: adae.xpt; Software: R; FDA reviewer analysis

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs; PT, preferred term; SOC, system organ class

Table 119. Participants With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Blinded Open-Label, Long-Term Extension Periods, LUNA 3

System Organ Class Preferred Term	Double-Blind		Open-Label		Long-Term Extension	
	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Rilzabrutinib to Rilzabrutinib N=115 n (%)	Placebo to Rilzabrutinib N=65 n (%)	Rilzabrutinib to Rilzabrutinib N=33 n (%)	Placebo to Rilzabrutinib N=17 n (%)
Any SAE	12 (9.0)	8 (11.6)	8 (7.0)	9 (13.8)	2 (6.1)	1 (5.9)
Blood and lymphatic system disorders (SOC)	2 (1.5)	3 (4.3)	3 (2.6)	2 (3.1)	1 (3.0)	0
Immune thrombocytopenia	1 (0.8)	1 (1.4)	0	0	1 (3.0)	0
Thrombocytopenia	1 (0.8)	2 (2.9)	3 (2.6)	2 (3.1)	1 (3.0)	0
Eye disorders (SOC)	0	1 (1.4)	0	0	0	0
Conjunctival haemorrhage	0	1 (1.4)	0	0	0	0
Gastrointestinal disorders (SOC)	1 (0.8)	2 (2.9)	0	0	0	0
Oesophageal varices haemorrhage	1 (0.8)	0	0	0	0	0
Haematemesis	0	1 (1.4)	0	0	0	0
Mouth haemorrhage	0	1 (1.4)	0	0	0	0
Hepatobiliary disorders (SOC)	1 (0.8)	0	0	0	0	0
Hepatic cirrhosis	1 (0.8)	0	0	0	0	0
Infections and infestations (SOC)	4 (3.0)	0	0	2 (3.1)	0	0
COVID-19	1 (0.8)	0	0	0	0	0
Pneumonia	1 (0.8)	0	0	0	0	0
Renal abscess	1 (0.8)	0	0	0	0	0
Urinary tract infection	1 (0.8)	0	0	0	0	0
Wound infection	1 (0.8)	0	0	0	0	0
Bronchopulmonary aspergillosis	0	0	0	1 (1.5)	0	0
Cytomegalovirus viraemia	0	0	0	1 (1.5)	0	0
Sepsis	0	0	0	1 (1.5)	0	0
Injury, poisoning and procedural complications (SOC)	1 (0.8)	0	2 (1.7)	0	0	0
Periorbital haematoma	1 (0.8)	0	0	0	0	0
Seroma	0	0	1 (0.9)	0	0	0
Subdural haematoma	0	0	1 (0.9)	0	0	0
Investigations (SOC)	2 (1.5)	0	1 (0.9)	0	0	0
Hepatic enzyme increased	1 (0.8)	0	0	0	0	0
Platelet count decreased	1 (0.8)	0	1 (0.9)	0	0	0

NDA 219685
WAYRILZ (rilzabrutinib)

System Organ Class Preferred Term	Double-Blind		Open-Label		Long-Term Extension	
	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Rilzabrutinib to Rilzabrutinib N=115 n (%)	Placebo to Rilzabrutinib N=65 n (%)	Rilzabrutinib to Rilzabrutinib N=33 n (%)	Placebo to Rilzabrutinib N=17 n (%)
Nervous system disorders (SOC)	0	0	1 (0.9)	0	1 (3.0)	1 (5.9)
Paraesthesia	0	0	1 (0.9)	0	0	0
Peripheral motor neuropathy	0	0	0	0	1 (3.0)	0
Peripheral sensory neuropathy	0	0	0	0	0	1 (5.9)
Renal and urinary disorders (SOC)	0	0	0	1 (1.5)	0	0
Haematuria	0	0	0	1 (1.5)	0	0
Reproductive system and breast disorders (SOC)	1 (0.8)	1 (1.4)	0	2 (3.1)	0	0
Vaginal haemorrhage	1 (0.8)	0	0	1 (1.5)	0	0
Heavy menstrual bleeding	0	1 (1.4)	0	1 (1.5)	0	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.8)	0	2 (1.7)	1 (1.5)	0	0
Epistaxis	1 (0.8)	0	1 (0.9)	0	0	0
Interstitial lung disease	0	0	0	1 (1.5)	0	0
Pulmonary embolism	0	0	1 (0.9)	0	0	0
Skin and subcutaneous tissue disorders (SOC)	0	1 (1.4)	0	0	0	0
Purpura	0	1 (1.4)	0	0	0	0
Vascular disorders (SOC)	1 (0.8)	0	1 (0.9)	1 (1.5)	0	0
Peripheral embolism	1 (0.8)	0	0	0	0	0
Deep vein thrombosis	0	0	1 (0.9)	0	0	0
Haematoma	0	0	0	1 (1.5)	0	0

Source: adae.xpt; Software: R; FDA reviewer analysis

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease of 2019; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SOC, system organ class

Table 120. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class, OND Custom Medical Query (Narrow) and Preferred Term, Double-Blind Treatment Period, LUNA 3

System Organ Class OCMQ (Narrow) Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Gastrointestinal disorders (SOC)			
Abdominal pain (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Abdominal discomfort	1 (0.8)	0	0.8 (-4.6, 4.1)
Diarrhea (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Diarrhoea	1 (0.8)	0	0.8 (-4.6, 4.1)
Dyspepsia (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Dyspepsia	1 (0.8)	0	0.8 (-4.6, 4.1)
Nausea (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Nausea	1 (0.8)	0	0.8 (-4.6, 4.1)
Hepatobiliary disorders (SOC)			
Hepatic injury (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Oesophageal varices haemorrhage	1 (0.8)	0	0.8 (-4.6, 4.1)
Infections and infestations (SOC)			
Pneumonia (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Pneumonia	1 (0.8)	0	0.8 (-4.6, 4.1)
Musculoskeletal and connective tissue disorders (SOC)			
Arthralgia (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Arthralgia	1 (0.8)	0	0.8 (-4.6, 4.1)
Nervous system disorders (SOC)			
Headache (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Headache	1 (0.8)	0	0.8 (-4.6, 4.1)
Vascular disorders (SOC)			
Hemorrhage (OCMQ)	1 (0.8)	0	0.8 (-4.6, 4.1)
Oesophageal varices haemorrhage	1 (0.8)	0	0.8 (-4.6, 4.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND medical query; OND, office of New Drugs; PT, preferred term; SOC, system organ class

17.2.2. Treatment-Emergent Adverse Events, LUNA 3

Table 121. Participants With Treatment Emergent Adverse Events, Any Grade, Preferred Term, Double-Blind Treatment Period, LUNA 3

Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Any AE	111 (83.5)	52 (75.4)	8.1 (–3.2, 20.8)
Diarrhoea	43 (32.3)	7 (10.1)	22.2 (10.5, 32.4) *
Nausea	27 (20.3)	4 (5.8)	14.5 (4.6, 23.2) *
Headache	24 (18.0)	5 (7.2)	10.8 (0.7, 19.6) *
COVID-19	18 (13.5)	3 (4.3)	9.2 (0.4, 16.9) *
Arthralgia	12 (9.0)	3 (4.3)	4.7 (–3.8, 11.6)
Dizziness	11 (8.3)	1 (1.4)	6.8 (–0.1, 13.1)
Abdominal pain	10 (7.5)	1 (1.4)	6.1 (–0.8, 12.1)
Vomiting	9 (6.8)	1 (1.4)	5.3 (–1.5, 11.2)
Nasopharyngitis	9 (6.8)	2 (2.9)	3.9 (–3.8, 10.0)
Abdominal pain upper	7 (5.3)	0	5.3 (–0.1, 10.5)
Dyspepsia	7 (5.3)	0	5.3 (–0.1, 10.5)
Cough	6 (4.5)	0	4.5 (–0.9, 9.5)
Asthenia	6 (4.5)	2 (2.9)	1.6 (–5.8, 7.2)

Source: adae.xpt; Software: R; FDA reviewer analysis

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease of 2019; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SOC, system organ class

Table 122. Participants With Adverse Events by System Organ Class and OND Custom Medical Query (Narrow), Blinded and Open-Label Treatment Periods, LUNA 3

System Organ Class OCMQ (Narrow)	Rilzabrutinib (BL Period) N=133 n (%)	Rilzabrutinib to Rilzabrutinib (OL Period) N=115 n (%)	Rilzabrutinib (BL+OL Periods) N=133 n (%)
Blood and lymphatic system disorders (SOC)			
Anemia	7 (5.3)	3 (2.6)	8 (6.0)
Thrombocytopenia	2 (1.5)	4 (3.5)	5 (3.8)
Cardiac disorders (SOC)			
Arrhythmia	2 (1.5)	0	2 (1.5)
Tachycardia	1 (0.8)	0	1 (0.8)
Systemic hypertension	0	1 (0.9)	1 (0.8)
Endocrine disorders (SOC)			
Hyperglycemia	2 (1.5)	1 (0.9)	3 (2.3)

System Organ Class OCMQ (Narrow)	Rilzabrutinib (BL Period) N=133 n (%)	Rilzabrutinib to Rilzabrutinib (OL Period) N=115 n (%)	Rilzabrutinib (BL+OL Periods) N=133 n (%)
Gastrointestinal disorders (SOC)			
Diarrhea	43 (32.3)	10 (8.7)	46 (34.6)
Nausea	27 (20.3)	7 (6.1)	29 (21.8)
Abdominal pain	19 (14.3)	4 (3.5)	21 (15.8)
Dyspepsia	14 (10.5)	1 (0.9)	15 (11.3)
Vomiting	9 (6.8)	3 (2.6)	11 (8.3)
Constipation	2 (1.5)	1 (0.9)	3 (2.3)
Dry mouth	1 (0.8)	0	1 (0.8)
General disorders and administration site conditions (SOC)			
Dizziness	12 (9.0)	5 (4.3)	17 (12.8)
Fatigue	10 (7.5)	4 (3.5)	14 (10.5)
Pyrexia	5 (3.8)	3 (2.6)	8 (6.0)
Decreased appetite	1 (0.8)	0	1 (0.8)
Fall	1 (0.8)	1 (0.9)	2 (1.5)
Local administration reaction	1 (0.8)	1 (0.9)	1 (0.8)
Peripheral edema	1 (0.8)	2 (1.7)	3 (2.3)
Hepatobiliary disorders (SOC)			
Hepatic injury	6 (4.5)	2 (1.7)	7 (5.3)
Infections and infestations (SOC)			
Viral infection	22 (16.5)	12 (10.4)	32 (24.1)
Nasopharyngitis	16 (12.0)	21 (18.3)	29 (21.8)
Bacterial infection	8 (6.0)	5 (4.3)	12 (9.0)
Pneumonia	2 (1.5)	0	2 (1.5)
Fungal infection	1 (0.8)	1 (0.9)	2 (1.5)
Opportunistic infection	1 (0.8)	0	1 (0.8)
Purulent material	1 (0.8)	0	1 (0.8)
Musculoskeletal and connective tissue disorders (SOC)			
Arthralgia	12 (9.0)	5 (4.3)	16 (12.0)
Back pain	5 (3.8)	2 (1.7)	6 (4.5)
Myalgia	3 (2.3)	2 (1.7)	5 (3.8)
Fracture	0	1 (0.9)	1 (0.8)
Osteoporosis	0	1 (0.9)	1 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy	0	1 (0.9)	1 (0.8)
Nervous system disorders (SOC)			
Headache	24 (18.0)	8 (7.0)	28 (21.1)
Paresthesia	1 (0.8)	1 (0.9)	2 (1.5)
Psychiatric disorders (SOC)			
Insomnia	4 (3.0)	1 (0.9)	4 (3.0)
Depression	2 (1.5)	0	2 (1.5)
Irritability	1 (0.8)	0	1 (0.8)
Renal and urinary disorders (SOC)			
Renal & urinary tract infection	3 (2.3)	5 (4.3)	8 (6.0)
Reproductive system and breast disorders (SOC)			
Abnormal uterine bleeding	1 (0.8)	0	1 (0.8)
Erectile dysfunction	1 (0.8)	0	1 (0.8)
Sexual dysfunction	1 (0.8)	0	1 (0.8)

System Organ Class OCMQ (Narrow)	Rilzabrutinib (BL Period) N=133 n (%)	Rilzabrutinib to Rilzabrutinib (OL Period) N=115 n (%)	Rilzabrutinib (BL+OL Periods) N=133 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)			
Cough	7 (5.3)	3 (2.6)	10 (7.5)
Dyspnea	1 (0.8)	1 (0.9)	2 (1.5)
Skin and subcutaneous tissue disorders (SOC)			
Rash	9 (6.8)	2 (1.7)	11 (8.3)
Pruritus	2 (1.5)	1 (0.9)	3 (2.3)
Alopecia	1 (0.8)	0	1 (0.8)
Urticaria	1 (0.8)	0	1 (0.8)
Vascular disorders (SOC)			
Hemorrhage	6 (4.5)	8 (7.0)	14 (10.5)
Thrombosis	0	1 (0.9)	1 (0.8)
Thrombosis venous	0	1 (0.9)	1 (0.8)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Duration is 24 weeks for the blinded period; 28 weeks for the open-label period.

Abbreviations: BL, blinded; incl, including; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND custom medical query; OL, open-label; OND, office of New Drugs; PT, preferred term; SOC, system organ class

Table 123. Participants With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 1% of Participants in Any Arm, Double-Blind Treatment Period, LUNA 3

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Any AE	111 (83.5)	52 (75.4)	8.1 (-3.2, 20.8)
Blood and lymphatic system disorders (SOC)	11 (8.3)	12 (17.4)	-9.1 (-20.5, 0.1)
Immune thrombocytopenia	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Neutrophilia	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Coagulopathy	0	1 (1.4)	-1.4 (-7.8, 1.4)
Haemorrhagic diathesis	0	1 (1.4)	-1.4 (-7.8, 1.4)
Leukocytosis	0	1 (1.4)	-1.4 (-7.8, 1.4)
Normochromic normocytic anaemia	0	1 (1.4)	-1.4 (-7.8, 1.4)
Anaemia	5 (3.8)	4 (5.8)	-2.0 (-10.6, 3.9)
Thrombocytopenia	1 (0.8)	2 (2.9)	-2.1 (-9.3, 1.7)
Iron deficiency anaemia	1 (0.8)	3 (4.3)	-3.6 (-11.4, 0.5)
Cardiac disorders (SOC)	2 (1.5)	2 (2.9)	-1.4 (-8.6, 2.9)
Bundle branch block right	0	1 (1.4)	-1.4 (-7.8, 1.4)
Palpitations	0	1 (1.4)	-1.4 (-7.8, 1.4)
Eye disorders (SOC)	5 (3.8)	2 (2.9)	0.9 (-6.5, 6.2)
Cataract	0	1 (1.4)	-1.4 (-7.8, 1.4)
Conjunctival haemorrhage	0	1 (1.4)	-1.4 (-7.8, 1.4)

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Gastrointestinal disorders (SOC)	71 (53.4)	16 (23.2)	30.2 (16.3, 42.4) *
Diarrhoea	43 (32.3)	7 (10.1)	22.2 (10.5, 32.4) *
Nausea	27 (20.3)	4 (5.8)	14.5 (4.6, 23.2) *
Abdominal pain	10 (7.5)	1 (1.4)	6.1 (-0.8, 12.1)
Vomiting	9 (6.8)	1 (1.4)	5.3 (-1.5, 11.2)
Abdominal pain upper	7 (5.3)	0	5.3 (-0.1, 10.5)
Dyspepsia	7 (5.3)	0	5.3 (-0.1, 10.5)
Abdominal discomfort	4 (3.0)	0	3.0 (-2.3, 7.5)
Abdominal distension	3 (2.3)	0	2.3 (-3.1, 6.4)
Gastritis	3 (2.3)	0	2.3 (-3.1, 6.4)
Oral pain	2 (1.5)	0	1.5 (-3.8, 5.3)
Constipation	2 (1.5)	1 (1.4)	0.1 (-6.4, 4.1)
Gastrointestinal disorder	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Gingival bleeding	0	1 (1.4)	-1.4 (-7.8, 1.4)
Haematemesis	0	1 (1.4)	-1.4 (-7.8, 1.4)
Mouth haemorrhage	0	1 (1.4)	-1.4 (-7.8, 1.4)
Pancreatic disorder	0	1 (1.4)	-1.4 (-7.8, 1.4)
Gastroesophageal reflux disease	1 (0.8)	2 (2.9)	-2.1 (-9.3, 1.7)
General disorders and administration site conditions (SOC)	20 (15.0)	9 (13.0)	2.0 (-9.2, 11.5)
Pyrexia	5 (3.8)	0	3.8 (-1.6, 8.5)
Asthenia	6 (4.5)	2 (2.9)	1.6 (-5.8, 7.2)
Influenza like illness	2 (1.5)	2 (2.9)	-1.4 (-8.6, 2.9)
Swelling face	0	1 (1.4)	-1.4 (-7.8, 1.4)
Fatigue	4 (3.0)	4 (5.8)	-2.8 (-11.3, 2.9)
Infections and infestations (SOC)	44 (33.1)	14 (20.3)	12.8 (-0.4, 24.5)
COVID-19	18 (13.5)	3 (4.3)	9.2 (0.4, 16.9) *
Nasopharyngitis	9 (6.8)	2 (2.9)	3.9 (-3.8, 10.0)
Influenza	4 (3.0)	0	3.0 (-2.3, 7.5)
Pneumonia	2 (1.5)	0	1.5 (-3.8, 5.3)
Skin infection	2 (1.5)	0	1.5 (-3.8, 5.3)
Urinary tract infection	2 (1.5)	1 (1.4)	0.1 (-6.4, 4.1)
Upper respiratory tract infection	5 (3.8)	3 (4.3)	-0.6 (-8.6, 5.0)
Bronchitis	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Gastroenteritis	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Viral infection	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Gingivitis	0	1 (1.4)	-1.4 (-7.8, 1.4)
Oral herpes	0	1 (1.4)	-1.4 (-7.8, 1.4)
Pyuria	0	1 (1.4)	-1.4 (-7.8, 1.4)
Pulpitis dental	0	2 (2.9)	-2.9 (-10.0, -0.0) *
Injury, poisoning and procedural complications (SOC)	11 (8.3)	4 (5.8)	2.5 (-6.5, 9.6)
Contusion	2 (1.5)	0	1.5 (-3.8, 5.3)
Ligament sprain	2 (1.5)	0	1.5 (-3.8, 5.3)
Fall	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Limb injury	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Meniscus injury	0	1 (1.4)	-1.4 (-7.8, 1.4)
Splenosis	0	1 (1.4)	-1.4 (-7.8, 1.4)

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Investigations (SOC)	12 (9.0)	6 (8.7)	0.3 (-9.5, 8.1)
Coombs test positive	2 (1.5)	0	1.5 (-3.8, 5.3)
Alanine aminotransferase increased	3 (2.3)	2 (2.9)	-0.6 (-7.9, 4.1)
Aspartate aminotransferase increased	3 (2.3)	2 (2.9)	-0.6 (-7.9, 4.1)
Hepatic enzyme increased	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Weight decreased	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Lymphocyte count decreased	0	1 (1.4)	-1.4 (-7.8, 1.4)
Weight increased	0	1 (1.4)	-1.4 (-7.8, 1.4)
Metabolism and nutrition disorders (SOC)	6 (4.5)	2 (2.9)	1.6 (-5.8, 7.2)
Hyperglycaemia	2 (1.5)	0	1.5 (-3.8, 5.3)
Hypokalaemia	3 (2.3)	1 (1.4)	0.8 (-5.7, 5.2)
Vitamin D deficiency	0	1 (1.4)	-1.4 (-7.8, 1.4)
Musculoskeletal and connective tissue disorders (SOC)	27 (20.3)	8 (11.6)	8.7 (-2.6, 18.5)
Arthralgia	12 (9.0)	3 (4.3)	4.7 (-3.8, 11.6)
Musculoskeletal pain	2 (1.5)	0	1.5 (-3.8, 5.3)
Neck pain	2 (1.5)	0	1.5 (-3.8, 5.3)
Myalgia	3 (2.3)	1 (1.4)	0.8 (-5.7, 5.2)
Back pain	4 (3.0)	2 (2.9)	0.1 (-7.2, 5.1)
Pain in extremity	4 (3.0)	2 (2.9)	0.1 (-7.2, 5.1)
Bursitis	0	1 (1.4)	-1.4 (-7.8, 1.4)
Musculoskeletal stiffness	0	1 (1.4)	-1.4 (-7.8, 1.4)
Nervous system disorders (SOC)	32 (24.1)	8 (11.6)	12.5 (0.9, 22.5) *
Headache	24 (18.0)	5 (7.2)	10.8 (0.7, 19.6) *
Dizziness	11 (8.3)	1 (1.4)	6.8 (-0.1, 13.1)
Neuropathy peripheral	2 (1.5)	0	1.5 (-3.8, 5.3)
Syncope	0	1 (1.4)	-1.4 (-7.8, 1.4)
Tremor	0	1 (1.4)	-1.4 (-7.8, 1.4)
Psychiatric disorders (SOC)	6 (4.5)	1 (1.4)	3.1 (-3.6, 8.3)
Depression	2 (1.5)	0	1.5 (-3.8, 5.3)
Insomnia	3 (2.3)	1 (1.4)	0.8 (-5.7, 5.2)
Renal and urinary disorders (SOC)	2 (1.5)	1 (1.4)	0.1 (-6.4, 4.1)
Stress urinary incontinence	0	1 (1.4)	-1.4 (-7.8, 1.4)
Reproductive system and breast disorders (SOC)	4 (3.0)	2 (2.9)	0.1 (-7.2, 5.1)
Heavy menstrual bleeding	0	2 (2.9)	-2.9 (-10.0, -0.0) *
Respiratory, thoracic and mediastinal disorders (SOC)	15 (11.3)	3 (4.3)	6.9 (-1.7, 14.3)
Cough	6 (4.5)	0	4.5 (-0.9, 9.5)
Oropharyngeal pain	3 (2.3)	1 (1.4)	0.8 (-5.7, 5.2)
Bronchitis chronic	0	1 (1.4)	-1.4 (-7.8, 1.4)
Rhinitis allergic	0	1 (1.4)	-1.4 (-7.8, 1.4)
Skin and subcutaneous tissue disorders (SOC)	15 (11.3)	8 (11.6)	-0.3 (-11.0, 8.4)
Rash	5 (3.8)	1 (1.4)	2.3 (-4.3, 7.3)
Eczema	2 (1.5)	1 (1.4)	0.1 (-6.4, 4.1)
Dermatitis	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Pruritus	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Urticaria	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Dermatitis acneiform	0	1 (1.4)	-1.4 (-7.8, 1.4)
Erythema	0	1 (1.4)	-1.4 (-7.8, 1.4)
Purpura	0	2 (2.9)	-2.9 (-10.0, -0.0) *

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Vascular disorders (SOC)	1 (0.8)	4 (5.8)	-5.0 (-13.3, -0.6) *
Peripheral venous disease	0	1 (1.4)	-1.4 (-7.8, 1.4)
Hypertension	0	3 (4.3)	-4.3 (-12.0, -1.4) *

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease of 2019; N, number of participants in treatment arm; n, number of participants with adverse event; SOC, system organ class

17.2.3. Infections, LUNA 3

Table 124. Participants With Infections and Infestations by System Organ Class and Preferred Term, Occurring in at Least 1% of Participants, Double-Blind Treatment Period, LUNA 3

System Organ Class Preferred Term	Rilzabrutinib N=133 n (%)	Placebo N=69 n (%)	Risk Difference % (95% CI)
Infections and infestations (SOC)	44 (33.1)	14 (20.3)	12.8 (-0.4, 24.5)
COVID-19	18 (13.5)	3 (4.3)	9.2 (0.4, 16.9) *
Nasopharyngitis	9 (6.8)	2 (2.9)	3.9 (-3.8, 10.0)
Influenza	4 (3.0)	0	3.0 (-2.3, 7.5)
Pneumonia	2 (1.5)	0	1.5 (-3.8, 5.3)
Skin infection	2 (1.5)	0	1.5 (-3.8, 5.3)
Urinary tract infection	2 (1.5)	1 (1.4)	0.1 (-6.4, 4.1)
Upper respiratory tract infection	5 (3.8)	3 (4.3)	-0.6 (-8.6, 5.0)
Bronchitis	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Gastroenteritis	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Viral infection	1 (0.8)	1 (1.4)	-0.7 (-7.1, 2.9)
Gingivitis	0	1 (1.4)	-1.4 (-7.8, 1.4)
Oral herpes	0	1 (1.4)	-1.4 (-7.8, 1.4)
Pyuria	0	1 (1.4)	-1.4 (-7.8, 1.4)
Pulpitis dental	0	2 (2.9)	-2.9 (-10.0, -0.0) *

Source: adae.xpt; Software: R; FDA reviewer analysis

Treatment-emergent adverse events defined as adverse events that developed, worsened, or became serious during the treatment-emergent period.

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

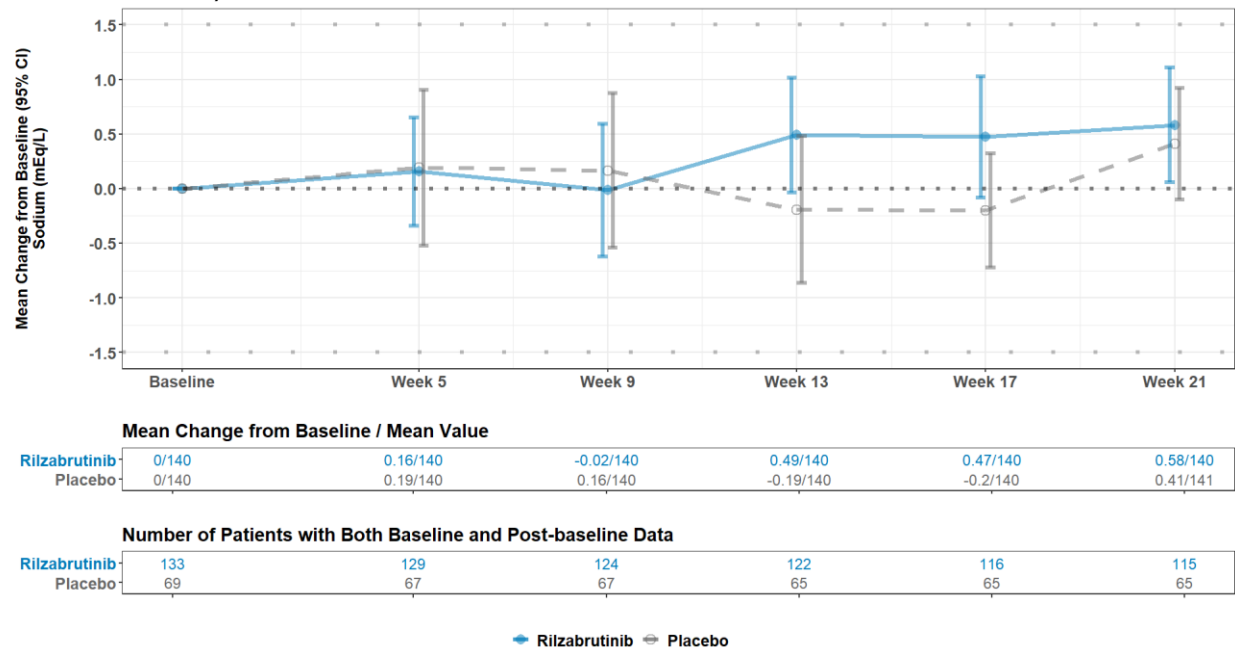
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease of 2019; N, number of participants in treatment arm; n, number of participants with adverse event; SOC, system organ class

17.2.4. Laboratory Analyses, LUNA 3

17.2.4.1. Change Over Time From Baseline, LUNA 3

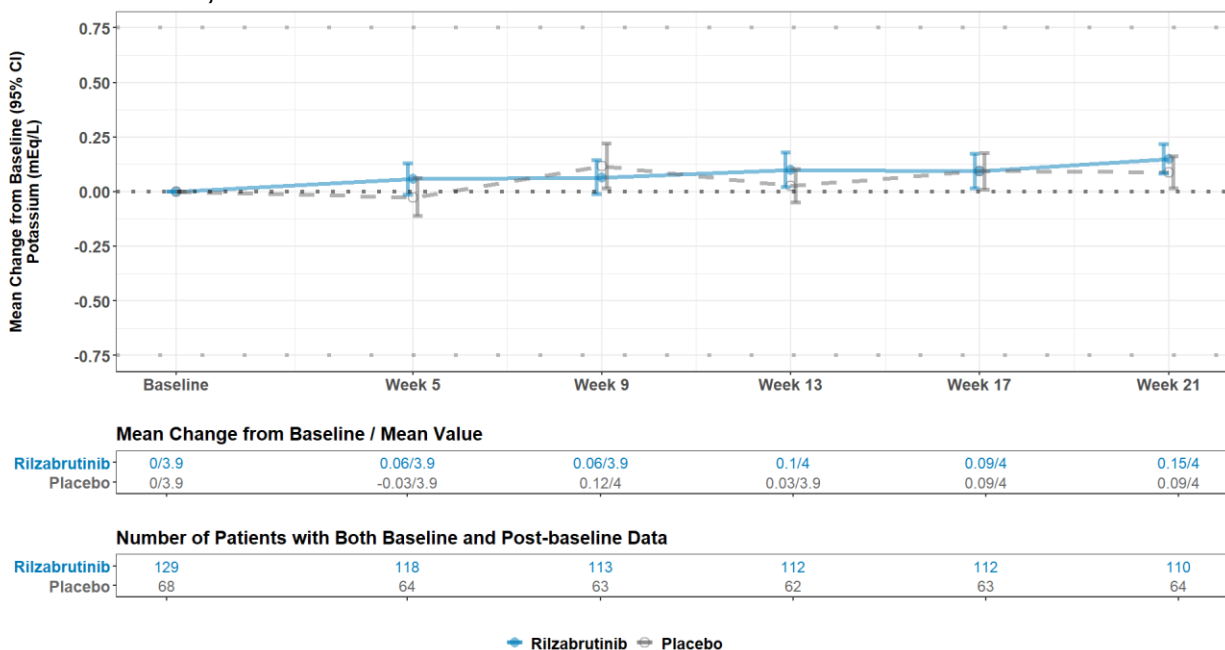
17.2.4.1.1. Chemistry Assessments, LUNA 3

Figure 29. Mean Laboratory Value Change From Baseline Over Time, Sodium, Double-Blind Treatment Period, LUNA 3



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

Figure 30. Mean Laboratory Value Change From Baseline Over Time, Potassium, Double-Blind Treatment Period, LUNA 3

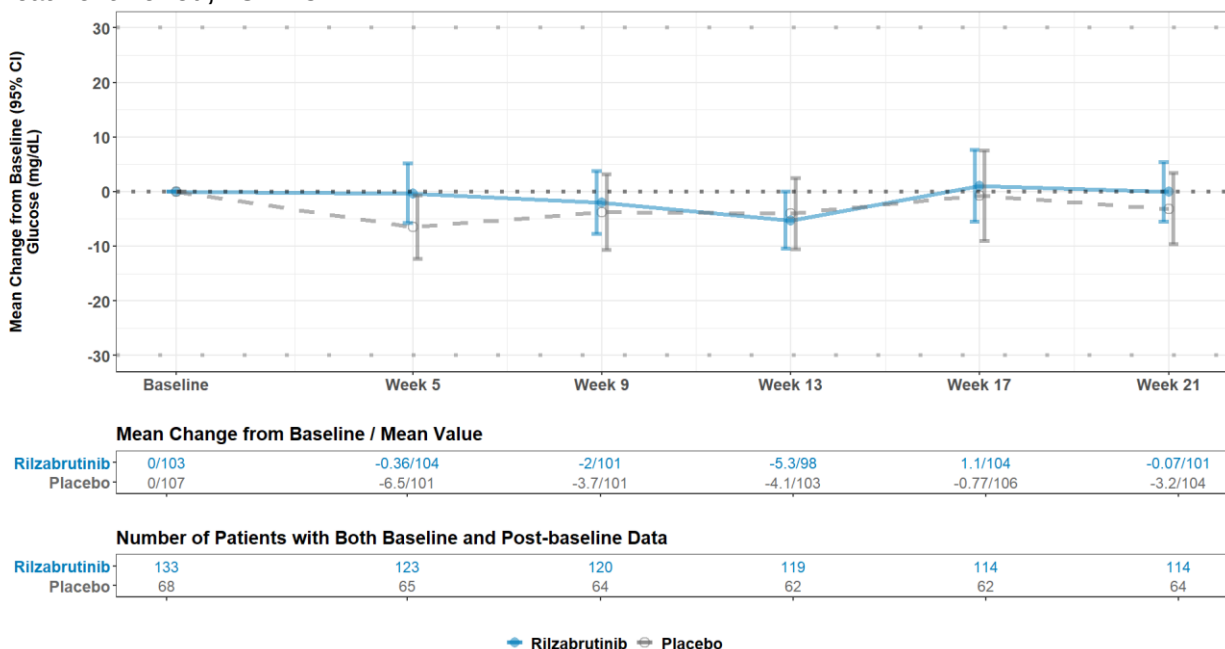


Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups. Only central laboratory data are included in the analysis.

Abbreviation: CI, confidence interval

Figure 31. Mean Laboratory Value Change From Baseline Over Time, Glucose, Double-Blind Treatment Period, LUNA 3

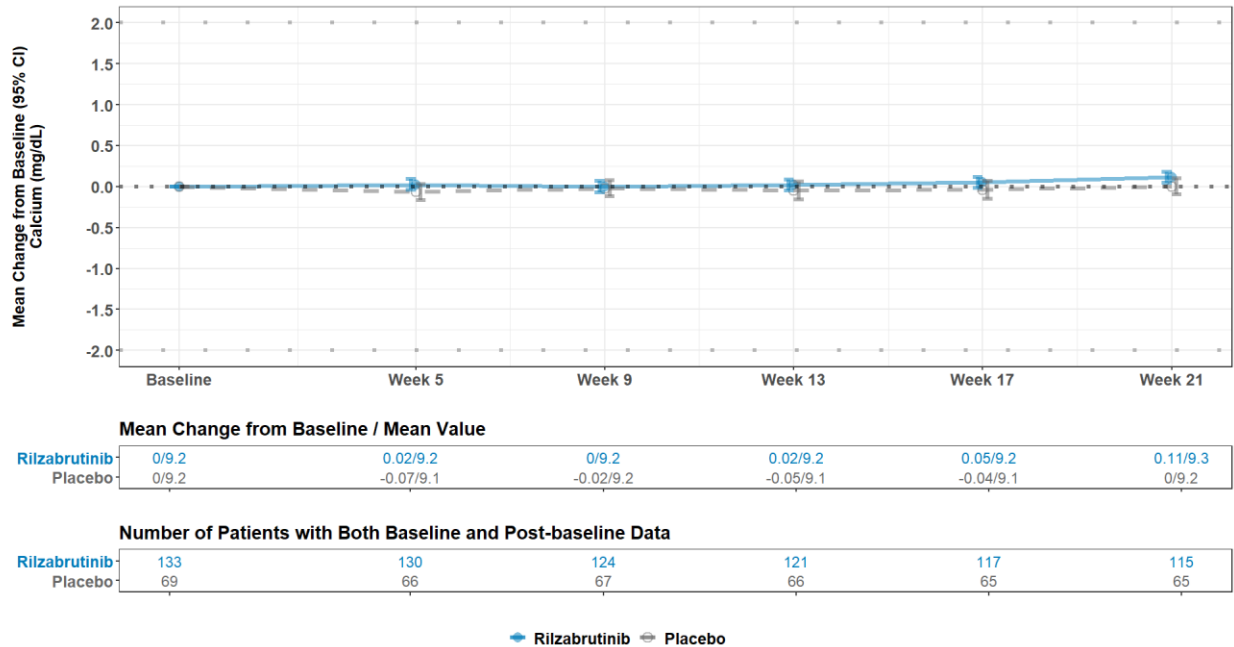


Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups. Only central laboratory data are included in the analysis.

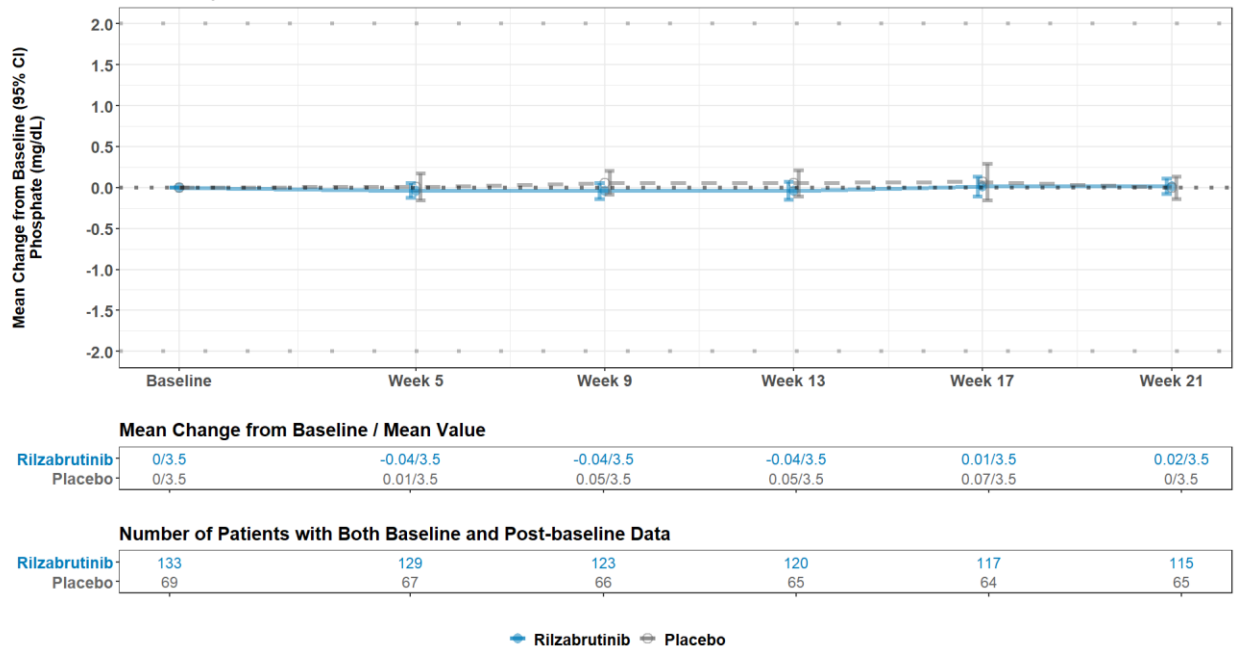
Abbreviation: CI, confidence interval

Figure 32. Mean Laboratory Value Change From Baseline Over Time, Calcium, Double-Blind Treatment Period, LUNA 3



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

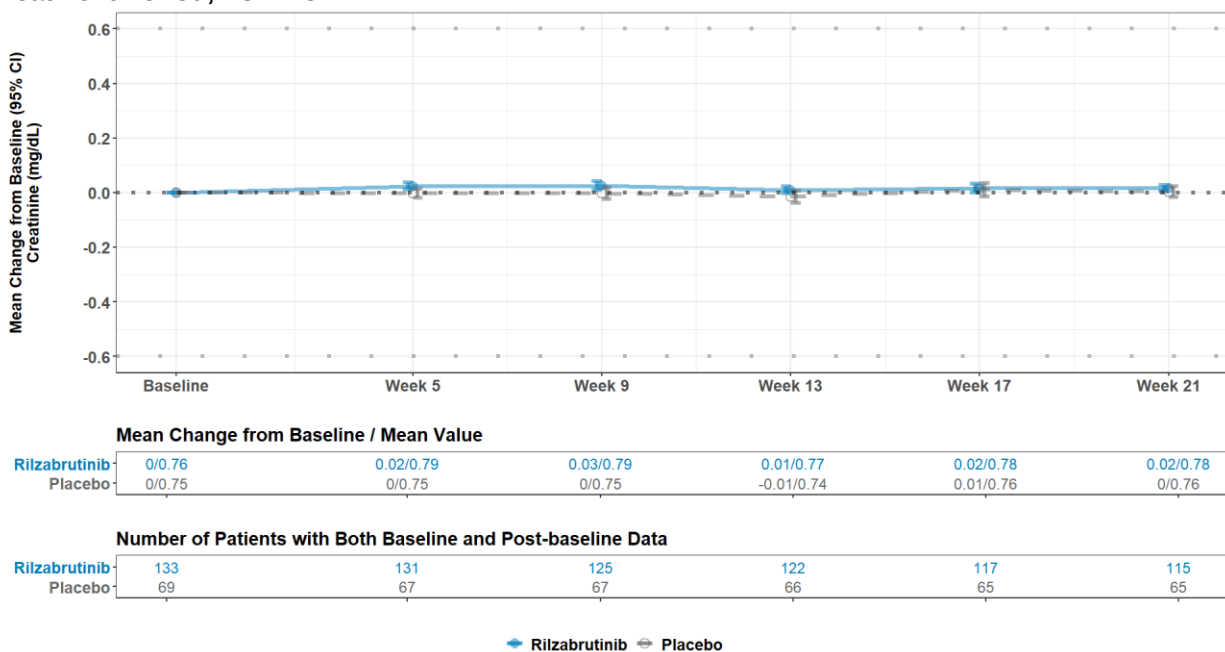
Figure 33. Mean Laboratory Value Change From Baseline Over Time, Phosphate, Double-Blind Treatment Period, LUNA 3



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

17.2.4.1.2. Kidney Function Assessments, LUNA 3

Figure 34. Mean Laboratory Value Change From Baseline Over Time, Creatinine, Double-Blind Treatment Period, LUNA 3



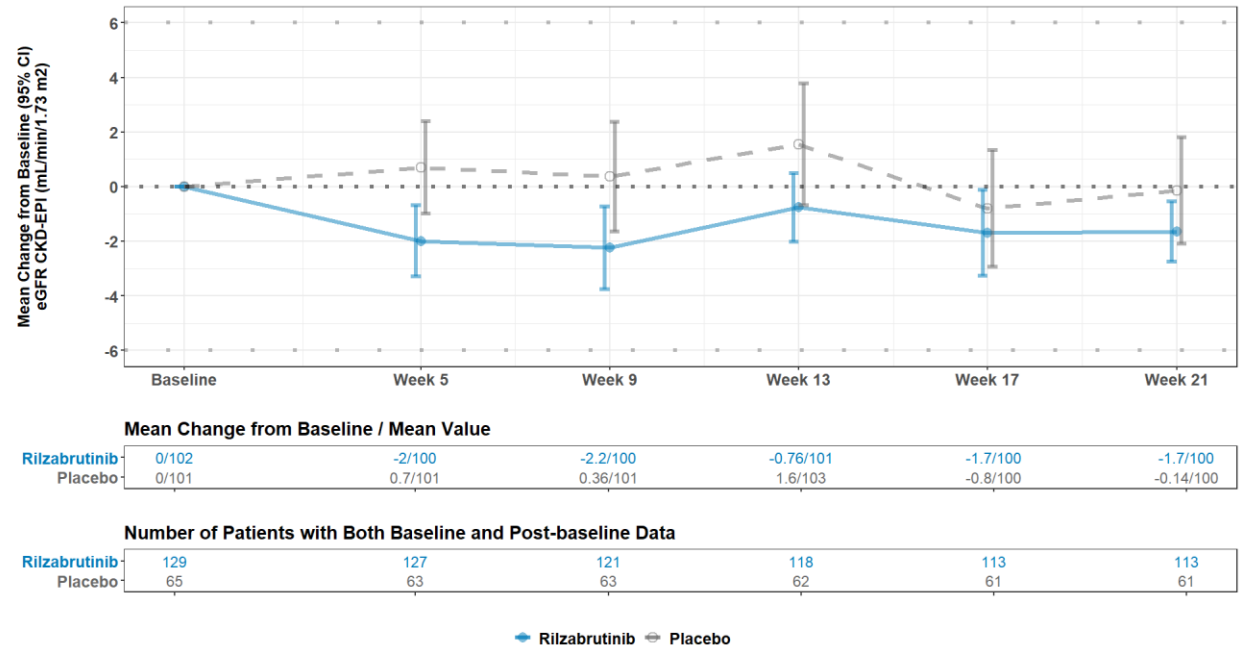
Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.

Only central laboratory data are included in the analysis.

Abbreviation: CI, confidence interval

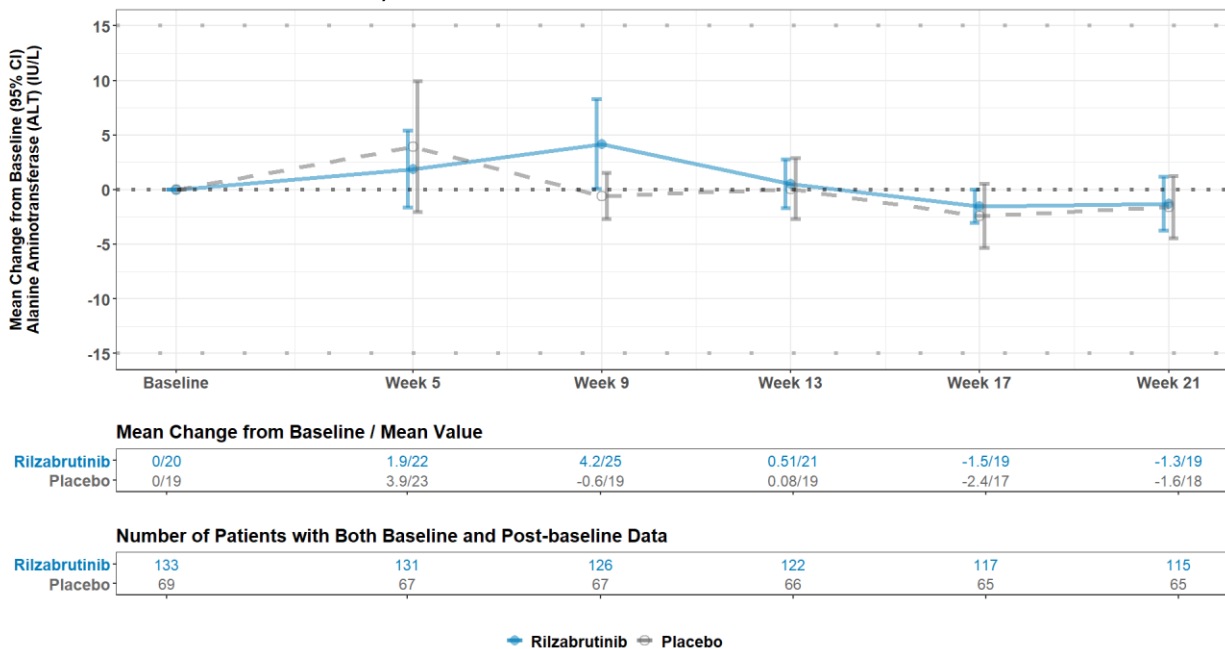
Figure 35. Mean Laboratory Value Change From Baseline Over Time, eGFR CKD-EPI, Double-Blind Treatment Period, LUNA 3



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate

17.2.4.1.3. Liver Assessments, LUNA 3

Figure 36. Mean Laboratory Value Change From Baseline Over Time, Alanine Aminotransferase, Double-Blind Treatment Period, LUNA 3



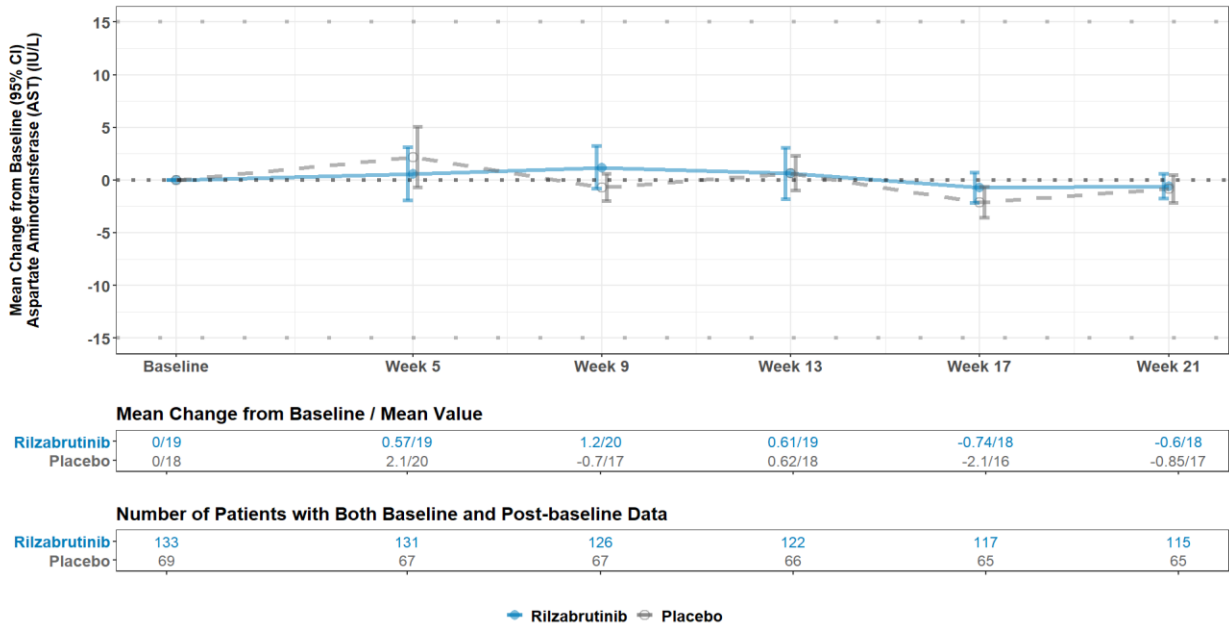
Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.

Only central laboratory data are included in the analysis.

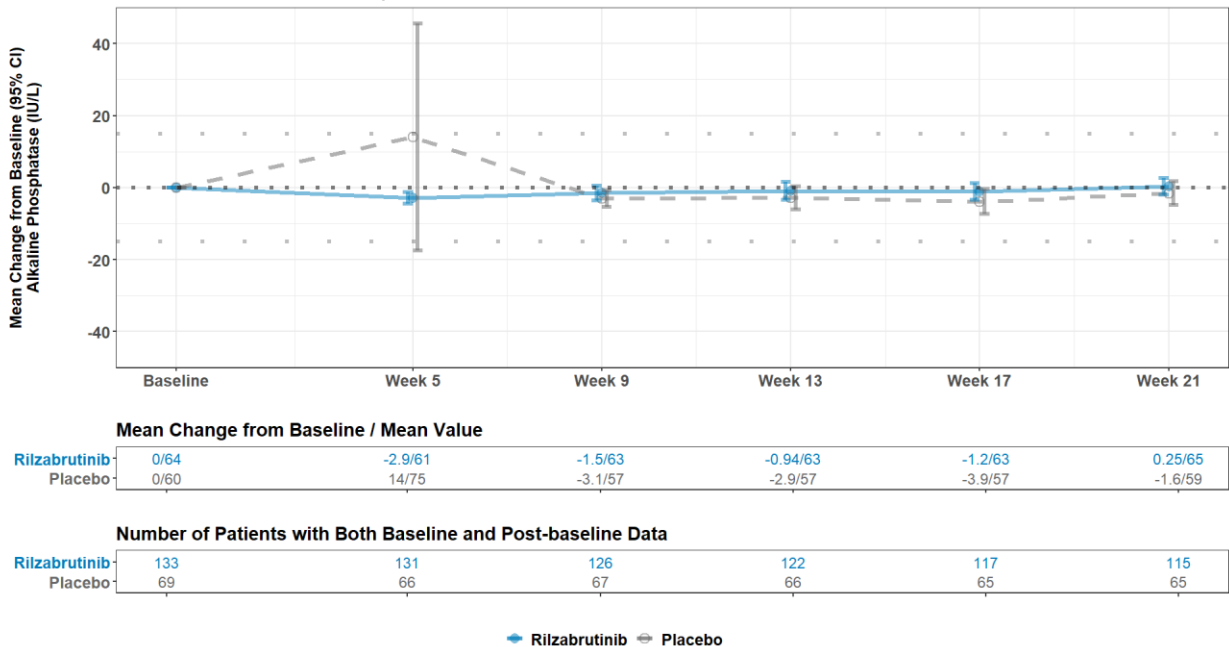
Abbreviation: CI, confidence interval

Figure 37. Mean Laboratory Value Change From Baseline Over Time, Aspartate Aminotransferase, Double-Blind Treatment Period, LUNA 3



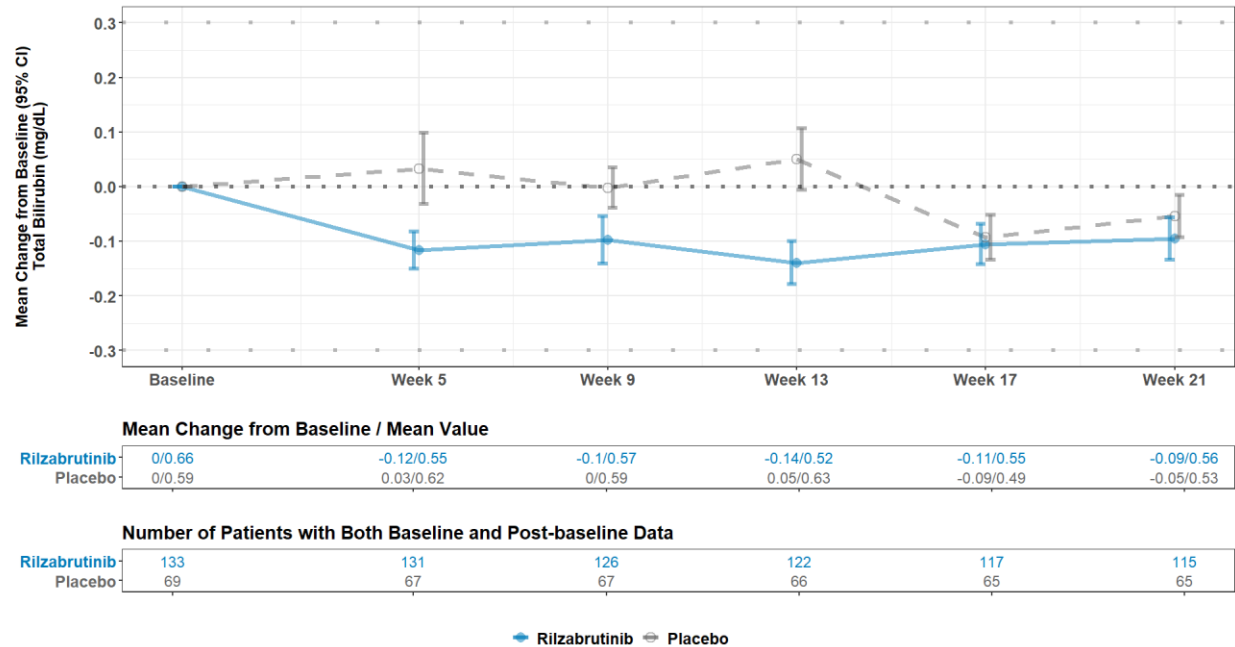
Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

Figure 38. Mean Laboratory Value Change From Baseline Over Time, Alkaline Phosphatase, Double-Blind Treatment Period, LUNA 3



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

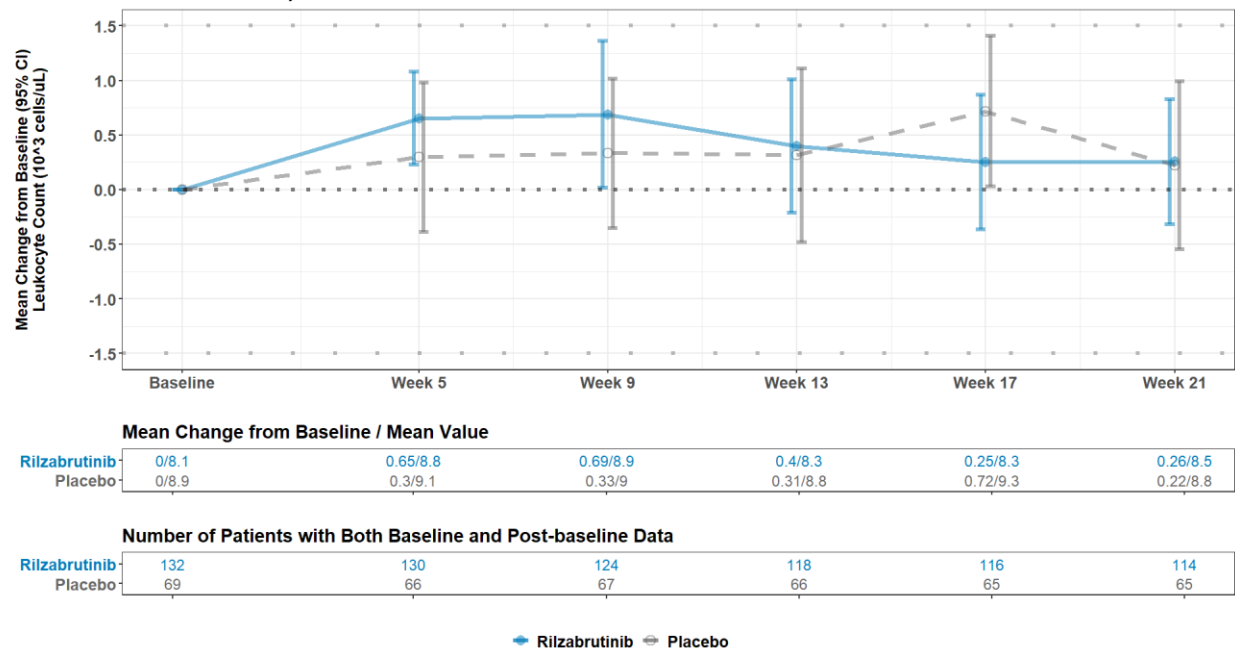
Figure 39. Mean Laboratory Value Change From Baseline Over Time, Total Bilirubin, Double-Blind Treatment Period, LUNA 3



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

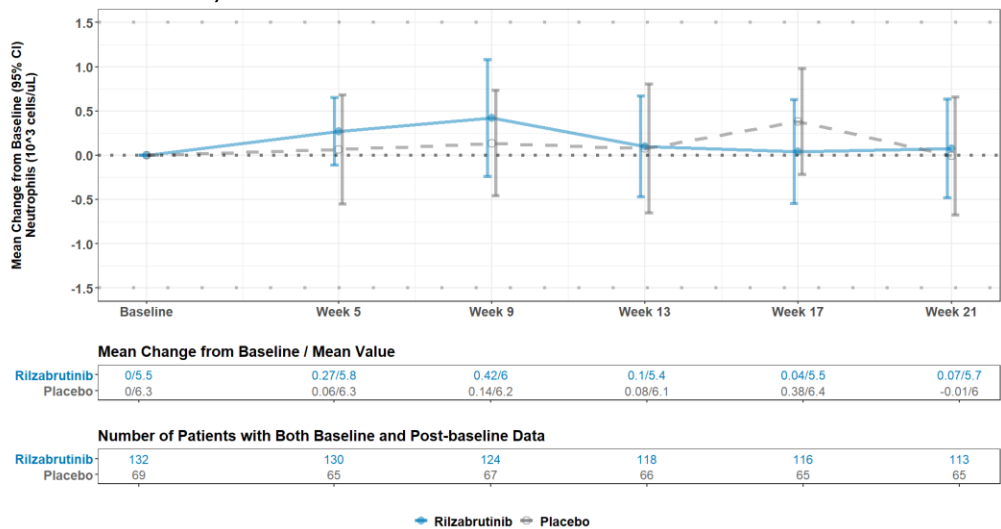
17.2.4.1.4. Hematology Assessments, LUNA 3

Figure 40. Mean Laboratory Value Change From Baseline Over Time, Leukocyte Count, Double-Blind Treatment Period, LUNA 3



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

Figure 41. Mean Laboratory Value Change From Baseline Over Time, Neutrophils, Double-Blind Treatment Period, LUNA 3

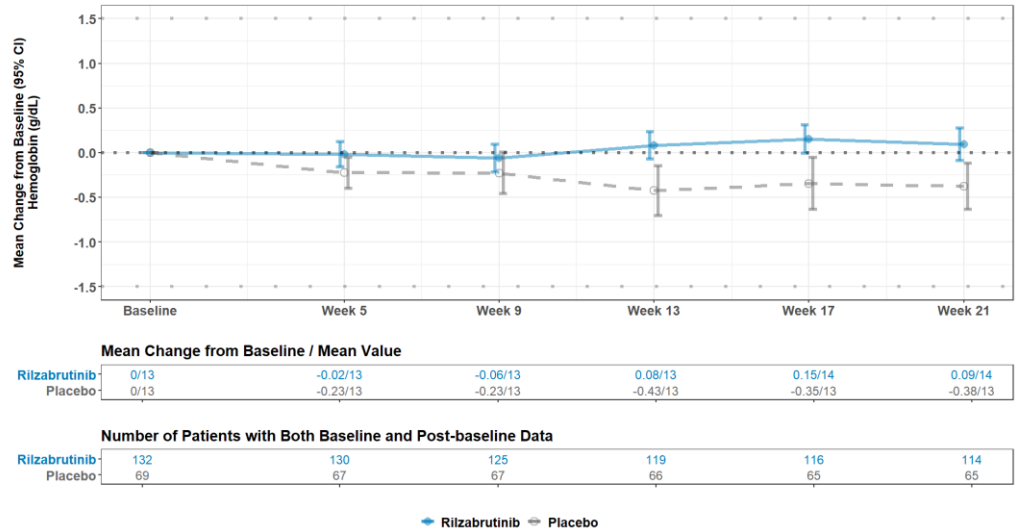


Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

Hemoglobin

The mean change from baseline over time for hemoglobin values for rilzabrutinib and placebo treated participants is shown in [Figure 42](#). At Week 13, the changes from baseline appear to diverge. This is likely due to response in the rilzabrutinib treated participants who remained on study in the DB treatment period and those treated with placebo who were permitted withdrawal due to nonresponse.

Figure 42. Mean Laboratory Value Change From Baseline Over Time, Hemoglobin, Double-Blind Treatment Period, LUNA 3



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

17.2.4.2. Outlier Analyses, LUNA 3

17.2.4.2.1. Chemistry, LUNA 3

Table 125. Frequency of Laboratory Values Exceeding Specified Levels for General Chemistry, Double-Blind Treatment Period, LUNA 3

Laboratory Parameter	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)	Rilzabrutinib vs. Placebo Risk Difference (%) (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	3/131 (2.3)	1/68 (1.5)	0.8 (−5.8, 5.3)
Level 2 (<130)	1/131 (0.8)	1/68 (1.5)	−0.7 (−7.2, 2.9)
Level 3 (<125)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Sodium, high (mEq/L)			
Level 1 (>150)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Level 2 (>155)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Level 3 (>160)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Potassium, low (mEq/L)			
Level 1 (<3.6)	38/128 (29.7)	15/68 (22.1)	7.6 (−5.7, 19.6)
Level 2 (<3.4)	16/128 (12.5)	5/68 (7.4)	5.1 (−4.7, 13.4)
Level 3 (<3)	0/128 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Potassium, high (mEq/L)			
Level 1 (>5.5)	3/128 (2.3)	0/68 (0)	2.3 (−3.1, 6.7)
Level 2 (>6)	0/128 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Level 3 (>6.5)	0/128 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Chloride, low (mEq/L)			
Level 1 (<95)	2/131 (1.5)	0/68 (0)	1.5 (−3.9, 5.4)
Level 2 (<88)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Level 3 (<80)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Chloride, high (mEq/L)			
Level 1 (>108)	11/131 (8.4)	9/68 (13.2)	−4.8 (−15.7, 3.8)
Level 2 (>112)	1/131 (0.8)	1/68 (1.5)	−0.7 (−7.2, 2.9)
Level 3 (>115)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Bicarbonate, low (mEq/L)			
Missing	NA	NA	NA
Bicarbonate, high (mEq/L)			
Missing	NA	NA	NA
Glucose, low (mg/dL)			
Level 1 (<70)	17/130 (13.1)	7/68 (10.3)	2.8 (−7.8, 11.6)
Level 2 (<54)	1/130 (0.8)	0/68 (0)	0.8 (−4.6, 4.2)
Level 3 (<40)	0/130 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Glucose, random, high (mg/dL)			
Level 2 (≥200)	4/130 (3.1)	2/68 (2.9)	0.1 (−7.3, 5.3)
Level 3 (>250)	2/130 (1.5)	1/68 (1.5)	0.1 (−6.5, 4.2)
Calcium, low (mg/dL)			
Level 1 (<8.4)	10/131 (7.6)	4/68 (5.9)	1.8 (−7.2, 8.8)
Level 2 (<8)	1/131 (0.8)	2/68 (2.9)	−2.2 (−9.4, 1.7)
Level 3 (<7.5)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Calcium, high (mg/dL)			
Level 1 (>10.5)	1/131 (0.8)	1/68 (1.5)	−0.7 (−7.2, 2.9)
Level 2 (>11)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)
Level 3 (>12)	0/131 (0)	0/68 (0)	0.0 (−5.4, 2.9)

Laboratory Parameter	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)	Rilzabrutinib vs. Placebo Risk Difference (%) (95% CI)
Phosphate, low (mg/dL)			
Level 1 (<2.5)	15/131 (11.5)	7/68 (10.3)	1.2 (-9.3, 9.7)
Level 2 (<2)	7/131 (5.3)	2/68 (2.9)	2.4 (-5.2, 8.3)
Level 3 (<1.4)	0/131 (0)	1/68 (1.5)	-1.5 (-7.9, 1.4)
Protein, total, low (g/dL)			
Level 1 (<6)	5/131 (3.8)	4/68 (5.9)	-2.1 (-10.7, 3.9)
Level 2 (<5.4)	0/131 (0)	2/68 (2.9)	-2.9 (-10.1, -0.0) *
Level 3 (<5)	0/131 (0)	0/68 (0)	0.0 (-5.4, 2.9)
Albumin, low (g/dL)			
Level 1 (<3.1)	1/131 (0.8)	2/68 (2.9)	-2.2 (-9.4, 1.7)
Level 2 (<2.5)	0/131 (0)	0/68 (0)	0.0 (-5.4, 2.9)
Level 3 (<2)	0/131 (0)	0/68 (0)	0.0 (-5.4, 2.9)
CPK, high (U/L)			
Level 1 (>3X ULN)	0/2 (0)	0/3 (0)	0.0 (-61.5, 70.6)
Level 2 (>5X ULN)	0/2 (0)	0/3 (0)	0.0 (-61.5, 70.6)
Level 3 (>10X ULN)	0/2 (0)	0/3 (0)	0.0 (-61.5, 70.6)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	10/131 (7.6)	4/68 (5.9)	1.8 (-7.2, 8.8)
Level 2 (>27)	4/131 (3.1)	2/68 (2.9)	0.1 (-7.3, 5.2)
Level 3 (>31)	1/131 (0.8)	0/68 (0)	0.8 (-4.6, 4.2)

Source: adlb.xpt; Software: R, FDA reviewer analysis

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide ([FDA 2021](#))

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal

17.2.4.2.2. Kidney Function, LUNA 3

Table 126. Participants With One or More Kidney Function Analyte Values Exceeding Specified Levels, Double-Blind Treatment Period, LUNA 3

Laboratory Parameter	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)	Rilzabrutinib vs. Placebo Risk Difference (%) (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5X baseline)	2/131 (1.5)	0/68 (0)	1.5 (-3.9, 5.4)
Level 2 (≥2X baseline)	0/131 (0)	0/68 (0)	0.0 (-5.4, 2.9)
Level 3 (≥3X baseline)	0/131 (0)	0/68 (0)	0.0 (-5.4, 2.9)
eGFR, low (mL/min/1.73 m ²)			
Level 1 (≥25% decrease)	7/127 (5.5)	0/64 (0)	5.5 (-0.3, 11.0)
Level 2 (≥50% decrease)	1/127 (0.8)	0/64 (0)	0.8 (-4.9, 4.3)
Level 3 (≥75% decrease)	0/127 (0)	0/64 (0)	0.0 (-5.7, 3.0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide ([FDA 2021](#)).

Duration is the 24-week double-blind treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data

17.2.4.2.3. Hematology, LUNA 3

Table 127. Participants With One or More Hematology Analyte Values Exceeding Specified Levels, Double-Blind Treatment Period, LUNA 3

Laboratory Parameter	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)	Rilzabrutinib vs. Placebo Risk Difference (%) (95% CI)
Complete blood count			
WBC, low (10 ³ cells/μL)			
Level 1 (<3.5)	10/132 (7.6)	3/68 (4.4)	3.2 (-5.3, 9.9)
Level 2 (<3)	6/132 (4.5)	0/68 (0)	4.5 (-0.9, 9.6)
Level 3 (<1)	0/132 (0)	0/68 (0)	0.0 (-5.4, 2.8)
WBC, high (10 ³ cells/μL)			
Level 1 (>10.8)	45/132 (34.1)	27/68 (39.7)	-5.6 (-19.9, 8.2)
Level 2 (>13)	25/132 (18.9)	21/68 (30.9)	-11.9 (-25.2, 0.4)
Level 3 (>15)	13/132 (9.8)	12/68 (17.6)	-7.8 (-19.4, 1.8)
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	13/131 (9.9)	7/68 (10.3)	-0.4 (-10.7, 8.0)
Level 3 (>2 g/dL dec. from baseline)	6/131 (4.6)	4/68 (5.9)	-1.3 (-10.0, 5.0)
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	2/131 (1.5)	1/68 (1.5)	0.1 (-6.5, 4.2)
Level 3 (>3 g/dL inc. from baseline)	2/131 (1.5)	0/68 (0)	1.5 (-3.9, 5.4)
Platelets, low (10 ³ cells/μL)			
Missing	NA	NA	NA
WBC differential			
Lymphocytes, low (10 ³ cells/μL)			
Level 1 (<1)	27/132 (20.5)	13/68 (19.1)	1.3 (-11.2, 12.3)
Level 2 (<0.75)	18/132 (13.6)	8/68 (11.8)	1.9 (-9.1, 11.0)
Level 3 (<0.5)	5/132 (3.8)	1/68 (1.5)	2.3 (-4.4, 7.4)
Lymphocytes, high (10 ³ cells/μL)			
Level 1 (>4)	19/132 (14.4)	12/68 (17.6)	-3.3 (-15.2, 6.9)
Level 2 (>10)	0/132 (0)	0/68 (0)	0.0 (-5.4, 2.8)
Level 3 (>20)	0/132 (0)	0/68 (0)	0.0 (-5.4, 2.8)
Neutrophils, low (10 ³ cells/μL)			
Level 1 (<2)	15/132 (11.4)	3/68 (4.4)	7.0 (-1.8, 14.4)
Level 2 (<1)	1/132 (0.8)	1/68 (1.5)	-0.7 (-7.2, 2.9)
Level 3 (<0.5)	1/132 (0.8)	0/68 (0)	0.8 (-4.6, 4.2)
Eosinophils, high (10 ³ cells/μL)			
Level 1 (>0.65)	6/132 (4.5)	4/68 (5.9)	-1.3 (-10.1, 4.9)
Level 2 (>1.5)	0/132 (0)	0/68 (0)	0.0 (-5.4, 2.8)
Level 3 (>5)	0/132 (0)	0/68 (0)	0.0 (-5.4, 2.8)
Coagulation studies			
PT, high (sec)			
Level 1 (>1.1X ULN)	25/129 (19.4)	9/68 (13.2)	6.1 (-5.5, 16.2)
Level 2 (>1.3X ULN)	2/129 (1.6)	4/68 (5.9)	-4.3 (-12.8, 0.8)
Level 3 (>1.5X ULN)	0/129 (0)	0/68 (0)	0.0 (-5.4, 2.9)

Laboratory Parameter	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)	Rilzabrutinib vs. Placebo Risk Difference (%) (95% CI)
PTT, high (sec)			
Level 1 (>1X ULN)	12/129 (9.3)	6/68 (8.8)	0.5 (-9.5, 8.5)
Level 2 (>1.21X ULN)	5/129 (3.9)	0/68 (0)	3.9 (-1.6, 8.8)
Level 3 (>1.41X ULN)	4/129 (3.1)	0/68 (0)	3.1 (-2.3, 7.7)

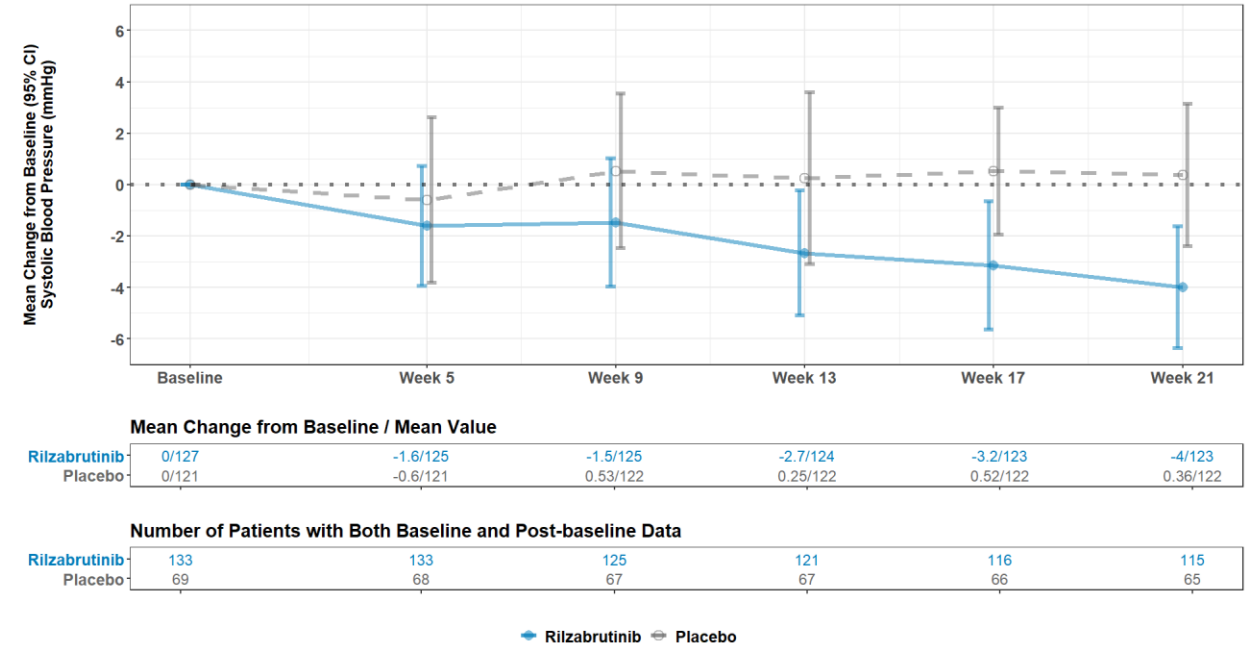
Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2021).
Duration is the 24-week double-blind treatment period.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants meeting criteria; NA, not available; N_w, number of participants with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells

17.2.5. Vital Signs Analyses

17.2.5.1. Change Over Time From Baseline

17.2.5.1.1. Systolic Blood Pressure

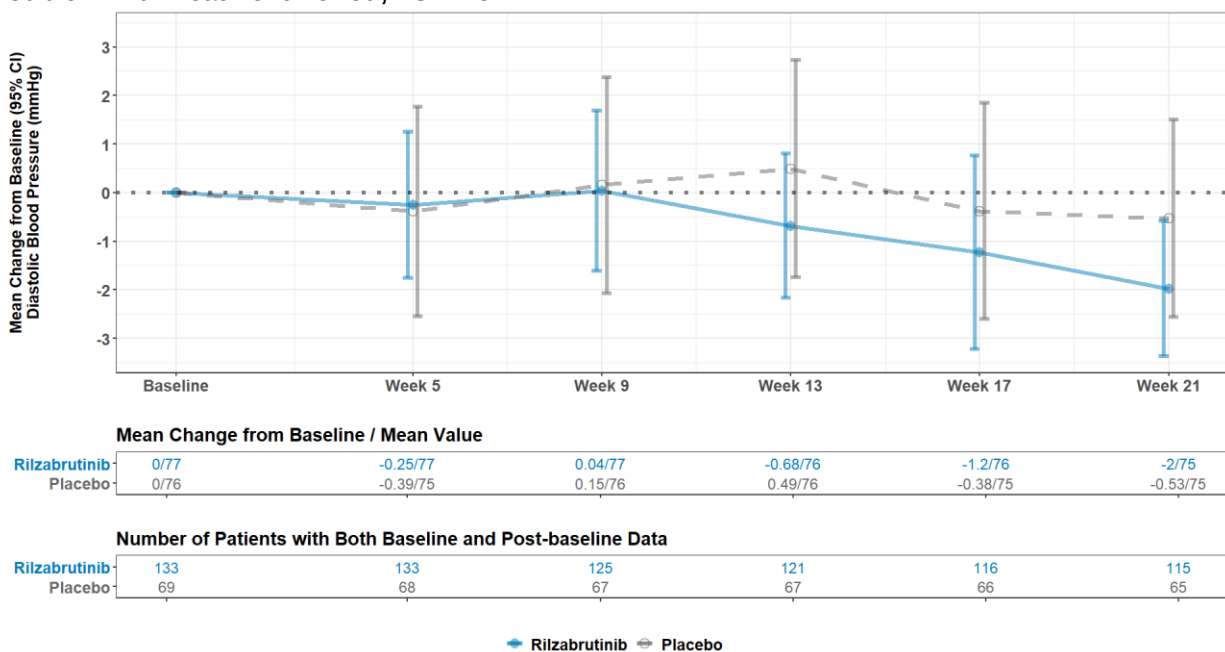
Figure 43. Mean Systolic Blood Pressure Change From Baseline Over Time by Treatment Arm, Double-Blind Treatment Period, LUNA 3



Source: advs.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Abbreviation: CI, confidence interval

17.2.5.1.2. Diastolic Blood Pressure

Figure 44. Mean Diastolic Blood Pressure Change From Baseline Over Time by Treatment Arm, Double-Blind Treatment Period, LUNA 3



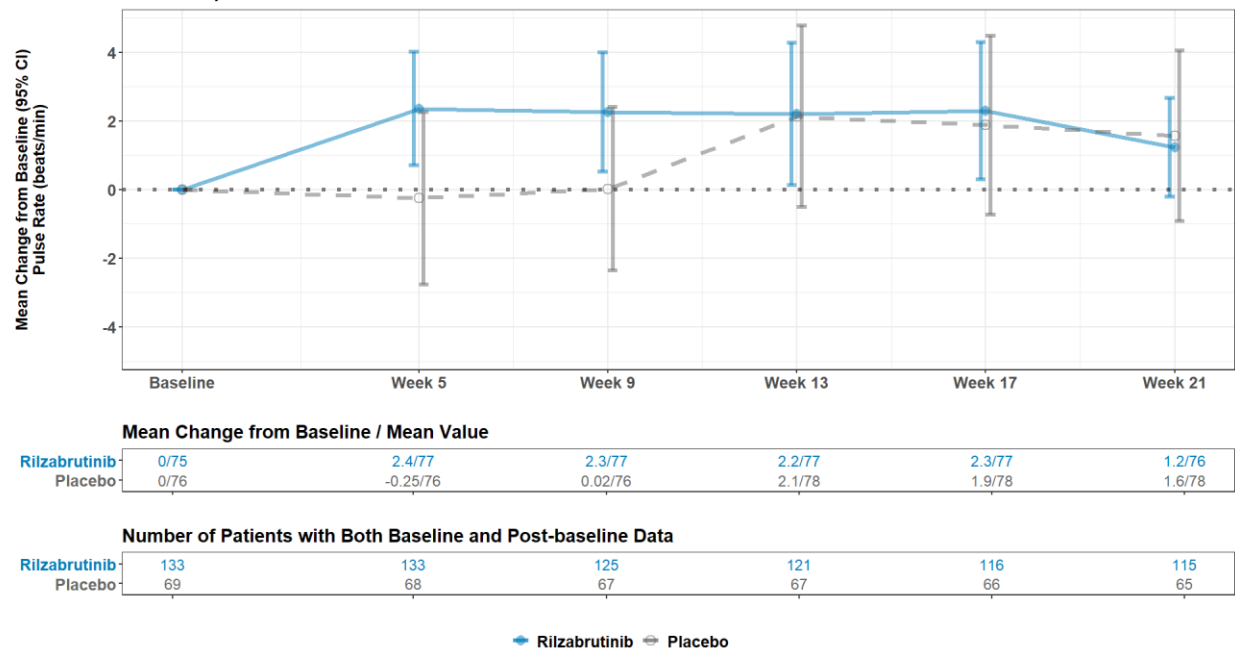
Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.

Abbreviation: CI, confidence interval

17.2.5.1.3. Pulse Rate

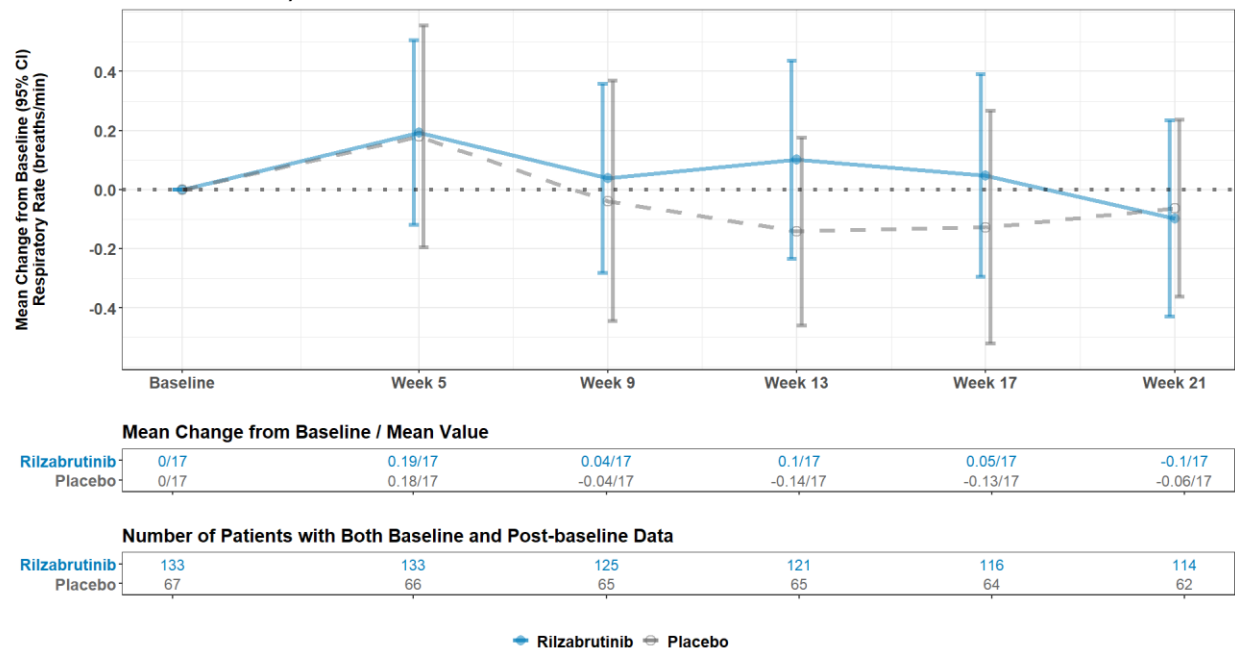
Figure 45. Mean Pulse Rate Change From Baseline Over Time by Treatment Arm, Double-Blind Treatment Period, LUNA 3



Source: advs.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Abbreviation: CI, confidence interval

17.2.5.1.4. Respiratory Rate

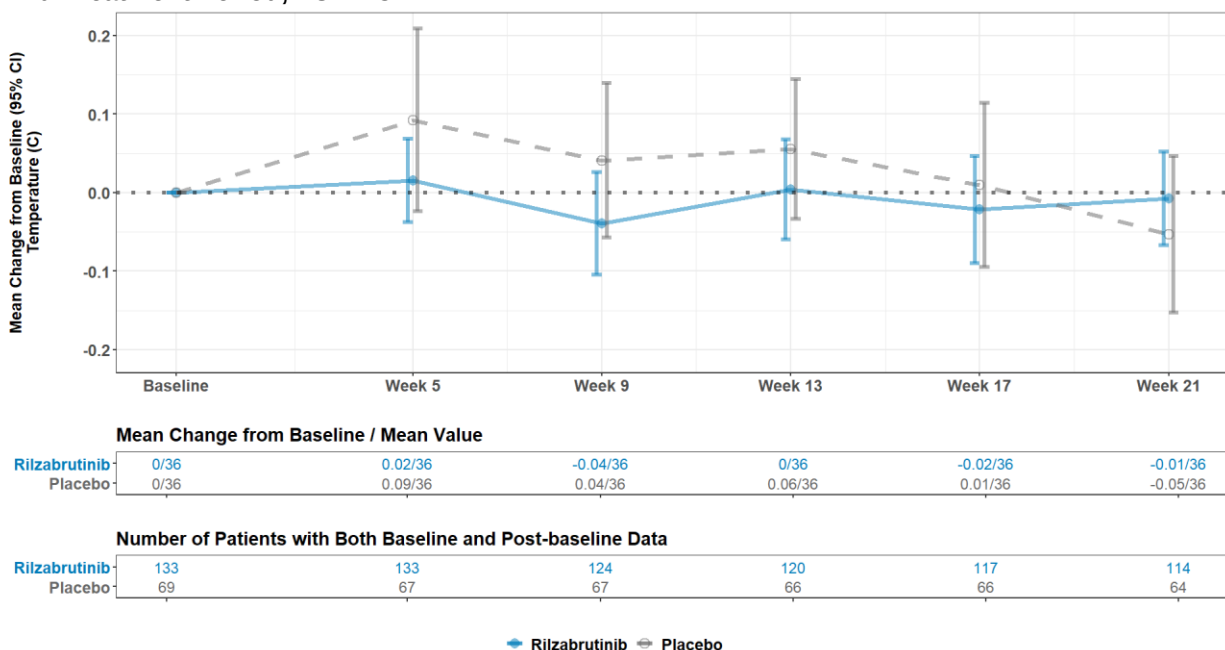
Figure 46. Mean Respiratory Rate Change From Baseline Over Time by Treatment Arm, Double-Blind Treatment Period, LUNA 3



Source: advs.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Abbreviation: CI, confidence interval

17.2.5.1.5. Body Temperature

Figure 47. Mean Body Temperature Change From Baseline Over Time by Treatment Arm, Double-Blind Treatment Period, LUNA 3



Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.

Abbreviation: CI, confidence interval

17.2.5.2. Outlier Analysis

17.2.5.2.1. Systolic Blood Pressure

Table 128. Percentage of Participants With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Double-Blind Treatment Period, LUNA 3

Systolic Blood Pressure (mm Hg)	Rilzabrutinib N=133 n/N _w (%)	Placebo N=69 n/N _w (%)	Rilzabrutinib vs. Placebo Risk Difference (%) (95% CI)
<90	0/133 (0)	0/68 (0)	0.0 (-5.4, 2.8)
≥90	133/133 (100)	68/68 (100)	0.0 (-2.8, 5.4)
≥120	114/133 (85.7)	49/68 (72.1)	13.7 (2.1, 26.5) *
≥140	34/133 (25.6)	14/68 (20.6)	5.0 (-8.0, 16.5)
≥160	5/133 (3.8)	1/68 (1.5)	2.3 (-4.4, 7.3)
≥180	1/133 (0.8)	0/68 (0)	0.8 (-4.6, 4.1)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data

17.2.5.2.2. Diastolic Blood Pressure

Table 129. Percentage of Participants With Maximum Diastolic Blood Pressure by Category of Postbaseline Blood Pressure, Double-Blind Treatment Period, LUNA 3

Diastolic Blood Pressure (mm Hg)	Rilzabrutinib N=133 n/N_w (%)	Placebo N=69 n/N_w (%)	Risk Difference % (95% CI)
<60	1/133 (0.8)	1/68 (1.5)	-0.7 (-7.2, 2.9)
≥60	132/133 (99.2)	67/68 (98.5)	0.7 (-2.9, 7.2)
≥90	27/133 (20.3)	11/68 (16.2)	4.1 (-8.0, 14.6)
≥110	0/133 (0)	0/68 (0)	0.0 (-5.4, 2.8)
≥120	0/133 (0)	0/68 (0)	0.0 (-5.4, 2.8)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data

17.2.5.2.3. Hypotension Levels

Table 130. Percentage of Participants Meeting Specific Postbaseline Hypotension Levels, Double-Blind Treatment Period, LUNA 3

Blood Pressure (mm Hg)	Rilzabrutinib N=133 n/N_w (%)	Placebo N=69 n/N_w (%)	Risk Difference % (95% CI)
SBP <90	2/133 (1.5)	1/68 (1.5)	0.0 (-6.5, 4.1)
DBP <60	12/133 (9.0)	3/68 (4.4)	4.6 (-3.9, 11.6)

Source: advs.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; SBP, systolic blood pressure

18. Clinical Virology

Not Applicable.

19. Clinical Microbiology

Not Applicable.

20. Mechanism of Action/Drug Resistance

Not Applicable.

21. Other Drug Development Considerations

Not Applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

A clinical inspection summary was completed by the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations with a signature date of May 27, 2025, with amended signature on July 31, 2025. Three clinical investigator inspections were completed for the study: Lei Zhang, M.D., Howard Liebman, M.D., and Wojciech Homenda, M.D. An inspection of the Contract Research Organization, (b) (4), was also completed. Based on the results of the inspections, the study data derived from the above inspected clinical investigator sites are considered acceptable. The Contract Research Organization's monitoring for the study appears adequate. In general, the clinical data submitted to the Agency for assessment appear to be acceptable in support of the proposed indication.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI ([Table 131](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 131. Key Labeling Changes and Considerations

(b) (4)



23.1. Approved Labeling Types

Upon approval of this [application/efficacy supplement], the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Package Insert

24. Postmarketing Requirements and Commitments

PMR 1

Conduct a clinical drug interaction study to evaluate the effect of WAYRILZ (rilzabrutinib) on the pharmacokinetics of P-gp, BCRP, OATP1B1, and OATP1B3 transporter substrates in adult healthy volunteers. The study will assess the magnitude of exposure change of the transporter substrates and inform appropriate drug interaction management strategy for coadministration of rilzabrutinib with these transporter substrates in adult patients with persistent or chronic immune thrombocytopenia. This study should be designed and conducted in accordance with the ICH guidance for industry *M12 Drug Interaction Studies* ([August 2024](#)).

PMR 2

Conduct a dedicated renal impairment study to evaluate the effect of severe renal impairment (eGFR <30 mL/min) on WAYRILZ (rilzabrutinib) pharmacokinetics compared to subjects with normal renal function. The study will assess the magnitude of exposure change of rilzabrutinib and inform appropriate dosing instructions for patients with severe renal impairment. This study should be designed and conducted in accordance with guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* ([July 2024](#)).

PMR 3

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to WAYRILZ (rilzabrutinib) during pregnancy to assess the risk of pregnancy and maternal complications and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

PMR 4

Perform a milk-only lactation study in lactating women who have received rilzabrutinib to measure concentrations of WAYRILZ (rilzabrutinib) in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

25. Financial Disclosure

Covered studies were LUNA 3 (PRN1008-018) and PRN1008-010 (Parts A and B). Financial disclosure information is provided for each of these studies in the tables below.

Table 132. Study PRN1008-018, LUNA 3

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: LUNA 3 Sites where participants were screened: Primary Investigators, 95; Subinvestigators, 548; Total: 643 Sites where no participants were screened: Investigators (nonspecified), 217		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Four investigators have disclosable financial interests/arrangements. In addition, while Sanofi was the Sponsor, updated financial disclosure information was not obtained for 158 investigators due to investigator leaving study site or site was closed before collection of updated form commenced (155), personal leave (2), or death of investigator (1).		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator: none Sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 158		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

Table 133. Study PRN1008-010, LUNA 2, Parts A and B

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: LUNA 2- Part A Sites where participants were screened: Primary Investigators, 24; Subinvestigators, 78; Total: 102 Sites where no participants screened: Investigators (nonspecified), 10 LUNA 2- Part B Sites where participants were screened: Primary Investigators, 17; Total: 17 Sites where no participants screened: Investigators (nonspecified), 10 Note: Some clinical investigators participated in several studies.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Five investigators have disclosable financial interests/arrangements. Of these five, two investigators did not acknowledge the amounts reported by the Sponsor during the covered period referenced. In addition, the Applicant reports initial (Principia Biopharma as the Sponsor) financial disclosure information was not obtained despite at least two attempts for six subinvestigators; all left clinical study sites prior to obtaining the required initial disclosure information. Under Sanofi sponsorship, 42 investigators were missing updated forms listing Sanofi as the Sponsor due to: investigators left the site before collection of updated forms occurred, sites closed before collection of updated forms started, personal leave, one investigator death.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator: none Sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 6		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Applicant Responses

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Electronic Book

NIDDK, 2012, LiverTox: Clinical and Research Information on Drug-Induced Liver Injury, Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases.

FDA Guidance Documents

NDA 219685
WAYRILZ (rilzabrutinib)

FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (August 2018), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products>.

FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (January 2020), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products>.

FDA guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* (July 2024), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing>.

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27. Review Team

Table 134. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Rolanda Bailey
Nonclinical reviewer(s)	Fred Alavi, C.M. Sabbir Ahmed
Nonclinical team leader	Pedro DelValle
OCP reviewer	Hebing Liu
OCP team leader	Sudharshan Hariharan
Clinical reviewer	Kristen Snyder
Clinical team leader	Margaret Thompson
Biometrics reviewer	Xiaoyan Yin
Biometrics team leader	Yeh-Fong Chen
Cross-discipline team leader	Margaret Thompson
Associate Director of Labeling	Virginia Kwitkowski
Deputy Director of Safety	Rosanna Setse
Division director (pharm/tox)	Calvin "Lee" Elmore
Division director (OCP)	Jayabharathi Vaidyanathan
Division director (OB)	Yuan Shen
Deputy Division director (clinical)	Tanya Wroblewski
Office director (or designated signatory authority)	Lisa Yanoff

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 135. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	DP Reviewers: Rao Kamphampati, Ted Carver (ATL) RBPM: Mickee Aguirre DS Reviewers: Daniel Jansen (Primary), Zhengfu Wang (Secondary) OPMA: Liya Tang, Feiyan Jin Biopharm: Kamrun Nahar, Tapash Ghosh Supervisor/BC: Mohan Sapru
Microbiology	
OPDP	Melissa Khashei, Jina Kwak
OSI	Anthony Orenca, Min Liu
OSE/DEPI	Kate Gelperin, Steve Bird
OSE/DMEPA	Sue Black, Nicole Iverson
OSE/DRM	Jacqueline Sheppard, Carla Darling
OSE/DPV	Mallika Mundkur, Sarah Kang
DPMH	Kerry Shaab, Tamara Johnson, Kerri-Ann Jennings, Rosemary Addy
DCOA	Sarah Rosenberg, Onyekachukwu Illoh, Selena Daniels
OCP - Pharmacometrics	Hui Wei, Vishnu Sharma (Secondary)
OCP - PBPK	Ying-Hong Wang, Yuching Yang (Secondary)
CDS	Zachary Osking, Qunshu Zhang

Abbreviations: CDS, clinical decision support; DCOA, Division of Clinical Outcome Assessment; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatrics and Maternal Health; DPV, Division of Pharmacovigilance; DRISK, Division of Risk Management; DRM, Division of Risk Management; OCP, Office of Clinical Pharmacology; OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; PBPK, Physiologically based pharmacokinetics

27.1. Reviewer Signatures

Table 27-136 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Virginia Kwitkowski Digitally signed by Virginia Kwitkowski Date: 8/29/2025 1:58 PM EDT GUID: 2025829175851				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Virginia Kwitkowski Digitally signed by Virginia Kwitkowski Date: 8/29/2025 1:59 PM EDT GUID: 2025829175918				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Hui Wei OCP DPM	Sections: section 6 and 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hui Wei Digitally signed by Hui Wei Date: 8/29/2025 2:00 PM EDT GUID: 202582918030				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Hebing Liu OCP DCEP	Sections: 5,6,8,14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hebing Liu Digitally signed by Hebing Liu Date: 8/29/2025 2:03 PM EDT GUID: 20258291834				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Kristen Snyder OCHEN DNH	Sections: 2, 3, 6, 7, 8, 10, 11, 12, 15, 17, 22, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kristen Snyder Digitally signed by Kristen Snyder Date: 8/29/2025 2:04 PM EDT GUID: 202582918442				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non- clinical Discipline Tertiary Reviewer	Calvin Elmore OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13.1-2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Calvin Elmore Digitally signed by Calvin Elmore Date: 8/29/2025 2:05 PM EDT GUID: 20258291856				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Yeh Fong Chen OB DBIX	Sections: 6, 15 and 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yeh Fong Chen		Digitally signed by Yeh Fong Chen Date: 8/29/2025 2:13 PM EDT GUID: 2025829181322		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Xiaoyan Yin OB DBIX	Sections: 6,15,16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Xiaoyan Yin		Digitally signed by Xiaoyan Yin Date: 8/29/2025 2:15 PM EDT GUID: 2025829181538		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Xiaoyan Yin OB DBIX	Sections: 6,15,16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Xiaoyan Yin Digitally signed by Xiaoyan Yin Date: 8/29/2025 2:16 PM EDT GUID: 2025829181640				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Margaret Thompson OCHEN DNH	Sections: 1,2,3,4,6.2, 6.3, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 10, 11, 12, 15, 16, 17, 18, 22, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Margaret Thompson Digitally signed by Margaret Thompson Date: 8/29/2025 2:19 PM EDT GUID: 2025829181920				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Rolanda Bailey ORO DROCHEN	Sections: 12	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Rolanda Bailey		Digitally signed by Rolanda Bailey Date: 8/29/2025 2:21 PM EDT GUID: 2025829182118		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Jayabharathi Vaidyanathan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jayabharathi Vaidyanathan		Digitally signed by Jayabharathi Vaidyanathan Date: 8/29/2025 2:23 PM EDT GUID: 2025829182346		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Sudharshan Hariharan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2,14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Yuan Shen OB DBIX	Sections: 6, 15,16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Ying-Hong Wang OCP DPM	Sections: 14.5.3	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline CPMS	Rolanda Bailey ORO DROCHEN	Sections: 12	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Pedro Delvalle OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	C M Sabbir Ahmed OCHEN DPTCHEN	Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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NDA 219685
WAYRILZ (rilzabrutinib)

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	C M Sabbir Ahmed OCHEN DPTCHEN	Sections: 5, 7, 8, and 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: C M Sabbir Ahmed Digitally signed by C M Sabbir Ahmed Date: 8/29/2025 2:58 PM EDT GUID: 2025829185848				

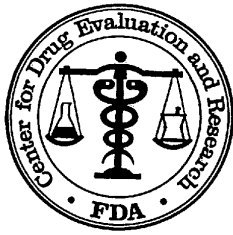
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Translational Sciences

Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number: NDA219685

Drug Name: rilzabrutinib (PRN1008)

Indication: Treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment.

Applicant: Genzyme Corporation

Test Facility for Rats Study: (b) (4)
(b) (4)
(b) (4)

Test Facility for Mice Study: (b) (4)
(b) (4)
(b) (4)

Documents Reviewed: Study reports and electronic data submitted on 08/29/2024 via NDA219685/0001

Biometrics Division: Division of Biometrics -6

Statistical Reviewer: Zhuang Miao, Ph.D.

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Keywords: Carcinogenicity, Dose response

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1. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of PRN1008, when administered via oral gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study:

Survival data analyses:

1. For male rats, the survival analyses did not show any statistically significant dose response relationship in mortality across the vehicle control group and the treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and any of the treated groups.
2. For female rats, the survival analyses did not show any statistically significant dose response relationship in mortality across the vehicle control group and the treated groups. However, p-value of the likelihood ratio test is $0.0295 < 0.05$ but the p-value of log-rank test is $0.1518 > 0.05$. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and any of the treated groups.

Tumor data analysis:

1. For female rats, the tumor data analysis showed statistically significant positive dose response relationships across the vehicle control and the treated groups in the incidence of adenoma, adrenocortical benign, gland adrenal (P-value= $0.0139 < 0.025$).
2. For female rats, the pairwise comparisons between the vehicle control and the medium dose group showed statistically significant increases in the incidence of carcinoma, follicular cell, malignant, gland thyroid (P-value= $0.0076 < 0.01$).

Mouse Study:

Survival data analyses:

1. The survival analyses did not show any statistically significant dose response relationship in mortality across the vehicle control group and the treated groups in

either male or female mice. The pairwise comparisons did not show statistically significant difference in mortality between the vehicle control group and any of the treated groups in either male or female mice.

2. The pairwise comparisons showed statistically significant increase in mortality in the positive control group than the vehicle control group male mice.

Tumor data analysis:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in the incidences of adenoma, benign, Lung (p-value<0.001) and carcinoma, malignant, Lung (p-value=0.0011 <0.05), hemangiosarcoma, malignant, Spleen (p-value<0.001), and combined tumors of hemangiosarcoma, whole body (p-value<0.001).
2. For female mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in the incidences of adenoma, benign, Lung (p-value<0.001) and carcinoma, malignant, Lung (p-value=<0.001), hemangiosarcoma, malignant, Spleen (p-value<0.001), and combined tumors of hemangiosarcoma, whole body (p-value<0.001).

2. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of PRN1008, when administered via oral gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases.

3. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and forty rats of each sex were randomly assigned to the four groups in equal size of 60 rats per group. The dose levels for treated groups were 10, 30 and 100 mg/kg/day for males and 5, 15 and 50 mg/kg/day for females. The study for the rats was designed to continue for up to 104 weeks.

Table 1: Study Design in Rat Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Vehicle	60	60
2	10/5	Low	60	60
3	30/15	Mid	60	60
4	100/50	High	60	60

3.1. Sponsor's analyses

3.1.1. Survival analysis

Kaplan-Meier estimates of group survival rates were calculated and shown graphically. A log-rank dose response trend test of survival rates was performed utilizing ordinal coefficients. In addition, a log-rank test for survival was used to make pair-wise comparisons of each treated group with the control group. Both the trend test and pair-wise comparisons were conducted

at the 0.05 significance level. Survival times in which the status of the animal's death is classified as an accidental death or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings: Sponsor's analysis showed the numbers (percents) of survival as 38 (63%), 46 (77%), 43 (72%), and 34 (57%) in vehicle, low, mid, high dose groups, respectively in males and 37 (62%), 35 (58%), 34 (57%), and 27 (45%) in vehicle, low, mid, high dose groups, respectively in females.

There were no statistically significant findings in survival rates when comparing active treatment groups with the control group

3.1.2. Tumor data analysis

The incidence of tumors was analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the context (incidental, fatal, or mortality independent) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: weeks 1-50, 51-80, 81-end of study (up to the initiation of terminal sacrifice), and scheduled terminal sacrifice.

Tumors classified as mortality-independent were analyzed with Peto's mortality-independent method incorporating the day of detection. Each diagnosed tumor type was analyzed separately. All metastases and invasive tumors were considered secondary and not included in the statistical analysis.

Each tumor type was analyzed with a 1-sided trend test using ordinal coefficients. In addition, pair-wise comparisons with the control group were conducted for each active treatment group. An exact permutation test was conducted for analyses with low tumor incidence.

Statistical significance was determined according to the following guidelines: trend tests were conducted at the 0.01 and 0.05 significance levels for common and rare tumors,

respectively. Pair-wise comparisons with the control group were conducted at the 0.05 significance level for both common and rare tumors. A rare tumor was defined as one in which the spontaneous tumor rate was less than 1%. The spontaneous tumor rate was determined based on the concurrent control groups and historical control data of the conducting laboratory and animal supplier.

Sponsor's findings:

1. For males, the tumor incidence of the granular cell tumor, benign in the brain was 0, 0, 4 and 2 for the vehicle, 10, 30 and 100 mg/kg/day treatment groups, respectively. The tumor was considered rare and the pairwise comparison of the 30 mg/kg/day group with the vehicle group was statistically significant (pvalue = 0.0498). In addition, the trend test across dose groups was statistically significant (p-value = 0.0363). No other pairwise comparisons were statistically significant.
2. For females, the tumor incidence of the adenoma, adrenocortical, benign in the adrenal gland was 0, 0, 1 and 3 for the vehicle, 5, 15 and 50 mg/kg/day treatment groups, respectively. The tumor was considered rare and the trend test across groups was statistically significant (p-value = 0.0339). None of the pairwise comparisons were statistically significant.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses.

3.2.1. Survival analysis

The survival distributions of animals in four groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested for the, vehicle control, low, medium and high dose groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 7 and 8 in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1 and 2 in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 9 to 10 in the appendix for males and females, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of survival were 31 (52%), 37 (62%), 35 (58%), and 31 (52%) in vehicle, and low, mid, high dose groups, respectively in males and 37 (62%), 32 (53%), 29 (48%), and 24 (40%) in vehicle, and low, mid, high dose groups, respectively in females.

Note that there is a discrepancy between the reviewer's survival rate and the sponsor's survival rate. The reason is that there were missing rats in the sponsor's data. The total number of rats in each of the groups were 52, 51, 51, 56 for males and 58, 56, 54, 53 for females.

For male rats, the survival analyses did not show any statistically significant dose response relationship in mortality across the vehicle control group and the treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and any of the treated groups.

For female rats, the survival analyses did not show any statistically significant dose response relationship in mortality across the vehicle control group and the treated groups. However, p-value of the likelihood ratio test is $0.0295 < 0.05$ but the p-value of log-rank test is $0.1518 > 0.05$. We consider the test results as a positive finding when both p-values are less than 0.05. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and any of the treated groups.

3.2.2. Tumor data analysis

The tumor data were analyzed for the positive dose response relationships and the pairwise comparison between each of the treated groups with control group. Both the dose response relationship tests and the pairwise comparisons were performed using the Poly-K method, described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $S_h = 1$. An animal that dies at week w_h without a tumor before the end of the study gets a score of $S_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted

group size is defined as $\sum S_h$. As an interpretation, an animal with score $S_h = 1$ can be considered as a whole animal while an animal with score $S_h < 1$ can be considered as a partial animal. The adjusted group size $\sum S_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes were then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons are listed in Tables 11 and 12 in the appendix for male and female rats, respectively.

Adjustment for multiple testing: For the chronic study in rats, the adjustment of multiple testing of the dose response relationship for a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for the chronic rat study. For pairwise comparisons for the chronic rat study in the above type of submission with one chronic rat study and one transgenic mouse study, the same guidance document suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for the chronic rat study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Tables 2 and 3 below show the p-values less than or equal to 0.05 for the positive dose response and the pairwise comparisons between vehicle control and treated groups for males.

Based on the criteria of adjustment for multiple testing discussed in the data analysis section, we make the following statistical conclusions:

1. For female rats, the tumor data analysis showed statistically significant positive dose response relationships across the vehicle control and the treated groups in the incidences of adenoma, adrenocortical benign, gland adrenal (P-value=0.0139<0.025).
2. For female rats, the pairwise comparisons between the vehicle control and the medium dose group showed statistically significant increases in incidences of carcinoma, follicular cell, malignant, gland thyroid (P-value=0.0076<0.01).

Table 2: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and the Treated Groups -Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=52) P-value - Trend	10 mg/kg/day Low (N=51) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=51) P-value - Vehicle vs. Med	100 mg/kg/day High (N=56) P-value - Vehicle vs. High
GLAND, THYROID	ADENOMA, FOLLICULAR CELL, BENIGN	7/52 (47) 0.0208	9/51 (45) 0.3554	8/51 (43) 0.4244	16/56 (50) 0.0399
PANCREAS	ACINAR-ISLET CELL TUMOR, BENIGN	1/51 (45) 0.0071	3/51 (44) 0.2997	0/50 (42) 1.0000	7/56 (46) 0.0314
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

Table 3: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and the Treated Groups -Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=58) P-value - Trend	5 mg/kg/day Low (N=56) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=54) P-value - Vehicle vs. Med	50 mg/kg/day High (N=53) P-value - Vehicle vs. High
GLAND, ADRENAL	ADENOMA, ADRENOCORTICAL, BENIGN	0/58 (47) 0.0139	0/56 (47) NC	1/53 (42) 0.4719	3/53 (41) 0.0971
GLAND, THYROID	CARCINOMA, FOLLICULAR CELL, MALIGNANT	2/58 (47) 0.1200	2/55 (47) 0.6916	10/54 (42) 0.0076	5/53 (41) 0.1644
LYMPH NODE, MESENT	HEMANGIOSARCOMA, MALIGNANT	0/58 (47) 0.0496	0/56 (47) NC	1/54 (42) 0.4719	2/53 (41) 0.2142

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=58) P-value - Trend	5 mg/kg/day Low (N=56) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=54) P-value - Vehicle vs. Med	50 mg/kg/day High (N=53) P-value - Vehicle vs. High
UTERUS	ADENOCARCINOMA, MALIGNANT	1/58 (47) 0.0139	3/56 (47) 0.3084	1/54 (42) 0.7240	6/53 (41) 0.0368
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

4. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group and one positive control group. One hundred and ten mice of each sex were randomly assigned to the treated and control groups. There were 25 mice in each of the vehicle control group and treated groups. The dose levels for treated groups were 30, 100, and 300 mg/kg/day for both males and females. There were ten mice in positive control group for each sex. Animals in positive control group were administered urethane on Days 1, 3, and 5

Table 4: Study Design in Mouse Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Vehicle	25	25
2	30	Low	25	25
3	100	Mid	25	25
4	300	High	25	25
5	1000	Positive	10	10

4.1. Sponsor's analyses

4.1.1. Survival analysis

Kaplan-Meier estimates of the group survival rates were calculated and shown graphically.

For Groups 1-4, a log-rank test for survival was used to compare the homogeneity of survival rates across the groups. If the survival rates are significantly different, a log-rank test was used to make pairwise comparisons of each treated group with the vehicle control group. In addition, Group 5 (positive control) was compared to the vehicle control group with a log-rank test. All tests were conducted at the 0.05 significance level.

Survival times in which the status of the animal's death is classified as an accidental death or terminal euthanasia were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings: The sponsor's analysis showed that the numbers (percents) of survival were 25 (100%), 24 (96%), 24 (96%), 25 (100%), and 5 (50%) in male mice, and 22 (88%), 24 (96%), 25 (100%), 23 (92%) and 9 (90%) in female mice in vehicle control, low, medium, high and positive control, respectively.

The sponsor concluded that, there were no statistically findings in survival rates when comparing test article groups with the vehicle control group. Among males, the survival rate in the positive control group was significantly lower when compared with the vehicle control group.

4.1.2. Tumor data analysis

For Groups 1-4, the incidence of tumors was analyzed by Peto's mortality prevalence method, without continuity correction, and incorporating the context (incidental, fatal, or mortality-independent) in which tumors were observed. Among males, one 30/mg/kg/day and one 100 mg/kg/day animal did not complete the study through the scheduled terminal sacrifice. Among females, three vehicle control, one 30/mg/kg/day and two 300 mg/kg/day animals did not complete the study through the scheduled terminal sacrifice. Because so few animals died during the study and, with the exception of one female vehicle control animal that died on day 55 with a multicentric lymphoma, all animals were at risk for at least 134 days, the fixed interval used for incidental tumor analysis was Days 1-end of study including scheduled terminal sacrifice. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis.

Tumors classified as mortality-independent were analyzed with Peto's mortality independent method incorporating the day of detection.

Each tumor type was analyzed with a 1-sided trend test using ordinal coefficients. In addition, pairwise comparisons with the vehicle control group were conducted for each active treatment group. An exact permutation test was conducted for analyses with low tumor incidence.

Incidence of tumors in the positive control group (Group 5) were compared to vehicle control group (Group 1) with Fisher's exact test. All tests were conducted at the 0.05 significance level.

Sponsor's findings: The sponsor concluded that there were no statistically significant tumor findings in the test article groups when compared to the vehicle control group.

There was a statistically significant increase in the following tumors when comparing the positive control group with the vehicle control group:

Sex	Organ	Tumor
M	LUNG	ADENOMA
		CARCINOMA
		CARCINOMA/ADENOMA
	SPLEEN	HEMANGIOSARCOMA
	WHOLE BODY	HEMANGIOSARCOMA
F	LUNG	ADENOMA
		CARCINOMA
		CARCINOMA/ADENOMA
	SPLEEN	HEMANGIOSARCOMA
	WHOLE BODY	HEMANGIOSARCOMA

4.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses.

4.2.1. Survival analysis

The survival distributions of three treated groups, one vehical control group, and one positive control group were estimated using the Kaplan-Meier product limit method. The dose response relationship in survival was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 3 and 4 in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 13 and 14 in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals among the water control, vehicle control, positive control and the

treated groups are given in Tables 15 to 16 in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed that the numbers (percents) of survival were 25 (100%), 24 (96%), 24 (96%), 25 (100%), and 5 (50%) in male mice, and 22 (88%), 24 (96%), 25 (100%), 23 (92%) and 9 (90%) in female mice in vehicle control, low, medium, high and positive control, respectively.

The survival analyses did not show any statistically significant dose response relationship in mortality across the vehicle control group and the treated groups in either male or female. The pairwise comparisons did not show statistically significant difference in mortality between the vehicle control group and any of the treated groups in either male or female mice.

The pairwise comparisons showed statistically significant increase in mortality in the positive control group in male mice compared to the vehicle control group.

4.2.2. Tumor data analysis

The reviewer used the same tumor data analysis methods for the mouse study as was used for rat study.

The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons between vehicle control and the treated groups, and between vehicle and positive control are listed in Tables 17 to 20 in the appendix for male and female mice, respectively.

Adjustment for multiple testing: For the adjustment of multiple testing of the dose response relationship for a submission with one 2 year chronic rat study and one 26 week mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.05$ for both common tumors and rare tumors for the mouse study. For pairwise, the same guidance document suggests the use of test levels $\alpha = 0.05$ for both common tumors and rare tumors for the mouse study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Tables 5 and 6 below showed p-values less than or equal to 0.05 in the tests between vehicle control and positive group.

Based on the criteria of adjustment for multiple testing discussed in the mouse data analysis section, we make the following statistical conclusions:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increase in the incidences of adenoma, benign, Lung (p-value<0.001) and carcinoma, malignant, Lung (p-value=0.0011 <0.05), hemangiosarcoma, malignant, Spleen (p-value<0.001), and combined tumors of hemangiosarcoma, whole body (p-value<0.001).
2. For female mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increase in incidences of adenoma, benign, Lung (p-value<0.001) and carcinoma, malignant, Lung (p-value=<0.001), hemangiosarcoma, malignant, Spleen (p-value<0.001), and combined tumors of hemangiosarcoma, whole body (p-value<0.001).

Table 5: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Positive Control -Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	300 mg/kg/day Positive (N=10) P-value - Vehicle vs. Positive
LUNG	ADENOMA, BENIGN	0/25 (25)	7/10 (8) <0.001
	CARCINOMA, MALIGNANT	0/25 (25)	3/10 (4) 0.0011
SPLEEN	HEMANGIOSARCOMA, MALIGNANT	0/25 (25)	7/10 (8) <0.001
Whold Body	C_Hemangiosarcoma	0/25 (25)	7/10 (8) <0.001

Table 6: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Positive Control -Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	300 mg/kg/day Positive (N=10) P-value - Vehicle vs. Positive
LUNG	ADENOMA, BENIGN	0/25 (24)	8/10 (8) <0.001
	CARCINOMA, MALIGNANT	0/25 (24)	7/10 (8) <0.001
SPLEEN	HEMANGIOSARCOMA, MALIGNANT	0/25 (24)	8/10 (8) <0.001
Whold Body	C_Hemangiosarcoma	2/25 (24)	8/10 (8) <0.001

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5. Appendix

Table 7: Intercurrent Mortality Rate -Male Rats

	0 mg/kg/day Vehicle (N=52)		10 mg/kg/day Low (N=51)		30 mg/kg/day Med (N=51)		100 mg/kg/day High (N=56)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	1	1.67	1	1.67	2	3.33	2	3.33
53 - 78	2	5.00	4	8.33	4	10.00	4	10.00
79 - 91	4	11.67	6	18.33	4	16.67	8	23.33
92 - 104	14	35.00	3	23.33	6	26.67	11	41.67
Ter. Sac.	31	51.67	37	61.67	35	58.33	31	51.67

Cum. %: Cumulative percentage except for Ter. Sac.

Table 8: Intercurrent Mortality Rate -Female Rats

	0 mg/kg/day Vehicle (N=58)		5 mg/kg/day Low (N=56)		15 mg/kg/day Med (N=54)		50 mg/kg/day High (N=53)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	3	5.00	.	.	3	5.00	2	3.33
53 - 78	9	20.00	6	10.00	9	20.00	5	11.67
79 - 91	2	23.33	4	16.67	2	23.33	10	28.33
92 - 104	7	35.00	14	40.00	11	41.67	12	48.33
Ter. Sac.	37	61.67	32	53.33	29	48.33	24	40.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 9: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Male Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.2613	0.1971	0.5342	0.6563
Homogeneity	Log-Rank	0.3659	0.1987	0.5333	0.6549

Table 10: Intercurrent Mortality Comparison between Treated Groups and Vehicle

Control - Female Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.0295	0.9245	0.6760	0.0567
Homogeneity	Log-Rank	0.1518	0.9240	0.6731	0.0540

Table 11: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Control and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=52) P-value - Trend	10 mg/kg/day Low (N=51) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=51) P-value - Vehicle vs. Med	100 mg/kg/day High (N=56) P-value - Vehicle vs. High
BONE	OSTEOSARCOMA, MALIGNANT	0/52 (46) 0.2570	0/51 (44) NC	0/51 (43) NC	1/56 (46) 0.5000
BONE MARROW, STERN	SARCOMA, HISTIOCYTIC, MALIGNANT	0/52 (46) 0.7444	1/51 (45) 0.4945	0/51 (43) NC	0/56 (46) NC
BRAIN	CARCINOMA, BASAL CELL, MALIGNANT	0/52 (46) 0.7430	1/51 (44) 0.4889	0/51 (43) NC	0/56 (46) NC
	GRANULAR CELL TUMOR, BENIGN	0/52 (46) 0.1570	0/51 (44) NC	4/51 (44) 0.0531	2/56 (46) 0.2473
	GRANULAR CELL TUMOR, MALIGNANT	0/52 (46) 0.2611	0/51 (44) NC	0/51 (43) NC	1/56 (47) 0.5054
	SARCOMA, HISTIOCYTIC, MALIGNANT	0/52 (46) 0.7444	1/51 (45) 0.4945	0/51 (43) NC	0/56 (46) NC
	SCHWANNOMA, MALIGNANT	0/52 (46) 0.7444	1/51 (45) 0.4945	0/51 (43) NC	0/56 (46) NC
EAR	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/52 (46) 0.2570	0/51 (44) NC	0/51 (43) NC	1/56 (46) 0.5000
EPIDIDYMIS	MESOTHELIOMA, MALIGNANT	1/51 (45) 0.1778	0/51 (44) 1.0000	2/51 (43) 0.4828	2/56 (46) 0.5083
	SCHWANNOMA, MALIGNANT	0/51 (45) 0.7486	1/51 (45) 0.5000	0/51 (43) NC	0/56 (46) NC
EYE	OSTEOSARCOMA, MALIGNANT	0/48 (43) 0.2543	0/49 (43) NC	0/50 (43) NC	1/52 (44) 0.5057
GANGLION	SCHWANNOMA, MALIGNANT	0/52 (46) 0.3203	1/51 (45) 0.4945	0/51 (43) NC	1/56 (47) 0.5054
GLAND, ADRENAL	ADENOMA, ADRENOCORTICAL, BENIGN	2/51 (45) 0.8342	0/51 (44) 1.0000	2/51 (44) 0.6833	0/56 (46) 1.0000
	CARCINOMA, ADRENOCORTICAL, MALIGNANT	0/51 (45) 0.7472	1/51 (44) 0.4944	0/51 (43) NC	0/56 (46) NC
	PHEOCHROMOCYTOMA, BENIGN	2/51 (45) 0.5074	2/51 (44) 0.6833	1/51 (43) 0.8707	2/56 (46) 0.7000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=52) P-value - Trend	10 mg/kg/day Low (N=51) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=51) P-value - Vehicle vs. Med	100 mg/kg/day High (N=56) P-value - Vehicle vs. High
	PHEOCHROMOCYTOMA, MALIGNANT	1/51 (45) 0.4573	0/51 (44) 1.0000	0/51 (43) 1.0000	1/56 (47) 0.7635
GLAND, COAGULATING	PAPILLOMA, SQUAMOUS CELL, BENIGN	0/52 (46) 0.2570	0/51 (44) NC	0/51 (43) NC	1/56 (46) 0.5000
GLAND, MAMMARY	FIBROADENOMA, BENIGN	1/47 (42) 1.0000	0/44 (39) 1.0000	0/42 (36) 1.0000	0/50 (41) 1.0000
	FIBROMA, BENIGN	1/47 (42) 1.0000	0/44 (39) 1.0000	0/42 (36) 1.0000	0/50 (41) 1.0000
GLAND, PARATHYROID	ADENOMA, BENIGN	3/46 (40) 0.7564	1/49 (43) 0.9503	2/45 (39) 0.8127	1/46 (39) 0.9392
	CARCINOMA, C-CELL, MALIGNANT	1/46 (40) 1.0000	0/49 (43) 1.0000	0/45 (39) 1.0000	0/46 (38) 1.0000
GLAND, PITUITARY	ADENOMA, PARS DISTALIS, BENIGN	26/52 (49) 0.9394	20/50 (45) 0.8512	26/51 (49) 0.5801	18/55 (49) 0.9665
	ADENOMA, PARS INTERMEDIA, BENIGN	2/52 (46) 0.6810	1/50 (44) 0.8708	1/51 (43) 0.8663	1/55 (46) 0.8791
	CARCINOMA, PARS DISTALIS, MALIGNANT	0/52 (46) 0.7430	1/50 (44) 0.4889	0/51 (43) NC	0/55 (46) NC
	GANGLIONEUROMA, BENIGN	0/52 (46) 0.2570	0/50 (44) NC	0/51 (43) NC	1/55 (46) 0.5000
	SCHWANNOMA, MALIGNANT	0/52 (46) 0.5000	0/50 (44) NC	1/51 (44) 0.4889	0/55 (46) NC
GLAND, PROSTATE	ADENOMA, BENIGN	2/52 (46) 0.8182	3/51 (44) 0.4787	1/51 (43) 0.8663	1/56 (47) 0.8830
GLAND, SALIVARY, S	SCHWANNOMA, MALIGNANT	0/52 (46) 0.5000	0/51 (44) NC	1/51 (44) 0.4889	0/56 (46) NC
GLAND, THYROID	ADENOMA, C-CELL, BENIGN	3/52 (46) 0.5241	3/51 (44) 0.6401	3/51 (43) 0.6289	3/56 (47) 0.6718
	ADENOMA, FOLLICULAR CELL, BENIGN	7/52 (47) 0.0208	9/51 (45) 0.3554	8/51 (43) 0.4244	16/56 (50) 0.0399
	CARCINOMA, C-CELL, MALIGNANT	3/52 (46) 0.9562	0/51 (44) 1.0000	1/51 (43) 0.9332	0/56 (46) 1.0000
	CARCINOMA, FOLLICULAR CELL, MALIGNANT	7/52 (46) 0.2515	5/51 (45) 0.8124	3/51 (44) 0.9477	8/56 (47) 0.5183
HEART	SARCOMA, HISTIOCYTIC, MALIGNANT	1/52 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
HEMOLYMPHORET ICULA	SARCOMA, HISTIOCYTIC, MALIGNANT	1/52 (46) 0.9159	3/51 (45) 0.3000	1/51 (44) 0.7416	0/56 (46) 1.0000
KIDNEY	LIPOSARCOMA, MALIGNANT	1/52 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
	NEPHROBLASTOMA, MALIGNANT	0/52 (46) 0.5000	0/51 (44) NC	1/51 (44) 0.4889	0/56 (46) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=52) P-value - Trend	10 mg/kg/day Low (N=51) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=51) P-value - Vehicle vs. Med	100 mg/kg/day High (N=56) P-value - Vehicle vs. High
	SARCOMA, HISTIOCYTIC, MALIGNANT	0/52 (46) 0.7444	1/51 (45) 0.4945	0/51 (43) NC	0/56 (46) NC
LIVER	ADENOMA, HEPATOCELLULAR, BENIGN	1/52 (46) 0.7486	0/51 (44) 1.0000	1/51 (43) 0.7357	0/56 (46) 1.0000
	LIPOSARCOMA, MALIGNANT	1/52 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
	SARCOMA, HISTIOCYTIC, MALIGNANT	1/52 (46) 0.9358	1/51 (45) 0.7473	0/51 (43) 1.0000	0/56 (46) 1.0000
	SARCOMA, MALIGNANT	0/52 (46) 0.2611	0/51 (44) NC	0/51 (43) NC	1/56 (47) 0.5054
LUNG	ADENOMA, BRONCHIOLOALVEOLAR, BENIGN	0/52 (46) 0.1926	0/51 (44) NC	1/51 (43) 0.4831	1/56 (47) 0.5054
	CARCINOMA, BASAL CELL, MALIGNANT	0/52 (46) 0.2570	0/51 (44) NC	0/51 (43) NC	1/56 (46) 0.5000
	CARCINOMA, BRONCHIOLOALVEOLAR, MALIGNANT	0/52 (46) 0.7430	1/51 (44) 0.4889	0/51 (43) NC	0/56 (46) NC
	CHORDOMA, MALIGNANT	0/52 (46) 0.7444	1/51 (45) 0.4945	0/51 (43) NC	0/56 (46) NC
	FIBROSARCOMA, MALIGNANT	1/52 (47) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
	SARCOMA, HISTIOCYTIC, MALIGNANT	1/52 (46) 0.9354	2/51 (45) 0.4917	0/51 (43) 1.0000	0/56 (46) 1.0000
	SARCOMA, MALIGNANT	0/52 (46) 0.2611	0/51 (44) NC	0/51 (43) NC	1/56 (47) 0.5054
LYMPH NODE	HEMANGIOSARCOMA, MALIGNANT	1/52 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
LYMPH NODE, CERVIC	HEMANGIOSARCOMA, MALIGNANT	0/52 (46) 0.7430	1/51 (44) 0.4889	0/51 (43) NC	0/56 (46) NC
	SARCOMA, HISTIOCYTIC, MALIGNANT	0/52 (46) 0.7444	1/51 (45) 0.4945	0/51 (43) NC	0/56 (46) NC
	SCHWANNOMA, MALIGNANT	0/52 (46) 0.5000	0/51 (44) NC	1/51 (44) 0.4889	0/56 (46) NC
LYMPH NODE, MESENT	HEMANGIOMA, BENIGN	0/52 (46) 0.1418	3/50 (43) 0.1087	0/51 (43) NC	3/55 (46) 0.1209
	HEMANGIOSARCOMA, MALIGNANT	1/52 (46) 0.1205	1/50 (43) 0.7357	1/51 (43) 0.7357	3/55 (46) 0.3083
	SARCOMA, HISTIOCYTIC, MALIGNANT	1/52 (46) 0.9350	1/50 (44) 0.7416	0/51 (43) 1.0000	0/55 (46) 1.0000
MESENTERY	LIPOMA, BENIGN	1/52 (46) 0.4663	3/51 (44) 0.2916	1/51 (43) 0.7357	2/56 (47) 0.5082

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=52) P-value - Trend	10 mg/kg/day Low (N=51) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=51) P-value - Vehicle vs. Med	100 mg/kg/day High (N=56) P-value - Vehicle vs. High
	LIPOSARCOMA, MALIGNANT	1/52 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
	MESOTHELIOMA, MALIGNANT	0/52 (46) 0.2570	0/51 (44) NC	0/51 (43) NC	1/56 (46) 0.5000
	SARCOMA, MALIGNANT	0/52 (46) 0.2611	0/51 (44) NC	0/51 (43) NC	1/56 (47) 0.5054
	SCHWANNOMA, MALIGNANT	0/52 (46) 0.1119	1/51 (44) 0.4889	0/51 (43) NC	2/56 (46) 0.2473
MUSCLE, BICEPS FEM	RHABDOMYOSARCOMA, MALIGNANT	0/52 (46) 0.5000	0/51 (44) NC	1/51 (44) 0.4889	0/56 (46) NC
NASAL TURBINATE	OSTEOSARCOMA, MALIGNANT	0/52 (46) 0.2570	0/51 (44) NC	0/51 (43) NC	1/56 (46) 0.5000
PANCREAS	ACINAR-ISLET CELL TUMOR, BENIGN	1/51 (45) 0.0071	3/51 (44) 0.2997	0/50 (42) 1.0000	7/56 (46) 0.0314
	ADENOMA, ACINAR CELL, BENIGN	0/51 (45) 0.4972	0/51 (44) NC	1/50 (42) 0.4828	0/56 (46) NC
	ADENOMA, BENIGN	0/51 (45) 0.1905	0/51 (44) NC	1/50 (42) 0.4828	1/56 (46) 0.5055
	SCHWANNOMA, MALIGNANT	0/51 (45) 0.2599	0/51 (44) NC	0/50 (42) NC	1/56 (46) 0.5055
SKIN	ADENOMA, SEBACEOUS, BENIGN	1/52 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
	CARCINOMA, BASAL CELL, MALIGNANT	1/52 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/52 (46) 0.7430	1/51 (44) 0.4889	0/51 (43) NC	0/56 (46) NC
	C_Squamous cell papillomas+carcinomas+keratoacanthomas	3/52 (46) 0.1177	1/51 (44) 0.9361	4/51 (43) 0.4619	5/56 (46) 0.3570
	FIBROMA, BENIGN	1/52 (46) 0.5065	1/51 (44) 0.7416	2/51 (43) 0.4744	1/56 (46) 0.7527
	FIBROSARCOMA, MALIGNANT	1/52 (47) 0.9336	1/51 (45) 0.7418	0/51 (43) 1.0000	0/56 (46) 1.0000
	HAIR FOLLICLE NEOPLASM, BENIGN	2/52 (46) 0.9800	2/51 (45) 0.6834	0/51 (43) 1.0000	0/56 (46) 1.0000
	HEMANGIOSARCOMA, MALIGNANT	0/52 (46) 0.3162	1/51 (44) 0.4889	0/51 (43) NC	1/56 (46) 0.5000
	KERATOACANTHOMA, BENIGN	2/52 (46) 0.0672	0/51 (44) 1.0000	2/51 (43) 0.6658	4/56 (46) 0.3384
	LIPOMA, BENIGN	1/52 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
	OSTEOSARCOMA, MALIGNANT	0/52 (46) 0.2611	0/51 (44) NC	0/51 (43) NC	1/56 (47) 0.5054

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=52) P-value - Trend	10 mg/kg/day Low (N=51) P-value - Vehicle vs. Low	30 mg/kg/day Med (N=51) P-value - Vehicle vs. Med	100 mg/kg/day High (N=56) P-value - Vehicle vs. High
	PAPILLOMA, SQUAMOUS CELL, BENIGN	1/52 (46) 0.3766	0/51 (44) 1.0000	2/51 (43) 0.4744	1/56 (46) 0.7527
	SARCOMA, HISTIOCYTIC, MALIGNANT	0/52 (46) 0.5000	0/51 (44) NC	1/51 (44) 0.4889	0/56 (46) NC
	SCHWANNOMA, MALIGNANT	0/52 (46) 0.1891	0/51 (44) NC	1/51 (43) 0.4831	1/56 (46) 0.5000
SMALL INTESTINE, D	SCHWANNOMA, MALIGNANT	0/48 (44) 0.2557	0/50 (44) NC	0/51 (43) NC	1/53 (45) 0.5056
SMALL INTESTINE, J	ADENOCARCINOMA, MALIGNANT	0/47 (43) 0.1921	0/49 (44) NC	1/51 (43) 0.5000	1/52 (45) 0.5114
	LEIOMYOMA, BENIGN	0/47 (43) 0.2529	0/49 (44) NC	0/51 (43) NC	1/52 (44) 0.5057
	LEIOMYOSARCOMA, MALIGNANT	0/47 (43) 0.3004	1/49 (44) 0.5057	1/51 (43) 0.5000	1/52 (44) 0.5057
SPLEEN	HEMANGIOSARCOMA, MALIGNANT	0/52 (46) 0.3162	1/51 (44) 0.4889	0/51 (43) NC	1/56 (46) 0.5000
	SARCOMA, HISTIOCYTIC, MALIGNANT	1/52 (46) 0.9354	2/51 (45) 0.4917	0/51 (43) 1.0000	0/56 (46) 1.0000
STOMACH	LEIOMYOSARCOMA, MALIGNANT	0/51 (46) 0.3162	1/51 (44) 0.4889	0/51 (43) NC	1/56 (46) 0.5000
	LIPOSARCOMA, MALIGNANT	1/51 (46) 1.0000	0/51 (44) 1.0000	0/51 (43) 1.0000	0/56 (46) 1.0000
	SARCOMA, HISTIOCYTIC, MALIGNANT	0/51 (46) 0.7444	1/51 (45) 0.4945	0/51 (43) NC	0/56 (46) NC
	SCHWANNOMA, MALIGNANT	0/51 (46) 0.2570	0/51 (44) NC	0/51 (43) NC	1/56 (46) 0.5000
TESTIS	LEYDIG CELL TUMOR, BENIGN	5/52 (46) 0.8079	5/51 (45) 0.6161	3/51 (43) 0.8440	3/56 (47) 0.8733
	MESOTHELIOMA, MALIGNANT	0/52 (46) 0.2068	0/51 (44) NC	2/51 (43) 0.2306	1/56 (46) 0.5000
THYMUS	SARCOMA, HISTIOCYTIC, MALIGNANT	0/50 (45) 0.7384	1/48 (42) 0.4828	0/51 (43) NC	0/51 (42) NC
	THYMOMA, BENIGN	2/50 (45) 0.7444	2/48 (41) 0.6559	1/51 (43) 0.8707	1/51 (43) 0.8707
Whold Body	C_Hemangiosarcoma+Hemangioma	2/52 (46) 0.0539	5/51 (44) 0.1990	1/51 (43) 0.8663	7/56 (46) 0.0789
	C_LYMPHOMA MALIGNANT	1/52 (46) 0.3962	0/51 (44) 1.0000	1/51 (43) 0.7357	1/56 (46) 0.7527

**Table 12: Tumor Rates and P-Values for Dose Response Relationship and
Pairwise Comparisons between the Vehicle Control and the Treated Groups-
Female Rats**

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=58) P-value - Trend	5 mg/kg/day Low (N=56) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=54) P-value - Vehicle vs. Med	50 mg/kg/day High (N=53) P-value - Vehicle vs. High
BODY CAVITY, ORAL	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/58 (47) 0.4689	0/56 (47) NC	1/54 (42) 0.4719	0/53 (41) NC
BONE	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/58 (47) 0.4689	0/56 (47) NC	1/54 (42) 0.4719	0/53 (41) NC
BRAIN	CARCINOMA, BASAL CELL, MALIGNANT	1/58 (47) 0.7194	0/56 (47) 1.0000	1/54 (42) 0.7240	0/53 (41) 1.0000
	GRANULAR CELL TUMOR, BENIGN	0/58 (47) 0.4719	0/56 (47) NC	1/54 (43) 0.4778	0/53 (41) NC
	GRANULAR CELL TUMOR, MALIGNANT	1/58 (47) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
	OLIGODENDROGLIOMA, MALIGNANT	1/58 (48) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
CERVIX	CARCINOMA, BASAL CELL, MALIGNANT	0/57 (46) 0.7900	2/56 (47) 0.2527	0/54 (42) NC	0/52 (40) NC
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/57 (46) 0.7371	1/56 (47) 0.5054	0/54 (42) NC	0/52 (40) NC
	CHOLANGIOCARCINOMA, MALIGNANT	0/57 (46) 0.2286	0/56 (47) NC	0/54 (42) NC	1/52 (40) 0.4651
	GRANULAR CELL TUMOR, BENIGN	1/57 (46) 0.4059	0/56 (47) 1.0000	0/54 (42) 1.0000	1/52 (40) 0.7168
	LEIOMYOSARCOMA, MALIGNANT	1/57 (46) 0.3302	0/56 (47) 1.0000	2/54 (44) 0.4831	1/52 (41) 0.7233
	POLYP, ENDOMETRIAL STROMAL, BENIGN	0/57 (46) 0.7386	1/56 (48) 0.5106	0/54 (42) NC	0/52 (40) NC
	SARCOMA, MALIGNANT	0/57 (46) 0.0512	0/56 (47) NC	0/54 (42) NC	2/52 (40) 0.2134
	SCHWANNOMA, MALIGNANT	2/57 (47) 0.1440	0/56 (47) 1.0000	4/54 (44) 0.3073	3/52 (41) 0.4348
GLAND, ADRENAL	ADENOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/53 (42) NC	1/53 (41) 0.4659
	ADENOMA, ADRENOCORTICAL, BENIGN	0/58 (47) 0.0139	0/56 (47) NC	1/53 (42) 0.4719	3/53 (41) 0.0971
	PHEOCHROMOCYTOMA, BENIGN	1/58 (47) 1.0000	0/56 (47) 1.0000	0/53 (42) 1.0000	0/53 (41) 1.0000
	PHEOCHROMOCYTOMA, MALIGNANT	0/58 (47) 0.7360	1/56 (48) 0.5053	0/53 (42) NC	0/53 (41) NC
GLAND, MAMMARY	ADENOCARCINOMA, MALIGNANT	5/58 (47) 0.3602	12/56 (50) 0.0708	8/54 (42) 0.2060	8/53 (42) 0.2060

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=58) P-value - Trend	5 mg/kg/day Low (N=56) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=54) P-value - Vehicle vs. Med	50 mg/kg/day High (N=53) P-value - Vehicle vs. High
	ADENOMA, BENIGN	1/58 (47) 0.4106	0/56 (47) 1.0000	0/54 (42) 1.0000	1/53 (41) 0.7176
	FIBROADENOMA, BENIGN	13/58 (48) 0.9606	11/56 (48) 0.7600	15/54 (47) 0.3854	5/53 (41) 0.9794
	FIBROMA, BENIGN	0/58 (47) 0.4689	0/56 (47) NC	1/54 (42) 0.4719	0/53 (41) NC
GLAND, PITUITARY	ADENOMA, PARS DISTALIS, BENIGN	43/58 (53) 0.8048	43/56 (54) 0.6692	37/54 (47) 0.7095	35/53 (47) 0.8519
	ADENOMA, PARS INTERMEDIA, BENIGN	1/58 (47) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
	CARCINOMA, PARS DISTALIS, MALIGNANT	1/58 (47) 0.7194	0/56 (47) 1.0000	1/54 (42) 0.7240	0/53 (41) 1.0000
GLAND, THYROID	ADENOMA, C-CELL, BENIGN	3/58 (47) 0.2785	1/55 (47) 0.9415	3/54 (43) 0.6181	3/53 (41) 0.5943
	ADENOMA, FOLLICULAR CELL, BENIGN	5/58 (47) 0.9853	4/55 (48) 0.7676	5/54 (43) 0.5719	0/53 (41) 1.0000
	CARCINOMA, C-CELL, MALIGNANT	1/58 (47) 1.0000	0/55 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
	CARCINOMA, FOLLICULAR CELL, MALIGNANT	2/58 (47) 0.1200	2/55 (47) 0.6916	10/54 (42) 0.0076	5/53 (41) 0.1644
KIDNEY	ADENOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	CHOLANGIOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	LIPOMA, BENIGN	1/58 (47) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
LARGE INTESTINE, C	ADENOCARCINOMA, MALIGNANT	0/57 (47) 0.2273	0/56 (47) NC	0/54 (42) NC	1/52 (40) 0.4598
LARGE INTESTINE, R	ADENOCARCINOMA, MALIGNANT	0/57 (47) 0.2316	0/55 (47) NC	0/54 (42) NC	1/52 (41) 0.4659
	LEIOMYOSARCOMA, MALIGNANT	0/57 (47) 0.4660	0/55 (47) NC	2/54 (44) 0.2310	0/52 (41) NC
LIVER	ADENOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	ADENOMA, HEPATOCELLULAR, BENIGN	1/58 (47) 0.8025	1/56 (47) 0.7527	1/54 (42) 0.7240	0/53 (41) 1.0000
	CARCINOMA, HEPATOCELLULAR, MALIGNANT	0/58 (47) 0.2624	1/56 (47) 0.5000	1/54 (42) 0.4719	1/53 (41) 0.4659
	CHOLANGIOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	CHOLANGIOMA, BENIGN	0/58 (47) 0.7345	1/56 (47) 0.5000	0/54 (42) NC	0/53 (41) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=58) P-value - Trend	5 mg/kg/day Low (N=56) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=54) P-value - Vehicle vs. Med	50 mg/kg/day High (N=53) P-value - Vehicle vs. High
LUNG	ADENOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	CARCINOMA, BASAL CELL, MALIGNANT	1/58 (47) 0.1345	0/56 (47) 1.0000	0/54 (42) 1.0000	2/53 (41) 0.4483
	CHOLANGIOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	LEIOMYOSARCOMA, MALIGNANT	0/58 (47) 0.4719	0/56 (47) NC	1/54 (43) 0.4778	0/53 (41) NC
	MESOTHELIOMA, MALIGNANT	1/58 (47) 0.4106	0/56 (47) 1.0000	0/54 (42) 1.0000	1/53 (41) 0.7176
LYMPH NODE, MESENT	ADENOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	HEMANGIOMA, BENIGN	1/58 (47) 0.4670	1/56 (48) 0.7579	1/54 (43) 0.7301	1/53 (41) 0.7176
	HEMANGIOSARCOMA, MALIGNANT	0/58 (47) 0.0496	0/56 (47) NC	1/54 (42) 0.4719	2/53 (41) 0.2142
MEDIASTINUM	MESOTHELIOMA, MALIGNANT	1/58 (47) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
MESENTERY	ADENOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	CHOLANGIOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	LEIOMYOSARCOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	LIPOMA, BENIGN	6/58 (47) 0.9271	1/56 (47) 0.9939	2/54 (42) 0.9581	1/53 (41) 0.9901
MUSCLE, BICEPS FEM	HEMANGIOSARCOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
MUSCLE, DIAPHRAGM	CHOLANGIOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
OVARY	ADENOCARCINOMA, MALIGNANT	0/57 (47) 0.2312	0/52 (44) NC	0/54 (42) NC	1/51 (40) 0.4598
	ADENOMA, TUBULOSTROMAL, BENIGN	0/57 (47) 0.4740	0/52 (44) NC	1/54 (42) 0.4719	0/51 (40) NC
	CHOLANGIOCARCINOMA, MALIGNANT	0/57 (47) 0.2312	0/52 (44) NC	0/54 (42) NC	1/51 (40) 0.4598
	CYSTADENOCARCINOMA, MALIGNANT	0/57 (47) 0.4740	0/52 (44) NC	1/54 (42) 0.4719	0/51 (40) NC
	GRANULOSA CELL TUMOR, BENIGN	0/57 (47) 0.4740	0/52 (44) NC	1/54 (42) 0.4719	0/51 (40) NC
	GRANULOSA CELL TUMOR, MALIGNANT	0/57 (47) 0.1653	0/52 (44) NC	1/54 (42) 0.4719	1/51 (40) 0.4598

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=58) P-value - Trend	5 mg/kg/day Low (N=56) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=54) P-value - Vehicle vs. Med	50 mg/kg/day High (N=53) P-value - Vehicle vs. High
	LUTEOMA, BENIGN	0/57 (47) 0.0524	0/52 (44) NC	0/54 (42) NC	2/51 (40) 0.2085
	SCHWANNOMA, MALIGNANT	0/57 (47) 0.7283	1/52 (44) 0.4835	0/54 (42) NC	0/51 (40) NC
	SERTOLI CELL TUMOR, BENIGN	1/57 (47) 1.0000	0/52 (44) 1.0000	0/54 (42) 1.0000	0/51 (40) 1.0000
OVIDUCT	LEIOMYOMA, BENIGN	0/58 (47) 0.7360	1/56 (48) 0.5053	0/54 (42) NC	0/53 (41) NC
PANCREAS	ACINAR-ISLET CELL TUMOR, BENIGN	0/58 (47) 0.7882	2/56 (48) 0.2526	0/54 (42) NC	0/53 (41) NC
	ADENOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	ADENOMA, BENIGN	1/58 (47) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
	CARCINOMA, ISLET CELL, MALIGNANT	2/58 (47) 0.8703	0/56 (47) 1.0000	1/54 (42) 0.8572	0/53 (41) 1.0000
	CHOLANGIOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	HEMANGIOMA, BENIGN	1/58 (48) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
	LEIOMYOSARCOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	SCHWANNOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
PEYER'S PATCH	CHOLANGIOCARCINOMA, MALIGNANT	0/54 (45) 0.2086	0/52 (44) NC	0/52 (40) NC	1/42 (34) 0.4304
SKIN	CARCINOMA, BASAL CELL, MALIGNANT	0/58 (47) 0.2863	1/56 (48) 0.5053	0/54 (42) NC	1/53 (41) 0.4659
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/58 (47) 0.7345	1/56 (47) 0.5000	0/54 (42) NC	0/53 (41) NC
	FIBROSARCOMA, PLEOMORPHIC, MALIGNANT	1/58 (48) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
	HAIR FOLLICLE NEOPLASM, BENIGN	0/58 (47) 0.4719	0/56 (47) NC	1/54 (43) 0.4778	0/53 (41) NC
	HEMANGIOSARCOMA, MALIGNANT	1/58 (48) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
	LIPOMA, BENIGN	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	MESOTHELIOMA, MALIGNANT	1/58 (47) 1.0000	0/56 (47) 1.0000	0/54 (42) 1.0000	0/53 (41) 1.0000
SMALL INTESTINE, D	CHOLANGIOCARCINOMA, MALIGNANT	0/56 (47) 0.2241	0/54 (47) NC	0/53 (41) NC	1/49 (39) 0.4535

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=58) P-value - Trend	5 mg/kg/day Low (N=56) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=54) P-value - Vehicle vs. Med	50 mg/kg/day High (N=53) P-value - Vehicle vs. High
SMALL INTESTINE, I	CHOLANGIOCARCINOMA, MALIGNANT	0/54 (46) 0.2209	0/54 (47) NC	0/53 (41) NC	1/46 (38) 0.4524
SMALL INTESTINE, J	LEIOMYOMA, BENIGN	1/54 (46) 0.3869	0/54 (47) 1.0000	0/51 (41) 1.0000	1/46 (37) 0.6959
SPLEEN	ADENOCARCINOMA, MALIGNANT	0/58 (47) 0.2316	0/55 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	HEMANGIOMA, BENIGN	0/58 (47) 0.7345	1/55 (47) 0.5000	0/54 (42) NC	0/53 (41) NC
	HEMANGIOSARCOMA, MALIGNANT	0/58 (47) 0.4659	0/55 (47) NC	2/54 (42) 0.2199	0/53 (41) NC
STOMACH	ADENOCARCINOMA, MALIGNANT	0/57 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	CHOLANGIOCARCINOMA, MALIGNANT	0/57 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	LEIOMYOSARCOMA, MALIGNANT	0/57 (47) 0.1632	0/56 (47) NC	1/54 (42) 0.4719	1/53 (41) 0.4659
THYMUS	ADENOCARCINOMA, MALIGNANT	0/53 (43) 0.2381	0/54 (45) NC	0/52 (40) NC	1/51 (40) 0.4819
	MESOTHELIOMA, MALIGNANT	1/53 (43) 1.0000	0/54 (45) 1.0000	0/52 (40) 1.0000	0/51 (40) 1.0000
	THYMOMA, BENIGN	5/53 (43) 0.8686	12/54 (47) 0.0777	7/52 (41) 0.3444	4/51 (40) 0.7209
URINARY BLADDER	LEIOMYOSARCOMA, MALIGNANT	0/57 (47) 0.4655	0/55 (46) NC	1/52 (42) 0.4719	0/50 (39) NC
UTERUS	ADENOCARCINOMA, MALIGNANT	1/58 (47) 0.0139	3/56 (47) 0.3084	1/54 (42) 0.7240	6/53 (41) 0.0368
	LEIOMYOSARCOMA, MALIGNANT	0/58 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/53 (41) 0.4659
	POLYP, ENDOMETRIAL STROMAL, BENIGN	0/58 (47) 0.4442	2/56 (47) 0.2473	3/54 (42) 0.1011	1/53 (41) 0.4659
	POLYP, GLANDULAR, BENIGN	1/58 (47) 0.0564	2/56 (47) 0.5000	1/54 (42) 0.7240	4/53 (41) 0.1406
	STROMAL SARCOMA, ENDOMETRIAL, MALIGNANT	1/58 (47) 0.4984	1/56 (48) 0.7579	0/54 (42) 1.0000	1/53 (41) 0.7176
VAGINA	ADENOCARCINOMA, MALIGNANT	0/57 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/52 (41) 0.4659
	CARCINOMA, BASAL CELL, MALIGNANT	0/57 (47) 0.7345	1/56 (47) 0.5000	0/54 (42) NC	0/52 (41) NC
	CHOLANGIOCARCINOMA, MALIGNANT	0/57 (47) 0.2316	0/56 (47) NC	0/54 (42) NC	1/52 (41) 0.4659
	LEIOMYOSARCOMA, MALIGNANT	0/57 (47) 0.4660	0/56 (47) NC	2/54 (44) 0.2310	0/52 (41) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=58) P-value - Trend	5 mg/kg/day Low (N=56) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=54) P-value - Vehicle vs. Med	50 mg/kg/day High (N=53) P-value - Vehicle vs. High
	POLYP, ENDOMETRIAL STROMAL, BENIGN	0/57 (47) 0.1640	0/56 (47) NC	1/54 (43) 0.4778	1/52 (41) 0.4659
	SCHWANNOMA, MALIGNANT	0/57 (47) 0.1534	1/56 (48) 0.5053	3/54 (44) 0.1090	2/52 (42) 0.2199
Whold Body	C_Hemangiosarcoma+Hemangioma	3/58 (48) 0.1990	2/56 (48) 0.8192	4/54 (43) 0.4380	4/53 (41) 0.4115
	C_LEUKEMIA MONOCYTIC MALIGNANT	0/58 (47) 0.4689	0/56 (47) NC	1/54 (42) 0.4719	0/53 (41) NC
	C_LYMPHOMA MALIGNANT	0/58 (47) 0.4719	0/56 (47) NC	1/54 (43) 0.4778	0/53 (41) NC

Table 13: Intercurrent Mortality Rate -Male Mice

Week	0 mg/kg/day Vehicle (N=25)		30 mg/kg/day Low (N=25)		100 mg/kg/day Med (N=25)		300 mg/kg/day High (N=25)		1000 mg/kg/day Positive (N=10)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	.	.	.	.	2	20.00
14 - 26	.	.	1	4.00	1	4.00	.	.	3	50.00
Ter. Sac.	25	100.00	24	96.00	24	96.00	25	100.00	5	50.00

Table 14: Intercurrent Mortality Rate -Female Mice

Week	0 mg/kg/day Vehicle (N=25)		30 mg/kg/day Low (N=25)		100 mg/kg/day Med (N=25)		300 mg/kg/day High (N=25)		1000 mg/kg/day Positive (N=10)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	1	4.00	.	.	.	.	.	.	.	.
14 - 26	2	12.00	1	4.00	.	.	2	8.00	1	10.00
Ter. Sac.	22	88.00	24	96.00	25	100.00	23	92.00	9	90.00

Table 15: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Male Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.4264	0.2390	0.2390	.	0.0002
Homogeneity	Log-Rank	0.3978	0.3173	0.3173	.	<0.0001

Table 16: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Female Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.6565	0.5283	0.0886	0.5518	0.5517

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Homogeneity	Log-Rank	0.5416	0.5315	0.1446	0.5554	0.5336

Table 17: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	30 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	100 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	30 mg/kg/day High (N=25) P-value - Vehicle vs. High
GLAND, HARDERIAN	ADENOMA, BENIGN	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000
LIVER	HEMANGIOSARCOMA, MALIGNANT	0/25 (25) 0.7475	1/25 (24) 0.4898	0/25 (25) NC	0/25 (25) NC
LUNG	ADENOMA, BENIGN	0/25 (25) 0.1084	1/25 (24) 0.4898	0/25 (25) NC	2/25 (25) 0.2449
SKIN/SUBCUTIS	HEMANGIOSARCOMA, MALIGNANT	0/25 (25) 0.5051	0/25 (24) NC	1/25 (25) 0.5000	0/25 (25) NC
	PAPILLOMA, BENIGN	0/25 (25) 0.5051	0/25 (24) NC	1/25 (25) 0.5000	0/25 (25) NC
SPLEEN	HEMANGIOSARCOMA, MALIGNANT	0/25 (25) 0.6287	1/25 (24) 0.4898	1/25 (25) 0.5000	0/25 (25) NC
THYMUS	LYMPHOMA, MALIGNANT WITHOUT METASTASIS	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000
TONGUE	PAPILLOMA, MALIGNANT	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000
Whold Body	C_Hemangiosarcoma	0/25 (25) 0.7496	2/25 (24) 0.2347	2/25 (25) 0.2449	0/25 (25) NC

Table 18: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	30 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	100 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	30 mg/kg/day High (N=25) P-value - Vehicle vs. High
GLAND, HARDERIAN	ADENOMA, BENIGN	0/25 (24) 0.6426	1/25 (24) 0.5000	2/25 (25) 0.2551	0/25 (24) NC
LUNG	ADENOMA, BENIGN	0/25 (24) 0.5052	0/25 (24) NC	1/25 (25) 0.5102	0/25 (24) NC
	CARCINOMA, MALIGNANT	0/25 (24) 0.5052	0/25 (24) NC	1/25 (25) 0.5102	0/25 (24) NC
LYMPH NODE, MESENT	HEMANGIOSARCOMA, MALIGNANT	0/25 (24) 0.5052	0/25 (24) NC	1/25 (25) 0.5102	0/25 (24) NC
SKIN/SUBCUTIS	HEMANGIOSARCOMA, MALIGNANT	1/25 (24) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000
	PAPILLOMA, BENIGN	0/25 (24) 0.5052	0/25 (24) NC	1/25 (25) 0.5102	0/25 (24) NC
SPLEEN	HEMANGIOSARCOMA, MALIGNANT	0/25 (24) 0.7349	2/25 (25) 0.2551	1/25 (25) 0.5102	0/25 (24) NC
STOMACH	HEMANGIOSARCOMA, MALIGNANT	1/25 (24) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000
THYMUS	LYMPHOMA, MALIGNANT WITHOUT METASTASIS	0/24 (23) 0.1921	0/25 (24) NC	1/25 (25) 0.5208	1/25 (24) 0.5106
	THYOMA, BENIGN	1/24 (23) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000
URINARY BLADDER	HEMANGIOSARCOMA, MALIGNANT	0/25 (24) 0.5000	0/25 (24) NC	1/24 (24) 0.5000	0/25 (24) NC
Whold Body	C_Hemangiosarcoma	2/25 (24) 0.9149	2/25 (25) 0.7110	3/25 (25) 0.5200	0/25 (24) 1.0000
	C_LYMPHOMA MALIGNANT	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000

Table 19: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	300 mg/kg/day Positive (N=10) P-value - Vehicle vs. Positive
LARGE INTESTINE, R	ADENOMA, BENIGN	0/25 (25)	1/10 (3) 0.1071
LUNG	ADENOMA, BENIGN	0/25 (25)	7/10 (8) <0.001
	CARCINOMA, MALIGNANT	0/25 (25)	3/10 (4) 0.0011
	KERATOACANTHOMA, BENIGN	0/25 (25)	1/10 (3) 0.1071
SPLEEN	HEMANGIOSARCOMA, MALIGNANT	0/25 (25)	7/10 (8) <0.001
STOMACH	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/25 (25)	1/10 (3) 0.1071
Whold Body	C_Hemangiosarcoma	0/25 (25)	7/10 (8) <0.001

Table 20: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and Positive Control- Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	300 mg/kg/day Positive (N=10) P-value - Vehicle vs. Positive
LUNG	ADENOMA, BENIGN	0/25 (24)	8/10 (8) <0.001
	CARCINOMA, MALIGNANT	0/25 (24)	7/10 (8) <0.001
SKIN/SUBCUTIS	HEMANGIOSARCOMA, MALIGNANT	1/25 (24)	1/10 (3) 0.2137
SPLEEN	HEMANGIOSARCOMA, MALIGNANT	0/25 (24)	8/10 (8) <0.001
STOMACH	HEMANGIOSARCOMA, MALIGNANT	1/25 (24)	1/10 (3) 0.2137
Whold Body	C_Hemangiosarcoma	2/25 (24)	8/10 (8) <0.001

Figure 1: Kaplan-Meier Survival Functions for Male Rats

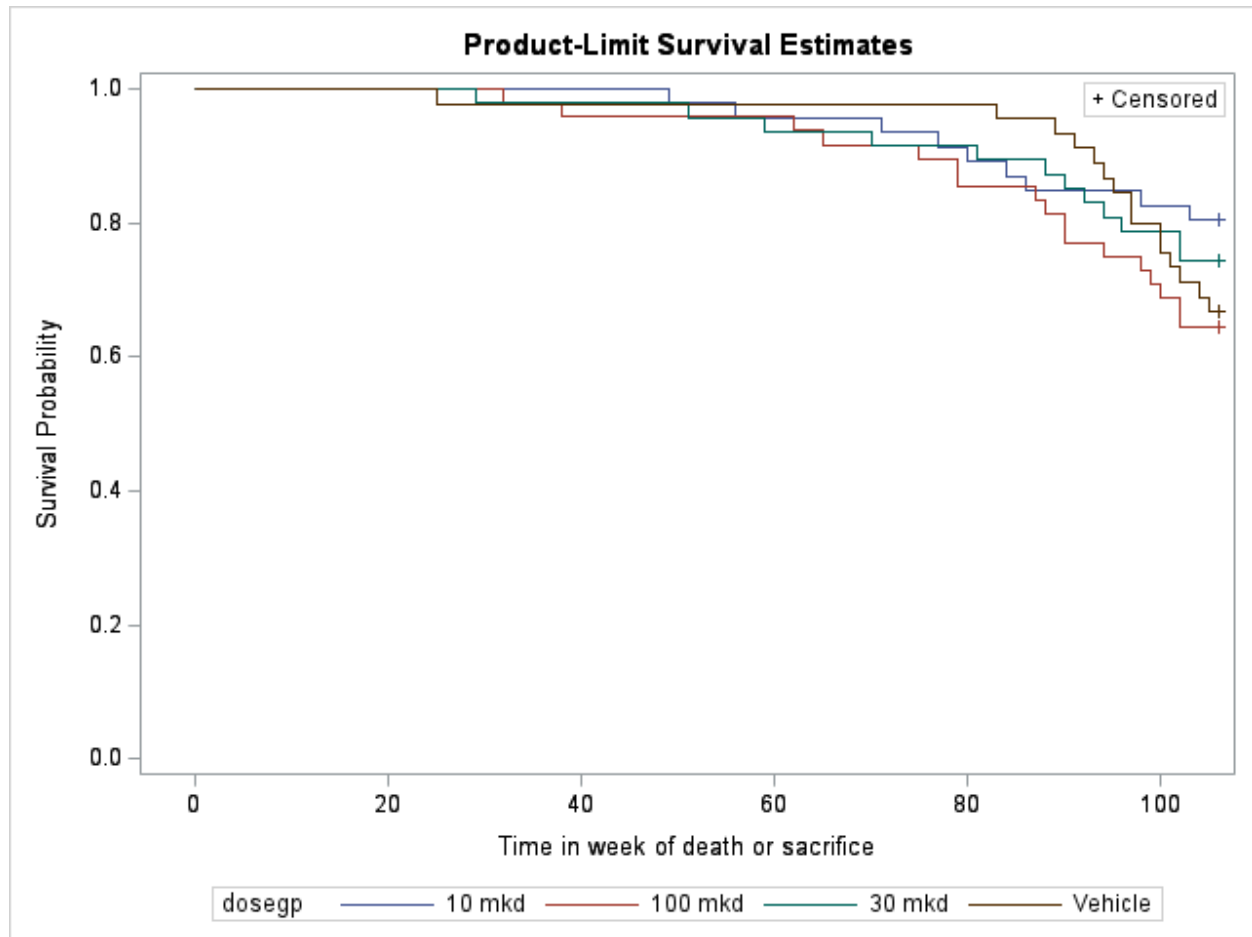


Figure 2: Kaplan-Meier Survival Functions for Female Rats

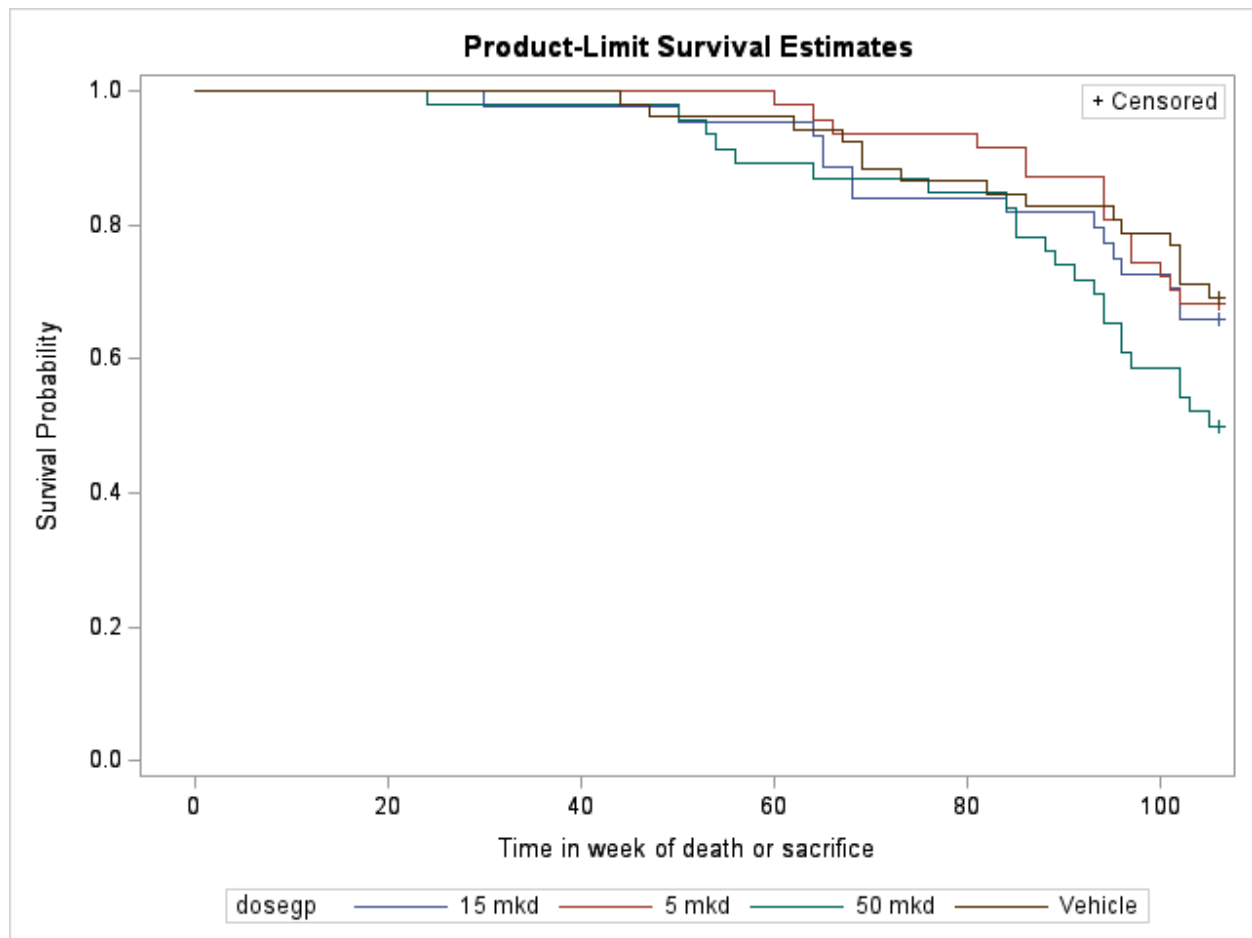


Figure 3: Kaplan-Meier Survival Functions for Male Mice

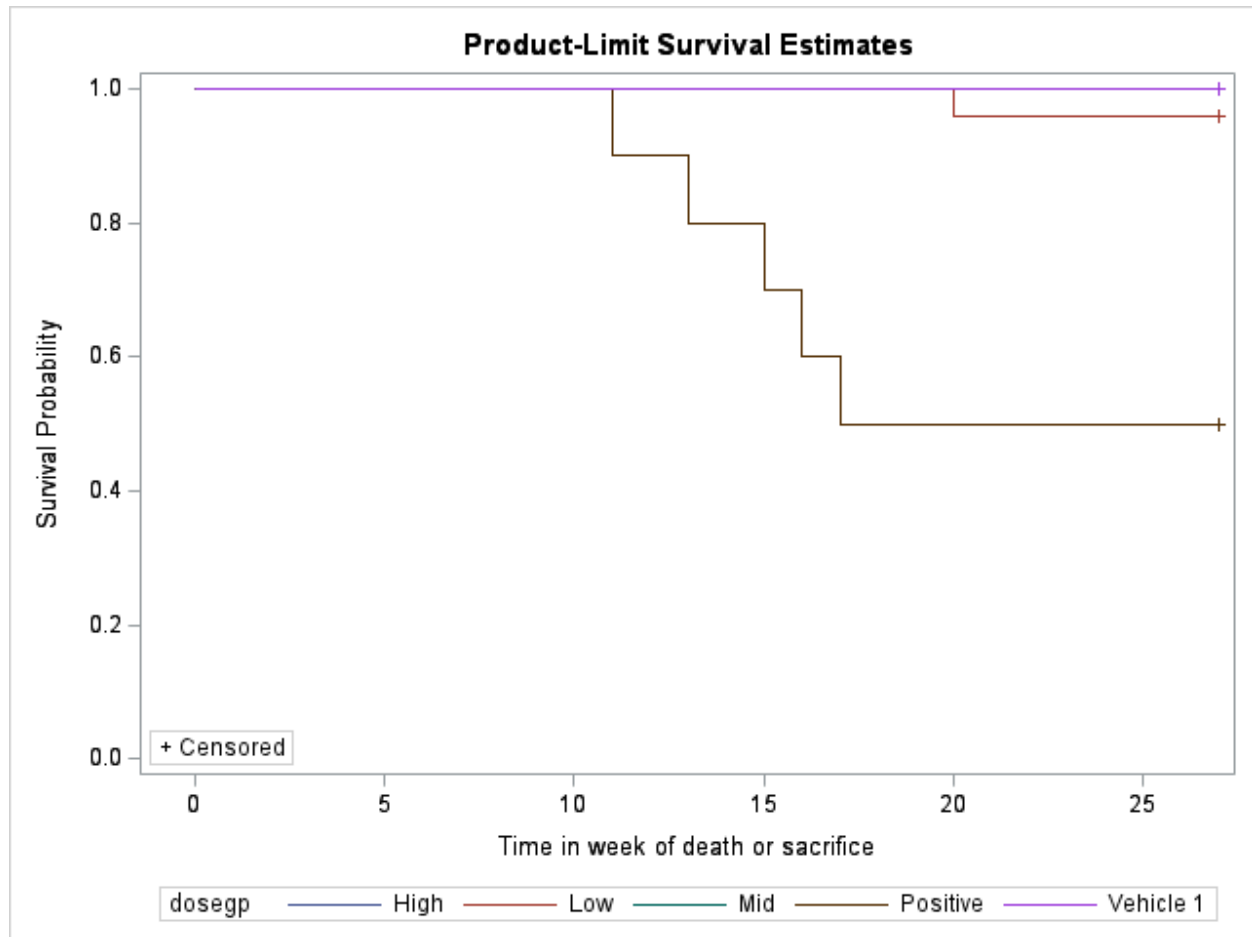
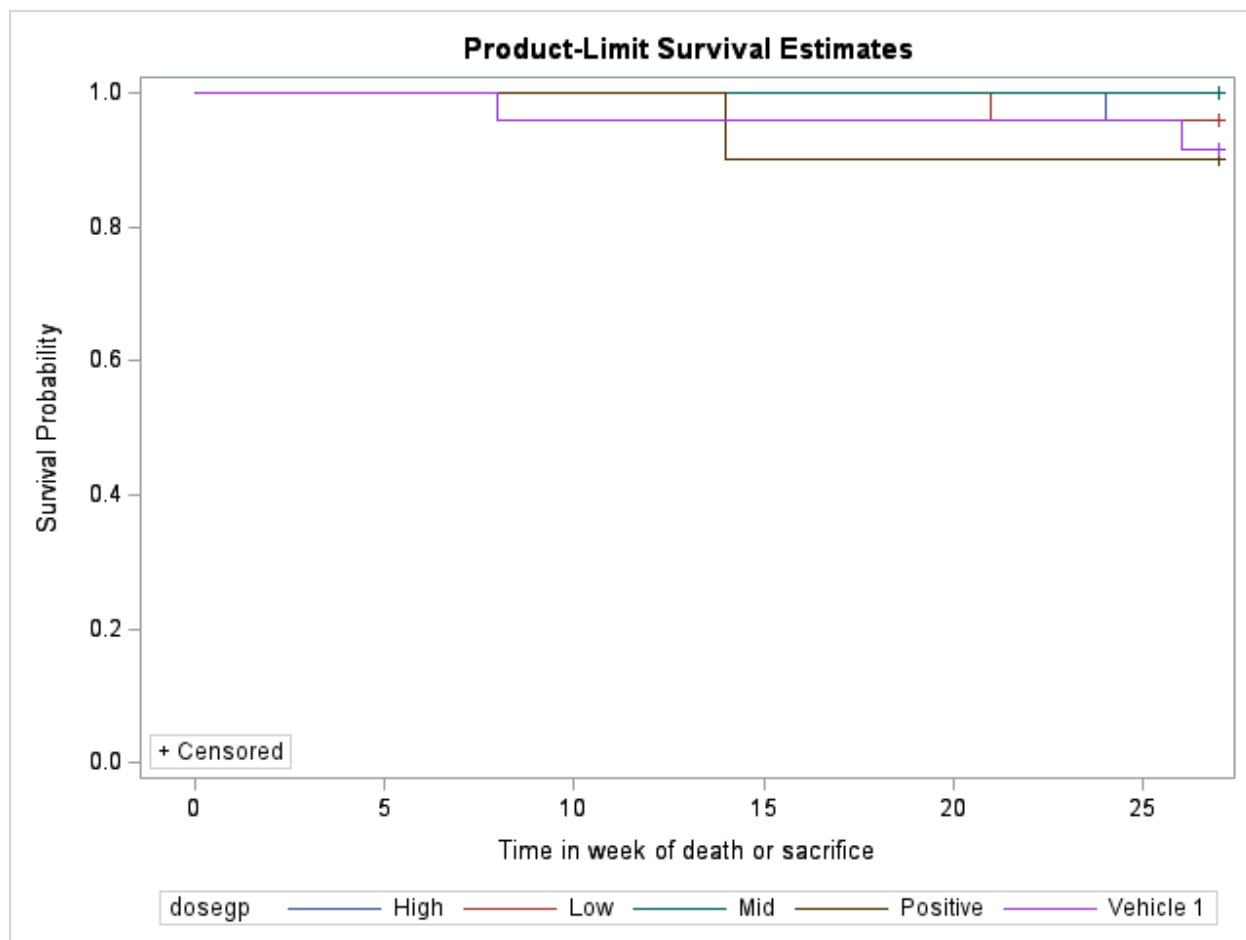


Figure 4: Kaplan-Meier Survival Functions for Female Mice



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