16 October 2025
EMA/348131/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

WAYRILZ

International non-proprietary name: Rilzabrutinib

Procedure No. EMEA/H/C/006425/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

(Q)SAR	(Quantitative) structure-activity relationship
6TG	6-thioguanine
ADCC	Antibody dependent cellular cytotoxicity
ADME	Absorption, distribution, metabolism, and excretion
ADP	Adenosine diphosphate
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANOVA	Analysis of variance
AP	applicant's Part (or Open Part) of a ASMF
API	Active pharmaceutical ingredient
APTT	Activated partial thromboplastin time
AR	Assessment Report
ASC:	apoptosis-associated speck-like protein containing a caspase recruitment domain
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	Aspartate transaminase
ATP	Adenosine triphosphate
AUC	Area under the plasma-concentration time curve
AUC_{0-24}	Area under concentration-time curve from 0 to 24 hours
AUC_{0-t}	Area under concentration-time curve from 0 to time t (h)
AUC_{inf}	Area under the curve from time 0 to infinity
AUC_{last}	Area under the plasma-concentration time curve from time zero to last measurable concentration
AUCss	Area under the curve at steady state
BCR	B cell receptor
BCRP:	breast cancer resistance protein
BCS:	biopharmaceutics classification system
BET	Brunauer-Emmett-Teller
BID	Twice daily
BLK	B-cell lymphocyte kinase
BLOQ	Below the limit of quantification
BMX	Bone marrow tyrosine kinase in chromosome X
BP	British Pharmacopoeia
BRK	Breast tumor kinase
BSA	Bovine serum albumin
BSEP:	bile salt export pump
BTK	Bruton’s tyrosine kinase
BTKi	BTK inhibitor
BUN	Blood urea nitrogen
C_0	Concentration at naught conditions
Caco	Cancer coli, "colon cancer"

CAS	Chemical abstracts service
CEP	Certificate of Suitability of the European Pharmacopoeia
CI:	confidence interval
CIA	Collagen induced arthritis
CL	Clearance
CLCr:	creatinine clearance
CLEC4F	C-type lectin receptor
Cmax	Maximum concentration
Cmax,ss	Maximum steady-state concentration
C_{max}:	maximum concentration
CMH:	Cochran-Mantel-Haenszel
CMQ:	customized MedDRA query
CMS	Concerned Member State
CNS	Central nervous system
CoA	Certificate of Analysis
CP	Cyclophosphamide
CPCA	Carcinogenic potency categorisation approach
CQA	Critical quality attribute
CRS	Chemical Reference Substance (official standard)
CS	Corticosteroids
CSF	Cerebro-Spinal Fluid
CV	Cardiovascular
CVO	Circumventricular organ
CYP	Cytochrome P450
CYP3A:	cytochrome 450 3A
DALA	Drug abuse liability assessment
DB:	double-blind
DIPNA	N-nitroso-isopropylethylamine
DMF	Drug Master File = Active Substance Master File
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DNP	Dinitrophenyl
DP	Decentralised (Application) Procedure
DP	Drug product
dpm	Disintegrations per minute
DS	Drug substance
DSC	Differential scanning calorimetry
DVS	DVS
eCAC	Executive carcinogenicity assessment committee
EC	European Commission
ECG	Electrocardiogram
EDC.HCl	1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EIPNA	N-nitroso-isopropylethylamine
ELISA	Enzyme-linked immunosorbent assay

EMA	European Medicines Agency
EMS	Ethyl methanesulfonate
ERB	Erythroblastic leukemia viral oncogene homolog
EU:	European Union
F	Female
FcR	Fragment crystallizable receptor
FcγR	Fragment crystallizable gamma receptor, Fcγ receptor
FcεR	Fragment crystallizable epsilon receptor
FDA	U.S. Food and Drug Administration
FGFR2	Fibroblast growth factor receptor 2
FGR	Fibroblast growth factor
FLT-3	FMS-related tyrosine kinase 3
FLT-4	FMS-related tyrosine kinase 4
fm	Fraction of metabolism
FOB	Functional observational battery
FRET	Fluorescence resonance energy transfer
GC	Gas Chromatography
GD	Gestation Day
GFAP	Glial fibrillary acidic protein
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GPVI	Glycoprotein VI
GST	Glutathione-s-transferase
H&E	Hematoxylin and eosin
H2:	histamine 2
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
hERG	Human ether-a-go-go-related gene
HI:	hepatic impairment
HLT:	high level term
HPBL	Human peripheral blood lymphocytes
HPLC-MS/MS	High performance liquid chromatography coupled to mass spectrometry
hprt	Hypoxanthine-guanine phosphoribosyl transferase
HRQoL	health-related quality-of-life
HWB	Human whole blood
IBA-1	Ionized calcium-binding adaptor molecule 1
IBLS:	ITP Bleeding Scale
IC_{50}	Inhibitory concentration 50% (concentration causing half-maximal inhibition)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGS	International Genetic Standardization
IHC	Immunohistochemistry

IJ	Intra-jejunal
IKr	Rectifier potassium channel current
IL-4	Interleukin-4
IMP:	investigational medicinal product
INN	International Nonproprietary Name
IP	Intraperitoneal
IPC	In-process control
IR	Infrared
IR:	immediate release
IS	Internal Standard
ITK	Interleukin-2-inducible T-cell kinase
ITP	Immune thrombocytopenia
ITP-PAQ:	Immune Thrombocytopenic Purpura Patient Assessment Questionnaire
ITT:	intent-to-treat
IU	International Units
IV	Intravenous
IVIG	Intravenous immunoglobulins; Immune globulin injection for infusion
I-WISH	ITP World Impact Survey
JAK3	Janus Kinase 3
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
KCN	Potassium cyanide
KF	Karl Fiscer Titration
KSCN	Potassium thiocyanate
LBA:	ligand binding assay
LC/MS	Liquid chromatography/mass spectrometry
LCK	Lymphocyte-specific protein tyrosine kinase
LD	Lactation Day
LD_{50}	lethal dose for 50% of animals
LDH	Lactate dehydrogenase
LDPE	Low density polyethylene
LE	Long-Evans
LLN:	lower limit of normal
LLOQ	Lower Limit of Quantification
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification
LoQ	List of Questions
LS:	least square
LSC	liquid scintillation counter
LTE:	long-term extension
LYN	LCK/YES-related novel protein tyrosine kinase
M	Male
M/P	Metabolite to parent ratio
M2	Muscarinic acetylcholine receptor
MA	Marketing Authorisation

MA	Maximum aggregation
MAD	Mutual acceptance of data
MAD:	multiple ascending dose
MAH	Marketing Authorisation holder
MCL	Mantle cell lymphoma
MedDRA:	Medical Dictionary for Regulatory Activities
MEI	Microsomal enzyme inducer
MF	Mutation frequencies
MI	Mutagenic impurity
MK	Megakaryocyte
MMRM:	mixed-effect model with repeated measures
MN	Micronuclei
MNBN	Micronucleated binucleate
MnPCE	Micronucleated PCE
MNT	Micronucleus test
MPE	Mean photo effect
MS	Mass Spectrometry
MTD	Maximum tolerated dose
NA	Not applicable
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
ND	Not detected
ND	No data
NDA	New drug application
NDEA	N-nitroso-diethylamine
NE	Not evaluated
NFAT	Nuclear factor of activated T cells
NI	Not identified
NK	Natural killer
NK2	Neurokinin 2 receptor
NLRP3:	Nod-like receptor protein containing pyrin 3
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect-level
NOGEL	No-observed-genotoxic-effect level
NPYR	N-nitroso-pyrrolidine
NR	Not reportable
NRU	Neutral red uptake
NZW	New Zealand White
OAT:	organic anion transporter
OATP1B1:	organic anion transporting polypeptide 1B1
OATP1B3:	organic anion transporting polypeptide 1B3
OCT:	organic cation transporter
OD	Optical density
OECD	Organisation for Economic Co-operation and Development

OL:	open-label
OOS	Out of Specifications
PBMC	Peripheral blood mononuclear cells
PBPK:	physiologically based pharmacokinetic
PBS	Phosphate buffered saline
PCE	Polychromatic erythrocyte
PCSA:	potentially clinically significant abnormality
PCTFE	Polychlorotrifluoroethylene
PD	Pharmacodynamics
PDE	Permitted daily exposure
PDAI	Pemphigus disease area index
PDE	Permitted Daily Exposure
PF	Pemphigus foliaceus
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIF	Photo irritation factor
PK	Pharmacokinetics
PL	Patient Leaflet
PNT	Pneumotachograph
PO	Oral
PopPK:	population PK
PR	Time from the beginning of the P wave to the beginning of the QRS complex
PRN35	ibrutinib
PT:	preferred term
PVC	Polyvinyl chloride
PYY	Peptide YY
Q2D	Every other day
QC	Quality control
QD	administered once per day
QD:	once daily
QoL	quality-of-life
QOS	Quality Overall Summary
Qp	Qualified person
QRS	Q, R and S waves of an echocardiogram
QT	Time between the start of the Q wave and the end of the T wave
QTc	Corrected QT interval
QTPP	Quality target product profile
QWBA	Quantitative whole-body radiography
RBC	Red blood cell
RH	Relative Humidity
RI:	renal impairment
RIPK2	Receptor-interacting serine/threonine-protein kinase 2
RMS	Reference Member State
RNA	Ribonucleic acid
RP	Restricted Part (or Closed Part) of a ASMF
RPM	Revolutions per minute

RR	Interval between heart beats, used to calculate heart rate
RRT	Relative retention time
RS	Relative survival
RSD	Relative standard deviation
RT	Room temperature
S9	Aroclor ™ 1254-induced rat liver S9 (metabolic activation system)
SAD:	single ascending dose
SAE:	serious adverse event
SCN	Thiocyanate
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SEM	Scanning electron microscopy
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ:	standardized MedDRA query
SOC:	system organ class
SRC	Sarcoma viral oncogene homolog
STAT6	Signal transducer and activator of transcription 6
STP	Society of Toxicologic Pathology
SULT	Sulfotransferase
SUSAR:	suspected unexpected serious adverse reaction
t1/2	Half life
t1/2z	Terminal half life
TBIL	Total bilirubin
TCR	T cell receptor
TEAE:	treatment-emergent adverse event
TEC	Tyrosine kinase expressed in hepatocellular carcinoma
TGA	Thermo-gravimetric Analysis
TgHRAS	Transgenic mouse
TK	Toxicokinetic
tmax	First time to reach C_{max}
TNFα	Tumor necrosis factor alpha
TP	Thromboxane receptor
TPGS	Tocophenol-polyethylene glycol succinate
TPO-RA	Thrombopoietin-receptor agonists
TRAP	Thrombin receptor activating peptide
TR-FRET	Time-resolved fluorescence resonance energy transfer
TSH	thyroid stimulating hormone
TTC	Threshold of toxicological concern
TXK	T cell X chromosome kinase
UGT	UDP-glucuronosyltransferase
UHPLC	Ultra-high-performance liquid chromatography
UK:	United Kingdom
ULN:	upper limit of normal

ULOQ	Upper limit of quantification
US:	United States
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
v	Volume
V_z	Volume of distribution
w	Weight
WBC	White blood cell
Wistar	Wistar han
XRD	X-Ray diffraction
XRPD	X-ray powder diffraction
YES	Yamaguchi sarcoma virus oncogene

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi B.V. submitted on 26 September 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for WAYRILZ, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2023. WAYRILZ, was designated as an orphan medicinal product EU/3/20/2278 on 4 June 2020 in the following condition: Treatment of immune thrombocytopenia.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Wayrilz as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Wayrilz

The applicant applied for the following indication WAYRILZ is indicated for the treatment of persistent or chronic immune thrombocytopenia (ITP) in adult patients who are refractory to a previous treatment.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0306/2020 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP EMEA-002438-PIP02-19 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance rilzabrutinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
15/10/2020	EMEA/H/SA/3795/2/2020/PA/SME/III	Brigitte Schwarzer-Daum and Ole Weis Bjerrum
23/06/2022	EMA/SA/0000090350	Ole Weis Bjerrum and Andreas Kirisits
14/12/2023	EMA/SA/0000152978	Vilma Petrikaite and Karri Penttila

The applicant received Scientific Advice pertained to the following quality, non-clinical and clinical aspects:

- The data, methodology and rationale to support the evaluation on New Active Substance (NAS) status.
- Adequacy of the non-clinical package for a marketing authorisation application (MAA).
- The design of the proposed randomised, double-blind, placebo-controlled, parallel-group Phase 3 pivotal trial with respect to dose selection, inclusion/exclusion criteria, endpoints, and statistical design to support an MAA.
- The proposed ITP-PAQ and KIT instruments as endpoints regarding patient disease experience.
- The design of the proposed open-label Part B of the ongoing Phase 2 PRN1008-010 trial as a supportive study, with respect to dose selection, eligibility criteria, endpoints, and statistical design to provide supportive evidence for an MAA.
- Adequacy of the clinical pharmacology plan to support a marketing authorisation application.
- Adequacy of the proposed safety database to characterise the safety profile of rilzabrutinib and form the basis for approval.
- Proposal to modify the primary endpoint for the ongoing pivotal study PRN1008-018 and inclusion of ITP-PAQ item 10 (Fatigue Scale) as part of the key secondary endpoint, while downgrading the bleeding scale to exploratory objective.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	26 September 2024
The procedure started on	31 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all	20 January 2025

CHMP and PRAC members on	
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	04 February 20
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	03 February 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 May 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	24 July 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	03 September 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	18 September 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 September 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to WAYRILZ on	16 October 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	16 October 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The intended indication for rilzabrutinib is for the treatment of persistent or chronic immune thrombocytopenia (ITP) in adult patients who are refractory to a previous treatment.

Immune thrombocytopenia (ITP) is an acquired rare autoimmune blood disease. ITP is primarily characterized by autoantibody-mediated platelet destruction and impaired platelet production, which results in thrombocytopenia (i.e., platelet count below 100,000/µL), an increased risk of bleeding and thrombosis, and diminished quality of life and increased mortality (Adelborg et al., 2019; Efficace et al., 2016; Rodeghiero et al., 2009). Typical symptoms include fatigue in addition to purpura, which may be mild or severe. Bleeding and fatigue associated with ITP negatively impact patients' quality of life (QoL). Anxiety is common due to fear of bleeding, patients have restricted activities, and treatment and monitoring impose significant burden.

The ITP World Impact Survey (I-WISH) collected QoL-related information from 1,507 patients with ITP and 472 physicians who treat patients with ITP across 13 countries. Patients reported reduced energy levels (85%), reduced capacity to exercise (77%), and limitations in ability to perform daily tasks (75%) due to their disease. Most (80%) physicians reported that ITP symptoms reduced patients' health-related quality of life (HRQoL); 66% indicated a substantial reduction from ITP-related fatigue. Approximately half (49%) of the patients surveyed had either reduced or seriously considered reducing their work hours (Cooper et al., 2021). Adults with ITP also experience cognitive impairment, difficulties in memory and concentration, which reduce their ability to perform complex daily living activities and their engagement in education and employment (Frith et al., 2012; Newton et al., 2011).

The disease burden is more significant in patients with symptomatic, persistent, and chronic thrombocytopenia requiring ongoing treatment and those who are unresponsive to current therapy, contributing to elevated mortality rates relative to the general population (Nørgaard et al., 2011; Frederiksen et al., 2014). Adult patients with chronic thrombocytopenia have up to a 10% risk of bleeding or haemorrhage that increases with age, and intracranial haemorrhage has been reported in approximately 1–2% of patients (Adelborg et al., 2019; Nørgaard et al., 2011; Neunert et al., 2015). Additionally, patients with chronic and refractory ITP may experience significant fatigue, cognitive impairment, fear of bleeding, and a negative impact on social and work activities, reinforcing the significant unmet need for these patients (Frith et al., 2012; Trotter & Hill, 2018; Terrell et al., 2020).

2.1.2. Epidemiology

ITP is an acquired rare autoimmune blood disease with epidemiology studies reporting an estimated worldwide prevalence of 10–20 per 100,000 persons (Liang et al., 2021; Terrell et al., 2012). A more recent Danish study highlights the increase in prevalence of ITP over time, from an estimated 25 per 100,000 persons in the year 2000 to 60 per 100,000 persons in 2015 (Lawrie et al., 2023). The prevalence of chronic ITP ranges from 10–23.6 per 100,000 persons (Saleh et al., 2009; Feudjo-Tepie et al., 2008; Pogna et al., 2021). The annual incidence of ITP is 6.1 per 100,000 persons (Weycker et al., 2020; Lawrie et al., 2023).

2.1.3. Aetiology and pathogenesis

The underlying pathophysiology of ITP is complex and includes pathogenic anti-platelet immunoglobulin G (IgG) autoantibodies that target surface antigens (e.g., glycoproteins αIIbβ3 [GPIIb/IIIA], GPIa/IIa, and/or GPIb-IX-V) (Al-Samkari et al., 2020; Zufferey et al., 2017; Grodzielski et al., 2018). The interaction of autoantibodies to various platelet glycoproteins results in platelet phagocytosis through binding of autoantibodies to Fcγ receptors (FcγR) on macrophages, platelet clearance by a C-type lectin receptor (CLEC4F) on hepatic Kupffer cells, platelet lysis by the membrane attack complex and/or phagocytosis due to classical complement pathway activation, T cell-mediated cytotoxicity, and/or impaired megakaryocyte viability (Zufferey et al., 2017; Grodzielski et al., 2018; Peerschke et al., 2010; Jiang et al., 2021; Reis et al., 2019). Considering the heterogeneity of mechanisms underlying ITP development, a single therapy that targets multiple pathogenic pathways is likely to be needed to induce sufficient and durable platelet response.

2.1.4. Clinical presentation, diagnosis

ITP is primarily characterized by autoantibody-mediated platelet destruction and impaired platelet production, which results in thrombocytopenia (i.e., platelet count below 100,000/μL), an increased risk of bleeding and thrombosis, and diminished quality of life and increased mortality (Adelborg et al., 2019; Efficace et al., 2016; Rodeghiero et al., 2009). Typical symptoms include fatigue in addition to purpura, which may be mild or severe.

2.1.5. Management

Treatment goals for ITP primarily focus on the prevention of bleeding by elevating the patient's platelet count. The standard therapy for adult patients with newly diagnosed ITP consists of corticosteroids (CS), such as oral high-dose dexamethasone or oral prednisone/prednisolone, but their prolonged use should be avoided due to associated adverse event (AE) burden (Cooper & Ghanima, 2019; Kuter, 2022; Neunert et al., 2019). Although most patients respond to initial CS therapy, responses are typically not durable, are associated with significant toxicities, and have a low rate of lasting remission (Cooper & Ghanima, 2019). First-line therapies also include intravenous immunoglobulins (IVIG) and anti-D immunoglobulin.

Recommended second-line treatments include rituximab, thrombopoietin-receptor agonists (TPO-RAs), and splenectomy. Splenectomy is an effective treatment choice with durable off-treatment remission rates of 60–70%; however, splenectomy might be associated with short-term surgery-related complications, infections, and thromboembolisms.

While rituximab and TPO-RAs have shown initial response rates of over 60% in randomized clinical trials (RCTs), high percentages of patients relapse after variable duration of treatment. In addition, infections, thromboembolisms, and other severe side effects have been associated with available treatments (Neunert et al., 2019; Singh et al., 2021; Mingot-Castellano et al., 2022; Kuter et al., 2008; Bussel et al., 2007; Kuter et al., 2010; Bussel et al., 2009; Tomiyama et al., 2012; Yang et al., 2014; Cheng et al., 2011; Wong et al., 2017).

Fostamatinib, a tyrosine kinase inhibitor against spleen tyrosine kinase (SYK)is also approved for patients with ITP who are refractory to other treatments. Placebo-adjusted durable response rates of 15% have been reported with fostamatinib in ITP patients (Bussel et al., 2018; Connell & Berliner, 2019; Center for Drug Evaluation and Research, 2016).

2.2. About the product

Rilzabrutinib (PRN1008/SAR444671) is a novel oral, reversible, covalent Bruton tyrosine kinase inhibitor (BTKi) developed for the treatment of autoimmune and inflammatory diseases. It mediates its therapeutic effect through a dual mechanism of action: (1) inhibition of B-cell activation and (2) interruption of antibody-coated cell phagocytosis by FcγR in the spleen and liver.

The intended indication was: WAYRILZ is indicated for the treatment of persistent or chronic immune thrombocytopenia (ITP) in adult patients who are refractory to a previous treatment.

The final approved indication is: WAYRILZ is indicated for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments

The posology is 400 mg twice daily (BID).

2.3. Type of Application and aspects on development

As mentioned above, the applicant received protocol assistance/scientific advice from the CHMP on the development for the ITP indication which pertained to the following quality, non-clinical, and clinical aspects.

EMEA/H/SA/3795/2/2020/PA/SME/III: The first scientific advice in the development of rilzabrutinib for the treatment of immune thrombocytopenia concerned the planned phase 3 study design. CHMP agreed to the overall study design with some exceptions. Inclusion/exclusion criteria were overall acceptable, but CHMP did not support the inclusion of adolescent patients in the trial. CHMP did not agree to the applicant's plan to initiate an open-label Part B of the ongoing phase 2 single arm trial in patients who had an insufficient response to prior treatments, with a historical placebo cross study comparison/control. This was because the part B would compete with the patient population of the phase 3 study, without providing significantly more or better results. Instead, eligible patients from the Phase 2 were recommended to be included in the proposed phase 3 study.

EMA/SA/0000090350: This advice related to the primary endpoint definition. The primary endpoint in ITP trials should represent a stable platelet count above the safe threshold for bleeding of 50 $x10^9$/l, to be durable and not to exceed a level with increased risk for thrombosis. The applicant sought to revise the definition of the primary endpoint in the then ongoing trial to address some challenges with conducting the trial. The CHMP criticized the revised primary endpoint for compromising trial integrity, questioned its clinical interpretation, noted a lack of comprehensive strategy for addressing missing data/ICEs, questioned the reference to precedence, and stated that the switching from central to local reading should be separated from considerations on endpoint definition. The CHMP also noted the need to address the durability of effect more appropriately and to consider the impact of external circumstances separately from the responder definition.

EMA/SA/0000152978: This advice concerned the applicant's proposal to demonstrate significant benefit of the product over authorised therapies through the use of an indirect treatment comparison (ITC) to compare the results of the PRN1008-018 study and the phase 3 studies from other approved drugs. CHMP found that while providing the efficacy results by ITC could be an acceptable approach, comparison of the proposed studies was problematic due to differences between the studies.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a film-coated tablet containing 400 mg of rilzabrutinib as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (E 460(i)), crospovidone (Type A) (E 1202), and sodium stearyl fumarate.

Film coating: polyvinyl alcohol (E 1203), macrogol (E 1521), titanium dioxide (E 171), talc (E 553b), and sunset Yellow FCF (E 110).

The product is available in a white, opaque, polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE)-aluminium blister pack as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of rilzabrutinib is (*EZ*)-2-[(3*R*)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile corresponding to the molecular formula $C_{36}H_{40}FN_9O_3$. It has a relative molecular mass of 665.77 g/mol and the following structure:

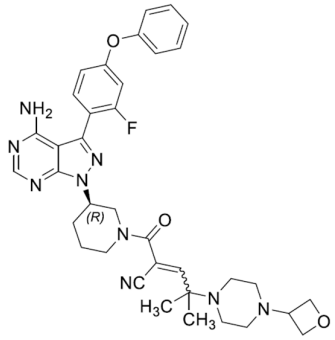


Figure 1: active substance structure

The chemical structure of rilzabrutinib was elucidated by a combination of techniques including elemental analysis, IR spectroscopy, UV spectroscopy, NMR spectroscopy, and mass spectrometry. The solid-state properties of the active substance were measured by such techniques as XRPD, DSC, TGA, SEM, BET analysis, DVS, and laser light diffraction.

The active substance is a white to off-white solid powder, it is moderately hygroscopic. The aqueous solubility of rilzabrutinib is pH dependent, it shows high solubility at low pH and this begins to decrease at pH values above 4.

Rilzabrutinib exhibits stereoisomerism due to the presence of one chiral centre. The chiral centre originates in one of the starting materials, and a test for chiral purity is controlled in the starting material and in the drug substance specification. The active substance is also present as a mixture of *E* & *Z* isomers across the double bond, and a consistent result is achieved using the proposed

manufacturing process and upon storage. The ratio of the *E*/*Z* isomers is controlled in the specification of the active substance.

Polymorphism has not been observed in conditions relevant to the manufacture and storage of the rilzabrutinib E/Z isomer mixture. The applicant has demonstrated that the isomeric E/Z mixture is present in an amorphous form which is consistently produced and sufficiently stable.

2.4.2.2. Manufacture, characterisation and process controls

The active substance process is conducted across two manufacturing sites. Satisfactory information with respect to GMP compliance has been provided in the QP declaration.

Rilzabrutinib is synthesized in eight main steps using well defined starting materials with acceptable specifications, some of which are commercially available.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The synthetic route was practically unchanged during the development process, and minor changes introduced for example to improve process efficiency and safety, have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance packaging complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for: appearance (visual), identity (IR, HPLC), assay (HPLC), *E*:*Z* isomer ratio (HPLC), impurities (HPLC, GC), chiral impurity (HPLC), water content (KF), residue on ignition (Ph. Eur.), elemental impurities (ICP-MS), residual solvents (GC), crystallinity (XRPD), and microbiological quality (Ph. Eur.).

The specification and test parameters are sufficient to ensure the quality of the active substance and are in line with relevant guidelines.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for batches manufactured throughout the development programme were provided. This included 18 batches representative of the commercial active substance, of which 3 commercial scale qualification batches were included. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from two commercial scale batches and one pilot scale batch of the active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 48 months under long term conditions (25 °C / 60% RH), 12 months under intermediate conditions (30 °C / 65% RH), and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. Photostability testing following ICH guideline Q1B was performed on one batch, the active substance is photosensitive when stored outside of the intended container closure system.

Results under stressed conditions were also provided on one batch. The conditions studied involved the effect of acidic, basic, hydrolytic, and oxidative exposure in the liquid phase. In the solid phase the impact of photolysis, dry heat, and heat with humidity was investigated.

The following parameters were tested: appearance, assay E/Z isomer ratio, impurities, chiral impurity, water content, crystallinity, and microbial enumeration. The analytical methods used were the same as for release and were stability indicating.

For the long-term stability studies all tested parameters were within the specifications under all conditions studied. Certain degradation products increased slightly under accelerated and intermediate conditions but remained within specification.

The stress testing study showed that rilzabrutinib is sensitive to acid, base, heat (dry heat or in presence of water/humidity), peroxide, and light.

With respect to ongoing stability studies, any confirmed out-of-specification result, or significant negative trend, should be reported to the rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 48 months, and the applicant's selected storage condition of do not store above 25 °C in the proposed container. While the stability results indicate the active substance could be stored at higher temperatures, the applicant's selected temperature storage condition does not impact the patient and is therefore acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a film-coated tablet containing 400 mg of rilzabrutinib. It is an orange tablet, capsule-shaped of 16.6 x 8.1 mm size, debossed with "P" on one side and "400" on the other side.

The aim of development was to create a safe and effective immediate release formulation, and a Quality target product profile (QTTP) was defined.

Critical quality attributes (CQAs) identified to be evaluated during product development were assay, degradation products, uniformity of dosage units, water content, and dissolution.

The active substance is practically insoluble in water and its solubility is pH dependent (high solubility at acidic conditions and low solubility at neutral and basic condition). The applicant has shown that the particle size of the active substance does not impact bioavailability or the dissolution of the finished product and therefore, it is not necessary to control the particle size of the active substance. The active substance is present in an amorphous form and the crystalline form is controlled in the specification of the active substance. It has been shown that the amorphous form is stable during the manufacture and storage of the finished product.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards, with the exception of the in-house film-coating for which an acceptable specification has been provided. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Early clinical studies involved the development of oral liquid formulations, hard capsules and various tablet formulations of different strengths. For the phase 3 clinical study program relevant to this indication, the applicant used the same formulation and active substance process proposed for commercial use.

Early development of the immediate release tablet formulation consisted of testing various excipients and processing techniques to produce a robust immediate release tablet formulation. The manufacturing process was performed at various scales during development and the information gained was used to inform the process parameters and in-process controls applied to the commercial process. In view of the intended commercialisation an additional manufacturing site was proposed. It was confirmed that the quality of the finished product manufactured at the two sites is equivalent, and this was supported by comparative dissolution data. Minor adaptions to the manufacturing process are needed between the sites in order to accommodate different equipment installations, these are suitably described and are acceptable.

The applicant's approach to the development of the dissolution method was initially not considered acceptable. The applicant had developed a method that was claimed to be discriminatory for certain finished product characteristics. However, the selected time-point for measuring the dissolution was set at a late time-point, but at this time-point all batches had already achieved similar dissolution values and no discriminatory power was therefore evident. The applicant was requested to tighten the dissolution limit and a Major Objection (MO) was raised by the CHMP on this aspect. In response, the applicant agreed to implement the dissolution specification testing at an earlier time-point however they also lowered the proposed dissolution value to be achieved. The lowering of this value was stated to be related to sticking of coated tablets. However, this justification was not acceptable and the MO was maintained. To resolve this MO the applicant provided further information on the investigations into tablet sticking and minimising variability of the method. It was demonstrated that it was currently not feasible to reduce variability of the method while ensuring the discriminatory power without significantly slowing the dissolution profiles or impacting the robustness of the method. As a result of this, the applicant implemented two dissolution time-points in their specification to be in line with the Ph. Eur. requirements for immediate release oral solid dosage forms. This approach was considered acceptable and the MO resolved.

The primary packaging is a white, opaque, polyvinyl chloride PVC/PCTFE-aluminium blister pack in a cardboard wallet. The primary materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at two manufacturing sites. Satisfactory information concerning GMP compliance has been provided.

The manufacturing process consists of eight main steps: milling, blending, granulation , sieving, final blending, compression, coating and packaging. At one of the manufacturing sites, a pre-blending step also takes place. The processes are considered to be the same with only minor adaptations between the sites to account for differences in equipment.

The manufacturing process is considered to be standard. Process validation has been conducted on three consecutive batches at one of the manufacturing sites. For the other site, process validation will be conducted, and a suitable process validation protocol has been provided. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The proposed bulk hold times at each of the sites have also been suitably justified by bulk stability data.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; appearance (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), a nitrosamine impurity (LC-MS/MS) microbiological quality (Ph. Eur.).

The specification and test parameters are sufficient to ensure the quality of the finished product and are in line with relevant guidelines.

Degradation products which are present above the ICH Q3B qualification threshold are appropriately qualified by toxicological studies.

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three commercial scale batches from each of the proposed manufacturing sites using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The risk assessment provided by the applicant concerning the potential presence of nitrosamine impurities was not considered acceptable and a MO was raised by CHMP and maintained during the procedure. To support their theoretical arguments that there was no-risk of such impurities, the applicant provided supportive testing data for small molecule nitrosamines in the active substance (NDEA, DIPNA, EIPNA) and supportive testing in the finished product for a potential nitrosamine impurity derived from the secondary amine impurity. While the supportive testing results demonstrated that the acceptable intakes would not be exceeded, a number of deficiencies were noted. The analytical method used for the active substance testing was not sufficiently sensitive to confirm that the small molecule nitrosamines would be present at <10% of their respective acceptable intakes. The applicant resolved this aspect by providing analytical data showing the methods were suitably sensitive to detect potential levels >10% of the acceptable intakes. For the finished product, the applicant had identified one potential nitrosamine and demonstrated that potential levels would not be >10% of the acceptable intake derived in accordance with the carcinogenic potency categorisation approach (CPCA) in four commercial scale batches. However, the approach of the applicant to identify only this potential impurity as a candidate for finished product testing was questioned and the applicant was requested to investigate the potential formation of other nitrosamines from secondary and tertiary amines of the active substance and its related substances. As part of this evaluation, another potential nitrosamine impurity was identified, and confirmatory testing was conducted. Four commercial scale batches were tested. The majority of these batches were 50 months in age which is beyond the proposed shelf life of the finished product. The results showed that the acceptable intake derived based on the CPCA was not exceeded. However, in the aged batches the amounts detected were >10% of the acceptable intake (up to 40% at 50 months). For this reason, it is necessary to control this impurity in the specifications of the finished product. The applicant was requested to update the dossier with the information on the analytical methods and standards used to

control said nitrosamine impurity and to provide an updated nitrosamines risk assessment. The applicant suitably updated the finished product specifications to control for this impurity. The control strategy for potential nitrosamine impurities is now considered acceptable and the MO is resolved.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results for 15 commercial scale batches (12 from the one of the manufacturing sites and 3 from the other site) were provided, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 36 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The batches were packaged in a transparent blister pack which is different to the white opaque blister proposed for marketing. The applicant provided information to demonstrate that both packaging types are comparable including up to 12 months long term and 6 months accelerated stability data for three commercial scale batches in the proposed commercial blister. The data was considered comparable between the packaging types, which are thus considered equivalent for the purposes of stability testing.

Samples were tested using the same methods proposed for the release specification. The analytical procedures used are stability indicating. Under long-term and accelerated conditions, no significant changes were observed. There were some small increases in degradation products, however the product remained within specification.

With respect to ongoing stability programs, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product is not photosensitive. Sensitivity to moisture was observed in an open dish study at 40 °C/75 %RH where a significant increase in water was observed.

Based on available stability data, the proposed shelf-life of 3 years, stored in the original package in order to protect from moisture as stated in the SmPC is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure two major objections concerning quality were raised by CHMP, these were related to the development of the dissolution method and the assessment of potential nitrosamine impurities. To resolve the major objection connected to the method proposed for the dissolution testing of the finished product, the applicant implemented two suitable specification time points. Concerning nitrosamine impurities, the applicant updated their risk assessment providing further theoretical and confirmatory testing data for potential nitrosamine impurities. A suitable limit for nitrosamine impurity

is now included in the specification of the finished product. While the relevant acceptable intake for this impurity is not exceeded, the levels present in certain aged batches are above 10% of the acceptable intake meaning that control is warranted. This approach ensures that this impurity will not exceed the acceptable intake and the control strategy and risk assessment for potential nitrosamine impurities is acceptable.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Rilzabrutinib was investigated in a full range of nonclinical pharmacology, pharmacokinetic, and toxicology studies.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Specificity and mechanism of action (*in vitro*)

The biochemical characterization of rilzabrutinib demonstrated the compound to be a potent inhibitor of BTK with durable target occupancy with an IC_{50} against the purified BTK of 1.3 nM. The kinetic characterization demonstrated rilzabrutinib to have a fast on-rate and slow off-rate (half-life of 7 days). The mechanism of inhibition is through competitive inhibition of ATP binding which leads to a shift of the IC_{50} to 3-9 nM depending on the presence of physiological ATP concentrations. Importantly, the interaction of rilzabrutinib with BTK, despite the covalent binding to cysteine (Cys481), is reversible.

In order to show reversibility of the binding and to control for possible BTK peptides linked to rilzabrutinib (which may result from physiological BTK protein turnover), the purified recombinant BTK has been incubated with rilzabrutinib. Following trypsinization, 137% of rilzabrutinib was recovered in the solution, while 0% ibrutinib was obtained under the same conditions (DRV0102).

Further the reversibility of the BTK inhibitory effect of rilzabrutinib may be further amplified by quantitative BTK protein turn-over. The biological half-life of BTK within B cells reaches 12 hours

(Saffran et a., 1994). Hence, reversibility of the rilzabrutinib effect is due to dissociation of rilzabrutinib from BTK and BTK protein turnover.

The durability, potency, and selectivity of rilzabrutinib were assessed in multiple cell-based systems in which BTK inhibition by rilzabrutinib further corroborated the mechanisms of action *in vitro*. The cellular occupancy and durability of rilzabrutinib was confirmed in Ramos cells, which are BTK expressing human B cells. The IC_{50} for rilzabrutinib was 8 nM and occupancy determined at washout times of 4 and 18 hours were 76% and 60%, respectively (DRV0070). Thus, affinity and occupancy for rilzabrutinib to bind BTK from a cell free system was retained in Ramos cells.

The functional ability of rilzabrutinib to inhibit BCR-driven activation of B cells, as assessed by CD69 expression, was also confirmed in HWB and PBMCs. The CD69 surface expression reveals an early lymphoid activation signal leading to inflammation and autoimmune conditions with downstream signals like NFkB, AP1 and early growth response protein (EGR-1). The IC_{50} values for CD69 surface expression varied from 123±38 nM to 233±75 nM rilzabrutinib in both cell bases assays, $CD20^{+}$ B cells and PBMCs respectively (DRV0070). Rilzabrutinib inhibition of BTK was also shown to inhibit anti-IgM-induced human B cell proliferation with an IC_{50} of 5 nM rilzabrutinib (DRV0167).

The ability of rilzabrutinib to inhibit IgG-mediated activation of monocytes and IgE-mediated activation of basophils, assessed by inhibition of TNF-alpha production and CD63 expression, respectively, was confirmed in two additional assays. In human monocytes IgG mediated TNF-alpha production was inhibited by rilzabrutinib with an IC_{50} 55.7±45 nM indicating a potent anti-inflammatory potential (DRV0286). In human whole blood, anti-IgE mediated activation of basophil granulocytes by BTK dependent Fc receptor-epsilon crosslinking was monitored via CD63 expression. Rilzabrutinib inhibited CD63 surface expression with an IC_{50} of 490±130 nM (DRV0070). Together these results confirm the expected on-target effects of rilzabrutinib on BCR and Fc receptor signalling.

Off-target effects

The lack of off-target rilzabrutinib activity was confirmed in multiple cellular cross screens using either cells that do not express BTK or processes that are not mediated by the BTK pathway. In T cells, BTK is not expressed and was therefore used to detect off-target effects. The T cell receptor activation including the crucial down-stream transcription factor NFAT was hardly affected by nanomolar concentrations and revealed an IC_{50} for rilzabrutinib >5 µM (DRV0070).

Similarly, the BTK independent pathway of IL4-induced STAT6 activation in human Ramos B cells revealed an IC_{50} for rilzabrutinib >5 µM, indicating no off-target effect in these cells (DRV0070).

Investigation of the EGF-receptor pathway (activation of the transcription factor AP1) in human cervical carcinoma cells (ME-180), which do not contain BTK, revealed an IC50 for rilzabrutinib >5 µM. Again, although the EGFR represents a binding target (IC_{50}: 520 nM) a concentration of 5 µM rilzabrutinib inhibited the EGFR pathway only 19-30% (DRV0070).

Rilzabrutinib had virtually no activity in a cytotoxicity assay (IC_{50} 16 µM) using in a transformed human epithelial HCT-116 cell line, which also do not express BTK (DRV0070).

Potent activity against off-target kinases was few in number and demonstrated reduced durability of inhibition compared to other kinases. Similar to BTK, closely related TEC kinases (TEC, BMX, TXK) were inhibited with an IC50 between 0.8 and 1.2 nM rilzabrutinib and, importantly, also showed an occupancy between 36 and 59% at 24 hours (DVR0102). In addition, the receptor tyrosine-protein kinase ERBB4 is also inhibited with high affinity (IC_{50} = 11 ± 7 nM). Kinase occupancy data are not provided or discussed.

In an *in vitro* study, 5 µM rilzabrutinib inhibited TCR-mediated T cell activation up to 48%. A study was carried out *in vitro* to demonstrate that rilzabrutinib has no inhibitory effect on ADCC up to 1 µM.

Hence, given a rilzabrutinib C_{max} of 1 µM in humans, and a free rilzabrutinib concentration of 3.75ng/ml such off-target effects are considered unlikely and clinically not relevant.

Similarly, in the CEREP screening profile, rilzabrutinib showed activity >50% against only 4 targets (muscarinic M2 receptor, neurokinin NK2 receptor, sodium channel site 2, and dopamine transporter), whereas activity against all other receptors, transporters, and ion channels in this panel was less than 50% (DVR0095). However, the pharmacological consequences due to potential off-target activity is considered to be low, as the concentration tested for rilzabrutinib was 10 µM. Thiocyanate, the main metabolite of rilzabrutinib showed no activity over 50% in the CEREP radioligand binding assay (100056422_014-I&I-21).

Platelet function

Rilzabrutinib had no effect on platelet aggregation *in vitro*, although significant expression of BTK is observed in these cells. Irrespective, whether healthy donor platelets or ITP patient derived platelets were used, up to 1 µM rilzabrutinib had no impact on agonist induced aggregation (PRN1008-008; DVR0307).

Metabolites of rilzabrutinib

Three major metabolites of rilzabrutinib were identified and further investigated, thiocyanate (PRN4400; 94% of total exposure), PRN834 (5% of total exposure) and PRN618 (<1%) (DRV0528). The major human metabolite thiocyanate was not able to inhibit BTK up to 5 µM and showed no measurable occupancy of BTK and no inhibition of BCR-induced CD69 expression in the HWB cellular assay (DVR0528). In a radio ligand binding assay testing for competition at possible new targets, 10 µM thiocyanate was not found to compete with the ligands up to 50%. Since thiocyanate is an endogenous compound in human serum between concentrations of 3-15 mg/L. Hence, impact on the overall thiocyanate concentration due to metabolism from rilzabrutinib seems negligible.

Comparison of the IC_{50} values reveals that PRN834 inhibited BTK with an IC_{50} of 14.5 nM and PRN618 with an IC_{50} of 0.4 nM, comparable to rilzabrutinib (1.3 nM). Although PRN618 also showed a BTK enzyme occupancy of 53%, all three metabolites were not able to inhibit BCR-induced CD69 expression in human B cells more potent than rilzabrutinib.

The BTK biochemical activities of the (E) and (Z) isomers of rilzabrutinib were assessed and were determined to be indistinguishable based on their similar BTK enzymatic activities and occupancies. Rilzabrutinib also contains a single stereogenic center with the (R)-configuration. The corresponding compound with the (S)-configuration, PRN1418, was determined to be a less potent inhibitor of BTK and to have faster off-rate kinetics than rilzabrutinib (DV0308).

Rilzabrutinib was shown to be a more potent inhibitor of BTK than its major metabolites, impurities, and stereoisomers.

Biological activity *in vivo*

Assessments of rilzabrutinib effects were conducted in a variety of *in vivo* disease models but focus on anti-inflammatory mechanisms not directly associated to ITP. Only a single ITP-model covers the projected indication of rilzabrutinib.

Rats administered rilzabrutinib were shown to have high percent occupancy of BTK in the spleen at 1 hour after administration. Target occupancy was maintained (61 to 75%) in these animals after the plasma levels of rilzabrutinib dropped to levels <10 ng/mL. This demonstrates that *in vivo* binding of rilzabrutinib to BTK is durable after plasma levels of rilzabrutinib have cleared systemic circulation (DRV0106).

In a murine model for ITP, rilzabrutinib pretreated animals were stressed with an intraperitoneal injection of an anti-CD41 antibody to induce thrombocytopenia (DVR0288). The drop in platelets was significantly reduced in the presence of 10-40 mg /kg rilzabrutinib in a dose dependent manner compared to vehicle. However, this effect was only seen 6 hours after anti-CD41 antibody application, while no significance difference with the vehicle was observed at 24 and 48 hours. Moreover, platelet counts were higher in rilzabrutinib pretreated animals at the time point of anti-CD41 antibody application. Consequently, the velocity of the drop in platelets with rilzabrutinib is indistinguishable from vehicle (zero-6 hours).

Hence, in the pivotal animal model, rilzabrutinib was not able to prevent full drop in platelets, was not able to reduce the drop velocity of platelets and was not able to significantly accelerate the recovery in platelet numbers. Although BTK occupancy determined after the last drug application ranged from 51-91%, this BTK inhibition could not translate into a significant biological effect mirrored in platelet counts.

Rilzabrutinib (10, 20 and 40 mg/kg) was effective in a collagen-induced arthritis model in rats and was comparable to dexamethasone (0.075 mg/kg) (DVR0200). Animals treated with 20 mg/kg rilzabrutinib BID showed complete reduction of arthritis Ankle score as dexamethasone. Interestingly, reduction of arthritis Ankle score with a 20 mg/kg BID dosing was more effective than 40 mg/kg rilzabrutinib QD.

Rilzabrutinib was also shown to be effective at passive Arthus reaction (DVR0287) in rats. BTK occupancy by rilzabrutinib correlated with disease suppression in this rat study, indicating rilzabrutinib mediated BTK inhibition may prevent IgG-mediated Fc-gamma receptor downstream signalling.

Rilzabrutinib was tested in passive cutaneous anaphylaxis (DVR0447) in mice. The extravasation area and intensity was significantly inhibited by prednisolone and the H1-blocker cyproheptadine, whereas only the highest dose of 80mg/kg rilzabrutinib reached significance level in both readout parameters. Occupancy of BTK in all dose groups was > 85% when analysed 3.5 hours after the last dosage. Again, robust occupancy of spleen BTK is not correlating with biological efficacy, nor reaching the efficacy of the positive controls.

When four dogs with naturally occurring canine pemphigus foliaceus were treated with rilzabrutinib, all showed complete or substantial clinical improvement by week 20 without the need for usual corticosteroid treatment (DVR0372). Clinical improvement in canine PDAI score was 77-100% indicating robust efficacy as a monotherapy. Elevated liver aminotransferases and reduced appetite were observed in two animals and resolved upon dose reduction. However, this study lacks a proper control and comparison to an alternative drug so that it is not possible to deduce any conclusion on the level of efficacy.

Together these *in vivo* studies demonstrate that rilzabrutinib, when given orally, can achieve BTK occupancy levels that result in the inhibition of B cell activation and FcγR signalling to inhibit progression and reverse antibody- and immune cell-mediated inflammation in various preclinical models.

2.5.2.2. Secondary pharmacodynamic studies

To investigate the etiology of decreased appetite observed in the dogs treated with rilzabrutinib, the secondary pharmacology of rilzabrutinib on the gut-brain axis was assessed in canine and rodent models.

Decreased appetite was observed in dogs receiving 15-500 mg/kg rilzabrutinib (DVR0173, DVR0206, DVR0377). Since emesis and anorexigenic effect were observed in all three beagle dogs treated with 30mg/kg rilzabrutinib, this immediate effect is considered of therapeutic relevance (DVR0226).

Significant elevations of peptide YY and leptin were measured and in the applicant's interpretation are deemed to participate in the above described anorexigenic effect. In a similar study in rats oral rilzabrutinib (500 mg/kg) resulted after 4 days in significantly elevated stomach weight, decreased food consumption and reduced body weight (DRV0235).

Beside peptide YY and leptin also glucagon and pancreatic polypeptide were elevated at all time points investigated in study DVR0226. The potent regulators of blood glucose, GIP and insulin were also fluctuating between mainly reduced but also significantly elevated at a single time point (7 h post dose).

In longer chronic GLP toxicological studies, direct contact of rilzabrutinib with stomach mucosa was reduced by using a capsule formulation (DRV0301 and DRV0206). Administration in a capsule reduced stool changes, emesis and initial weight loss compared to liquid vehicle formulation. Protection from reduced gastric emptying was also seen when rilzabrutinib was applied intrajejunally (100 mg/kg) (DRV0235).

2.5.2.3. Safety pharmacology programme

In a core battery of safety pharmacology studies, there were no rilzabrutinib-related adverse effects on CNS, CV, and respiratory systems.

In a rat study to evaluate the potential effects of rilzabrutinib on the CNS, no rilzabrutinib-related changes on gross behaviour profile, physiological and neurological state, or body temperature were observed at doses up to 500 mg/kg.

In vitro, the hERG IC_{50} of rilzabrutinib was 3.5 µM (2328.7 ng/mL). The risk of QT prolongation in humans is considered to be low since rilzabrutinib is highly protein bound (97.5%) so the plasma free fraction projected at a C_{max} (150 ng/mL) corresponding to a 400 mg BID dose would be as high as 3.75 ng/mL, assuming free fraction is 2.5%.

In vivo, the no observed adverse effect level (NOAEL) for effects on the CV and respiratory systems in male dogs was considered to be 500 mg/kg rilzabrutinib (mean C_{max} and AUC_{last} values were 3760 ng/mL and 20 200 ng h/mL, respectively).

2.5.2.4. Pharmacodynamic drug interactions

No non-clinical studies investigated pharmacodynamics drug interactions.

2.5.3. Pharmacokinetics

The applicant conducted a comprehensive non-clinical pharmacokinetic program, including *in vitro* and *in vivo* studies in relevant non-clinical species and humans.

Analytical Methods

The applicant submitted six validation reports (PDV0226, DVR0161, AV21-244, DVR0506, DVR0507, DVR0508) for HPLC/MS/MS analysis to determine plasma concentrations of rilzabrutinib and/or its metabolites PRN834, PRN618 and PRN4400, if applicable, within the scope of GLP compliant pharmacokinetic and toxicity studies [repeat dose PK study in rats (study 1281-21219), single dose toxicity studies in rats (study DVR0178) and dogs (DVR0179), repeat dose toxicity studies in rats (studies DVR0174, DVR0207 and DVR0376) and dogs (DVR0184, DVR0206 and DVR0377), embryo-fetal development studies in rats (study DVR0378) and rabbits (DVR0379)]. Due to the low extraction recovery of rilzabrutinib, PRN618 and PRN834 in rat plasma, an LCMS/MS assay validation report for

the determination of PRN1088 and PRN834 from rat plasma (study PDV0296) was resubmitted upon request, using the same acetonitrile precipitation extraction method as before, but with matrix ions present in the extraction recovery QCs. This time, the results of recovery were close to 100% for PRN1008 and PRN834. All validation studies were performed according to standard operating procedures (SOPs) in a facility compliant with applicable FDA GLP regulations.

Calibration curves for rilzabrutinib, PRN834 and PRN618 were ranging from 1 ng/mL to 1000 ng/mL, whereas for thiocyanate (SCN, PRN4400) a calibration curve ranging from 1000 ng/mL to 50000 ng/mL was used. Overall, evaluated validation endpoints, e.g. curve parameters, inter and intra assay accuracy and precision (calibration standards, quality control (QC) and dilution QC samples), reproducibility (accuracy and precision of haemolyzed QCs, assay transfer and matrix factor), recovery, selectivity and sensitivity (double blank, blank and IS samples; ULOQ QC samples without IS; carryover), matrix stability (benchtop stability, freeze-thaw stability, long term stability), post-preparative stability (reinjection stability, batch size determination, injection order determination) and whole blood stability, met their pre-specified limits, as applicable, in all analysis, with the exemption of reinjection stability of the metabolites thiocyanate and PRN618, which failed in study AV21-244 and DVR0507, respectively, and carryover, which failed for PRN618 in study DVR0506, therefore requiring monitoring during sample analysis/reinjection.

Absorption

Single dose studies

Non-GLP single dose absorption studies to evaluate pharmacokinetic parameters and bioavailability after IV (2mg/kg) and PO (equal or approximately 20mg/kg and 100mg/kg) administration of rilzabrutinib were conducted in female Sprague-Dawley rats (study DVR0077), male beagle dogs (study DVR0078) and male cynomolgus monkeys (DVR0080). Plasma concentrations of rilzabrutinib were determined by LC/MS/MS analysis.

The mean clearance rate (CL) after the intravenous route of administration was 65.9 ml/min/kg in rats (n=2), 40.3 ml/min/kg in dogs (n=3) and 22.8 ml/min/kg in cynomolgus monkeys (n=3), representing approximately liver blood flow in rats and dogs and approximately half liver blood flow in monkeys, comparable to values published by Davies and Morris 1993, suggesting, that the clearance of rilzabrutinib could be accomplished by hepatic mechanisms. The volumes of distribution (V_z) in rats, dogs and monkeys, were 0.33, 13.31 and 2.62 L/kg, respectively. Elimination half-life ($t_{1/2}$) was 0.6, 0.7 and 0.4 hours in rats, dogs and monkeys, respectively. IV administration of 2mg/kg resulted in C_{max} and AUC values of 1608 ng/mL and 505 ng*h/mL, 2066 ng/mL and 827ng*h/mL and 2790 ng/mL and 1464 ng*h/mL, respectively, in rats, dogs and monkeys.

After oral administration of 20mg/kg or 100mg/kg rilzabrutinib in female rats (n=4), a t_{max} of 0.5 and 1 hour, a C_{max} of 270 and 2795 ng/mL, a $t_{1/2}$ of 1.5 and 2.6 and an AUC_{inf} of 622 and 13 310 ng*h/mL was observed, respectively. The increase in exposure at the 100mg/kg was more than dose-proportional and showed a higher oral bioavailability (F of 52.7%) when compared to the 20mg/kg dose (F of 12.3%). Comparable rilzabrutinib exposures were found in male dogs (n=3) (with a t_{max} of 0.5 and 4 hours, a C_{max} of 378 and 2050 ng/mL, a $t_{1/2}$ of 2.2 and 2.0 and an AUC_{inf} of 695 and 11 667 ng*h/mL for 20mg/kg and 100mg/kg, respectively), with a moderate oral bioavailability (F) of 28.2% at the higher, and 7.5% at the lower dose.

Oral administration of 20mg/kg or 100mg/kg rilzabrutinib in male monkeys (n=3) led to a t_{max} of 1 and 4 hours, a C_{max} of 181 and 431 ng/mL, a $t_{1/2}$ of 1 and 2.5 and an AUC_{inf} of 473 and 2 772 ng*h/mL, respectively. The oral bioavailability (F) was low at both doses, with 3.2 and 3.8%, respectively.

Further single dose studies

A non-GLP pharmacokinetic study in CD-1 mice (study DVR0406; 18 mice/group) was conducted to compare and evaluate pharmacokinetic parameter of rilzabrutinib and its metabolites PRN834 and PRN618 after single oral administrations of 100, 300 or 600 mg/kg precipitated or micronized rilzabrutinib.

T_{max} values of rilzabrutinib and its metabolites ranged from 0.25 to 1 hour at all doses with the exception for the metabolite PRN834 at the 300 and 600mg/kg dose, where t_{max} was 4 and 6 hours, respectively. C_{max} of rilzabrutinib increased less than and AUC_{last} approximately dose proportional for both formulations, the first indicating possible dose limiting absorption. Comparable rilzabrutinib and metabolite exposures were observed for both formulations, however, the micronized formulation was further used in toxicology studies in mice. The non-GLP Study DVR0233 was conducted to determine differences in pharmacokinetic parameter due to different methods of blood sample collection, comparing anesthetized (Non-JVC) versus non-anesthetized (jugular vein cannulated, JVC) female rats, after a single oral administration of 20, 50 and 100 mg/kg rilzabrutinib.

Systemic exposure (T_{max}, C_{max} and AUC_{last}) after oral rilzabrutinib administration in jugular vein cannulated rats was similar as observed in the non-GLP rat PK study DVR0077. Since there was an issue with the dose solution (not homogenous) in the non-JVC groups, data of these groups should be considered with precaution. However, systemic exposure (C_{max} and AUC_{last}) in Non-JVC female rats was 2-fold less when compared to JVC female rats.

Repeat dose studies

A GLP-compliant fourteen-day pharmacokinetics study in male and female Wistar-Han rats (14/sex/group) was conducted to bridge between animal and human studies to demonstrate exposure of PRN4400 (SCN, thiocyanate), the major but inactive metabolite of rilzabrutinib in humans, which is also physiologically present in plasma, and the exposure of the metabolites PRN834 and PRN618, after single and repeated dosing of 150 or 500mg/kg rilzabrutinib.

Mean plasma pharmacokinetic parameter (T_{max}, C_{max} and AUC_{last}) of rilzabrutinib after a single 150mg/kg dose in female rats were similar as observed in the single 100 mg/kg oral PK study in female rats DVR0077. Only a minor increase in C_{max} and AUC_{last} was seen in females after a single administration of 500 mg/kg when compared to a single administration of 150 mg/kg. Repeated administration of 150 mg/kg resulted in similar exposure values (C_{max} and AUC_{last}) when compared to a single administration of the same dose. Repeated 500 mg/kg doses in females increased C_{max} and AUC_{last} less but almost dose-proportionally. In male rats, exposure (C_{max} and AUC_{last}) was markedly lower (ranging from 1.2 to 3.6-fold less) when compared to female animals.

Mean plasma exposures (C_{max} and AUC_{last}) of PRN618 increased less than dose-proportionally after a single dose administration and approximately dose-proportional after repeated dosing. No differences in sex were observed. T_{max} ranged from 0.5 to 1 hour.

Mean plasma exposures (C_{max} and AUC_{last}) of PRN834 in female rats were almost the same after a single administration of 150 or 500 mg/kg but increased about 2-fold after repeated dosing in the higher dose group. In males, exposures increased after single and repeated dosing in a slightly less than dose-proportional manner. Exposures in females were ≥ 2-fold higher when compared to males at 150 mg/kg dosing, whereas at 500 mg/kg, the difference was apparently less. T_{max} ranged from 0.5 to 8 hours.

Concentrations of PRN4400 at baseline ranged from 1130 to 2660ng/mL at day 1. Apparent differences in exposure were only noticed after repeated dosing (at day 14), with approximately 2-fold higher exposure values at 500 mg/kg (C_{max} values of 7160 ng/mL and 8020 ng/mL, and AUC_{last} values of

149 000 ng*h/mL and 184 000 ng*h/mL, respectively, in females and males) when compared to 150 mg/kg (C_{max} values of 3170 ng/mL and 4860 ng/mL, and AUC_{last} values of 58 100 ng*h/mL and 96 200 ng*h/mL, respectively, in females and males). Systemic accumulation (accumulation ratio values >2.0 for C_{max} and AUC_{last}) was only observed at the high dose groups. T_{max} ranged from 0.5 to 24 hours. No apparent differences in sex were observed.

In vitro studies

A bi-directional transport assay in Caco-2 cells was used to investigate, if rilzabrutinib is a substrate of the P-glycoprotein (P-gp) efflux transporter.

Results suggest, that rilzabrutinib could be a potential substrate of efflux transporters in this cell type, showing a Net Flux ratio of greater than 2 (namely 3.1) for rilzabrutinib and a ratio of 8.3 for its positive reference compound digoxin. No further studies with a selective transporter inhibitor for P-gp were performed to confirm this result.

Distribution

Protein binding and blood partitioning

An equilibrium dialysis method was used to investigate protein binding of rilzabrutinib (1 µM; 0.667 µg/mL) in human and rat (study DVR0093) as well as in dog and mouse (study DVR0094) plasma.

Rilzabrutinib was found to be bound to proteins (mean values) with 97.51% in human, 98.69% in rat, 95.94% in dog and 99.21% in mouse plasma, whereas % recovery was low in rat (45.65%) and in mouse (30.92%) plasma, when compared to human (83.01%) and dog (75.85%) plasma, presumably due to lower stability in rat and mouse plasma, as determined by stability testing after 6 hours incubation.

Distribution of rilzabrutinib (5 µM) in red blood cells and plasma of rats, dogs and humans was investigated in blood partitioning experiments (study DVR0083).

The RBC to plasma ratio ($K_{RBC/Pl}$) for rilzabrutinib was 0.27 in rat, 0.40 in dog, and 0.47 in human, demonstrating, that rilzabrutinib rather remained in the plasma compartment than partitioning to red blood cells.

Tissue distribution

Excretion mass balance (MB) and tissue distribution by quantitative whole-body autoradiography (QWBA) after a single oral administration of [^{14}C]PRN1008 at 40 mg/kg to male albino rats (Sprague Dawley; SD) was investigated in the non-GLP compliant study DVR0159. QWBA was also conducted in pigmented male rats (Long-Evans; LE).

Mean pharmacokinetic parameter in male Sprague Dawley (n=6) after an oral dose of [^{14}C]PRN1008 40mg/kg were determined to be 2.407±0.472 µg equiv/mL, 96.862±20.257 µg equiv·h/mL, 42.4±4.2 h and 4±2 h for C_{max}, AUC_{last}, $t_{1/2}$ and T_{max}, respectively. 72 h post-dose concentrations in plasma decreased to 0.691±0.151 equiv/mL.

Blood to plasma concentration ratios increased with time, showing approximately equal concentrations in blood and plasma up to almost 4 hours and reaching a maximum ratio of 1.55 at 168 hours post-administration, the latest time point investigated.

In both strains, [^{14}C]PRN1008-derived radioactivity was found to be well distributed in most tissues at all time-points with concentrations slightly lower or comparable as seen in blood and a C_{max} of ≥ 1.0 µg equiv/g at 4 hours post-dose. Afterwards, tissue concentrations decreased constantly, whereas at 168 h post-dose, in about 40% of tissues of pigmented rats, radioactivity was eliminated again. In

pigmented (LE) rats, the highest tissue concentrations at C_{max} of > 10.0 µg equiv/g were observed in stomach, small intestine, esophagus and liver, whereas the lowest concentrations at C_{max} of < 0.6 µg equiv/g found in mammary gland region, bone, white adipose and eye lens. In the brain and spinal cord, no radioactivity could be determined in pigmented (LE) rats, whereas low and punctual radioactivity was measured in albino (SD) rats. Contents of the alimentary canal, urinary bladder and bile showed the highest concentrations of radioactivity, being in line with the supposed route of excretion via the bile and thus faeces. Overall, concentrations of radioactivity in pigmented tissues, as eye uveal tract and pigmented skin, were higher and more persistent when compared to non-pigmented tissues, suggesting an association with melanin, but considered reversible, as a decrease was observed again with time.

CSF

Study DVR0212 was conducted to further investigate possible penetration of rilzabrutinib and five of its metabolites (PRN618, PRN834, PRN1186, PRN835, and PRN438) to cerebral spinal fluid (CSF) in non-pigmented female Wistar Han rats, since 2 out of 3 rats of this species showed punctually and low levels of rilzabrutinib in the brain and/or spinal cord in study DVR0159.

Comparable concentrations of rilzabrutinib and its metabolites PRN618 and PRN834 were found in plasma of female Wistar Han rats after an oral dose of 50mg/kg rilzabrutinib in this study (DVR0212), and the 13-week toxicology study DVR0207, whereas in the latter, PRN1186, PRN835 and PRN438 concentrations were not determined, but detected in study DVR0212 after 1 and 4 hours post-dose. In CSF, rilzabrutinib concentrations and those of its metabolites PRN618, PRN834, PRN1186, PRN835 and PRN438 were below the limit of quantification (<1.25ng/mL).

No studies regarding placental transfer or excretion to milk were conducted. Please refer to the discussion of the pre- and postnatal development studies in the toxicology section.

Metabolism

in vitro

Study DVR0092 and DVR0096 investigated the stability of rilzabrutinib in human, dog and rat plasma or pooled liver S9 fractions of humans, male rats and male dogs, respectively, *in vitro*.

In human and dog plasma, rilzabrutinib (5 µM) stayed stable approximately up to 30 minutes and then decreased after 120 minutes to 82.69% and 67.36%, respectively. In rat, rilzabrutinib concentrations in plasma decreased more continuously, reaching 68.94% after 2-hours. After 60 minutes and in the presence of NADPH, rilzabrutinib (2µM) concentrations in pooled human, dog and rat S9 fractions decreased to 25.30%, 12.17%, and 5.15%, respectively, with calculated intrinsic clearance values of 23.48, 44.77 and 83.90 µL/min/mg protein and half-life values of 29.51, 15.48 and 8.26 minutes, respectively.

In study DVR0105, rilzabrutinib's *in vitro* metabolic stability and metabolite formation (PRN618, PRN834 and PRN 1186) at 1 and 10 µM was assessed up to two hours in human liver, lung and intestinal S9 fractions. Additionally, microbial biotransformation of rilzabrutinib was investigated for 24 hours under anaerobic conditions in fresh human faeces at the same concentrations (1 and 10 µM).

In the presence of human liver, lung and intestinal S9 fractions and cofactors (NADPH and NADPH), moderate to extensive degradation of rilzabrutinib at 1 µM after 2 hours was observed, with 9.6%, 48.7% and 4.7% of the initial rilzabrutinib concentration remaining in the liver S9 fraction, lung S9 fraction and intestinal S9 fraction, respectively. At 10 µM rilzabrutinib, degradation to 22.8% and 36.9% of the initial concentration was seen in human liver and intestinal S9 fractions, respectively, whereas rilzabrutinib concentrations stayed stable in human lung S9 fractions. Since rilzabrutinib was stable in medium without S9 fractions and cofactors, it is assumed, that rilzabrutinib is degraded

through biotransformation rather than chemical degradation. This is additionally supported by the observed slower degradation of rilzabrutinib at higher concentrations presumably due to supposed enzyme saturation. Half-life of rilzabrutinib (with cofactors) was 0.13 h and 0.83 h at 1 µM and 10 µM in human liver S9 fractions, and 2.31 h at 1 µM in human lung S9 fractions.

Because concentrations of determined metabolites after 2 hours incubation at 1 µM rilzabrutinib were low, 2.3% and 13.2% of PRN618 and PRN834, respectively, in human liver S9, and 5.2% and 14.1%, respectively, in the intestinal S9 fraction, other metabolites must have been formed as well.

Under anaerobic conditions in the human intestinal flora from human faeces, rilzabrutinib at 1 and 10 µM moderately degraded after 24 hours to 56.7% and 61.8%, whereas 44.0% and 44.4% of the original rilzabrutinib concentration accounted for metabolite PRN834.

The *in vitro* metabolic stability of rilzabrutinib (2 µM) was investigated in pooled male dog and male rat liver microsomes (DVR0089) and pooled human liver microsomes (DVR0090), as well as in dog, rat (study DVR0180) and human (study DVR0086) hepatocytes (at 1 µM).

In the presence of NADPH, rilzabrutinib concentrations decreased rapidly within the first 15 and 30 minutes, with 7.06%, 4.51% and 3.05% of the original rilzabrutinib concentration remaining after 60 minutes in the samples, showing *in vitro* intrinsic clearance (CL_{int}) values of 163.79, 189.74 and 177.73 µL/min/mg protein and half-life ($t_{1/2}$) values of 8.46, 7.30 and 7.80 minutes in dog, rat and human liver microsomes. After 90 minutes, the percentage of remaining rilzabrutinib in dog, rat and human hepatocytes was 3.21%, 1.73% and 7.95%, with intrinsic clearance values of 76.16, 89.89 and 53.45 µL/min/10^6 cells, respectively.

CYPs

Study DVR0084 and DVR0085 were conducted to investigate rilzabrutinib's potential to induce the activity of CYP 1A2, CYP 2B6 and CYP 3A4 in cryopreserved human hepatocytes or to inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 in pooled human liver microsomes, respectively, by determination of specific metabolites of known CYP substrates (e.g. Phenacetin, Testosterone) by LC/MS/MS. Positive controls (e.g. Omeprazole or furafylline, respectively) were included.

Rilzabrutinib at 10 µM did not induce significant activity of CYP 1A2, CYP 2B6 and CYP 3A4, whereas an inhibition of CYP1A2, 2C8, 2C9, 2C19 and 2D6 at 11.63, 30.61, 30.00, 51.16 and 9.97 %, respectively, was noticed. For CYP3A4, an inhibition percentage of 70.87 and 58.37 was observed, depending on the used substrate (Midazolam or Testosterone, respectively).

In study DVR0108, CYP reaction phenotyping of rilzabrutinib (1 µM) and other test articles (e.g. Midazolam) was assessed in human recombinant supersomes (containing CYP enzymes) and in mock supersomes (without CYP), the latter serving as control to detect non-CYP degradation. The remaining parent was quantitated by LC/MS/MS.

CYP-dependent elimination rate constant CL_{int} and half-life ($T_{1/2}$) were determined for rilzabrutinib with CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4, whereas the highest intrinsic clearance and shortest half-life were observed for CYP 3A4 (6.8µL $min^{-1}pmol^{-1}$ and 4.1 min, respectively), followed by CYP 2D6 by a considerable margin (0.2µL $min^{-1}pmol^{-1}$ and 121 min, respectively).

To conclude, CYP 3A4 emanates from study DVR0108 and DVR0085 to be the main CYP involved in rilzabrutinib's metabolism.

Metabolic profiling

In study DVR0088, *in vitro* metabolic profiling of rilzabrutinib (10 µM) was investigated in liver S9 fractions (1 mg/mL) from rats, dogs and humans (with Co-factor NADPH, 2mM) by LC-MS/MS.

Rilzabrutinib was metabolised via oxidation, dealkylation, and/or hydrogenation with a total of 14 metabolites found in dog and human and 11 in rat liver S9 fractions, whereas metabolites M7, M8 and M12 were not observed in rats but in humas and dogs. Most metabolites were found to be minor with a 1-10% relative peak area (mass spectrometry). Major metabolites (> 10% relative peak area) were M8, M12 and M13 in humans, M7, M8 and M11 in dogs and M3, M5 and M11 in rats.

In study DVR0527, metabolite profiling and characterization, after administration of a single oral dose of 40 mg/kg of [^{14}C]-rilzabrutinib to Sprague Dawley rats (Study DVR0527), was conducted in plasma, bile, urine and faecal samples by HPLC-tandem mass spectrometry coupled with a radio flow-through detector (RFD). Rilzabrutinib was metabolised via N-dealkylation, oxidation and sulfation, resulting in a total of 11 metabolites (M1-M11), whereas rilzabrutinib itself was only observed in the faeces of rats.

In pooled rat plasma from jugular vein cannulated rats (up to 72 hours post-dose), two metabolites, M1 (PRN4400, thiocyanate) at 1.6 and M11 (PRN834) at 0.1 µg Equiv/mL, were identified, representing approximately 94 and 6 %, respectively, of total drug exposure in plasma. In this study, M1 was first reported as co-eluting with cyano acetic acid but identified as PRN4400 (thiocyanate) at a later stage in a human ADME study (study PRN1008-015). Because of its endogenous nature and its occurrence in baseline values, thiocyanate was not detected in previous studies with unlabelled rilzabrutinib. Therefore, a GLP-compliant fourteen-day oral pharmacokinetic study in Wistar Han rats (see study 1281-21219) was conducted to demonstrate its occurrence in animal species and to bridge between human and non-clinical toxicology studies.

In pooled rat urine (0-72 h post-dose) from intact rats, M1 (PRN4400, thiocyanate) was found to be the only metabolite with 1.5 % of the administered dose, whereas in bile duct cannulated rats, 2.0, 0.7 and 0.3 % of dose were determined to be metabolite M1, M8 (dioxidation of PRN834) and M10 (PRN618), respectively.

In pooled rat bile (0-72 h post-dose) of bile duct cannulated rats, metabolite M2 (unknown), M3 (sulfate conjugate of PRN618), M4 (oxidation and sulfate conjugation of PRN834), M7 (unknown), M8 (dioxidation of PRN834) and M11 (PRN834) were found to be present with about 2.8, 25.5, 10.5, 5.1, 4.5 and 9.6 % of the administered dose.

In pooled rat faeces (up to 24 h post-dose), rilzabrutinib itself was present at 3.1 and 8.8 % of the administered dose in intact rats and bile duct cannulated rats, respectively. In the latter (BDC rats), only two metabolites were found, namely M10 (PRN618) with 7.3 and M11 (PRN834) with 0.8 % of dose, which were seen in intact rats as well with 6.2 and 3.3 %, respectively. Additionally, in intact rats, metabolite M3 (sulfate conjugate of PRN618), M5 (protonated PRN1008), M6 (oxidation of PRN1008), M8 (dioxidation of PRN834) and M9 (oxidation of PRN834) were determined with 15.3, 8.4, 15.7, 4.7 and 8.9 % of dose.

Metabolite Identification

In study DVR0189 and DVR0188, plasma samples were collected at day 1 and 14 for metabolite identification and quantitation by LC/MS/MS after daily oral administration (oral gavage) of 50, 150, and 500 mg/kg/day rilzabrutinib to Wistar Han rats (2-week toxicity range-finding study DVR0172) and Beagle dogs (2-week oral gavage toxicity range-finding study DVR0173), respectively.

The hydrolysis product PRN834 (M16) and the dealkylation product PRN618 (M6, M9 or M11) represent the two major metabolites in rats and dogs, the two being almost equally present in dogs (C_{max} values in % and AUC in % (metabolite to parent ratio) ranged from 31.8 to 79.5 % and 55.5 to 163.2 %, respectively, for PRN618 and from 32.6 to 97.1 % and 90.2 to 205.9 %, respectively for PRN834), whereas the hydrolysis product PRN834 (C_{max} and AUC in %: 50 to 75 % and 81 to 149%, respectively) was far more present than the dealkylation product PRN618 (C_{max} and AUC in %: 9 to 16 % and 14 to 37%, respectively) in rats. Further, low percentages of other metabolites were observed

in rats (C_{max} and AUC in %: 4 to 5 % and 4 to 6.9 %, respectively, for M8; from 1 to 2 % (both) for M5) and dogs (C_{max} and AUC in %: 11.7 to 25.9 % and 14.3 to 28.9 %, respectively, for M8; 1.1 to 2.9 % and 1.9 to 8.1 %, respectively, for M5). Additionally, the hydrolysis product PRN834 (M16) was not determined in any *in vitro* study but observed in all *in vivo* samples, suggesting an extrahepatic, non-CYP mediated, metabolism.

Isomer interconversion

Study DVR0186 investigated isomer conversion in Wistar-Han rats following administration of PRN1008 at 50 mg/kg as either pure isomer E or Z. Samples were taken up to 24 hours and analysed by LC/MS/MS.

In both groups, an E to Z isomer ratio of about 85:15 was reached.

In study DVR0162, plasma samples were obtained after dosing with rilzabrutinib (90:10 E:Z-isomer ratio) from a 28-day oral repeat dose toxicology studies in rats and dogs (DVR0174 and DVR0184, respectively) and from a healthy human volunteer study (Study PRN1008-00), and evaluated for their quantity of E and Z isomers at various time points by LC/MS/MS analysis.

In human plasma samples of healthy volunteers after a single dose of 300 mg rilzabrutinib, the E isomer was the major isomer detected (C_{max} of 76 ng/mL and AUC_{last} of 216.92 hr*ng/mL), whereas the Z isomer only represented 3.4 and 2.1% of the total C_{max} and AUC_{last}, respectively.

No apparent differences in interconversion were noted for different genders or doses in rats and dogs. At steady state, a slight increase in the amount of Z isomer was noted in dogs, but not in rats. As in humans, the major isomer was the E isomer in both species, in dogs similar or slightly higher when compared to humans, whereas in rats an increase of interconversion with a Z-isomer plasma concentration of approximately 25% was observed.

Overall, attained E and Z isomer ranges observed in the non-clinical toxicology species comprise E/Z isomer levels observed in humans, e.g. with a safety margin of 40- to 100-fold on total AUC and 400- to 1000-fold on Z isomer AUC in rats.

R/S isomer interconversion was evaluated in an exploratory study in rats after pure administration of the R or S enantiomer of rilzabrutinib. The R isoform represents the predominant form of rilzabrutinib, which shows comparable potency to the S form but a higher durability of the pharmacodynamic effect. After dosing with pure R, hardly no conversion to the S form was noticed. An S impurity is controlled by specification limits. A conversion from the S to R enantiomer up to 23% was noticed after pure administration of the S form of the drug.

Excretion

Excretion mass balance (MB) after a single oral administration of [^{14}C]PRN1008 at 40 mg/kg to male albino rats (Sprague Dawley; SD) was investigated in study DVR0159.

Biliary excretion (about <70%) was identified as the major route of elimination, followed with about >20% in faeces in bile duct-cannulated (BDC) rats (n=3), which is consistent with an excretion rate in faeces of about 90% in intact rats (n=3), suggesting an absorption of approximately 80% of radioactivity after oral administration. Excretion via the urine was observed to be low (up to approximately 3.5%). Total recovery of radioactivity averaged about 93% in both groups of rats.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Rilzabrutinib was evaluated in single-dose toxicity studies (rats, dog) and in the repeat-dose toxicity studies in rats (13-day; 2-week; 1-, 3-, and 6-month), and dogs (4-day; 2- and 12-week, 1-, 3-, and 9-month); in genotoxicity studies in vitro (Ames test and in vitro chromosome aberration test) and in vivo (micronucleus test in rats); reproductive toxicology studies (male and female fertility study in rats; embryo-fetal toxicity in rats and rabbits, pre- and postnatal development toxicity study in rats), and carcinogenicity studies (6-month TgHRAS mouse and a 2-year rat study).

In terms of **single dose toxicity studies**, toxicity and toxicokinetics of rilzabrutinib after oral gavage administration were evaluated in rats (10/sex/group + 6/sex/group) at 0, 50, 150 and 500 mg/kg rilzabrutinib (Study DVR0178) and Beagle dogs (5/sex/group) at 0, 50, 150 or 500 mg/kg rilzabrutinib (Study DVR0179). Both studies included a recovery group which was necropsied 14 days after dosing. Both studies were GLP-compliant.

Rilzabrutinib was well tolerated in the submitted single dose toxicity studies. Clinical effects related to rilzabrutinib administration were emesis in dogs (Study DVR0179), which was not considered adverse. Observed compound-related differences in microglial cell distribution patterns in periventricular (lateral and third ventricle) regions of the brain (compared to vehicle control rats) at mid- and high-dose groups in study DVR0178 were not considered adverse by the applicant. This first indication of neutrophilic infiltration and microgliosis (increased presence of microglia) in rat brain upon rilzabrutinib treatment is recapitulated in long term studies and will be discussed later.

In both studies, a sex-related difference in systemic exposure (C_{max} and AUC_{last}) was observed, with higher exposures noted for the females (2.0- to 4.1-fold higher exposures than males in rat).

Overall, no particular concerns were identified in DVR0178 and DVR0179.

2.5.4.2. Repeat dose toxicity

Six GLP-compliant repeat dose toxicity studies were performed covering durations of 1 (rat DVR0174, dog DVR0184), 3 (rat DVR0207, dog DVR0206), 6 (rat DVR0376), and 9 months (dog DVR0377).

Rat

For the 6-month rat study (DVR0376) (with a 4-week recovery period) animals were treated daily with rilzabrutinib at doses of 0, 15, 50, 150 and 300 mg/kg/day (in citric acid formulation). A sufficient number of animals was selected in order to provide a main study group (toxicity assessment), a toxicokinetic group and a recovery group. In total, 8 animals died over the course of the study. Six (5 found dead, 1 euthanized) deaths were considered related to rilzabrutinib in the 150 mg/kg/day group (3 females) and the 300 mg/kg/day (2 females, 1 male). The earliest of these deaths occurred on day 105. The average ((D89 + D182)/2) rilzabrutinib exposure levels for this time in the toxicokinetic groups were as follows:

50 mg/kg:	C_{max} ng/mL:	1805 in females
	AUC_{last} h*ng/mL:	6190 in females
150 mg/kg:	C_{max} ng/mL:	989 in males; 3440 in females
	AUC_{last} h*ng/mL:	5795 in males; 15850 in females
300 mg/kg:	C_{max} ng/mL:	1935 in males; 5360 in females
	AUC_{last} h*ng/mL:	15300 in males; 28550 in females

(Individual numbers on D89 and D182 were comparable.)
As no female animals died in the 50 mg/kg/day and no males died at 150 mg/kg/day the tolerated exposure levels for this event are roughly 1000 ng/mL for C_{max} and 6000 h*ng/mL for AUC_{last}. This provides a safety margin of at least 6× and 4×, respectively, considering clinical human exposures of 150 ng/mL C_{max} and 1540 h*ng/mL AUC_{24h}. Likewise, all other adverse events were detected at exposure levels high enough to provide a sufficient safety margin for clinical use.
One female animal (4F168) in the 150 mg/kg/day-group was found dead on Day 112 and death was considered related to rilzabrutinib and connected to inflammation of the brain. In general terms the study reports that administration at or above 150 mg/kg/day caused a low incidence of inflammation of the meninges and/or brain, which fully resolved during the recovery period. At 50 mg/kg/day (males) or 150 mg/kg/day (females) rilzabrutinib resulted in increased positivity for IBA-1 (microglia marker) and GFAP (astrocyte marker), especially around lateral ventricles. This finding partially reversed during the recovery period. Inflammation of the meninges/brain was considered adverse while IBA-1 and GFAP positivity was not. According to the pathology report, the implications of microglia cell activation are unclear and IBA-1 positivity was not consistently linked to brain inflammation, except for animal 4F168, in which sites of inflammation and IBA-1 positivity (microgliosis) overlapped.
Of note, IBA-1 positivity was considered non-adverse based on two observations: (i) it mostly disappeared after a 4-week recovery period and (ii) there was no neurodegeneration detectable in Fluoro-Jade B (FJB) stainings. As opposed to this, the observed inflammation was considered adverse although also fully reversible following the recovery period and although Bielschowsky silver and FJB stainigs also did not indicate brain tissue destruction or neuronal degeneration.

Two shorter GLP-compliant repeated dose toxicity studies (1-month DVR0174 and 3-month DVR0207) were conducted in rat. Overall, the findings in these studies are in good concordance with study DVR0376 and no specific concerns were identified.

Dog

For the 9-month dog study with a 4-week recovery period (study DVR0377) Beagle dogs were treated daily with rilzabrutinib at doses of 0, 15, 30, or 50 mg/kg/day (as capsule). Three dogs/sex/group were maintained for 4 weeks after the last dose to evaluate reversibility. Toxicokinetic assessment of rilzabrutinib, PRN618 (minor metabolite), and PRN834 (minor metabolite) was conducted by collecting blood samples from each animal on days 1, 127 and 273.

One male animal (4M30), which was subjected to 50 mg/kg/day, was euthanized on day 53 of the study because of weight loss (> 20%), lack of food consumption and poor body condition. Also, this animal had the highest plasma concentrations at the 0.5 through 4-hour timepoints on Day 1 as well as the highest C_{max} and AUC on that day. It is hence possible that the animal´s condition was test-article-related.

Rilzabrutinib at all dose levels caused emesis, resulting in occasional ejection of the gelatine-capsule. However, this was an infrequent event, and it was mostly possible to re-administer the dose. Hence, an influence of this aspect on total drug exposure is unlikely.

Adverse effects at 50mg/kg/day included decreased food consumption, microscopic gastric epithelial changes and increases in liver enzymes and the NOAEL was defined as 30 mg/kg/day. At this NOAEL (on day 273) the C_{max} was 257 and 339 ng/mL and the AUC_{0-24} was 747 and 812 hr*ng/mL for males and females, respectively. Of note, systemic exposure in humans at the anticipated clinical dose (i.e. 400 mg BID) accumulates to AUC_{0-24} = ~1540 hr*ng/mL at steady state.

In addition, two GLP-compliant shorter dog studies (1-month DVR0184 and 3-month DVR0206) were conducted. Of note, rilzabrutinib was not administered as capsules in these two studies but as citric

acid formulation (like in rat studies), which was found to be considerably less tolerable than capsules (see exploratory bridging study DVR0301). In both studies the dose levels were 0, 30, 100 and 300 mg/kg/day.
No deaths were documented for the 1-month study, whereas in the 3-month study two 100 mg/kg/day dogs, three 300 mg/kg/day females and all (5) 300 mg/kg/day males were euthanized in extremis.
Toxicokinetic parameters for rilzabrutinib were as follows:

Table 1: Toxicokinetic parameters for rilzabrutinib

Dose (mg/kg/day)	30		100		300	
Sex	**M**	**F**	**M**	**F**	**M**	**F**
			AUC_{last} (ng.h/mL)			
Rilzabrutinib						
Day 1	985	821	1500	5530	2170	12 100
Day 37	1350	903	3230	6160	14 700	4190
Day 91/92	1070	1040	1980	4410	ND	7350
			C_{max} (ng/mL)			
Rilzabrutinib						
Day 1	575	365	441	1280	718	1730
Day 37	591	444	844	918	2480	1140
Day 91/92	592	484	736	1670	ND	1780

Due to two (1 male, 1 female) deaths in the 100 mg/kg/day group, the NOAEL for this event appears to be 30 mg/kg/day. It is noted that at day 37 (point closest to death) C_{max} and AUC_{last} values at 100 mg/kg/day exceed the respective clinical parameters in human by ~6× and ~2 – 4×, respectively. However, as the AUC_{last} at the NOAEL falls below the respective clinical value, it is questionable if deaths in dogs may not also occur at (sub-)clinical exposures.
The NOAEL was defined as 30 mg/kg/day in males but could not be determined for females, as adverse events were detected in the 30 mg/kg/day dose group.

Overall, systemic exposure levels (in terms of AUC_{last}) at the defined NOAELs in dog studies are frequently below the corresponding human exposure levels during clinical trials. In studies DVR0377 (9 months) and DVR0206 (3 months) the NOAEL of 30 mg/kg/day corresponded to an AUC_{last} of ~750 – 1000 ng*h/mL (vs. 1540 ng*h/mL in humans at 400 mg BID). Hence, based on the provided dog studies, any adverse event observed at the next larger dose level (i.e., 50 mg/kg/day for study DVR0377 and 100 mg/kg/day for males and 30 mg/kg/day in females for study DVR0206) cannot be ruled out for human use.

Non-pivotal repeated dose toxicity (after oral administration) was evaluated in rats, rabbit and in Beagle dogs. In total, six studies were submitted. In the non-GLP compliant Study DVR0172, rilzabrutinib was administered at 0, 50, 150 and 500 mg/kg/day for a consecutive period of 14 days to male and female Wistar Han rats (5/sex/group). Toxicokinetics in the submitted rat repeated dose toxicity study was investigated in a satellite group (6/sex/group, treated at the same dosing regimens used in the main study). Microglia cell change – also reported for various other studies eg.: DVR0175 - was not considered adverse by the applicant due to no evidence of neurodegenerative changes with H&E and Fluoro-Jade B.

In another non-GLP compliant dose-finding study (Study DVR0300) 0, 50, 150 and 500 mg/kg/day of rilzabrutinib was administered for seven days to three female New Zealand White rabbits.

Based on the severity of the body weight loss, reduced food consumption, and the macroscopic observation of mottled liver, the maximum tolerated dose (MTD) was exceeded at 500 mg/kg/day. The

dose of 150 mg/kg/day was considered to be suitable as the high dose for inducing acceptable maternal toxicity in a subsequent dose range-finding study in pregnant rabbits.

Furthermore, in range finder study (Study DVR0173) one male and one female Beagle dog were treated with 0, 50, 150, and 500 mg/kg/day of rilzabrutinib for two weeks. Due to decreased food consumption (up to ≤-50% for one female) and body weight loss (up to -28% for females by day 14) the dose level of 500 mg/kg was considered to be a limit dose.

In a bridging study (Study DVR301), four male and four female Beagle dogs received 0, 30 and 50 mg/kg/day of rilzabrutinib for 12 weeks orally, formulated as a capsule to compare the tolerability and systemic exposure of rilzabrutinib administered by capsule compared to oral gavage (DVR0206).The capsule formulation was better tolerated than the liquid formulation. Observed adverse effects were sporadic emesis at 50 mg/kg/day (m) and ≥30 mg/kg/day (f), stool changes (total/diarrhoea) at ≥30 mg/kg/day, increased salivation at 50 mg/kg/day, decreased body weight (-15 to -18%) noted for two 50 mg/kg/day females compared to their pre-study weight and decreased food consumption in one 50 mg/kg/day female. Test article-related haematology changes were reported to be within reference ranges.

The incidences of emesis and stool changes were reported to be reduced compared to administration of rilzabrutinib by oral gavage in a 3-month repeat-dose study (Study DVR0206). In addition, the absence of early termination due to severe weight loss, was attributed to better tolerance of the capsule formulation.

Two additional non-pivotal but GLP-compliant repeated dose toxicity studies were submitted. Both were conducted with Rilzabrutinib in its bis-mesylate salt form, which is not being developed as the drug substance and was not intended for further use in clinical trials of rilzabrutinib.

In study DVR0175 Wistar Han rats (15/sex/group) including a recovery group (5/sex/group) and a toxicokinetics satellite group (9/sex/group), were dosed with 0, 150, 500, and 1000 mg/kg/day of rilzabrutinib for 13 days. Reversibility of effects was assessed 4 weeks after dosing. This study originally was intended as a 28-day study but was reduced in duration after high mortality in the high-dose group. Adverse and abnormal findings observed, were largely attributed to the mesylate content and acidic pH, as similar toxicities have not been observed with rilzabrutinib free-base. Toxicokinetic parameters C_{max} (ng/mL) and AUC_{last} (ng.h/mL) at Day 1 show to be in good concordance with data obtained in a single-dose oral toxicity study in rats (Study DVR0178). Similarly, as observed in study DVR0172, IBA-1 immunohistochemical (IHC) expression revealed (minimal to mild) increases in microglial cells in the lateral and third ventricles of mid- and high-dose males and females. The pattern of differences showed evidence of reversibility during the recovery period and was not considered an adverse event.

In study DVR0168 three male and three female Beagle dogs received 0, 30, 100, and 300 mg/kg/day of rilzabrutinib for 20 days (m), 21 days (f). Reversibility of effects was assessed in two animals/sex/group. No toxicologically significant findings were reported by the applicant. All observations made during the trial (increases in ALT ≥100 mg/kg/day in males, a slight increase in mean ALP at 300 mg/kg/day in females, mild single cell necrosis of hepatocytes at 300 mg/kg/day in males, minimal to moderate decreased cellularity of Peyer's patches for ≥100 mg/kg/day in males and at 300 mg/kg/day in females) were not considered to be adverse by the applicant. ALT elevations were observed already pre-dose in one animal but decreased across dosing days in this animal. Furthermore, ALT elevations were found not to be associated with microscopic pathology findings in any organs (e.g. liver) and appeared to fully recover following a one-month recovery period. Microscopic findings were considered spontaneous disease lesions or incidental findings. According to the applicant, these findings occurred at essentially comparable incidences and severity in control and treated animals, and they were the usual number and type commonly seen in dogs of this age and the

decreased cellularity of Peyer's patches fully recovers following a one month recover period. Assessment of potential test article related effects were not conducted. The study had been shortened, and no flow cytometry specimens had been collected after the beginning of dosing. Thus, no conclusion was drawn on rilzabrutinib-related changes in immunophenotyping (flow cytometry).

2.5.4.3. Genotoxicity

A standard battery of GLP-compliant genotoxicity studies (2 *in vitro* and 1 *in vivo*) was submitted. Specifically, a bacterial reverse mutation assay with *Salmonella typhimurium* and *Escherichia coli* (Study DVR0169), an *in vitro* Chromosomal Aberration test in human peripheral blood lymphocytes (Study DVR0170), and the *in vivo* Rat Bone Marrow Micronucleus Assay (Study DVR0185). The *in vitro* assays included two independent experiments and were conducted in the presence and absence of microsomal enzymes prepared from Aroclor™ 1254-induced rat liver S9 fraction (S9).

The applicant reported clearly negative results for the Reverse Mutation Assay (study DVR0169), which indicated, that rilzabrutinib "did not cause a positive mutagenic response with any of the tester strains in either the presence or absence of Aroclor-induced rat liver S9." Also, no significant or dose-dependent increases in structural or numerical aberrations were observed in treatment groups with or without S9, while all criteria for a valid study were reported to be met. Rilzabrutinib was considered negative for the induction of structural and numerical chromosome aberrations in the non-activated and S9-activated test systems in the *in vitro* mammalian chromosome aberration test using HPBL (DVR0170). *In vivo* micronucleus assessment in rats was performed as an independent study (DVR0185). As reported, the results of the micronucleus assay indicated that rilzabrutinib did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes at doses up to 2000 mg/kg in males, which is the recommended top dose for short-term studies (ICH S2 (R1); for females, the MTD was determined to be 1500 mg/kg in a range finder study, and thus was concluded to be negative. A TK-satellite group of 3 animals/sex was included in the study for determination of rilzabrutinib plasma levels, which showed systemic exposure at a multiple over clinical exposure (for males, the C_{max} and AUC0-24 at the lowest dose 500 mg/kg were 1580 ng/mL and 10 700 ng.h/mL, respectively. For females, the C_{max} and AUC_{0-24} at the lowest dose 375 mg/kg were 2870 ng/mL and 27 800 ng.h/mL, respectively. Rilzabrutinib tested negative in all three assays.

2.5.4.4. Carcinogenicity

Two main studies served the assessment of the carcinogenic potential of rilzabrutinib: a GLP-compliant 24-month study in rats (1281-18051) and a GLP-compliant 26-week study in TgHRAS hemizygous mice (1281-20014). The latter study did not indicate any carcinogenicity over the entire observation period at dosages up to 300 mg/kg/day (resulting in Cmax of ~ 6000 ng/mL and AUClast of ~ 40000(m) – 70000(f) hr*ng/mL at day 66). The rat study revealed a variety of neoplastic findings over the observation period of 2 years.

The study concludes that rilzabrutinib "was not carcinogenic in Wistar Han rats at ≤ 30 mg/kg/day in males and ≤ 50 mg/kg/day in females. On day 176, the AUC0-24 values were 978 ng*h/mL for males at 30 mg/kg/day and 6930 ng*h/mL for females at 50 mg/kg/day." The applicant states that "based on available data, no rilzabrutinib-related tumors considered to be relevant to humans were observed following the oral administration of doses up to 100 and 50 mg/kg/day in males and females, respectively." (further data were provided during the procedure see discussions section).

At 15 mg/kg/day, females appear to develop follicular cell carcinoma/adenoma in the thyroid gland. It is noted that in the high-dose group (50 mg/kg/day) such events do not appear with higher frequency

than in the vehicle-group. The relationship between rilzabrutinib and neoplastic findings in the thyroid is also supported by data in males at 100 mg/kg/day.

Rilzabrutinib at 50 mg/kg/day (and possibly lower) appears to elicit malignant (metastatic) uterine adenocarcinoma, which seemed to be the cause of death for two group 4 animals (female 454 and female 476).
Not statistically significant hemangiosarcoma findings (0, 0, 1 and 2) in the mesenteric lymph node in females are also reported.

Upon request, the applicant has provided a comprehensive re-evaluation of the neoplastic findings in the uterus and mesenteric lymph nodes, under consideration of relevant literature on historical background levels of hemangiosarcoma and uterine adenocarcinoma in 2-year rat studies (see discussion section). The applicant conducted transcriptomic profiling in human and rat liver spheroids showing that rilzabrutinib induces several UGT-enzymes (study MCT0292).

2.5.4.5. Reproductive and developmental toxicity

- **Fertility and early embryonic development**

Aspects of fertility and early embryonic development with respect to rilzabrutinib treatment were assessed in a rat study (DVR0380). Male and female Wistar Han rats were treated with dosages up to 300 mg/kg/day of rilzabrutinib from day 28(m) or day 15(f) before cohabitation until gestation day (GD) 7. Males were necropsied after daily dosing for a minimum of 49 days and females were necropsied on GD13. The study concludes that there were no effects on mating, fertility, reproductive organ weights, or sperm parameters in males and no effects on estrous cycling, mating, fertility, or ovarian and uterine parameters in the females. The respective NOAEL for the tested reproductive and developmental parameters is 300 mg/kg/day

- **Embryo-foetal development**

Two main studies in rats and rabbits (DVR0378 and DVR0379) were conducted to assess effects of rilzabrutinib on embryo-foetal development. The two studies were preceded by respective dose range-finding studies (DVR0298 for rats and DVR0299 for rabbits). The dose levels defined by study DVR0298 to be used for the conduct of DVR0378 were 50, 150, 300 mg/kg/day and exposures (C_{max} and AUC_{inf}) at all dose levels used in DVR0298 (50, 150 and 500 mg/kg/day) provide sufficient toxicokinetic safety margins over the clinical exposure at 400 mg BID.

For the rat study DVR0378 pregnant Wistar Han rats were treated with dosages up to 300 mg/kg/day from GD 7 through GD 17. Rats were euthanized on GD 21 and embryo-foetal developmental parameters were assessed. Overall, the study concludes that rilzabrutinib has no adverse effect on any developmental parameter tested. However, the study shows a statistically significant increase in the incidence of supernumerary thoracic rib pairs associated with increased numbers of thoracic and decreased numbers of lumbar vertebrae at 300 mg/kg/day. A very similar observation was made in the rabbit study DVR0379 at 100 mg/kg/day (see below). Both studies conclude that this finding is unrelated to rilzabrutinib because the total number of presacral vertebrae appears unchanged.

For the rabbit study DVR0379 pregnant New Zealand White rabbits were treated with 0, 10, 30, or 100 mg/kg/day of rilzabrutinib. As indicated above, the choice of these dose levels is not understood as the dose range-finding study DVR0299 for rabbits demonstrated that dosing with 50 mg/kg/day is barely sufficient to reach clinical exposure levels in terms of AUC_{last} (at 50 mg/kg/day animals reached AUC_{last} of 1050 and 1760 hr*ng/mL on GD 6 and GD 19, respectively, as compared to AUC_{24h} of 1540 hr*ng/mL in humans during clinical trials). Dose levels of 10 and 30 mg/kg/day are hence not expected to reach total exposure levels to provide sufficient safety margins for clinical exposure.

Toxicokinetic assessment for study DVR0379: 30 mg/kg/day resulted in an AUC_{0-t} of 175 and 313 hr*ng/mL on GD 7 and GD 19. The applicant provided a comprehensive explanation for the selection of 0, 10, 30 and 100 mg/kg/day for the conduct of study DVR0379, which was based on the toxicokinetic data provided in study DVR0299.
Study DVR0299 reports fused sternebrae at the 50 and 150 mg/kg/day but regards them as incidental background findings. In study DVR0379 fused sternebrae were documented with a frequency of 1.9, 2.2, 2.4, and 3.3% of all fetuses at dose levels of 0, 10, 30, and 100 mg/kg/day, respectively. Hence, the synopsis of data rather indicates a slight but consistent increase in fused sternebrae upon rilzabrutinib-exposure. Hence, the synopsis of data rather indicates a slight but consistent increase in fused sternebrae upon rilzabrutinib-exposure.

Similar to rats (see study DVR0378), the highest dose level used in DVR0379 (i.e., 100 mg/kg/day caused a shift in the number of thoracic and lumbar vertebrae.
As a result of numerous rounds of responses as well as consultations of pertinent experts, the observed skeletal variations are not considered explicitly adverse, and the issue was appropriately addressed under SmPC section 5.3.

In addition, an increase in postimplantation loss was observed at the high dose level of 150 mg/kg/day in the rabbit dose range-finding study DVR0299. This was considered as possibly related to maternal toxicity and mainly driven by females #30 and #31 (3 resorptions each). This finding occurred at 5.6-fold clinical exposure and its reproducibility could not be fully explored in the definitive study using a lower high dose level corresponding to a small exposure multiple of 4.5.

- **Prenatal and postnatal development, including maternal function**

Aspects pertaining to prenatal and postnatal development were investigated in rat study DVR0492. The study assessed any effects on pregnancy, parturition, and lactation of dams as well as growth, viability, and development of F1 offspring. Reproductive performance of the F1 generation was also assessed. Pregnant rats were treated with 0, 50, 150, or 300 mg/kg/day of rilzabrutinib from gestation day 6 through lactation day 20. Three NOAELs were defined: toxicity to F0 mothers (NOAEL = 50 mg/kg/day), toxicity to F1 development (NOAEL = 150 mg/kg/day), and toxicity to F1 parental fitness (NOAEL = 300 mg/kg/day).
The study also states (e.g., under 12.2.4) that: "*F1 animals will not be directly dosed but may be exposed to the test article in utero and via maternal milk during lactation.*" Transfer of Rilzabrutinib into maternal milk was not assessed.

- **Juvenile animal toxicity**

A programme of juvenile animal studies was initiated in rats aged 10 days to support paediatric development of rilzabrutinib from 1 year of age, but subsequently deleted from the PIP due to extension of the waiver to patients below 10 years of age. The applicant submitted the results of the dose range-finding study wherein rilzabrutinib was not well-tolerated with treatment-related mortalities reported mainly at ≥100 mg/kg on PND10-13. The cause of these unscheduled deaths is not clear.

2.5.4.6. Local Tolerance

No local tolerance studies were submitted. As Wayrilz will be administered orally, this is acceptable.

2.5.4.7. Other toxicity studies

Antigenicity

No antigenicity studies were submitted "because there were no general toxicology study findings that indicated that such studies were needed to assist in the interpretation of any study results". This is acceptable.

Immunotoxicity

No dedicated immunotoxicity studies were submitted in Module 4.2.3.7.2 of this dossier. Immunotoxicity endpoints (hematology, immunophenotyping (flow cytometry), anatomic pathology) were assessed in several GLP repeat-dose toxicity studies and are commented on in the respective sections of this assessment report. The applicant arguments, that immunotoxicity studies were not conducted "because there were no general toxicology study findings that indicated that such studies were needed to assist in the interpretation of any study results".

Results in rats demonstrated non-adverse microscopic findings in lymphoid tissues as mentioned in the repeat dose toxicity studies in rats (minimal decreased numbers of lymphocytes, thymus: increased numbers of tangible body macrophages) and dogs (reversible lymphoid tissue changes at 30 mg/kg/day: germinal canters of lymph nodes, Peer's patches in the intestine, and thymus).

Drug abuse liability

No dedicated drug abuse liability studies, eg. specific behavioural studies evaluating the risk of drug dependence and abuse of rilzabrutinib were submitted. Drug abuse liability potential was assessed and discussed using data/information on the molecular structure, CEREP evaluation, and *in vivo* evaluation in safety pharmacology and general toxicology studies of rilzabrutinib and its major metabolite, thiocyanate.

In a radioligand binding assay against a panel of receptors, ion channels, and transporters sourced from various cells or cell lines (see 2.6.3 Nonclinical TS Pharmacology, Study DVR0095 [TS 2.6.3.1]) at a supratherapeutic concentration of 10 µM Rilzabrutinib showed notable activity against 4 targets: muscarinic M2 receptor (50.7%), neurokinin NK2 receptor (50.2%), sodium channel site 2 (59.3%), and dopamine transporter (81.8%). Though these 4 targets play a role in the central nervous system, it has been demonstrated that rilzabrutinib does not cross the blood brain barrier (53).

Consequently, given the absence of rilzabrutinib exposure in the central nervous system, the binding to muscarinic M2 receptor, neurokinin NK2 receptor, sodium (Na+) channel site 2, and dopamine transporter observed in the CEREP assay is reported to have no substantive clinical relevance.

Besides other repeated dose studies, a single dose oral (gavage) study in rats (Study DVR0176) was cited to deduce abuse potential or withdrawal via a Functional Observational Battery (including assessment of behavioural, physiological, and neurological changes). The relevance of this cross-reference remains questionable, considering the limitations of a single dose administration to capture the complexities of abuse potential or withdrawal, which typically require more detailed and prolonged observations like conditioned place preference, self-administration assays, and withdrawal symptom monitoring.

The molecular structures of rilzabrutinib and its major metabolite thiocyanate, benchmarked against a published list of scheduled substances showed low similarity to scheduled substances and thus a low probability to share an abuse-related mode of action, despite Rilzabrutinib binding to receptors implicated in neurological dependence: muscarinic M2, neurokinin NK2, sodium channel site 2, and dopamine transporter. Moreover, in the brain and cerebral spinal fluid (CSF) concentrations or rilzabrutinib (distribution studies) the sponsor concluded that neither rilzabrutinib nor its metabolites

penetrate the CSF to a detectable level, except for thiocyanate. Another point is that according to the sponsor and the distribution study, rilzabrutinib does not cross the blood brain barrier. Indeed, minimal rilzabrutinib was detected in the brain or spinal cord of pigmented rats (<0.6 µg equivalents/g at C_{max}), and only very low levels (<0.20 µg equivalents rilzabrutinib/g tissue) were observed in these tissues in non-pigmented rats.

Studies on metabolites

The *in vivo* metabolism of rilzabrutinib was assessed in rats, dogs and in humans. Rilzabrutinib is first metabolized via CYP 3A4 and in minority via CYP2D6. Three notable metabolites of rilzabrutinib are described. Specifically, one major metabolite PRN4400 (thiocyanate), representing 94.2% of total radioactivity exposure in plasma, which is an endogenous compound with safety and toxicity well characterized in the literature, as claimed by the applicant.

Thiocyanate is an endogenous element of the serum (the normal human range are 50 to 250 µmol/L (3 to 15 mg/L) with a long half-life (approximately 3 days in rat). Thiocyanate systemic exposure/AUC was determined in rats following repeated administration of rilzabrutinib in a dedicated GLP-compliant bridging PK study (Study 1281-21219) with the objective to demonstrate that PRN4400 (thiocyanate) is formed *in vivo* and to generate exposure data for comparison to the exposure observed in humans. In view of additional data obtained from previous nonclinical *in vivo* metabolite ID studies (Studies DVR0188, DVR0189, DVR0527) the applicant concluded, that dogs and rats metabolized rilzabrutinib to PRN4400 (thiocyanate), PRN834 and PRN618 to a similar or greater degree than humans and thus, the potential toxicological effects of these metabolites had been adequately covered. Furthermore, the applicant reported results from a literature search on nonclinical safety studies with thiocyanate in rodents and non-rodents, with no safety concerns identified for thiocyanate.

Minor metabolites identified were PRN834 (accounting for 1.09% of total plasma radioactivity exposure) and PRN618, which was found in trace amounts (<1% of total plasma radioactivity exposure) in plasma.

None of the metabolites were described to contribute significantly to the pharmacological activity of rilzabrutinib. No unique human metabolites have been identified.

Studies on impurities

This section must also be read in reference to the quality aspects on Drug Subtance and Drug Product.

Actual and potential mutagenic impurities were assessed according to ICH M7(R2). Several actual and potential mutagenic impurities were identified and classified in an internal mutagenicity hazard assessment using database search, as well as two (Q)SAR *in silico* system models (Study MAR0248). Impurities classified as Cohort of Concern, class 1, class 2 and class 3 impurities were treated as required by respective guidelines. No risk of presence of nitrosamines in the drug substance above 10% of the acceptance limit was claimed by the applicant. For class 1, class 2 and class 3 impurities acceptable intake and appropriate controls were defined as per ICH M7 (R2).

In total, 15 GLP-compliant mutagenicity studies on actual and potential mutagenic impurities were submitted in Module 4.2.3.7.6.

Except for two studies, which were considered exploratory studies and confirmed by separate GLP-studies, all of the 15 submitted *in vitro* mutagenicity studies as part of the evaluation of actual and potential mutagenic impurities (HIS2453, HIS2449, HIS2472, DVR0522 (exploratory, non-GLP), DVR0521 (exploratory, non-GLP), HIS2490, LYM0377, HIS2456, HIS2460, HIS2461, HIS2473, HIS2462, HIS2454, HIS2455, AG58XF.502ICH.BTL) were conducted in compliance with GLP principles.

Considering the present mutagenicity hazard assessment and information on the control strategies, no non-clinical concern is raised on these impurities.

According to ICH Q3A(R2) non-clinical qualification of impurities of the drug substance for general toxicity was conducted for impurities present at levels predicted to be ≥0.15% or a predicted daily intake of ≥ 1 mg. Furthermore, genotoxicity assays were conducted for impurities with a predicted daily intake of ≥1 mg. For this, 18 studies were submitted, all relevant studies were conducted in compliance with GLP principles.

The qualification of ten specified impurities was evaluated by comparison of the impurity exposure (mg/kg) at the NOAEL in GLP repeat-dose toxicity studies in rats and the impurity exposure in a 60 kg patient at the therapeutic dose of 800 mg/day, taking into account the proposed acceptance criterion for each impurity. Pivotal repeat-dose toxicity studies chosen for this evaluation were rat-studies DVR0174 (1-month toxicity study), study DVR0207 (3-month toxicity study), study TXC1711 (3-month toxicity study), and study DVR0376 (6-month toxicity study). The NOAELs considered appropriate for calculation of a safety margin were 500 mg/kg/day in the 1-month toxicity study, 150 and 100 mg/kg/day in the 3-month toxicity studies, and 150 (males) / 50 (females) mg/kg/day in the 6-month toxicity study. All impurities had a dose margin sufficient to consider respective impurity qualified, since appropriately tested in toxicity studies as per ICH Q3A(R2).

The applicant also conducted two dedicated repeat-dose qualification studies (TXC1679 and TXC1711) using spiked material by comparing the new drug substance containing a representative amount of the new impurity (rilzabrutinib spiked with the impurity) with previously qualified material (unspiked rilzabrutinib). (See also discussions section)

Phototoxicity studies

As mentioned in ICH S10, "The initial consideration for assessment of photoreactive potential is whether a compound absorbs wavelengths between 290 and 700 nm". As rilzabrutinib absorbs in UV-visible at 254 and 284 nm its phototoxic potential was assessed in line with OECD 432 and ICH S10 guideline.

Two phototoxicity studies were submitted in Module 4.2.3.7.7 to conclude on the potential phototoxic effect of rilzabrutinib. One explorative study (Study DVR0374) and a GLP-compliant study (Study PHV0082). Both studies used the 3T3 neutral red uptake phototoxicity test in BALB/C 3T3 cells according to OECD Guideline 432. Confirmatory "Definitive Assays 3 and 4", met all OECD 432-recommended criteria for cell survival, OD540, and promethazine cytotoxicity and phototoxicity indicating that the assays were valid. Studies were well performed and concentration ranges chosen comprehensibly. Based on the results of Definitive Assays 3 and 4, up to the highest soluble concentration tested (56.2 µg/mL), rilzabrutinib did not demonstrate phototoxic potential in the neutral red uptake phototoxicity assay and no further photosafety evaluations were performed.

Given Rilzabrutinib's UV-visible absorption λ_{max} at 254 and 284 nm, which is not typical for phototoxic substances, this is supported. No concerns were identified.

Excipients studies

No dedicated toxicology studies were conducted. It is not mandatory as no novel excipients are used.

2.5.5. Ecotoxicity/environmental risk assessment

For the **Phase I risk assessment**, the calculation of $PEC_{surfacewater}$ (PEC_{SW}) is mandatory. Under the assumption of a daily dose of 800mg Rilzabrutinib and a prevalence of <3 in 10000 for ITP, resulting in

a Fpen (market penetration factor) of 0.0003, a PEC_{SW} of 0.120 µg/L was reached, which triggered the need for a further Phase II assessment as it was above 0.01µg/L.

Within the scope of the **PBT/vPvB hazard screening assessment**, the octanol/water partition coefficient was investigated using a HPLC method according to OECD 117. Since the log K_{ow} did not exceed 4.5, a further persistence, bioaccumulation and toxicity (PBT) assessment was not indicated. However, because a Phase II risk assessment was triggered (see PEC_{SW}) and the log K_{ow} value was greater than 3.0, the determination of a Bioconcentration factor (BCF) according to OECD 305 to evaluate the potential of secondary poisoning was implicated. The bioaccumulation study, conducted in zebrafish (Danio rerio), resulted in a whole fish Lipid normalised (5%) Bioconcentration Factor (BCF_{SSL}) of 2 L/kg, which did not trigger the need for a further secondary poisoning assessment, as it was below the trigger value of 100 L/kg.

In the **Phase II ERA assessment**, physico-chemical properties, fate properties, aquatic toxicity, functioning of sewage treatment plant (STP) and sediment toxicity were investigated.

The examination of Rilzabrutinib's physico-chemical properties included the determination of water solubility (shake flask method according to OECD 105), octanol/water partitioning (HPLC method according to OECD 117; also see PBT/vPvB hazard screening) and its dissociation in water (OECD 112). Results indicate, that rilzabrutinib is soluble in water at the expected environmental pH range, as solubility in water ranged from 26.6 mg/L at pH 7 to 109.1 mg/L at pH 5, however, the octanol/water partition coefficient log K_{OW} of 4 also assumes lipophilic properties and therefore indicates a possible tendency to bioconcentrate in organic materials, such as soils, aquatic or terrestrial life forms. Due to technical issues, no or unprecise dissociation constants, pKa and pKb, respectively, could be determined, however, due to rilzabrutinib's amine moieties, its measured but unprecise pKb of about 6.6, as well as pH values in test item solutions of slightly above 7, rilzabrutinib is expected to react as a very weak base in water.

Fate properties were investigated by determination of the adsorption coefficient (K_{OC}) (according to OECD 106 batch equilibrium protocol in three soils and two sludges), ready biodegradability (manometric respirometry test according to OECD 301F), aerobic transformation in aquatic sediment systems (two sediments, OECD 308) and aerobic transformation in soil (OECD 307). Tier 2 assessment of the adsorption study revealed moderately binding of rilzabrutinib to organic material including sludge and soil (adsorption coefficient K_{OC} ranged from 1371.28 – 11816.06 mL/g). In Tier 3, Freundlich adsorption coefficients (K_F^{ads}) were ranging from 39.41 (Soil A) to 1098.66 (Sludge U) $\mu g^{1-1/n}(cm^3)^{1/n}g^{-}1$, and organic carbon normalized Freundlich adsorption coefficients (K_{FOC}^{ads}) values were ranging from 1812.11 (Sludge R) to 50242.46 (Soil C) $\mu g^{1-1/n}(cm^3)^{1/n}g^{-1}$. According to the current EMA guideline for ERA, a K_{FOC} for sludge of > 10 000 L/kg or < 1000 L/kg would trigger the need for a soil or groundwater assessment via bank filtration, respectively, independently of $PEC_{sufacewater}$ values, whereas K_{FOC} values ranging from 1000 to 10 000 combined with a PEC_{SW} of at least 1 or more (as indicated per guideline) would result in both, further soil and groundwater assessments. Therefore, with regard to the highest K_{FOC}^{ads} value for sludge (2726.21 $\mu g^{1-1/n}(cm^3)^{1/n}g^{-1}$ for Sludge U) and the $PEC_{surfacewater}$ value of 0.12 µg/L, no further assessment in soil and groundwater compartments was triggered. However, rilzabrutinib was shown not to be readily biodegradable in the manometric respirometry test. Radioactive-labelled ^{14}C-rilzabrutinib partitioned primary to sediment and disappeared quickly from the water layer. It was degraded in both sediment systems during an incubation period of 101 days at 20°C (DT_{50} values [in days] for the water phase, sediment phase and total system of 4.16, 89.3, 61.8, respectively, for sediment A and 4.42, 72.1 and 66.1, respectively, for sediment B) and degraded to several transformation products, whereas the two major transformation products, with more than 10% of the applied radioactivity, were identified. The maximum mineralisation to CO_2 was 5.19% of the applied radioactivity. These results indicate a slow degradation of rilzabrutinib. Aerobic transformation of rilzabrutinib at 20°C in four different soils

revealed DT_{50} values ranging from 57.5 to 95.4 days, assuming, that rilzabrutinib is unlikely to accumulate in the soil compartment. However, after request, the applicant provided transformation half-live values extrapolated from the experimental temperature of 20°C to 12°C according to Eq.45 of the current ERA-GL. For the aerobic transformation study in aquatic sediment systems (OECD 308) $DT_{50,water}$ values of 4.16 and 4.42 days (at 20°C) were extrapolated to 8.84 and 9.39 days at 12°C. For the aerobic transformation in soil study (OECD307), DT_{50} values for soil A, B, C and D were extrapolated from 85.8, 57.5, 68.3 and 95.4 days at 20°C to 182.3, 122.2, 145.1 and 202.7 days at 12°C, respectively. Therefore, results indicate that Rilzabrutinib fulfils the criteria for persistence (>120 days) or even very persistent (>180 days) in fresh water sediment and soil.

For evaluation of aquatic toxicity according to the current ERA guideline, studies on algae growth inhibition (OECD 201), Daphnia sp. Reproduction (OECD 211) and Fish early life stage toxicity (OECD210) should be performed. Besides, two acute toxicity studies in Daphnia magna (investigation of immobilization according to OECD 202) and fish (investigation of zebrafish embryo development according to OECD 236) were conducted, revealing an EC_{50} of 33.1 mg/L and a NOEC of 16.4 mg/L and a LC_{50} of > 34.7 mg/L and NOEC of 8.37 mg/L, respectively. In the algae (Pseudokirchneriella subcapitata) growth inhibition test according to OECD 201, a no observed effect concentration (NOEC) of 4.7 mg/L for biomass and growth rate was determined. The chronic toxicity test to Daphnia sp. according to OECD 211 revealed the lowest calculated EC_{10} value of 3.91 mg test item/L for reproduction per introduced adult. In the fish early life stage toxicity test according to OECD 210, the lowest value was determined to be the NOEC of 2.82mg test item/L for body length, whereas the lowest reliable EC_{10} value of 5.38 mg test item/L was observed for wet body weight. According to the current EMA guideline, chronic ecotoxicity data for species from at least three trophic levels (algae, daphnia and fish) are required to derive a predicted no effect concentration for surface water ($PNEC_{SW}$; $PNEC_{SW}$ = EC_{10} or NOEC [mg L^{-1}] / Assessment factor [AF] of 10) which is then related to PEC_{SW} to receive a risk quotient (RQ; RQ = PEC/PNEC), which itself triggers the need for a further Phase II Tier B assessment if RQ ≥1. For the $PNEC_{SW}$ calculation a NOEC of 2820 µg/L from the fish early life stage toxicity test was used. The RQ for surfacewater was far below 1, indicating, that rilzabrutinib is unlikely to pose a risk to surface water. Furthermore, PEC_{SW} was used for $PEC_{groundwater}$ (PEC_{GW}) calculations ($PEC_{groundwater}$ = 0.25 × $PEC_{surfacewater}$), whereas the $PNEC_{surfacewater}$ of 282.0 µg/L was used to further calculate the $PNEC_{groundwater}$ (28.2 µg/L) of rilzabrutinib. The risk quotient for ground water (RQ_{GW}) was far below 1 as well.

Functioning of sewage treatment plant (STP) was followed up by an activated sludge respiration inhibition test (OECD 209). For total and heterotrophic respiration, the LOEC and NOEC were determined to be ≤ 10 mg/L and < 10 mg/L, respectively, whereas the NOEC for respiration based on nitrification was set to ≥ 1000 mg/L since no statistically significant difference to the control could be determined, except for the lowest concentration (10mg). For the effect assessment for STP, PEC ($PEC_{STP/microorganism}$ = $PEC_{surfacewater}$ * 10) and PNEC ($PNEC_{microorganism}$ = EC_{10} or NOEC [mg L^{-1}] / 10) were calculated (using a NOEC of 1000 mg/L), and a risk quotient was determined ($RQ_{microorganism}$ = $PEC_{STP}/PNEC_{microorganism}$) and again found to be far below 1. The OECD 209 Activated Sludge Respiration Inhibition Test will be repeated (post-marketing setting) at lower test concentrations in order to definitively determine no observed effect concentration (NOEC) values and the $PNEC_{microorganism}$ calculation will be refined, if applicable.

Sediment toxicity was investigated by a sediment water toxicity test in Chironomus riparius (OECD 218). An emergence rate and development rate NOEC of 359 mg test item/kg dry sediment (d.s.) was determined at 2.24% organic carbon and recalculated to a NOEC of 1603 mg/kg for standard sediment with an OC content of 10% according to the current ERA -GL (Eq. 18). Due to the lacking concentration/response no valid ECx values could be derived. For the risk characterisation for sediment, several calculations were performed, including those for the solids/water partition coefficient

for suspended matter (K_{Psusp}), the partition coefficient between suspended matter and water $K_{(susp-water)}$, the predicted environmental concentration in sediment related to wet or dry weight ($PEC_{SED,ww}$ of 131.16 µg/kg and $PEC_{SED,DW}$ of 603 µg/kg, respectively) and the predicted no effect concentration in aquatic sediments ($PNEC_{sediment}$), which was based on the Chironomid NOEC of 1603 mg/kg and an Assessment factor (AF) of 100. The risk quotient (PEC/PNEC ratio) for sediment was below 1.

Table 2: Summary of main study results

Substance (INN/Invented Name): Rilzabrutinib			
CAS-number (if available): NA			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	Log K_{OW} of 4	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4 L/kg	B
	BCF_{SSL}	2 L/kg	not B
Persistence	OECD308 (recalculated to 12°C), for 1/2 Sediment 1 = slit loam Sediment 2 = sand OECD307 (recalculated to 12°C) Soil 1 = Loamy sand Soil 2 = Sandy loam Soil 3 = Sandy loam Soil 4 = Clay Ready biodegradability	$DT_{50, water}$ = 8.84/9.39d $DT_{50, sediment}$ = 189.58/ 153.07d $DT_{50, whole\ system}$ = 131.20/140.33d $DT50_{soil1}$ = 182.3 d $DT50_{soil2}$ = 122.2 d $DT50_{soil3}$ = 145.1 d $DT50_{soil4}$ = 202.7 d Not readily biodegradable	vP
Toxicity	NOEC (fish, OECD 210) CMR	2.82 mg/L Non-carcinogenic, non-mutagenic, Presumed human reproductive toxicant (animal studies)	N Y
PBT-statement:	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence, literature)	0.120	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)	NA		N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1 = Loamy Sand Soil 2 = Loam Soil 3 = Clay Sludge 1 = Rural	OECD 106	$K_{oc, soil\ 1}$ = 8406.73 L/kg $K_{oc, soil\ 2}$ = 1806.58 L/kg $K_{oc, soil\ 3}$ = 11816.06 L/kg $K_{oc, sludge\ 1}$ = 1371.28 L/kg $K_{oc, sludge\ 2}$ = 2812.37 L/kg	

Sludge 2 = Urban					
Ready Biodegradability Test	OECD 301F	0% (28 d) not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = slit loam Sediment 2 = sand	OECD 308	$DT_{50, water}$ = 4.16/4.42 d $DT_{50, sediment}$ = 89.3/72.1 d $DT_{50, whole\ system}$ = 61.8/66.1 d $DT_{50, water}$ = 8.84/9.39d $DT_{50, sediment}$ = 189.58/ 153.07d $DT_{50, whole\ system}$ = 131.20/140.33d % shifting to sediment = 82.2% CO_2 = 5.19% NER = 30.8% $NER_{type\ I}$ = 4.1% Transformation products >10% = Y, TP1 = 20.2%, DT50 M1: NA			DT50s at 20°C 1 / 2 DT50s extrapolated to 12°C 1 / 2 at day 29 at test end at test end at day 29, total system
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	4700	µg/L	
Daphnia sp. Reproduction Test	OECD 211	EC_{10}	3910	µg/L	
Fish, Early Life Stage Toxicity Test/ *Danio rerio*	OECD 210	NOEC EC_{10}	2820 5380	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC / EC_{10} NOEC / EC_{10}	<10000 / NA ≥1000000 / NA	µg/L	Total and heterotrophic respiration Nitrification respiration To be repeated at lower test concentration (post-marketing)
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF_{SS} BCF_{SSL}	3 2	L/kg	%lipids:7.5% %lipids: 5%
Aerobic and anaerobic transformation in soil Soil 1 = Loamy sand Soil 2 = Sandy loam Soil 3 = Sandy loam Soil 4 = Clay	OECD 307	DT50 $\%CO_2$	$DT50_{soil1}$ = 85.8/182.3 d $DT50_{soil2}$ = 57.5/122.2 d $DT50_{soil3}$ = 68.3/145.1 d $DT50_{soil4}$ = 95.4/202.7 d CO_2 (max) = 20% NER (max) = 52.3%		At 20°C/12°C at test end, soil3 at test end, soil2 at test end,

			$NER_{type\ I}$ = 6.6 % Transformation products >10% = Y, M1 = 15.3%, DT50 M1: NA		soil2 at day 120; soil 1 chemical formular: $C_{36}H_{41}O_4N_9F^+$ $[M+H]^+$ m/z = 682.32660
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	359/1603	mg/kg	Organic carbon content of 2.24%/10% For emergence and development rate

2.5.6. Discussion on non-clinical aspects

Preclinical studies provided evidence on rilzabrutinib's mechanism of action, its safety and tolerability for the treatment of autoimmune diseases. Pharmacokinetic and pharmacodynamic data collected from *in vitro* and *in vivo* studies were used to select the dose for the first in human studies as well as define the expected efficacious dose (400 mg BID) in the clinic. The dose of 400 mg BID was confirmed as the optimal dose in Phase 2 (DFI17124, including dose escalation and expansion parts) and Phase 3 (EFC17093, including successively placebo-controlled, open-label and long-term extension parts).

The toxicology profile of Rilzabrutinib was evaluated in mouse, rat, rabbit, and dog. Rilzabrutinib was evaluated in single-dose toxicity studies (rat, dog) and in repeat-dose toxicity studies in rats (13-day; 2-week; 1-, 3-, and 6-month), mice (1- or 2-day; 2-week; and 1-month), and dogs (4-day; 2- and 12-week (bridging); 1-, 3-month, and 9-month); genotoxicity studies *in vitro* (Ames test and *in vitro* chromosome aberration test) and *in vivo* (micronucleus test in rats); reproductive toxicology studies (male and female fertility study in rats; embryo-fetal toxicity in rats and rabbits, pre- and postnatal development toxicity study in rats), and carcinogenicity studies (6-month TgHRAS mouse and a 2-year rat study). The applicant considered investigations for local tolerance, antigenicity, immunotoxicity, unnecessary/not applicable on a regulatory point of view or based on a scientific rationale; this is endorsed based respectively on the route of administration, pharmacology of the product and the immunotoxicology parameters that were evaluated in repeat dose toxicity studies in rats and dogs.

Relevance of pharmacological and toxicological species

The pharmacodynamic effects of BTK blockage are expected to be the same in the mouse, rat, rabbit, and dog. This is because mouse, rat, dog, and rabbit BTK are nearly identical to the human version of the protein (approximately 99% homologous amino acid sequence), with no differences in the sites where rilzabrutinib binds. Since BTK is highly conserved across these species, the potency of rilzabrutinib is also expected to be the same. Selection of the animal species for toxicity studies (mouse, rat, and dog) was also based on the standard use of these species in the corresponding study types and the robust historical database. Based upon the pharmacokinetics and pharmacologic properties of rilzabrutinib, the rat and dog were considered appropriate primary models for nonclinical safety studies, based on the similarity of oral bioavailability and metabolite profiles in these species to

the human while the low oral bioavailability in the monkey at all doses factored into the selection of the dog as the nonrodent species for safety testing. The rabbit was chosen as the non-rodent species in the embryo-foetal toxicity studies because of the large historical control database.

GLP aspects

Pivotal GLP safety/toxicology studies were performed in test facility site within a period part of an EU or an OECD/MAD accepted GLP monitoring programme. Indeed, for rilzabrutinib, all facilities where the studies were conducted are either currently part of or have previously participated in a GLP (Good Laboratory Practice) verification program in the USA or France. When deviations had been reported in the appropriate study reports, it is agreed these deviations did not negatively impact the quality or integrity of the data nor the conclusions.

Pharmacology

Rilzabrutinib is a covalent reversible BTK inhibitor. It binds covalently to a cysteine present in the ATP-binding pocket of BTK with high selectivity. BTK is involved in the activation of hematopoietic cells, notably basophils, mast cells, macrophages, neutrophils and platelets. B lymphocytes are key players in the pathogenesis of autoimmune thrombocytopenia. Their abnormal activation leads to the production of antibodies that target and destroy platelets, resulting in thrombocytopenia. Rilzabrutinib inhibits BCR signalling and Fc receptor pathways and is therefore being developed as a treatment for autoimmune thrombocytopenia.

Primary Pharmacology *in vitro*

Rilzabrutinib is a highly potent BTK inhibitor with an IC_{50} of 1.3 nM and demonstrates durable target occupancy due to its fast binding and slow dissociation (half-life of 7 days). It inhibits BTK by competitively blocking ATP binding, with IC_{50} values shifting to 3–9 nM under physiological ATP conditions. Although it forms a covalent bond with Cys481, the binding is reversible, as shown by recovery of 137% rilzabrutinib after trypsinization, compared to 0% for ibrutinib. This reversibility is further supported by BTK turnover in B-cells, which has a biological half-life of 12 hours, contributing to the compound's reversible pharmacological effect.

Rilzabrutinib shows cellular BTK inhibition with an IC_{50} of 8 ± 2 nM, aligning with its BTK occupancy. It effectively reduces B-cell activation, as evidenced by decreased CD69 expression, and inhibits B-cell proliferation with an IC_{50} of 5 ± 2.4 nM, confirming its mechanism of action. However, its effect on the IL-4/STAT6 pathway is weak (IC_{50} > 5 µM). In monocytes, rilzabrutinib inhibits TNF-α production (IC_{50} = 55.7 nM), indicating anti-inflammatory potential. It also suppresses IgE-mediated basophil activation, though with lower potency (IC_{50} = 490 ± 130 nM), and notable variability. Platelet aggregation was shown to be unaffected by Rilzabrutinib at mean and maximum human concentrations of 0.3 and 1 µM respectively.

Non-BTK targets

Rilzabrutinib shows limited off-target kinase activity, with potent inhibition of TEC family kinases (TEC, BMX, TXK; IC_{50} = 0.8–1.2 nM), but lower occupancy (36–59% at 24h). It partially inhibits T-cell activation (48% at 5 µM) and has no effect on ADCC up to 1 µM, suggesting low clinical relevance of these effects. Receptor tyrosine-protein kinase ERBB4 is inhibited with high affinity (IC_{50} = 11 ± 7 nM). Although this inhibition is considered modest, kinase occupancy data are not provided or discussed. Therefore, the risk of functional consequences related to ERBB4 inhibition cannot be completely excluded. Non-clinical and clinical data available today suggest that the risk of an adverse effect related to an effect on ERBB4 is low. Although BTK is expressed and involved in T-cell signalling pathways, its role in T-cell activation is minor. In a broad receptor screen (CEREP), rilzabrutinib showed >50% activity against only 4 targets at 10 µM, with minimal activity across other receptors

and ion channels, indicating a low risk of off-target pharmacology. Rilzabrutinib has a covalent non-permanent binding mechanism and increased selectivity by bonding to a specific cysteine residue, therefore reduced off-target effects are expected.

Metabolites

Three metabolites were identified: thiocyanate (PRN4400; 94%), PRN834 (5%), and PRN618 (<1%). Thiocyanate showed no BTK inhibition or occupancy, and no off-target activity at 10 µM, with negligible impact on serum thiocyanate levels. PRN834 and PRN618 inhibited BTK with IC_{50} values of 14.5 nM and 0.4 nM, respectively, but were less effective than rilzabrutinib in cellular assays. The (E) and (Z) isomers of rilzabrutinib showed similar BTK activity, while the (S)-enantiomer (PRN1418) was less potent and had faster off-rate kinetics, confirming rilzabrutinib's superior potency and durability.

Pharmacology *in vivo*

Several models have been used to demonstrate the effectiveness of Rilzabrutinib on various autoimmune pathologies. Concerning the choice of non-clinical species, the rat and the dog are generally used for this type of pathologies since the function as well as the structure of BTK are largely conserved between humans and the chosen species.

Rilzabrutinib (10, 20 and 40 mg/kg) was effective in a collagen-induced arthritis model in rats and was comparable to dexamethasone (0.075 mg/kg) (DVR0200). Animals treated with 20 mg/kg rilzabrutinib BID showed complete reduction of arthritis Ankle score as dexamethasone. Interestingly, reduction of arthritis Ankle score with a 20 mg/kg BID dosing was more effective than 40 mg/kg rilzabrutinib QD. Over the course of this procedure, the applicant resolved the concern regarding the discrepancy between high occupancy and plasma concentration of rilzabrutinib and the efficacy in reducing the Ankle Score.

Decreased appetite was observed in dogs receiving 15-500 mg/kg rilzabrutinib (DVR0173, DVR0206, DVR0377). Since emesis and anorexigenic effect were observed in all three beagle dogs treated already with 30mg/kg rilzabrutinib, this immediate effect is of therapeutic relevance (DVR0226). Significant elevations of peptide YY and leptin were measured and, according to the applicant's interpretation, are deemed to contribute to the above described anorexigenic effect. In a similar study in rats, oral rilzabrutinib (500 mg/kg) resulted after 4 days in significantly elevated stomach weight, decreased food consumption and reduced body weight (Figure 15; DRV0235).

Beside peptide YY and leptin also glucagon and pancreatic polypeptide were elevated at all time points investigated in study DVR0226. The potent regulators of blood glucose GIP and insulin were also fluctuating between mainly reduced but also significantly elevated at a single time point (7 h post dose). Overall, these hormone patterns are in favour of elevated blood glucose levels and suggest pursuing monitoring these hormones throughout the clinical usage program.

Safety Pharmacology

In a core battery of safety pharmacology studies (rats and dogs), there were no rilzabrutinib-related adverse effects on CNS, CV, and respiratory systems, up to 500 mg/kg rilzabrutinib, which is also considered the no observed adverse effect level (NOAEL). Although the *in vitro*, IC_{50} of rilzabrutinib was 3.5 µM (2328.7 ng/mL) to inhibit the hERG, the risk of QT prolongation in humans is considered to be low since rilzabrutinib is highly protein bound (97.5%) so the plasma free fraction projected at a C_{max} (150 ng/mL) corresponding to a 400 mg BID dose would be as high as 3.75 ng/mL, assuming free fraction is 2.5%.

Pharmacokinetics

The *in vitro* and *in vivo* data provided by the applicant on absorption, distribution, metabolism and excretion (ADME) are agreed and regarded as supportive for the proposed indication. The detailed description of the ADME and the toxicokinetic(s) (TK) of Rilzabrutinib has been reflected in the SmPC. HPLC/MS/MS was applied as the analytical method in order to determine Rilzabrutinib and its metabolites (PRN834, PRN618 and PRN4400) plasma concentration. Methods were sufficiently validated.

Appropriate animal models (mice, rats, dogs and cynomolgus monkeys) were used, as applicable. Besides the robust historical database for mice, rats and dogs in toxicity studies and for the rabbit in embryo-fetal toxicity studies, BTK is considered highly conserved across these species (approximately 99% homologous amino acid sequence to human BTK). Furthermore, rats and dogs were selected for non-clinical safety studies due to their similarity of oral bioavailability and metabolite profiles compared to humans, while the oral bioavailability in monkeys was low. In pharmacokinetic studies, animals received the drug either by intravenous (IV) route followed by oral route, oral route only or intra-jejunal (IJ) route (TK study in rats repeat dose study). The IJ route was performed to understand the impact of avoiding gastric exposure. Rilzabrutinib is a combination of the E (> or equal to 90%, predominant) and the Z geometric isomer (minor) with same pharmacological activity. Their interconversion was studied in rats. Because oral bioavailability was low in monkeys, the dog was used as non-rodent species.

In general, rilzabrutinib was rapidly absorbed with a high plasma clearance representing approximately liver blood flow in rats and dogs and approximately half liver blood flow in monkeys. It was often noted, especially in rats, that females showed higher systemic exposures compared to males. The applicant states that due to observed gender-related exposure differences in rats, dose-adjustment was performed in subsequent toxicological evaluations. A similar trend was observed in clinical PK data (PopPK analysis with data from healthy participants and participants with ITP revealed that sex had statistically an impact on clearance and volume of distribution, with a median Cmax and AUC0-24 at steady state reduced by about 21% and 24% in male participants), however, differences were considered not clinically significant for a dose adjustment (<25% difference in exposure, no difference in efficacy or safety response) in male participants.

Almost no accumulation of rilzabrutinib in plasma occurred. *In vitro* studies demonstrated a high plasma protein binding in humans, dogs and rats, with an approximately 2-fold occurrence of the drug in plasma than blood. Radioactive-labelled rilzabrutinib well distributed to almost all tissues, whereas the highest tissue concentrations (>10.0 µg equiv/g) were observed in stomach (it corroborates with the gastro-intestinal findings in rats, dogs and humans), followed by small intestine, esophagus and liver and the highest concentrations were seen in the contents of the alimentary canal, urinary bladder and bile, which is in line with the supposed route of excretion via the bile and thus faeces. Only small amounts of radioactivity were found in the urine of animals. Tissues with the lowest concentrations (<0.6 µg equiv/g) at C_{max} were the mammary gland region, bone, white adipose, spinal cord, brain, and eye lens.

Due to higher exposures to pigmented skin, a phototoxicity study was further conducted. Furthermore, because low and punctual radioactivity was found in the brain and/or spinal cord of albino (SD) rats (<0.2 µg equivalent/g tissue), an additional study was performed in non-pigmented female Wistar Han rats, where concentrations of rilzabrutinib and the metabolites PRN618, PRN834, PRN1186, PRN835 and PRN438 in the cerebral spinal fluid (CSF) were below the limit of quantification. The RBC to plasma ratio (KRBC/Pl) for rilzabrutinib was below 0.5 in all species.

The metabolic pathways of rilzabrutinib included N-dealkylation, oxidation, and sulfation. The main metabolite identified in plasma was thiocyanate (PRN4400), which is also endogenous in nature.

Additionally, since the hydrolysis product PRN834 (M16) was not determined in any *in vitro* study but observed in all *in vivo* samples, an extrahepatic, non-CYP mediated metabolism is suggested. Importantly, no unique human metabolite has been detected so far. CYP 3A4 seems to be the main CYP involved in rilzabrutinib's metabolism, followed, but far behind, by CYP2D6. It is to note, that no studies regarding placental transfer or excretion to milk were conducted. Please refer to the discussion of the pre- and postnatal development studies in the toxicology section.

Toxicology

Repeat-dose Toxicity

Rat repeat-dose toxicity studies demonstrated increased IBA-1 (microglia activity/microgliosis) and GFAP (astrocytes) positivity in the brain at systemic exposures to rilzabrutinib, which are below the expected exposure during human use. It is agreed that the observations pertaining to IBA-1 and GFAP may not be adverse as their meaning is currently unknown. The NOEL for IBA-1 and GFAP expression was 50 mg/kg/day for males and 15 mg/kg/day for females and the according exposure levels (AUC_{last}) are slightly above (males) or even below (females) the exposure expected during clinical use (AUC_{24h} = ~1540 ng*h/mL). On basis of further correspondence with the applicant, it is considered unlikely that increased fluorescent signals for IBA-1 and GFAP indicate an adverse reaction of the brain to rilzabrutinib.

After subsequent correspondence, it is agreed with the applicant, that the dog might be particularly susceptible to the effects of rilzabrutinib but still represents a useful and sensitive model for estimating some clinical effects. Definitive conclusions on safety should derive from human studies. To appropriately conclude on safety endpoints that are clinically inaccessible (e.g., carcinogenicity), rat data, which provide sufficient exposure margins are considered more reliable.

Genotoxicity

A standard battery of GLP-compliant genotoxicity studies (2 *in vitro* and *1 in vivo*) were submitted. Specifically, a bacterial reverse mutation assay with *Salmonella typhimurium* and *Escherichia coli* (Study DVR0169), an *in vitro* Chromosomal Aberration test in human peripheral blood lymphocytes (Study DVR0170), and the *in vivo* Rat Bone Marrow Micronucleus Assay (Study DVR0185).

Clearly negative results for the Reverse Mutation Assay (study DVR0169) were reported, indicating that rilzabrutinib did not cause a positive mutagenic response with any of the tester strains in either the presence or absence of rat liver S9. Also, rilzabrutinib was considered negative for the induction of structural and numerical chromosome aberrations in the non-activated and S9-activated test systems in the *in vitro* mammalian chromosome aberration test using HPBL (DVR0170). Results of the micronucleus assay indicated that rilzabrutinib did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes at doses up to 2000 mg/kg in males, which is the recommended top dose for short-term studies (ICH S2 (R1); for females, the MTD was determined to be 1500 mg/kg in a range finder study, and thus was concluded to be negative. Rilzabrutinib plasma levels showed systemic exposure at a multiple over clinical exposure. Rilzabrutinib tested negative in all three assays. The non genotoxic potential of rilzabrutinib is reflected in the SmPC Section 5.3.

Carcinogenicity

In the 2-year rat carcinogenicity study, a statistically significant increase in follicular cell carcinoma/adenoma in the thyroid gland was observed at 15 mg/kg/day in females and at 100 mg/kg/day in males. Fewer incidences of this finding at 50 mg/kg/day in females are presently regarded incidental. Insufficient evidence was provided to rule out a possible relevance for human, as direct comparison of the influence of rilzabrutinib on thyroid hormones and/or TSH in rat and human is absent.

Upon request, the applicant has provided a comprehensive re-evaluation of the neoplastic findings in the uterus and mesenteric lymph nodes, under consideration of relevant literature on historical background levels of hemangiosarcoma and uterine adenocarcinoma in 2-year rat studies. This, in connection with appropriate safety margins in the high dose groups in the conducted rat carcinogenicity study, provides sufficient certainty that the respective risks in humans are low.

Hence, the applicant was requested to adapt the SmPC. The non-carcinogenic dose was adjusted from 50 mg/kg/day to 5 mg/kg/day in females. Of note, at 30 mg/kg/day in males (i.e., NOAEL in males) as well as at 5 mg/kg/day (and at 15 mg/kg/day) in females the total exposure to rilzabrutinib is below the human exposure at steady state. Upon subsequent rounds of questions/responses, it was also agreed to revise the SmPC as follows: "Transcriptomic analysis suggests that thyroid tumors in rats derive from rilzabrutinib-mediated perturbation of thyroid hormone maintenance. This nongenotoxic effect was discovered to be specific for rats with a mechanism not considered to be relevant to human' therefore, the potential for thyroid tumors in humans is considered low."

Additionally, the applicant mentioned erythrocytosis in the mesenteric lymph node as a potential rilzabrutinib-related long-term non-neoplastic effect in Section 5.3 of the SmPC.

Reproductive and developmental toxicity

For the embryo-foetal rabbit study DVR0379, dose levels were 0, 10, 30, or 100 mg/kg/day of rilzabrutinib. Although dose levels of 10 and 30 mg/kg/day did not reach clinical systemic exposure levels to provide sufficient safety margins, the dose range is considered adequate due to inclusion of 100 mg/kg/day and absence of exaggerated maternal toxicity at higher doses.

Embryo-foetal development studies (DVR0378 and DVR0379) in both animal models (rats and rabbits) demonstrated the occurrence of a shift in the number of thoracic and lumbar vertebrae upon rilzabrutinib at the highest dose (300 mg/kg/day in rats; 100 mg/kg/day in rabbits). The rat study describes a statistically significant increase in the incidence of supernumerary thoracic rib pairs.

In the rabbit study DVR0379 at 30 mg/kg/day (the NOAEL for this effect) the systemic exposure falls vastly below exposure levels reached during clinical use. After several rounds of responses, this matter has been clarified and reflected in section 5.3 of the SmPC.

Prenatal and postnatal development, including maternal function: NOAELs presented are agreeable. The applicant upon request provided a comprehensive explanation for the lack of toxicokinetic assessment in F1-offspring as well as transfer of rilzabrutinib into maternal milk. It is agreed that ICH S5 (see 3.5.) does not strictly demand the toxicokinetic assessment of substances in maternal milk. The issue is considered resolved.

Juvenile animal toxicity: It is agreed that additional JAS is not needed to support the current MAA for the treatment of adult patients. The following statement in the SmPC Section 4.2 is supported: "The safety and efficacy of rilzabrutinib in children and adolescents below 18 years of age with ITP have not been established. No data are available."

Qualification of Impurities

Several impurities (impurities with structural alert that warranted a mutagenicity study), present at levels ≥0.15% or a predicted daily intake of ≥1 mg in the drug, structurally related to rilzabrutinib, were subjected to toxicological qualification through a pivotal oral toxicology study in rats (1-, 3- and 6-months studies) administered by oral gavage. Mutagenic impurities were assessed in accordance with ICH M7 (R2).

A dose margin was calculated for the comparison of the impurity exposure in human and rats, expressed in mg/kg. Different batches were used for the pivotal toxicity studies. Impurities in

rilzabrutinib drug substance batches were qualified in rats in line with ICH Q3 A (R2). Batch specification for the impurities are agreed to be covered by toxicological data.

The main impurities in the finished product are PRN2960 and PRN834.

While *in silico* structure- activity (Q)SAR predictions systems (expert rule-based Derek Nexus version 2.1 and Leadscope version 2022.0.0) determined these impurities as Class 1 (known mutagenic carcinogens) to Class 5 (non-mutagenic) according to their structural alerts, these impurities were subjected to Ames test (for mutagenicity in Salmonella typhimurium/TA100, TA1535, TA1537, TA98; E. coli, +/- S9) and *in vitro* micronucleus test (clastogenicity assay in human lymphocytes) studies in line with ICH S2 requirement, *in vivo* Comet assay test was realized when the micronucleus test was positive (PRN3232, PRN3612). The presence of nitrosamines in the drug substances was also assessed with acceptable limit (no risk above 10 % of the acceptance limit).

All mutagenicity tests for the mutagenic impurities were realized globally in compliance with GLP except the tests for the impurities, PRN835-EDCI adduct (PRN1319) and PRN3220.

Regarding the Ames tests provided for impurities, the sponsor was asked to justify the absence of the preincubation method. The sponsor justified the use of the incorporation plate in accordance with OECD 471, given that the impurities did not contain chemical structures requiring the preincubation method.Ten specified impurities were qualified by comparison of the impurity exposure (mg/kg) at the NOAEL in GLP repeat-dose toxicity studies in rats and the impurity exposure in a 60 kg patient at the therapeutic dose of 800 mg/day, taking into account the proposed acceptance criterion for each impurity. Pivotal repeat-dose toxicity studies chosen for this evaluation were rat-studies DVR0174 (1-month toxicity study), study DVR0207 (3-month toxicity study), study TXC1679 (3-month toxicity study), and study DVR0376 (6-month toxicity study). According to the applicant, all impurities had a margin greater than or equal to 4 and were therefore considered qualified since they were appropriately tested in toxicity studies as per ICH Q3A(R2). A generic acceptability criterium of 4 to regard impurities as qualified is not explained any further. Although there are no specifications regarding an acceptable margin to qualify an impurity at a specific level, a 4-fold dose margin is generally considered at the lower end of what's typically accepted, given uncertainties resulting from interspecies variability and individual patient variability or taking into account long-term, chronic treatment.

Ideally, an impurity should be present at levels at or above its proposed specification in batches tested in toxicity studies. Cases, where the proposed specification is higher than the tested level AND a low dose margin is seen are considered highly critical.

A 4-fold *in vivo* margin above the requested drug substance specification limit is not considered robust enough to extrapolate a safe dose from an actual impurity level which is lower by a factor of 2,6 (0,05% vs 1.3%) compared to the proposed limit, as this is the case for PRN3232 and its presence in batches used in study TXC1679.

On the other hand, in light of the arguments provided by the applicant (same *in-silico* structural alerts as rilzabrutinib, negative genetic toxicity results), a 4-fold *in vivo* margin above the requested drug substance specification level appears justified for impurities tested at levels at or above its proposed specification, as this is the case for PRN3590.

Nevertheless, both impurities in question were subjected to a dedicated 3-month repeat-dose impurity qualification study in rat (Study TXC1711) separately spiked with six impurities and performed as a GLP study from 29 Jan 2024 to 12 Feb 2025. Dose margins of rilzabrutinib impurities qualified under ICH Q3A(R2) were revised based on the results from study TXC1711. This is acknowledged and listed impurities (specifically PRN3232, PRN3590 and PRN1418) are considered qualified at their respective proposed specification levels.

Impurity PRN834, which is also a metabolite of rilzabrutinib in humans and laboratory animal species and well characterized in animal repeat-dose toxicity studies is considered qualified at specified levels as adequately tested in toxicity studies (rat 1-month toxicity study DVR0174 and rat 3-month toxicity study DVR0207).

Environmental Risk Assessment

Overall, the applicant submitted a thorough Environmental Risk Assessment (ERA) with this Marketing Authorization Application, including a Phase I, PBT/vPvB hazard screening and Phase II Tier A assessment.

However, two follow-up concerns need to be adequately addressed by the applicant post-approval:

a) The OECD 209 test will be repeated (post-marketing setting) at lower test concentrations in order to definitively determine no observed effect concentration (NOEC) values. Results of the OECD 209 test have to be provided as soon as they are available, as agreed with the applicant. b) The PNECmicroorganism value will be refined or confirmed as necessary after the OECD 209 test is repeated at lower test concentrations (Post-marketing setting), as agreed with the applicant. The applicant provided a letter of recommendations containing all agreed commitments regarding the ERA.

Rilzabrutinib is not a PBT substance. As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of rilzabrutinib to the environment.

2.5.7. Conclusion on the non-clinical aspects

A full panel of preclinical *in vitro* and *in vivo* studies was performed to characterize rilzabrutinib and to analyse its efficacy and safety in various disease models. Rilzabrutinib potently and covalently inhibits BTK and thereby downstream signals of BCR and FcγR signalling, which are implicated in the pathogenesis of ITP. Rilzabrutinib showed beneficial effects in *in vivo* models of antibody-mediated disease, including a single immune thrombocytopenia study. These preclinical pharmacology studies supported the clinical evaluation of rilzabrutinib.

The applicant provided a comprehensive study package on toxicological aspects of rilzabrutinib. Overall, the preclinical safety profile is regarded acceptable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A request for GCP inspection has been adopted for the following clinical study: PRN1008-018. The outcome of this inspection was provided on 4th of June 2025 with one critical finding raised (EMA/IN/0000239123). Still, it was concluded by inspectors that identified major and critical findings do not compromise GCP compliance, ethical standards or the quality of data from trial PRN1008-018.

- **Tabular overview of clinical studies**

Study Number/ formulation/ Status as of data cutoff date (14 March 2024)	Study design	Population (sample size)	Primary Study Objective	Dose Levels
Study participants with ITP				
PRN1008-018 (EFC17093) (pivotal Phase 3) IR tablet 24-week double-blind (adults) Complete; Open-label (OL)/ Long-term extension (LTE) Ongoing	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)	Adult ITP patients: 202 (2:1) (133 rilzabrutinib, 69 placebo)	To demonstrate the efficacy of rilzabrutinib versus placebo in participants with persistent or chronic 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	400 mg BID or placebo
PRN1008-010 (DFI17124) Phase 1/2 IR tablet Parts A and B Complete; LTE ongoing	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 ITP	ITP patients Part A: (N=60) Part B: (N=26) LTE: (N=16 from Part A and N=11 from Part B)	Part A: To explore the clinical activity of up to 4 dose levels of rilzabrutinib in relapsed/refractory participants with ITP; To identify a potential dose regimen to use in future studies of rilzabrutinib in participants with ITP; and Part B: To further explore the clinical activity and durability of response of the selected dose of 400 mg BID of rilzabrutinib in patients with ITP who have relapsed or have an insufficient response to prior therapies	Part A: 200 mg QD (n=9, starting dose); 400 mg QD (n=1, starting dose); 600 mg per day (300 mg BID; n=5, starting dose); 800 mg per day (400 mg BID; n=45, starting dose) Part B: 400 mg BID (n=26 exposed to this dose) LTE: 400 mg BID (Parts A and B, N=27)
Phase 1 studies				
PRN1008-001 (TDU17293) Oral liquid Complete	A Phase 1, Randomized, Double-blind, Placebo-controlled, Ascending-dose Study of the Safety, Tolerability, and Pharmacokinetics of Orally Administered Rilzabrutinib	Healthy participants SAD (N=30 active; N=10 PBO) MAD (N=32 active; N=8 PBO)	To assess the safety and tolerability of single and multiple oral doses of rilzabrutinib when administered to healthy adult participants	SAD: 50, 150, 300, 600, 1200 mg (6 active: 2 PBO per group) MAD: 300 mg, 600 mg QD; 300 mg, 450 mg BID × 10 days (8 active: 2 PBO per group)
PRN1008-002 (INT17284) Liquid Complete	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	Healthy participants (N=12)	To evaluate the effect of a single oral dose of rilzabrutinib on the single-dose PK of midazolam, a CYP3A4 substrate, in healthy participants	600 mg single dose
PRN1008-004 (PKM17285) Liquid and capsule Complete	A Phase 1, Single-center, Open-label Study to Evaluate the Pharmacokinetics of Rilzabrutinib in Healthy Male and Female Volunteers	Healthy participants (N=12)	To evaluate the relative bioavailability of a single oral dose of rilzabrutinib when administered as a liquid formulation and a capsule formulation in the fasted state	300 mg single dose
PRN1008-006 (PKM17286) Liquid and IR tablet Complete	Relative Bioavailability and Effect of Food and Esomeprazole on the Pharmacokinetics of Rilzabrutinib in Healthy Volunteers	Healthy participants (N=12)	Relative bioavailability of liquid versus tablet formulation in the fasted state and the impact of food and esomeprazole on the PK of tablet formulation	300 mg single dose
PRN1008-008 (PKM17289) IR and DR tablet Complete	A Phase 1, Single-Center, Open-label Study to Evaluate the Safety and Pharmacokinetics of Two Tablet Formulations of Rilzabrutinib	Healthy participants (N=16)	To evaluate the relative oral bioavailability of a single oral dose of rilzabrutinib when administered as an IR and DR tablet formulation in the fasted state. To assess the effect of food on the PK of single oral doses of the DR tablet formulation.	DR tablet 200 mg single dose, DR or IR tablet 400 mg single dose
PRN1008-011 (INT17290) IR tablet Complete	A Phase 1 Study of the Relative Bioavailability of Two Rilzabrutinib Tablet Formulations, Effect of Rilzabrutinib on Midazolam Pharmacokinetics, and Impact of Famotidine on PRN1008 Pharmacokinetics in Healthy Participants	Healthy participants (N=14)	Relative bioavailability of 2 rilzabrutinib tablet formulations, effect of rilzabrutinib on midazolam pharmacokinetics, and impact of famotidine on rilzabrutinib PK	400 mg single dose
PRN1008-014 (PKM17291) IR tablet Complete	A Two-Part Study to Assess the Effects of Ritonavir on Rilzabrutinib Pharmacokinetics, and the Effects of Rilzabrutinib on QTc Interval Compared to Placebo and Moxifloxacin in Healthy Participants	Healthy participants Part A: (N=12) Part B: (N=39; 37 of whom received at least 1 dose of study drug)	A 2-part study to assess the effects of ritonavir on rilzabrutinib PK, and the effects of rilzabrutinib on QTc interval compared to placebo and moxifloxacin in healthy participants	Part A: 100 mg, 1200 mg single dose Part B: 400 mg single dose

PRN1008-015 (POP17292) Part 1: IV solution/ IR tablet Part 2: liquid Complete	A Two Part Phase 1, Open-Label Study of the Absorption, Metabolism, Excretion and Absolute Bioavailability of [14C]-rilzabrutinib in Healthy Male Participants	Healthy participants Part 1: (N=8) Part 2a: (N=7) Part 2b: (N=3)	Part 1: Absolute oral bioavailability of rilzabrutinib and IV PK of [14C]-rilzabrutinib Part 2: Mass balance recovery, PK, and routes and rates of elimination along with metabolite identification of a single oral dose of [14C]-rilzabrutinib	Part 1: single oral dose of 400 mg and IV micro tracer dose of [14C]-rilzabrutinib (100 µg in approximately 2 mL) Part 2: single oral dose of 300 mg in approximately 100 mL [14C]-rilzabrutinib
PRN1008-020 (POP17091) IR tablet Complete	An Open-Label, Phase 1 Study to Evaluate the Effect of Mild and Moderate Hepatic Impairment on the Single-Dose Pharmacokinetics of Rilzabrutinib	Participants with hepatic impairment Child-Pugh A: N=8 Child-Pugh B: N=8 Matched control: N=13	To compare the PK of rilzabrutinib in adult participants with mild and moderate hepatic impairment/insufficiency to participants with normal hepatic function; and To evaluate the safety and tolerability of rilzabrutinib in participants with hepatic impairment/insufficiency	400 mg single dose
PRN1008-022 (PKM17088) IR tablet Complete	A Phase 1, Single-center, Open-label Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Rilzabrutinib (PRN1008/SAR444671) in Chinese Healthy Male and Female Participants	Chinese healthy participants (N=10)	To evaluate the PK of a single dose of rilzabrutinib in healthy Chinese participants	400 mg single dose
PRN1008-023 (PKM17089) IR tablet Complete	A Phase 1, Single-Center, Open-Label Study to Evaluate the Pharmacokinetics and Tolerability of Rilzabrutinib (PRN1008) in Japanese and Caucasian Healthy Male and Female Participants	Healthy participants Cohort 1 - Japanese origin: N=11 Cohort 2 - Caucasian: N=12	To evaluate the PK of rilzabrutinib in Japanese and Caucasian healthy participants following single and multiple doses	Cohort 1: Period 1: 100 mg tablet on Day 1 Period 2: 200 mg tablet (2×100 mg tablet) on Day 5 Period 3: 400 mg tablet BID on Days 9 to 12 and 400 mg tablet SD on Day 13 Cohort 2: Period 1: 400 mg tablet BID on Days 1 to 4 and 400 mg tablet SD on Day 5
PRN1008-024 (INT17090) IR tablet Complete	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 (PRN1008) in Healthy Male and Female Volunteer	Healthy participants Part A: N=16 Part B: N=16	To evaluate the impact of quinidine co-administration on rilzabrutinib PK (Part A). To evaluate the impact of rifampin co-administration on rilzabrutinib PK (Part B).	Part A: Period 1: 400 mg rilzabrutinib on Day 1 Period 2: quinidine 300 mg q8h on Days 7 to 11; 400 mg rilzabrutinib on Day 10 Part B: Period 1: 400 mg rilzabrutinib on Day 1 Period 2: rifampin 600 mg QD on Days 7 to 17; 400 mg rilzabrutinib on Day 16
PRN1008-025 (PKM17098) IR tablets (FC, SDD) Complete	A Randomized, Open-label, Phase 1 Study to Assess the Effects of Food and Formulation on the Pharmacokinetics of a Single Dose of Rilzabrutinib (SAR444671 [Formerly PRN1008]) in Healthy Male and Female Participants	Healthy participants N=24	To evaluate the impact of food on the PK of rilzabrutinib following a single oral 400 mg dose to healthy participants. To evaluate the impact of formulation on the PK of rilzabrutinib following a single oral 400 mg dose to healthy participants	400 mg single dose

Abbreviations: Abbreviations: BID = twice daily; BTK = Bruton's tyrosine kinase; 14C = radio labeled carbon-14; CYP = cytochrome P450; DR = delayed release; FC = film coated; IR = immediate release; ITP = immune thrombocytopenia; IV = intravenous; LTE = long term extension; MAD = multiple ascending dose; N = the number of subjects in the analysis population; PBO = placebo; PK = pharmacokinetic; q8h = every 8 hours; QD = once daily; QTc = QT interval corrected for heart rate; SAD = single ascending dose; SD = single dose; SDD = spray-dried dispersion

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalytical Methods

Several bioanalytical methods were used throughout the clinical development program to quantify Rilzabutinib alone or simultaneously with one metabolite (PRN834) in plasma (AV14-PRN1008601 & addendums 01-06, AV21-PRN1009-01 & addendum 01, PDV0143) and in urine (DRV0523) or to quantify thiocyanate (PRN4400) in plasma (DRV0529 and PDV0143-Thyocyanate). Cross validation were provided by the applicant for methods AV14-PRN1008601 & AV21-PRN1009-01 and between analytical sites of AV21-PRN1009-01 & of PDV0143. Achiral bioanalytical methods were used to quantify the analytes.

Absorption

PK studies were performed in healthy volunteers as well as in patients with ITP [Studies 015, 022, 023, 010, 018]. Across the clinical studies after single dose administration in healthy volunteers or single/multiple dose in patients of 400 mg rilzabrutinib, absorption was rapid with a median Tmax at 2 h (ranging from 1 to 2.25h). Absorption is approximately dose proportional up to doses of 600mg, but less than dose proportional at higher doses.

At a 400 mg single dose with the commercial formulation, in healthy volunteers, geometric mean Cmax ranged from 108 to 175 ng/mL and AUCinf from 334 to 589 ng.h/mL (Studies 015, 022, 023). In patients (Study 018), predicted geometric mean Cmax was 150 ng/mL and AUC24h 1540 ng.h/mL.

The ADME study (PRN-1008-025) explored the **absolute bioavailability** of oral rilzabrutinib in comparison to [^{14}C]-PRN1008 administered intravenously. A low bioavailability of 4.7% was estimated after a single oral dose of 400mg using the commercial tablet formulation which was also employed in the pivotal clinical trial.

Rilzabrutinib demonstrated a **pH-dependent solubility**, with a decrease in solubility with increasing pH. For the description of the dissolution studies, please see the Quality AR of this procedure. Low bioavailability and high variability due to low penetration result in a classification as a **BSC IV compound** for rilzabrutinib.

Across the clinical program several formulations (7) were developed. Four drug substances were used and the manufacturing site was transfer to a different site. Generally the different formulations were bridged together either by formal rBA study or by *in vitro* dissolution profiles. Initial Phase 1 clinical studies were conducted with liquid and capsule formulations, before the **tablet formulation** was selected for further development. Tablets of 100 and 300 mg strengths were developed for early clinical studies, and then the 400 mg strength was developed following final dose selection for the ITP program, with the three strengths being homothetic. Afterwards, the tablet formulation remained unchanged during clinical development, except for minor changes in nonfunctional film coating agent and changes in tablet shape (from oval to capsule shape). Thus, the to-be-marketed tablet formulation is the same as the tablet formulation used in the ITP Phase 3 pivotal study (Study PRN1008-018). Throughout tablet formulation development, amorphous drug substance (DS) batches produced by spray drying or precipitation by different drug substance suppliers were used.

The liquid formulation used in early PK studies had a higher bioavailability than the immediate release tablet formulation later introduced into the clinical development programme. A capsule and a delayed release tablet formulation were tested as well, but were not selected for further development. The tablet formulation chosen for use in the pivotal trial and commercialisation is an immediate release 400mg tablet, which PK characteristics were shown to be similar to the earlier IR tablet formulation. Formal bioequivalence criteria between the three IR tablet formulations tested in study PRN1008-011 were not fulfilled due to high variability of the PK parameters of rilzabrutinib and low subject numbers. Confidence intervals were wide for both AUC and C_{max}. However, as the pivotal study as well as the food effect study PRN1008-025 used the foreseen commercial IR tablet formulation and as PK data from ITP patients as well as several PopPK models exploring PK parameters under different circumstances are available, the lack of bioequivalence between the different formulations used in the clinical trial programme is considered acceptable.

Four clinical studies explored the **effect of food** on the PK parameters of rilzabrutinib. Three studies investigated the influence of a moderate fat meal (500 calories; 30% from fat) and one from a high fat meal (800-1000 calories; 50% fat). Study PRN-1008-025 investigated the effect of a high fat meal on the PK of the commercial tablet formulation of rilzabrutinib. A slightly lower exposure and delayed T_{max} were observed in the fed versus the fasted state. As inter- and intra-subject variability is high, these variations were not considered clinically relevant, which is agreed. The pivotal trial PRN1008-018 did not specifically prescribe fasted or fed tablet administration, but the protocol stated that the frequency and/or severity of GI AEs may be improved if rilzabrutinib/placebo was taken with food.

Distribution

Generally ***in vitro* protein binding** (PB) is investigated across a wide concentration range to identify whether PB is concentration dependent or not. In study DVR0093, one concentration level at 1 µM

(equiv. to 666 ng/mL) which represents 4-time the predicted geometric mean Cmax at steady state in the target population (150 ng/mL) was studied. Since the fu (%) has been confirmed *in vivo* (in spiked samples), concentration dependent PB is probably unlikely. However, for a complete characterization of the rilzabrutinib PK, the applicant was asked to clarify to which plasma protein rilzabrutinib is mainly bound (HAS, AAG…) and to update the SmPC accordingly. The requested clarification was partially provided by the applicant. In study DVR0495, only the binding to HSA was investigated and demonstrated a 95% PB in the presence of 40 mg/mL of HAS. The PB was concentration independent. Therefore, it appears that rilzabrutinib is predominantly bound to HSA since only PB to HSA was investigated.

The ***in vitro*** **blood-to-plasma partitioning** of rilzabrutinib showed higher concentration in plasma (by ~2 fold) in Study DVR0083. This was confirmed *in vivo* (Study PRN1008-015), where the blood-to-plasma ratio of total radioactivity was 0.786, indicating low association of radioactivity with blood cells. The preferential distribution in plasma supports the choice of plasma as the matrix for monitoring the PK of the drug.

Volume of distribution

In the terminal phase (Vz) after IV administration was estimated to be 149 L (Study PRN1008-015, ADME). This is well above the volume of plasma (3 L) and total body water of 42 L in humans, indicating toward a high distribution of the compound.

Based on rilzabrutinib's molecular size, structure, poor permeability as well as its transport by P-gp, penetration of human blood-brain barrier by rilzabrutinib is estimated to be unfavourable and likely to be negligible. This interpretation of the physico-chemical properties of rilzabrutinib is consistent with the results of the rat tissue distribution study in which rilzabrutinib associated radioactivity was only detected in the brain in few animals with low level of radioactivity, and the absence of quantifiable rilzabrutinib or PRN834 metabolite in the CSF of rats dosed with rilzabrutinib.

Study PRN1008-001 (FIH study in HV): Mean apparent volume of distribution (Vz/F) ranged from 6720 to 4890 L.

Study PRN1008-010A (Single dose PK in ITP patients): Mean apparent volume of distribution (Vz/F) ranged from 656 to 2520 L.

Estimates from Main PopPK Model POH1156: Mean predicted apparent volume of distribution of the central compartment was 1390 L and of the peripheral compartment was 463 L.

Elimination

In healthy participants receiving single and multiple ascending oral doses of rilzabrutinib over a wide range (Study PRN1008-001), the **mean $t_{1/2}$** ranged from 1.4 to 3.9 hours after a single dose and from 3.8 to 4.5 hours after multiple doses. Following a single IV dose of 100 ug [14C]rilzabrutinib, the $t_{1/2}$ was 3.2 h. The mean $t_{1/2}$ was consistent across the studies in healthy volunteer participants ($t_{1/2}$ ~ 3−4 h). Consistency of $t_{1/2}$ after single and repeated oral administration points to the absence of time-dependent changes in the systemic clearance. In participants with ITP, the mean $t_{1/2}$ was about 1.4 hours after 400 mg BID doses (PRN1008-010-A).

Clearance was shown to be 904 L/h in healthy volunteers in mass balance study PRN1008-015 and ranged from 246 to 911 L/hr in ITP patients in study PRN1008-010.

Following oral administration of a single 400 mg [^{14}C]-rilzabrutinib dose, radioactivity was predominantly **excreted** in **faeces (~86% of dose**) and to a lesser extent in urine (~ 5% of dose) and bile (~ 6% of dose).

Rilzabrutinib was the most abundant radiolabelled component in faeces (~9% of the dose in non-bile collection participants and a trace component in bile), and ~0.03% of dose recovered unchanged in urine, indicating negligible renal or biliary elimination. 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 faeces. The prevalence of metabolites in faeces indicate that liver metabolism is the major mechanism of elimination of rilzabrutinib in humans.

Rilzabrutinib undergoes extensive **metabolism**, mediated primarily by dealkylation, oxidative N-dealkylation, and oxidation, as well as secondary reduction, oxidation, sulfonation, and sulfuration as noted in the clinical ADME study following dosing with [14C]-rilzabrutinib in healthy male participants (PRN1008-015), where a total of 46 radiolabeled components were detected, 25 of which were characterized and/or identified.

Unchanged drug was a trace component in plasma and accounted for 0.76% of total radioactivity exposure in plasma. PRN4400 (thiocyanate, M1) was identified as the prominent circulating metabolite, representing 94.2% of total radioactivity exposure in plasma. This metabolite was initially not identified in the *in vitro* metabolic profiling studies (DVR0088). The dealkylated inactive metabolite, PRN834 accounted for 1.09% of total plasma radioactivity exposure and appears to be formed by non-CYP mediated pathway as a substantial decrease in PRN834, similar to that for the parent drug, was seen when rilzabrutinib was co-administered with rifampin (Study PRN1008-024). The other metabolites were observed in trace amounts (<1%) in plasma. The metabolites, PRN4400 (thiocyanate, M1) and PRN834, do not contribute significantly to pharmacological activity. Additionally, thiocyanate is a normal physiological constituent of serum, with normal levels typically in the range of 50 to 250 µmol/L (3 to 15 µg/mL) in humans, and elevated levels in smokers. Thiocyanate concentrations measured in studies with rilzabrutinib were in the range of 1.8 to 6.6 µg/mL.

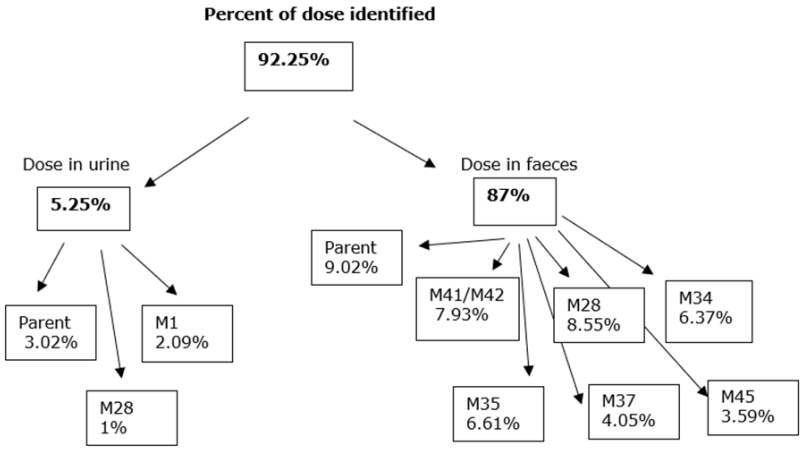


Figure 2: Mass balance study

Dose proportionality and time dependencies

Rilzabrutinib shows approximately dose proportional increase of exposure at clinically relevant doses of 300 mg to 600 mg. Absorption is limited at higher doses and exposure considerably less than dose proportional. Steady state is rapidly reached due to the low half-life of approximately 2 hours. The mean accumulation ratio after a dose of 450mg BID was 1.53. However, given the estimated half-life of 3-4h and a BID schedule, based on the general formula, accumulation is expected to be closed to 1.1. See section 2.6.3. for further discussion.

Intra-and inter-individual variability

In healthy participants, rilzabrutinib exhibited a high total variability in AUC (20 to 86%) and C_{max} (37 to 65%) over a range of single and multiple doses. The variability appeared to be moderate to high in participants with ITP (%CV >50% for AUC, Study PRN1008-010-A) over the range of 200 to 400 mg BID doses.

PopPK analysis showed high inter-individual variability in rilzabrutinib clearance, central volume of distribution, peripheral volume of distribution, and absorption constant (66.4%, 66.4%, 55.5%, and 72%, respectively). The residual (intra-individual) variability was also large (72%).

Population PK analysis

One population pharmacokinetic analysis (PPK, Report POH1156) aiming to characterize the PK of rilzabrutinib in healthy volunteers and in the target population, and to evaluate the effect of covariates on the variability of both compounds was developed. From this analysis predicted exposure metrics were used for the subsequent ER analysis (Report POH1157).

Methods

Twelve studies were included in the PPK analysis, 10 in healthy volunteers, two in patients with ITP. The concentration-time data of rilzabrutinib was modelled using a compartmental approach. Covariates of interest in rilzabrutinib trials were baseline demographic covariates (age, weight, gender, race/ethnicity), formulation, dose, hepatic function measure (albumin, bilirubin, ALT, AST and ALP), renal function measure (CLCr), disease state and concomitant medications.

PPK was built using nonlinear mixed effects model with the importance sampling estimation (IMP) method for parameter estimation implemented in NONMEM (version 7.5.1). Covariates were explored first graphically and then selected using a SCM approach. The PPK model was evaluated using standard diagnostic plots, visual predictive check and bootstrap. After model validation, the final Pop PK model was used to generate individual PK parameters and post-hoc exposures in participants with ITP.

Results

The final dataset contained 7076 rilzabrutinib concentrations from 545 participants (255 healthy participants and 290 participants with ITP). The final PK parameter estimates and the associated GOF and pcVPC plots are provided below.

The final PPK model consisted of a two compartment PK model with first order absorption and linear elimination, ka, CL/Fs, Vd/Fs. IIV was considered on all PK parameters except Q2/F. RUV was modelled using a proportional error. All PK parameters were estimated with a good precision (RSE <10% for the fixed effects and <35% for the random effects). Eta-shrinkage was particularly low for CL/F and V2/F (8.4%) reasonable for ka (26.4%) and high for V3/F (55.5%). The condition number was 110. The following covariates were identified as statistically significant: disease, body weight, gender, formulation and dose. Simulations were conducted to assess their impact on PK parameters. Gender and different formulations were identified to have the biggest effects on Cmax and AUC with male subjects showing a decreased Cmax and AUC by approximately 20%.

Table 3: Parameter estimates for final PopPK model

Parameter	Estimate (% RSE)	[95%CI]
CL/F (L/hour)	673 (5.46)	[600, 747]
V_2 /F (L)	1390 (5.64)	[1230, 1540]
K_a (1/hour)	0.725 (6.12)	[0.637, 0.814]
Q /F (L/ hour)	42.2 (5.49)	[37.5, 46.8]
V_3 /F (L)	463 (6.62)	[402, 525]
Coefficient of ITP disease on CL/F	-0.082 (44.7)	[-0.155, -0.009]
Coefficient of FORM=2 on CL/F	0.203 (21.9)	[0.114, 0.292]
Coefficient of FORM=0 on CL/F	0.153 (33.6)	[0.050, 0.256]
Coefficient of SEX on CL/F	0.325 (26.5)	[0.153, 0.497]
Coefficient of DOSE on F1	0.00213 (3.01)	[0.00200, 0.00225]
Coefficient of FORM=0 on F1	0.280 (23.6)	[0.148, 0.412]
Coefficient of DOSE on Ka	-0.00319 (10.5)	[-0.00386, -0.00252]
Coefficient of FORM=0 on Ka	0.599 (27.2)	[0.274, 0.925]
Coefficient of SEX on V_2/F	0.222 (40.1)	[0.044, 0.401]
Coefficient of WT on V_2/F	0.00375 (34.8)	[0.00114, 0.00637]
Inter-individual variability (IIV)		
	CV% (RSE%) [shrinkage%]	**[95%CI]**
IIV on CL/F and V_2/F	66.4 (7.15) [9.04]	[61.5, 71.0]
IIV on K_a	72.0 (9.65) [26.4]	[64.7, 78.7]
IIV on V_3 /F	55.5 (23.4) [55.5]	[40.4, 67.3]
Residual variability (RV)		
	Estimate (% RSE)	**[95%CI]**
Propotion term (mg/L)	0.725 (0.330)	[0.720, 0.730]

Abbreviations: CI: confidence interval; CL: linear clearance; CV: coefficient of variation; IIV: inter-individual variability; K_a: absorption rate constant; Q: apparent inter-compartment distribution clearance; V_2:volume of central compartment; V_3: volume of peripheral compartment; RSE: percentage of relative standard error (100% * SE / estimate); SE: standard error; RV: residual variability. FORM, WT

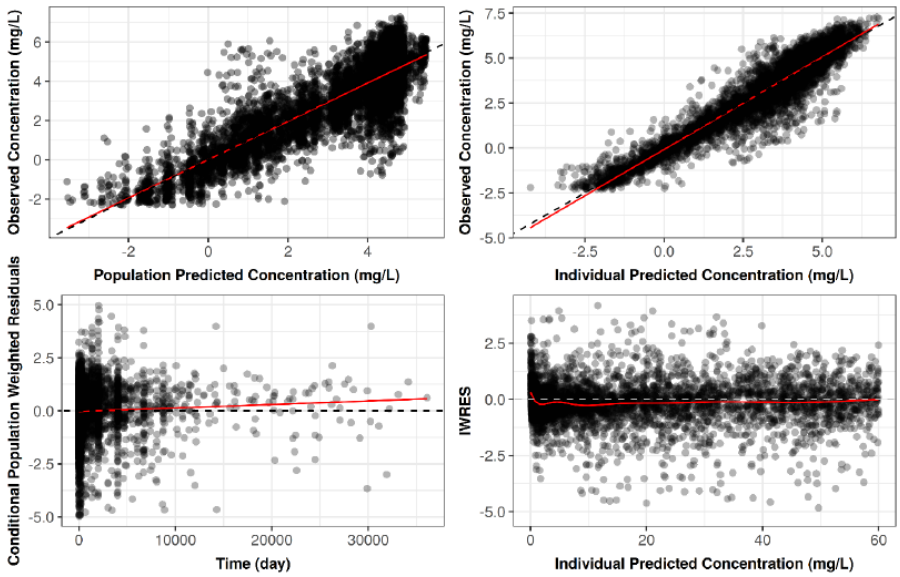
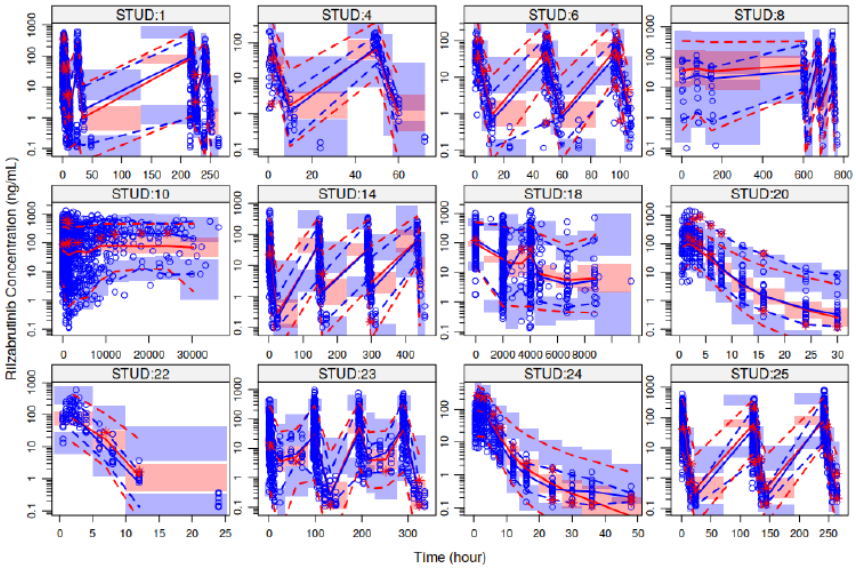


Figure 3: Goodness of fit plots from final PopPK model in participants with ITP



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.

Figure 4: Visual predictive checks for final PopPK model in participants with ITP

Special populations

Impaired renal function

Based on the mass balance study PRN1008-015, rilzabrutinib is excreted unchanged in urine at 3% suggesting that renal impairment (RI) is unlikely to have a clinically relevant effect on rilzabrutinib PK.

However as indicated by the applicant in the PBS0020 report, in patients with RI, uremic toxins can accumulate in the body fluids and down-regulate the expression of CYP enzymes, affecting therefore drug mainly eliminated through metabolism.

Instead of designing a dedicated clinical study where a single dose of rilzabrutinib would have been investigated in a small cohort of severe RI subjects, PBPK simulations were performed (with the known limits of this approach, highlighted in the introduction section of the report by the applicant). Results of this analysis indicate a 1.1 to 1.4 fold increase in PK parameter exposure in moderate/severe RI compared to HV and a 1.4 to 1.8 fold increase of fu. Please note the estimate half-life set in HV of 8h.

Table 4: Predicted exposure parameters, mean + SD (geometric mean) [CV%], following a single 400 mg dose of rilzabrutinib in healthy, and moderate and severe renal impairment populations based on total drug concentrations - Study PBS0020

PK parameters	HV	Moderate RI	Severe RI
C_{max} (ng/mL)	122 ± 79 (98) [65]	148 ± 85 (121) [57]	135 ± 76 (112) [57]
t_{max} (h)	1.48 (0.8-2.55)	1.65 (0.90-2.90)	1.75 (0.95-3.00)
AUC_{inf} (ng.h/mL)	510 ± 323 (419) [63]	688 ± 389 (578) [56]	654 ± 363 (555) [56]

PK parameters	HV	Moderate RI	Severe RI
$t_{1/2}$	8.31 ± 7.42 (6.66) [89]	20.13 ± 23.02 (13.09) [114]	19.27 ± 20.95 (13.16) [109]
CL/F (L/h)	1199 ± 1002 (954) [84]	896 ± 999 (692) [111]	904 ± 943 (720) [104]

Abbreviations: SD = standard deviation; CV = coefficient of variation ; RI = renal impairment ; C_{max} = maximum observed concentration ; t_{max} = time to peak concentration; AUC_{tau} = Area under the concentration-time curve from time zero to 24 hours postdose; AUC_{inf} = Area under the concentration-time curve extrapolated to infinity; $t_{1/2}$ = elimination half-life; CL = clearance from central compartment; F = oral bioavailability fraction.

Additional analysis based on the popPK model to study the Effect of Creatinine Clearance on PK-parameters

The Figure below shows a trend of increase of clearance with increase of creatinine clearance, suggesting that participants in the analysis dataset that have high creatinine clearance would have lower exposure.

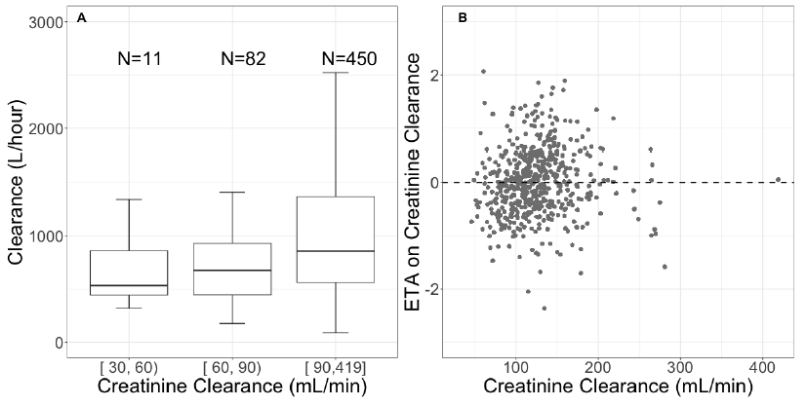


Figure 5: Effect of creatinine clearance on Rilzabritunib clearance

Based on the PPK analysis, median CLCr (min-max) was 122 (46-419) mL/min, with 82.6% having a normal renal function, 15% a mild RI (60-90 mL/min) and 2% a moderate RI (30-60 mL/min). Results of this analysis indicate that ITP subject with moderate RI have an increase of 1.1-1.2 dose normalized PK exposure metrics compared to ITP patients with normal renal function.

Impaired hepatic function

A dedicated hepatic impairment (HI) study PRN1008-020 was conducted in patients with mild hepatic impairment (Child-Pugh class A, moderate hepatic impairment (Child-Pugh class B) and matched (based on age, sex and BMI) healthy control subjects.

Total rilzabrutinib exposure (AUC and C_{max}) was approximately 1.4 to 1.5 fold higher in participants with mild HI and 4.2 to 4.8 fold higher in participants with moderate HI compared to healthy-matched controls. PRN834 exposures (AUCs and C_{max}) were approximately 1.2- to 1.3 fold higher in participants with mild HI and 1.7- to 2.0-fold higher in participants with moderate HI compared to the respective healthy-matched control cohorts. There was no appreciable increase in PRN4400 levels after administration of rilzabrutinib in participants with mild or moderate HI based on the limited data due to undetectable plasma levels in several participants.

A relationship could not be established between total rilzabrutinib exposure (based on AUCinf and C_{max}) and measures of HI (ie, Child-Pugh score, albumin levels, bilirubin levels, or PT) based on the exploratory scatter plots.

Rilzabrutinib was highly bound to plasma proteins across all cohorts, with mean percent unbound (%fu) of <3% across the cohorts that did not increase significantly in participants with HI.

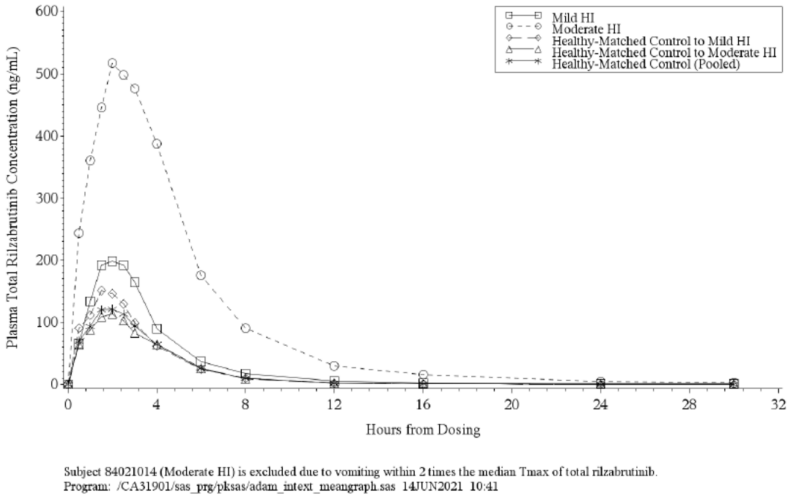


Figure 6: Arithmetic Mean of Plasma Total Rilzabrutinib Concentration-Time Profiles Following Administration of 400 mg Rilzabrutinib in Subjects with Mild or Moderate HI and Healthy-Matched Control Subjects (Linear Scale, PK Analysis Population

Gender

PopPK analysis with data from healthy participants and participants with ITP (39.3% male and 60.7% female) showed that sex had statistically an impact on clearance and volume of distribution V2. Simulations for male population versus reference female subjects showed that median C_{max} and AUC24,ss was reduced by about 21% and 24%.

Based on the subgroup analysis for the platelet response, male and female participants with ITP had similar response. Therefore, in the context of the ITP indication and of the observed safety profile of rilzabrutinib, sex is not considered significant for a dose adjustment.

Ethnic factors

The PK of rilzabrutinib was assessed in Chinese and Japanese populations in Studies PRN1008-022 and PRN1008-023, respectively, which demonstrated similar exposure to the Caucasian population. Consistent with these results, PopPK analysis, including data from healthy participants and participants with ITP, did not identify race as a covariate with the PopPK dataset consisting of 70.6% Caucasians, 3.12% Black, 21.5% Asians. Therefore, no dose adjustments are recommended based on race/ethnicity.

Weight

PopPK analysis with data from healthy participants and participants with ITP with median (range) body weight 76 kg (36-140 kg) showed that weight had statistically an impact on volume of distribution V2, with expected potential impact on C_{max}.

However, the simulations for body weight at the extremity of the population used in Study POH1156 (5th and 95th percentile, 52 and 109 kg versus the median 76 kg), showed that the difference on median C_{max} and $AUC_{24,ss}$ was less than 10%. Therefore, the impact on body weight was considered not relevant (Study POH1156). Therefore, although a statistical selection of this covariate was observed, no dose adjustments are recommended based on body weight.

Elderly

PopPK analysis with data from healthy participants, and participants with ITP with median (range) age of 47 years (12 to 80) years, with most participants younger than 65 years (16% >65 years, 3.4% >75 years); showed that age was not a significant covariate affecting the PK of rilzabrutinib (Study POH1156). Therefore, no dose adjustments are recommended for elderly patients.

Paediatrics

Based on the PPK analysis of POH1156the median (min-max) age in the target population was 47 (12-80) years, thus paediatric patients were included. However as indicated by the applicant in study PRN1008-018, only PK data from adults were presented.

Pharmacokinetic interaction studies

Rilzabrutinib as a "victim"

Impact of pH-modifying agents

Study PRN1008-006 investigated the influence of esomeprazole on the PK of PRN1008 in healthy volunteers and showed that PPIs esomeprazole significantly influenced the exposure parameters of rilzabrutinib. Study PRN1008-011 investigated the impact of famotidine on PRN1008 PK in healthy subjects and showed that administering an H2RA at least 10 hours after rilzabrutinib results in a reduction of the rilzabrutinib $AUC_{0-\infty}$ by 35.3% and C_{max} by 27.7%. This is further discussed in section 2.6.3.

In vitro studies revealed that rilzabrutinib is predominantly metabolized by CYP3A4 (fm > 89%), with a smaller contribution from CYP2D6 (fm < 16%), and identified as a substrate of the efflux transporter P-gp. To investigate potential interactions with these pathways, the applicant conducted clinical DDI studies.

Effect of a strong CYP3A inhibitor (ritonavir) on rilzabrutinib PK

Study PRN1008-014 assessed the effect of ritonavir on PRN1008 PK. Coadministration with ritonavir with 100 mg rilzabrutinib increased plasma AUC by ~18-fold, and C_{max} by ~8-fold. Coadministration of the therapeutic 400 mg rilzabrutinib dose with ritonavir increased the rilzabrutinib AUC by ~8-fold and C_{max} by ~5-fold. These results demonstrated a dose dependent effect of ritonavir on rilzabrutinib PK, 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.

Effect of a strong P-gp inhibitor (quinidine) and a strong CYP3A inducer (rifampin) on rilzabrutinib PK

Study PRN1008-024 evaluated the effects of quinidine and rifampin on the single-dose pharmacokinetics of rilzabrutinib. After coadministration of rilzabrutinib with quinidine, a strong P-gp inhibitor, a modest increase in exposure to rilzabrutinib, considered not to be clinically meaningful, was observed by 12.7% and 6.9% for AUCinf and AUClast, 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. Quinidine appeared to have little effect on the rate of absorption of rilzabrutinib, since the median t_{max} was the similar (2.25 vs 2.00 h) between the treatment periods. The plasma concentration-time profiles for PRN834 closely followed that of rilzabrutinib, with peak concentrations around 3 hours postdose and mean plasma concentration similar after both treatments.

Coadministration of rifampin, a strong CYP3A inducer, decreased rilzabrutinib exposure compared to rilzabrutinib alone, with ratio of the geometric means for AUClast, AUCinf, and C_{max} of 19.9%, 20.5%, and 19.5%, respectively. The rate of absorption of rilzabrutinib was unaffected by rifampin, with similar t_{max} for both treatment groups. There was a 69.7% and 72.4% decrease in C_{max} and AUCinf,

respectively, of PRN834, similar to that observed with the parent drug, rilzabrutinib. The substantial decreases seen in PRN834 exposure with rifampin treatment, suggests that its formation from rilzabrutinib is not mediated by CYP3A.

Rilzabrutinib as perpetrator

CYP inhibition:

The *in vitro* data indicate that Rilzabrutinib and its metabolite may pose a risk of DDIs with CYP3A4, particularly at the intestinal level, as the IC_{50} values are below the threshold of 0.1 × dose/250 mL (240.4 µM). To assess the inhibitory potential of Rilzabrutinib and its metabolite, PRN834, on various CYP450 enzymes, the applicant conducted several *in vitro* studies.

In study DVR0085, human liver microsomes were incubated with 10 µM of Rilzabrutinib to evaluate its effect on CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. This concentration exceeded the anticipated systemic exposure (50 × $C_{max,u}$, i.e., 0.36 µM) but was below the estimated intestinal concentration (0.1 × dose/250 mL, i.e., 240.4 µM). The results indicated that Rilzabrutinib did not significantly inhibit most CYP isoforms, except for CYP3A4, showing 70.87% inhibition with midazolam and 58.37% with testosterone as substrates, and CYP2C19, with 51.16% inhibition.

Subsequently, study DVR0500 determined IC_{50} of Rilzabrutinib for CYP2C19 and CYP3A4 across concentrations ranging from 0.001 to 50 µM. The IC_{50} values were 2.17 µM for CYP3A4 (midazolam), 5.11 µM for CYP3A4 (testosterone), and 11.1 µM for CYP2C19. These findings suggest that significant systemic inhibition is unlikely, as the IC_{50} values exceed the threshold of 50 × $C_{max,u}$ (0.36 µM). However, potential DDIs at the intestinal level cannot be excluded, given that the IC_{50} values are below the threshold of 0.1 × dose/250 mL (240.4 µM).

Further investigation in study ICH0140 assessed both direct and TDI potentials of Rilzabrutinib and its metabolite, PRN834, on various CYP enzymes using human liver microsomes. Concentration ranges were 2–40 µM for Rilzabrutinib and 5–60 µM for PRN834. Neither compound inhibited CYP1A2. Both exhibited direct inhibition of several CYP isoforms, with Rilzabrutinib showing IC_{50} values of 5.38 µM for CYP2B6, 22.6 µM for CYP2C8, 12.5 µM for CYP2C9, 11.3 µM for CYP2C19, 69.8 µM for CYP2D6, 1.09 and 5.93 µM for CYP3A4/5. PRN834 demonstrated IC_{50} values of 20.7 µM for CYP2B6, 15.2 µM for CYP2C8, 11.0 µM for CYP2C9, 16.5 µM for CYP2C19, 39.9 µM for CYP2D6, 38.7 and 12.0 µM for CYP3A4/5. No time-dependent inhibition was observed for any CYP isoforms with testosterone as the substrate. However, PRN834 exhibited TDI of CYP3A4 with midazolam as the substrate, with an IC_{50} shift of 2.08; kinetic parameters (KI and kinact) were not determined due to activation effects at low concentrations.

Effect of rilzabrutinib on PK of a sensitive CYP3A substrate (midazolam)

Based on the *in vitro* results rilzabrutinib was shown to be an inhibitor and inducer of CYP3A4 enzyme. Therefore, to assess its impact on a CYP3A4 substrates *in vivo* a clinical study (PRN1008-011) was conducted using midazolam as a CYP3A4 probe substrate. This was a single center, four-period, open-label, randomized, complete cross-over study in healthy adult volunteers (14 participants enrolled to achieve 12 completed). Results demonstrated that when midazolam was administered simultaneously with single 400 mg oral doses of rilzabrutinib, with the geometric mean ratio for AUC 0-∞ 172% (90% CI: 148 - 200%) and C_{max} 140% (90% CI: 117 - 168%). When midazolam was administered 2 hours post- rilzabrutinib dosing, the geometric mean ratios of midazolam exposure for AUC 0-∞ and C_{max} were 217% (90% CI: 187 - 252%) and 223% (90% CI: 187 - 267%), respectively, compared to midazolam alone.

Another clinical study (PRN1008-002) was conducted to evaluate the effect of a single 600 mg dose of rilzabrutinib as an oral liquid formulation on the PK of a sensitive substrate of CYP3A4, midazolam, in healthy participants (12 participants). 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. The results showed that midazolam exposure was 3.14 fold higher when it was administered 1 hour after rilzabrutinib compared to being administered alone

CYP induction:

To evaluate the potential of rilzabrutinib and PRN834 to act as an inducers of different CYP1A2, 2B6, and 3A4, the applicant has conducted several *in vitro* studies.

In the study DVR0084 rilzabrutinib at 10 µM was evaluated for induction of CYP1A2, 2B6, and 3A4 using cryopreserved human hepatocytes (3 donors). However, the study setups were not considered adequate since no viability cell neither the CYP mRNA expression were measured. Therefore, the results were not conclusive.

In another study (IHH0096), the concentration-dependent response of CYP induction was evaluated after 48-h incubations with 8 concentrations of rilzabrutinib or its metabolite ranged from 0.01 to 30 µM, or with positive control inducers. Based on this study findings, rilzabrutinib and the metabolite, PRN834, are considered a potential CYP3A inducer *in vitro*, indicating a possible DDI risk with CYP3A4 substrates when co-administered with rilzabrutinib. To further assess this risk, the applicant conducted a clinical DDI study using midazolam, a CYP3A4 probe substrate; details are discussed in the clinical assessment section below. Additionally, the metabolite is considered a CYP2B6 inducer *in vitro* at high concentrations, which are unlikely to be achieved at therapeutic doses; therefore, the DDI risk with CYP2B6 substrates can be ruled out.

Transporters inhibition:

The inhibitory effects of rilzabrutinib on transport of substrate by OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, P-gp or BSEP were investigated during an *in vitro* study (DVR0157) using different experimental systems. The study plan is generally appropriate, but the maximum concentration of 3 µM used does not reflect the expected *in vivo* intestinal concentration at the worst case (0.1 × dose/250 mL, i.e., 240.4 µM), making the results inconclusive for BCRP and P-gp inhibition. For other transporters, rilzabrutinib did not inhibit OAT3, OCT1, OCT2, or OATP1B3 at 3 µM, but it inhibited OAT1, OATP1B1, and BSEP transport by 28.8%, 18.4%, and 48.9%, respectively.

In addition, the ability of rilzabrutinib and its metabolite, PRN834, to inhibit human uptake transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2-K was investigated in another *in vitro* study (TRI0053) using transfected HEK293 cells. The inhibitory effect of these compounds on BCRP and BSEP efflux transporters was evaluated in the Caco-2/TC7 cell line and HEK membrane vesicles. This time, the study employed appropriate concentrations, encompassing worst-case scenarios at systemic, hepatic, and intestinal levels. The results showed that rilzabrutinib was an *in vitro* inhibitor of all the tested enzymes with an IC_{50} values of 0.705 µM, 0.180 µM, 2.93 µM, 5.36 µM, 22.2 µM, 36.4 µM, 2.91 µM, 6.71 µM, 1.42 µM and 7.61 µM for OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2-K, BSEP and BCRP transporters, respectively. Regarding the metabolite the results showed that it is not identified to inhibit P-gp *in vitro*. However, it is an *in vitro* inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2-K, BSEP and BCRP transporters with an IC_{50} values of 1.87 µM, 3.97 µM, 11.4 µM, 1.34 µM, 122 µM, 7.94 µM, 0.138 µM, 7.78 µM, 16.7 µM, 5.25 µM, respectively.

Based on these results the DDI risk between rilzabrutinib and OATB1B3 and BCRP substrates could not be ruled out. In fact, the IC_{50} values for these 2 transporters (i.e. 0.18 µM for OATB1B3 and 7.61 µM for BCRP) are below the concentrations expected in the worst case scenario at the hepatic and intestinal level (10 × Cu,inlet i.e. 0.34 µM for OATB1B3 and 240 µM for BCRP). This risk was further investigated by the applicant using the PBPK modelling.

The inhibition of the P-gp transporter was not investigated, or at least the results were not provided (the initial study (DVR0157) results are considered inconclusive regarding P-gp inhibition). According to the PBPK model report (parameter in-put used), it appears that the applicant may have conducted another *in vitro* study (TRI0055) to evaluate rilzabrutinib and its metabolite, PRN834, as inhibitors of the human efflux transporter P-gp, the results revealed that an inhibitor of hP-gp mediated NMQ uptake with an IC_{50} value of 2.17 µM (CV=3.0%) on transfected vesicle model. Taking into account this finding, the potential inhibitory effect of rilzabrutinib on P-gp cannot be fully excluded, however, the corresponding report was asked to be submitted for review. The applicant submitted the *in vitro* Study TRI0055, in which the inhibitory effect of rilzabrutinib was assessed using Caco-2/TC7 cell line and P-gp vesicles with 3H-digoxin [5 µM] and NMQ [2 µM] as probe substrates. The results showed that rilzabrutinib was identified as an *in vitro* inhibitor of hP-gp–mediated Digoxin and NMQ uptake, with an IC_{50} of 9.53 µM (CV = 11.8%) in the Caco-2/TC7 cell model, and as an *in vitro* inhibitor with an IC_{50} of 2.17 µM (CV = 3.0%) in the transfected vesicle model.

In Silico studies: Results are not shown here. Assessment of the models can be found in section 2.6.3.

Pharmacokinetics using human biomaterials

The submitted *in vitro* studies employed usual and accepted test setups (e.g. human liver microsomes, cell lines overexpressing the respective transporter, Caco-2 cells). The tested rilzabrutinib concentrations ranged from 0.1 µm up to 75 µM.

The observed median rilzabrutinib concentration at 2 hours post-dose on Week 25 was 193.00 ng/mL (= 0,193 µg/mL) in pivotal trial PRN1008-018. Due to the high protein binding, the unbound C_{max} equals 5.79 ng/mL, and therefore the relevant 50x C_{max}(u) is 0.435 µM.

The provided IC_{50} values indicate no interaction with most of the investigated transporters. All *in vitro* transporter model and experimental conditions were validated, including culture and transport assay conditions. Transport studies were performed under linear transport rate conditions as all probe substrate concentrations used were well below Michaelis constant (Km) values for each transporter. Appropriate positive controls were also included in the test study to ensure the validity of the study's results. Thus, the submitted IC50 values can be considered meaningful for the relevant transporter system.

2.6.2.2. Pharmacodynamics

Mechanism of action

Bruton tyrosine kinase (BTK) is expressed in cells of the B-cell lineage, including marrow-derived hematopoietic stem cells and other cells of hematopoietic lineage with the exception of T cells, natural killer cells and plasma cells. It is a key therapeutic target in immune-mediated diseases due to its role in B-cell differentiation and development, antibody production, and FcγR (FcγR)-mediated signalling pathways and its direct regulation of key innate inflammatory machinery, NLRP3 inflammasome.

A **BTK inhibitor** (BTKi) such as rilzabrutinib has the potential to target multiple pathways and cell types involved in inflammation and autoimmunity. These include B-cell receptor-mediated B-cell pathways, FcγR-induced cytokine release from monocytes and macrophages, and mediator release. Of relevance to ITP, phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) on the FcγR during auto-antibody mediated destruction of platelets allows the recruitment of spleen tyrosine kinase (Syk), which activates downstream signalling pathways including BTK activation of Rac and Rho

required for platelet phagocytosis. BTK inhibition has the potential to reduce FcγR–mediated macrophage function and reduce autoantibody production.

Rilzabrutinib (PRN1008/SAR444671) is a novel oral, reversible, covalent, potent BTK inhibitor (BTKi) developed for the treatment of autoimmune and inflammatory diseases. It mediates its therapeutic effect through a dual mechanism of action: (1) inhibition of B cell activation and (2) interruption of antibody-coated cell phagocytosis by FcγR in spleen and liver.

Primary and Secondary pharmacology

Primary pharmacology

In healthy volunteers as well as ITP patients, **BTK occupancy** was investigated as a PD marker, which is considered a suitable biomarker. The assay was however only fully validated only in late stage for the studies in ITP participants. Nevertheless, the early data in healthy participants suggested a dose-dependent and a durable target occupancy despite the short half-life of rilzabrutinib. For pivotal study 018, no BTK occupancy data were available at the time of this reporting and will be included in final CSR with data from OL period.

The therapeutically intended PD effect, impact on **thrombocyte levels**, was investigated as the primary efficacy endpoint in the phase 1/2 clinical trial 010 as well as the pivotal clinical study 018 in ITP patients. Please refer to the efficacy part of this AR for more details.

In non-clinical studies, the PD effect of rilzabrutinib was explored with *in vitro* and *in vivo* experiments:

Biochemical studies were performed to characterize: (1) the potency of rilzabrutinib for BTK in an *in vitro* kinase activity assay, (2) the selectivity of rilzabrutinib as assessed by kinase panel profiling, Inhibitory concentration 50% (IC_{50}) determination, and a CEREP radioligand binding assay against a panel of receptors, ion channels, and transporters, (3) the biochemical on-rate and off-rate of BTK for rilzabrutinib, and (4) the reversibility of the interaction between rilzabrutinib and BTK.

In addition, the inhibition of BTK function was confirmed in cell-based assays. Rilzabrutinib was tested for: (1) occupancy of BTK in both a human B cell line and peripheral blood mononuclear cells, (2) inhibition of B cell activation in human whole blood, (3) inhibition of basophil activation in human whole blood, (4) inhibition of antibody mediated Fc receptor activation, (5) effects on platelet aggregation, and (6) the potential for off target effects in a variety of cell types.

In vivo pharmacodynamics was investigated in an ITP mouse model. Please refer to the Non-clinical part of this AR for more details.

POH1157 - Exposure-response analyses to characterize relationship between rilzabrutinib exposures and efficacy and safety endpoints in patients with immune thrombocytopenia

Exposure-response (ER) models were developed for longitudinal platelet counts, key adverse events (AEs), and time-to-event for rescue therapy. The impact of selected intrinsic and extrinsic factors on response was quantified.

The 400 mg BID dosing regimen was evaluated in relevant subgroups with respect to the following endpoints:

1. Response rate as defined by the primary endpoint of Study PRN1008-018 (proportion of participants with platelet counts ≥ 50×109/L for at least two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period, provided that at least 2 non-missing weekly scheduled platelet measurements were ≥ 50×109/L during the last 6 weeks of the 24-week blinded treatment period).

2. Durability of response over the 24-week blinded treatment period in the absence of rescue therapy as defined by the following three metrics:

(i) number of weeks with ≥ 50 × 10^9/L during the last 12 weeks;

(ii) number of weeks with platelet count ≥ 50×109/L or between 30×109/L and 50×10^9/L and ≥ 2× baseline;

(iii) number of weeks with platelet count ≥ 30×10^9/L and ≥ 2× baseline.

3. Probability of the selected AEs.

4. Probability of rescue therapy.

Results

Platelet Count Modeling

An indirect exposure-response model adequately characterized platelet counts, including the magnitude of persistent and sometimes large fluctuations in platelet counts.

• Response to prior corticosteroid therapy and concomitant use of corticosteroids were associated with higher response rates;
• Baseline platelet counts below the median were associated with lower response rates; baseline counts above the median were associated with higher response rates;
• Response rate to the primary endpoint did not depend on exposure.

Safety Modeling

Participants with higher rilzabrutinib exposures had higher rates of nausea and diarrhoea.

• Participants with higher rilzabrutinib Cmin,ss values were generally more likely to experience a nausea event, and no other covariates were found to be predictive of nausea incidence. Participants with exposures at the mean of the fourth quartile had a 28.7% chance of a nausea event, while those with exposures at the mean of the first quartile had a 14.4% chance of a nausea event, and placebo participants had a 13.8% chance of a nausea event.

• Participants with higher rilzabrutinib AUC,ss values were more likely to experience a diarrhoea event, and race was the only covariate found to be predictive of diarrhoea incidence. Participants with exposures at the mean of the fourth quartile had a 37.9% chance of a diarrhoea event, while those with exposures at the mean of the first quartile had a 24.8% chance of a diarrhoea event, and placebo participants had a 17.2% chance of a diarrhoea event.

• Anaemia events were rare overall, with less than 5% of participants experiencing an anaemia event. Anaemia was not considered for further model development.

Time to Rescue Therapy and Dropout

There was a modest relationship between rilzabrutinib exposure and time to dropout and rescue therapy, and several additional covariates were identified as important predictors of both event times.

• Placebo participants had the shortest time to rescue therapy, but participants with higher rilzabrutinib exposures had shorter times to first rescue therapy than those with lower exposures, suggesting possible confounding between exposure and response. Rilzabrutinib exposure was not found to be predictive of time to rescue therapy or time to dropout.

• Several covariates were found to be predictive of time to first rescue therapy: those describing the effects of ALP, baseline platelet count, concomitant H2 receptor agonist use, race, and weight.

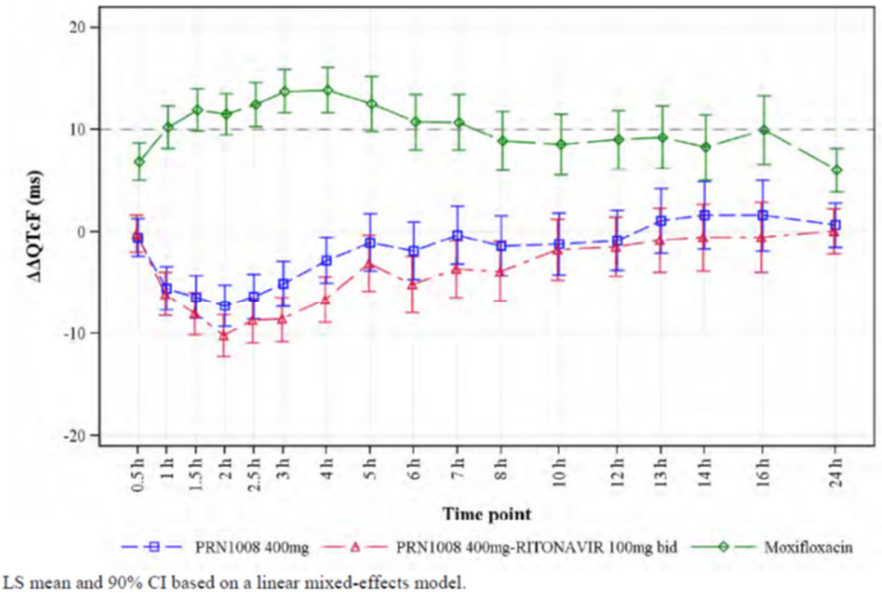
No covariates were found to be predictive of time to dropout.

Secondary pharmacology

A **thorough QTc study** (PRN1008-014) was conducted at therapeutic and supratherapeutic exposure of rilzabrutinib in healthy participants.

A supratherapeutic dose of 1200mg rilzabrutinib was dropped in part A of the thorough QT study due to tolerability issues. Supratherapeutic exposures were reached by combining 400mg of rilzabrutinib with two doses of 100mg ritonavir 12 hours apart. As ritonavir is a strong inhibitor of CYP3A4 and CYP2D6 as well as P-gp, plasma levels of rilzabrutinib, which is a substrate of CYP3A and G-pg were increased. AUC and C_{max} at the 400 mg therapeutic dose of PRN1008 were increased by approximately 8.3 and 5.2-fold, respectively.

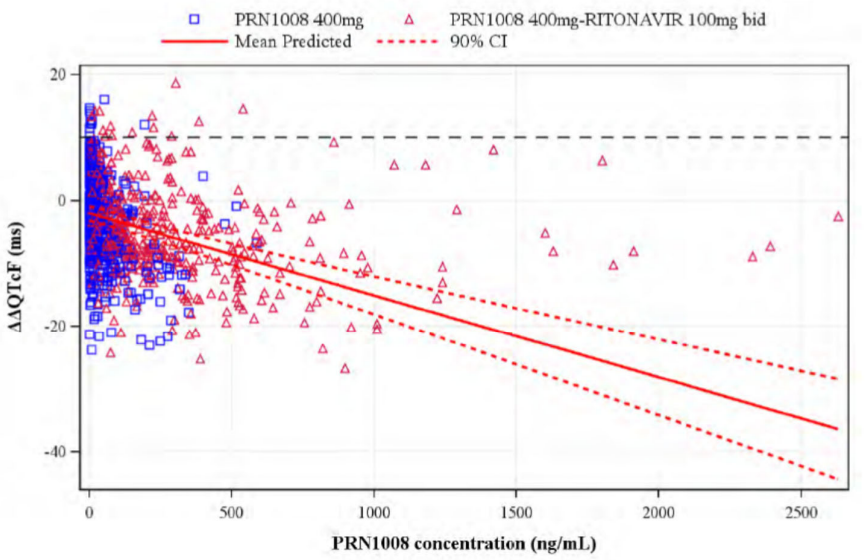
In the thorough QTc study, no prolongation of the QT interval at therapeutic or supratherapeutic doses was shown, while the active control with movifloxacin did show a clear increase of the QT interval, providing proof of assay sensitivity.



LS mean and 90% CI based on a linear mixed-effects model.

Figure 7: Placebo corrected change from baseline QTcF (ΔΔQTcF) across time points (QT/QTc analysis population in Part B)

While rilzabrutinib does not cause a prolongation of the QT interval, it is noticeable that a shortening of the QT interval could be observed even at clinical doses (Figure above).



The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90% CI. The blue squares and red triangles denote the pairs of observed PRN1008 plasma concentrations and observed ΔΔQTcF by subjects for the PRN1008 400 mg and PRN1008 400 mg-RITONAVIR 100 mg bid treatment groups, respectively.

Figure 8: Scatter plot of observed PRN1008 plasma concentrations on ΔΔQTcF (PK/QTc analysis population in Part B)

2.6.3. Discussion on clinical pharmacology

Bioanalytical methods

Generally, the used bioanalytical methods appear to comply with acceptance criteria regarding sensitivity accuracy and precision. Analytical validation reports were provided with satisfactory results for the method used. Short and long-term stability of the analytes in biological matrix were tested and shown to be satisfactory.

Pharmacokinetics

Rilzabrutinib's pharmacokinetics were studied in healthy volunteers and through a mass balance/ADME study to determine bioavailability and metabolism. Additional studies assessed the impact of intrinsic factors (ethnicity, hepatic impairment) and extrinsic factors (drug-drug interactions, gastric pH, food). PK data were also collected from ITP patients in clinical trials. Population and physiologically based PK models, along with PK/PD models, were developed to estimate exposure and explore correlations with efficacy, safety, and drug interactions.

Absorption

Rilzabrutinib is rapidly absorbed orally, reaching peak plasma levels in about two hours. Its absorption is dose-proportional up to 600 mg, with lower bioavailability at higher doses. The ADME study showed low oral bioavailability (4.73%). Early liquid formulations had higher bioavailability than the immediate-release (IR) tablet chosen for clinical use. Although other formulations were tested, the 400 mg IR tablet was selected commercially. Bioequivalence among IR tablets was not formally shown due to variability and small sample size, but this was acceptable given consistent use in the pivotal trial. Food slightly reduced exposure and delayed Tmax, but without clinical significance. Tablets may be taken with or without food, though food may help reduce gastrointestinal side effects. This is reflected in section 4.2 of the SmPC.

Distribution
Rilzabrutinib is highly protein bound (~97.5%) and mainly present in plasma. Following request, the applicant clarified which plasma protein rilzabrutinib primarily binds to. Study DVR0495 showed 95% binding to human serum albumin (HSA), independent of concentration, suggesting HSA is the main binding protein. The apparent volume of distribution is much higher after oral dosing than IV, likely due to its low bioavailability.

Elimination
Rilzabrutinib has a short half-life of 1–4 hours, slightly shorter in ITP patients than in healthy volunteers. Clearance ranged from 246 to 911 L/h in ITP patients and was 904 L/h in healthy volunteers. In the mass balance study using the 400 mg tablet, 92.5% of the dose was recovered—mostly in faeces (87%), indicating hepatic elimination. Rilzabrutinib undergoes extensive metabolism through various pathways, with its main metabolite, PRN4400, naturally present in plasma. Other metabolites are minimal and pharmacologically inactive. No enzymes linked to genetic polymorphism are involved in its metabolism. The main plasma metabolite of rilzabrutinib was thiocyanate, accounting for 94% of total radioactivity, indicating the radiolabel was placed on a metabolically unstable site. This led to loss of the label and potential under-identification of other metabolites. The applicant was asked to justify the adequacy of metabolite characterization. It is acknowledged that due to limited cleavage potential of the cyanide group, along with non-clinical *in vivo* studies and a PK bridging study in rats, the metabolic profile has been sufficiently characterized.

Dose proportionality and time dependency
Rilzabrutinib shows an approximately dose-proportional increase in exposure at clinically relevant doses between 300 mg and 600 mg. At higher doses, absorption becomes limited and exposure is considerably less than dose-proportional. All interaction studies used rilzabrutinib doses within the dose-proportional range.

Due to its short half-life of approximately 2 hours, steady state is reached quickly. In study PRN1008-010B, the mean accumulation ratio after a 450 mg BID dose was 1.53. However, based on the estimated half-life of 3–4 hours and a BID dosing schedule, the expected accumulation is closer to 1.1. The applicant was therefore asked to explain the observed accumulation of 1.5 to 3-fold in ITP patients, especially since study 010A estimated a mean half-life of 1.41 hours.

The applicant clarified that rilzabrutinib generally has a short half-life of 3–4 hours and shows mild accumulation (<2-fold). The reported 3-fold accumulation in study PRN1008-010B was based on median concentrations measured at Day 1 and Day 57, approximately 2 hours post-dose, assumed to represent Cmax. This method does not accurately reflect true accumulation and the reported accumulation was not confirmed in the Phase 3 study with a larger ITP population.

Based on population pharmacokinetic (PopPK) analysis, the applicant estimated accumulation ratios of 1.3 for Cmax and 1.2 for AUC, which are considered acceptable and have been included in the SmPC.

Although rilzabrutinib is a weak CYP3A4 inhibitor and could theoretically inhibit its own metabolism, no significant increases in plasma exposure were observed. This is likely due to its rapid clearance and metabolism via pathways independent of CYP3A4.

Variability
Rilzabrutinib shows high inter- and intraindividual variability. Sex and hepatic impairment were the main factors affecting exposure, with males showing ~20% lower exposure and moderate hepatic impairment causing a ~4.5-fold increase. Despite this, no dose adjustments are needed based on efficacy data.

PopPK model

The popPK model describes ITP patient data moderately well, capturing overall trends despite some misspecifications in the VPC and GOF plots. Individual fits are generally appropriate, though variability in the data is noted. The impact of anti-drug antibodies was not assessed. While acceptable for current use, further model refinement is recommended for future development.

PK in target population

In ITP patients, pharmacokinetics were comparable to healthy subjects, though exposure tended to be slightly lower.

Special populations

The applicant conducted three dedicated studies to assess the impact of intrinsic factors on rilzabrutinib pharmacokinetics, including hepatic impairment and ethnicity (Chinese and Japanese subjects). Mild hepatic impairment led to a ~1.5-fold increase in exposure, while moderate impairment caused a significant rise. Male subjects had ~20% lower exposure than females, but efficacy subgroup analyses revealed comparable platelet responses. SmPC section 4.2 indicates that rilzabrutinib is not recommended in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment and states that severe hepatic impairment has not been studied in clinical trials. Ethnicity and bodyweight had minimal impact, and no dose adjustments are needed. Renal impairment was evaluated through modelling and clinical data in a low number of patients; although mild and moderate impairment showed some exposure increase, safety profiles were comparable, and no concerning signals were observed.

DDI

Wayrilz displays a low solubility which decreases with increasing pH. Recommendations with regard to concomitant use with proton pump inhibitors and H2 receptor agonists are provided in the SmPC and, upon request, guidance pertaining to antacids was added by the applicant.

- Rilzabrutinib as a victim:

The first study (Study PRN1008-014) was with ritonavir (a strong inhibitor of CYP3A4 and P-gp), while the second study included rifampin (a potent CYP3A inducer) and quinidine (an inhibitor of both P-gp and CYP2D6). Based on the PK and safety results from these two studies and the PK results from the PBPK modelling simulations, the applicant recommends avoiding the concomitant use of moderate to strong CYP3A inhibitors or inducers during rilzabrutinib treatment. For short-term use of CYP3A inhibitors (e.g., anti-infectives for seven days or less), rilzabrutinib treatment should be temporarily interrupted. These recommendations were considered appropriate.

The applicant advises against co-administering proton pump inhibitors (PPIs) with rilzabrutinib due to their potential to interfere with drug absorption. If a gastric acid-reducing agent is necessary, an H2 receptor antagonist (H2RA) is preferred. Rilzabrutinib should be taken at least two hours before the H2RA. However, in real-world use, patients often take H2RAs for extended periods (4 to 8 weeks), which may still affect rilzabrutinib's pharmacokinetics. Even when rilzabrutinib is taken two hours before the H2RA, the residual effects of the H2RA may influence the next rilzabrutinib dose. Study PRN1008-011 showed that administering an H2RA ten hours after rilzabrutinib reduced the drug's $AUC_{0-\infty}$ by 35.3% and Cmax by 27.7%. The applicant addressed this concern by recommending H2RAs over PPIs and maintaining the two-hour separation. Based on the study, the reduction in exposure—around 30%—is considered minor and does not require dose adjustment. This approach is deemed acceptable.

- Rilzabrutinib as a perpetrator:

Based on results from studies PRN1008-011 and PRN1008-002 rilzabrutinib could be considered as a moderate inhibitor of drugs which are metabolized by CYP3A. However, these results could not be fully endorsed and should be interpreted with caution due to limitations in the study design. The single-dose protocol was not specifically designed to demonstrate the metabolite's induction effect on CYP3A4. To fully elucidate this effect, a multiple-dose regimen of 400mg would have been more appropriate. Such a protocol would allow for the accumulation of the metabolite and provide a more accurate assessment of its long-term impact on CYP3A4 activity. The applicant conducted a PBPK simulation to evaluate the effect of a multiple-dose regimen of rilzabrutinib on CYP3A4 activity. Nevertheless, the model demonstrated limitations in its applicability as a CYP3A4 perpetrator. The recommendation on the SmPC that caution should be exercised if co-administering rilzabrutinib with CYP3A substrates with narrow therapeutic range is considered appropriate. Additionally, information regarding its CYP3A4 induction effect, specifying that the effect of a multiple-dose regimen of rilzabrutinib on CYP3A4 activity is unknown is included in SmPC section 4.5.

In silico Studies:

The methodology used for model development and validation is considered appropriate. However, a few limitations have been identified that warrant consideration. Specifically, the model tends to overestimate the induction effect of rifampicin and the inhibition effects of ritonavir, with a slight overestimation observed in the impact on Cmax. This issue persists even after fm calibration, raising concerns about the model's reliability. That being said, these limitations do not significantly compromise the model’s applicability for assessing the impact of CYP3A4 modulators on the PK of rilzabrutinib, which will be more conservative.

Another notable limitation is the omission of the metabolite in the model development, as well as the lack of consideration of its induction effect on the CYP3A4 enzyme when simulating with midazolam as a CYP3A4 probe substrate. This omission compromises the model’s ability to fully assess rilzabrutinib as a potential CYP3A4 perpetrator (See assessment of clinical study with midazolam).

Regarding transporter-mediated inhibition by rilzabrutinib, the PBPK model simulation results suggest no significant inhibition effect on P-gp, BCRP, or OATP1B3 substrates. However, when the *in vitro* Ki values were lowered by 100-fold in the model, maximum interaction ratios for AUC ranged from 1.3 to 1.5, and for Cmax, from 1.5 to 2. Given the lack of qualification of PBPK models for reliably predicting transporter inhibition in general, along with the potential high variability in *in vitro* Ki values for transporters across different laboratories, these results do not fully rule out the risk of DDIs, particularly with sensitive substrates or those with a narrow therapeutic index (NTI). Caution should be exercised when co-administering rilzabrutinib with P-gp, BCRP, OATP1B1, or OATP1B3 sensitive substrates or those with a narrow therapeutic range.

Since the PBPK model was considered not to be sufficiently qualified to assess the DDI transporter mediated, a warning that caution should be exercised when co-administering rilzabrutinib with P-gp sensitive substrates with a narrow therapeutic range was added to the SmPC 4.5 section. This is accepted.

Other consideration for DDI:

The "Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Chronic Primary Immune Thrombocytopenia (EMA/CHMP/153191/2013)" notes that, in patients with chronic ITP, multiple therapies are often administered concurrently. The clinical implications of pre-medication (e.g., corticosteroids prior to anti-D Ig or IVIg), concomitant medications, or rescue medications should be assessed in line with the current CHMP Note for Guidance on the Investigation of Drug Interactions. Consequently, the applicant was requested to discuss the potential risk of DDIs

between rilzabrutinib and any possible concomitant drugs in this patient population. The applicant has adequately discussed the potential concomitant medications in the target patient population and their associated risk of DDIs (which is mainly related to CYP3A4 modulation as either a precipitant or an object drug). These risks are already addressed in the SmPC interaction section (section 4.5).

According to the EMA guideline on Investigation of drug interactions, it should be noted that there may still be mechanisms of induction which presently are unknown. Therefore, the applicant was asked to conduct a clinical DDI study with oral contraceptives, to assess the *in vivo* for effects of rilzabrutinib on contraceptive steroids as the drug is intended for use in fertile women, regardless of the *in vitro* induction study results. The applicant agreed to conduct a clinical DDI study with oral contraceptives, the final report is expected to be submitted in September 2027. Given the potential burden of a mechanical contraception (as recommended pending such DDI data), efforts should be made by the applicant to shorten the delay to obtain those data.

Until the results of the study are available, the applicant added a SmPC recommendation (section 4.6) that highly effective contraception should be used during treatment until 1 month after cessation of treatment. In addition, a statement has beec included in section 4.5 regarding potential interaction with hormonal contraceptives, under the subtitle *"Agents that may have their plasma concentrations altered by rilzabrutinib"*, as follows:

Hormonal contraceptives
The effect of rilzabrutinib on the plasma concentrations of hormonal contraceptives is unknown. Therefore, women of childbearing potential should use an alternative non-hormonal or additional highly effective method of contraception during treatment and for at least 1 month after discontinuation of rilzabrutinib (see section 4.6).

Pharmacodynamics

Primary Pharmacology: In healthy volunteers as well as ITP patients, BTK occupancy was investigated as a PD marker, which is considered a suitable biomarker. The therapeutically intended PD effect, impact on thrombocyte levels, was investigated as the primary efficacy endpoint in the phase 1/2 clinical trial 010 as well as the pivotal clinical study 018 in ITP patients.

Secondary Pharmacology: A thorough QT study, PRN1008-014, explored the influence of supratherapeutic doses of rilzabrutinib on cardiac repolarisation. While rilzabrutinib does not cause a prolongation of the QT interval, it is noticeable that a shortening of the QT interval could be observed even at clinical doses. The applicant argues that a shortening of the QT interval by 10 ms is not clinically relevant, however, a statement was added upon request to section 4.4 of the SmPC to alert treating physicians to this effect of rilzabrutinib and to enable a benefit risk consideration in patients with congenital short QT syndrome.

PK-PD modelling: The PK-PD model POH1157 illustrated that measurable plasma levels of rilzabrutinib did not necessarily correlate with effects on thrombocyte levels. Non-clinical data corroborate the PD effect on thrombocyte levels was not dependent on plasma levels. Durable BTK occupancy was maintained even in the absence of plasma exposure. The GI tract was one of the target tissues in non-clinical toxicity studies, and in the human PK-PD model, effects of rilzabrutinib were seen as dose dependent. Dose dependency of AEs in general was found in PK studies in healthy volunteers as well as in phase 1/2 dose finding study PRN1008-010 in ITP patients, and higher doses of rilzabrutinib (>600mg) were discontinued due to tolerability issues.

2.6.4. Conclusions on clinical pharmacology

The documentation of the clinical pharmacology of rilzabrutinib is based on 15 clinical trials and a wealth of *in vitro* studies as well as several modelling approaches (PopPK, PBPK, PKPD models). With regard to DDI, the applicant has conducted several *in vitro*, *in vivo*, and *in silico* studies to assess the DDI risk of rilzabrutinib as both an object and precipitant for all relevant enzymes and transporters. The clinical pharmacology part of the dossier is considered acceptable to support a MA for rilzabrutinib.

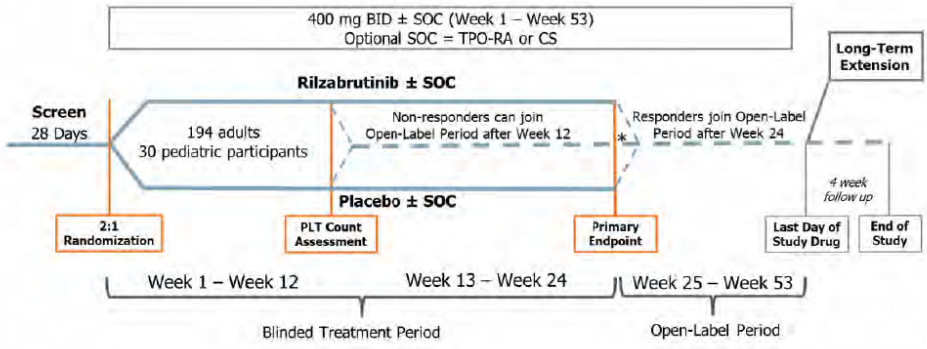
Effective contraception is required for women of childbearing potential based on preclinical findings. In line with EMA guidance, and despite in vitro results, the applicant has agreed to conduct a clinical DDI study with oral contraceptives to assess potential effects on contraceptive steroids. **(Cat 3. PAM-MEA)**

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

PRN1008-010 (DFI17124)

Study Design: Study PRN1008-010 (DFI17124) is a global, 2-part (Parts A and B) multicenter, adaptive, open-label dose finding study of oral rilzabrutinib in patients with refractory or relapsed ITP with no available approved therapeutic options. The planned number of patients (60 for part A and 25 for part B) was enrolled in 8 countries (Australia, Bulgaria, Canada, Czech Republic, Netherlands, Norway (Part A only), United Kingdom, United States of America).



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

At the end of 12 weeks of treatment, (ie, at the Week 13 visit) participants were assessed for a platelet response. Participants who met the criteria for response, continued in the blinded treatment period for a total of 24 weeks before entering the open-label period. Participants who did not meet the criteria for response, could discontinue from the study or enter the open-label period at the end of 12 weeks of treatment (ie, at the Week 13 visit).

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

Figure 9: Study design PRN1008-018

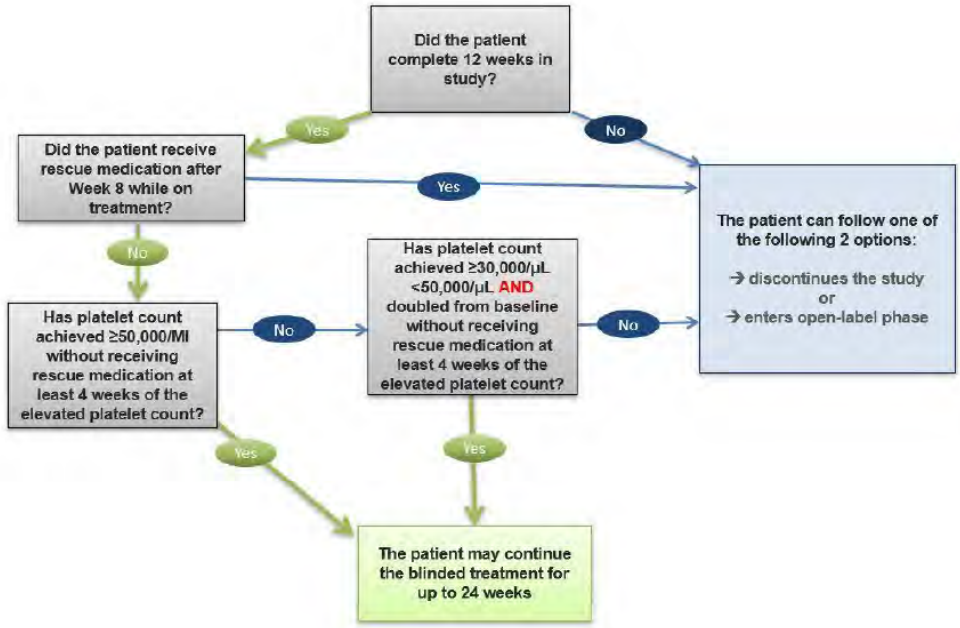


Figure 10 : Decision tree for assessing response at week 13

Study Population

Inclusion/Exclusion criteria

This Phase 1/Phase 2 study (Part A) enrolled adult, male and female patients with ITP who were refractory or relapsed with no available/approved therapeutic options, and with a platelet count <30,000/µL on 2 counts no sooner than 7 days apart in the 15 days prior to treatment start.

Part B (ongoing as of the data cutoff date) is enrolling adult, male and female patients with immune-related ITP (both primary and secondary) as defined by current guidelines with at least 3 months duration. Specifically, patients who had a response (achievement of platelet count ≥50,000/µL) to IVIg/anti-D or corticosteroid that was not sustained and failed at least 1 other ITP therapy (that was not IVIg or corticosteroid), and with a platelet count of <30,000/µL on 2 occasions no less than 7 days apart in the 15 days before treatment begins, and no platelet counts above 35,000/µL on study Day 1.

Patients who were receiving CS or TPO-RAs at the time of enrolment with inadequate platelet response were allowed to continue on stable doses of these medications.

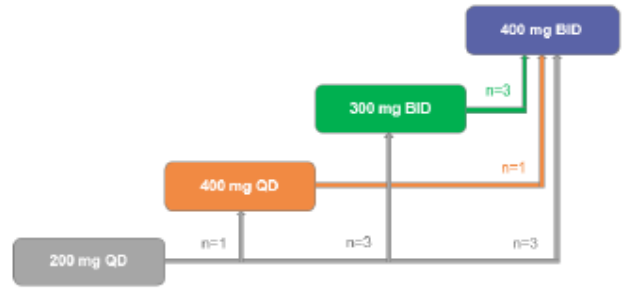
Objectives and Endpoints

Table 5: Primary Efficacy Objectives and Endpoints of study 010

Objectives	Endpoints
Primary	
Efficacy	
Part A	
• To explore the clinical activity of up to 4 dose levels of rilzabrutinib in relapsed/refractory patients with ITP • To identify a potential dose regimen to use in future studies of rilzabrutinib in patients with ITP	• The proportion of patients able to achieve 2 or more consecutive platelet counts, separated by at least 5 days, of ≥50,000/μL AND an increase of platelet count of ≥20,000/μL from baseline, by dose level, without use of rescue medication in the 4 weeks prior to the latest elevated platelet count
Part B	
• To further explore the clinical activity and durability of response of the selected dose of 400 mg BID of rilzabrutinib in patients with ITP who have relapsed or have an insufficient response to prior therapies • To evaluate the predictive value of platelet response to rilzabrutinib therapy in the first 8 weeks of active treatment for the achievement of the primary endpoint.	• Proportion of patients able to achieve platelet counts ≥50,000/μL on at least 8 out of the last 12 weeks of the 24-week treatment period without the use of rescue medication after 10 weeks of active treatment

Patient disposition

Sixty patients were enrolled and were assigned to one of 4 rilzabrutinib starting doses. The bars indicate the highest dose received. All received at least 1 dose of rilzabrutinib as follows:



Starting Dose	N=9	N=1	N=5	N=45
Maintained Dose	n=2	n=0	n=2	n=45
Dose-escalated	n=7	n=1	n=3	N/A

Figure 11: Patient disposition in study 010

At the completion of **Part A**, 35 (58.3%) patients had completed the main treatment period, and 34 (56.7%) had completed 24 weeks of treatment. Twenty-five (41.7%) patients did not complete the main treatment period. Reasons for patient discontinuation included AEs (not including DLT) (7 [11.7%]), patient decision (6 [10.0%]), need of rescue medication (6 [10.0%]), lack of response (5 [8.3%]), and patient erroneously enrolled into the study (1 [1.7%]).

As of the data cutoff date, 16 (26.7%) patients had entered the LTE. Of those, 12 (20.0%) were ongoing in the LTE, and 4 (6.7%) had withdrawn. Two of these (3.3%) patients discontinued due to AEs, 1 (1.7%) due to pregnancy of a female patient, and 1 (1.7%) due to need of rescue medication.

Of note, 2 patients completed 12 weeks of treatment under the initial protocol design and were therefore not considered discontinuations.

Twenty-six participants were enrolled and received rilzabrutinib 400 mg BID in the 24-week **Part B** main treatment period. A total of 22 (84.6%) participants completed 12 weeks of treatment, with 15 (57.7%) of them completing 24 weeks of treatment.

Eleven (42.3%) participants discontinued the main treatment period. The reasons for discontinuation were lack of response (per the investigator's judgement) for 5 participants, treatment-emergent adverse events (TEAEs) for 2 participants, a non-treatment-emergent AE for 1 participant, noncompliance for 1 participant, both lack of response and AE (diarrhoea) for 1 participant (which was recorded as "other" reason), and wrongly enrolled in the study for 1 participant.

As of the data cutoff date (31 Jan 2023), 11 (42.3%) participants had entered the LTE. Of those, all participants are ongoing in the LTE, ie, no participants have discontinued from the LTE.

Results – Part A

Table 6 Primary Platelet Response by Starting Dose and Overall - Main Treatment Period (ITT Population)

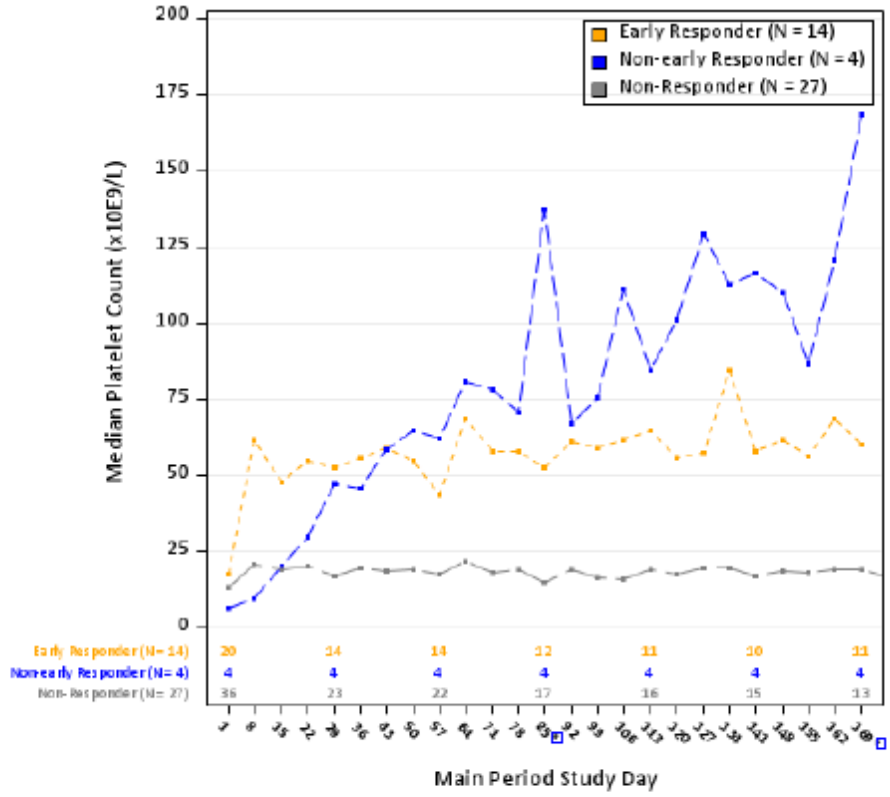
	Starting Dose 200 mg QD (N = 9)	Starting Dose 400 mg QD (N = 1)	Starting Dose 300 mg BID (N = 5)	Starting Dose 400 mg BID (N = 45)	Overall (N = 60)
Responder - n (%)	4 (44.4)	0 (0.0)	2 (40.0)	18 (40.0)	24 (40.0)
- 95% CI	13.70, 78.80	0.00, 97.50	5.27, 85.34	25.70, 55.67	27.56, 53.46

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

95% Confidence Interval is based on the Clopper-Pearson method.

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

Included platelet counts up to one day after the date of last dose of study drug.



Study days are based the nominal day for each visit, e.g. visit Cycle 1 Day 8 is mapped to Study Day 8. Baseline is mapped to Study Day 1.

Early Responder = Achieved primary efficacy response and platelet count >= 30,000/uL on Cycle 1 Day 8.

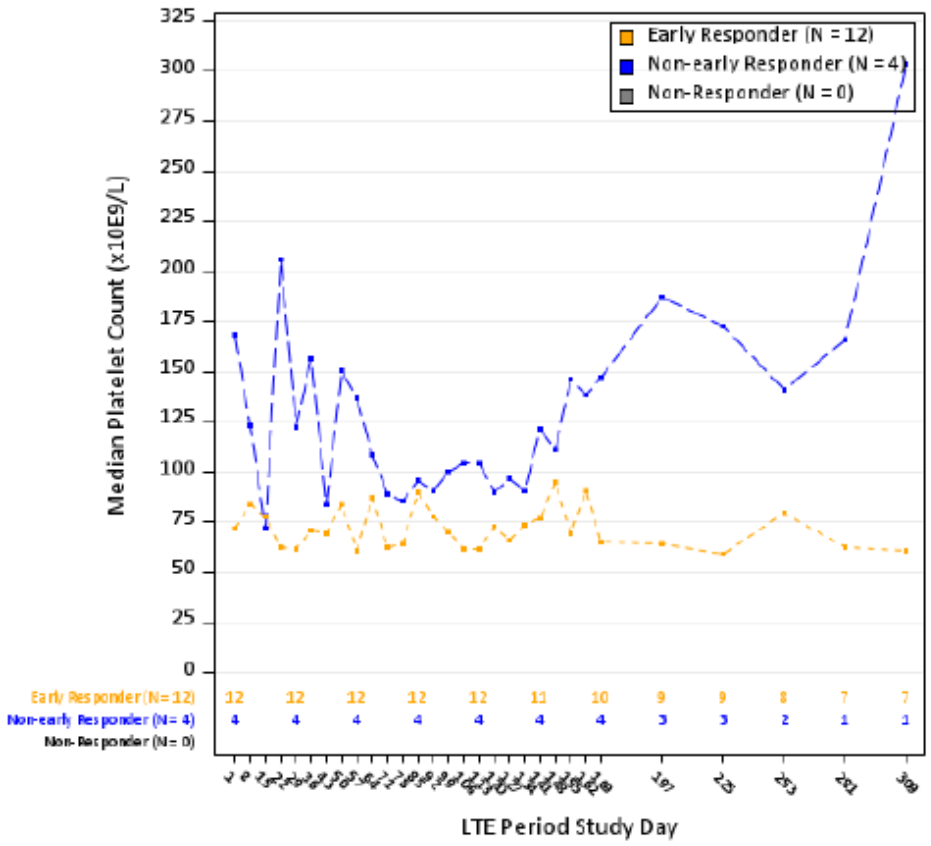
Non early Responder = Achieved primary efficacy response and platelet count < 30,000/uL on Cycle 1 Day 8.

Non-Responder = Did not achieve primary efficacy response.

Note of *: D169 may refer to visit D169, visit C1D1_LTE, or visit C7D1, depending on the availability of subject's visit information and duration of cycles.

Note of *: D85 may refer to visit D85 or visit C4D1, depending on duration of cycles.

Figure 12: Plot of Median Platelet Counts by Time of Response - Main Period (ITT population - Started with 400 mg BID)



Study days are based the nominal day for each visit, e.g. visit LTE Cycle 1 Day 8 is mapped to Study Day 8.
Early Responder = Achieved primary efficacy response and platelet count >= 30,000/uL on Cycle 1 Day 8.
Non early Responder = Achieved primary efficacy response and platelet count < 30,000/uL on Cycle 1 Day 8.
Non-Responder = Did not achieve primary efficacy response.

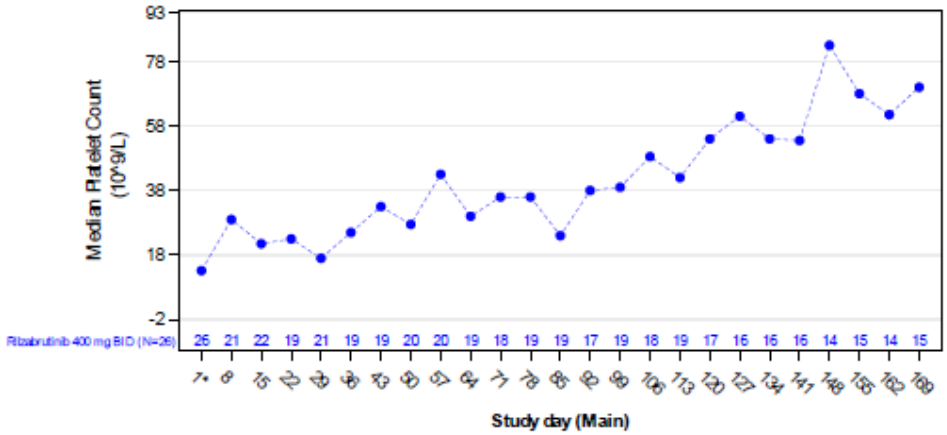
Figure 13: Plot of Median Platelet Counts by Time of Response - LTE Period (ITT population)

Results - Part B

Table 7: Platelet overall response during 24-week treatment period - ITT population

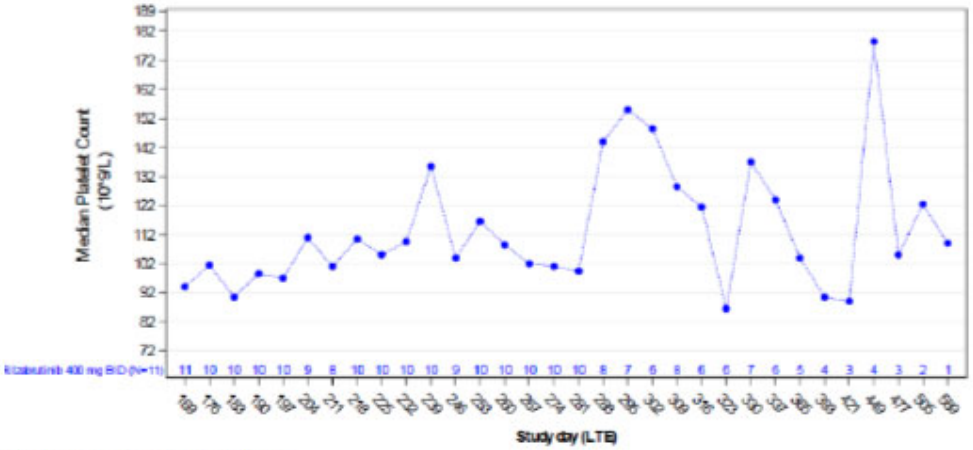
	Rilzabrutinib 400 mg BID (N=26)
At least 8 out of the last 12 platelet counts ≥ 50,000/μL	
n (%)	9 (34.6)
95% CI[a]	17.21 to 55.67

Abbreviations: BID = twice daily; CI = confidence interval.
[a] 95% CI is calculated using the Clopper-Pearson exact method.



Study day is relative to first dose date; study days are based the nominal day for each visit, for example, Week 2 is mapped to Study Day 8.
*This refers to baseline, which is the average of 1st, 2nd qualifying screening platelet counts, and Week 1 (Study Day 1) platelet count.

Figure 14: Median platelet counts by visit during 24-week treatment period - ITT population



Abbreviations: LTE = Long-term extension.
Study day is relative to first dose date; study days are based the nominal day for each visit, e.g., C1D1_LTE is mapped to Study Day 169

Figure 15: Median platelet counts by visit during long-term extension on-treatment period – ITT population

Table 8: Supplementary analyses of platelet durable response during 24-week treatment period - ITT population

	Rilzabrutinib 400 mg BID (N=26)
At least two-thirds of 8 non-missing of the last 12 platelet counts > 50,000/μL and at least 2 occurred during last 6 weeks	
n (%)	9 (34.6)
95% CI[a]	17.21 to 55.67
At least 8 out of the last 12 platelet counts ≥ 50,000/μL or entered LTE	
n (%)	11 (42.3)
95% CI[a]	23.35 to 63.08
At least 4 out of the last 6 platelet counts ≥ 50,000/μL biweekly	
n (%)	9 (34.6)
95% CI[a]	17.21 to 55.67

Abbreviations: BID = twice daily; CI = confidence interval; LTE = Long-term extension.

a 95% CI is calculated using the Clopper-Pearson exact method

2.6.5.2. Main study(ies)

PRN1008-018 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)

Methods

The adult part of the study was conducted at 92 centers with randomized adult participants in 25 countries.

Study period was 14 December 2020 to 14 March 2024 (last participant last visit for the double-blind period). The analyses presented in this report are based on a database lock dated 16 Apr 2024 (last adult completed blinded treatment period).

The results for the paediatric population will be presented in a separate CSR.

Study Design

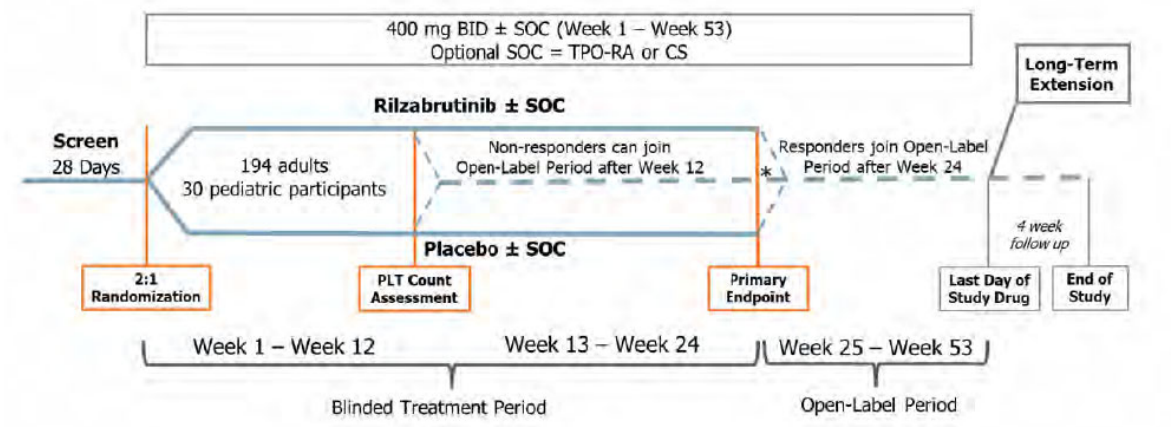
After randomization (2:1 rilzabrutinib:placebo) to one of two study arms: rilzabrutinib 400 mg BID or placebo, participants started a blinded treatment period of up to 24 weeks, followed by an open-label (OL) period of 28 weeks during which all participants received rilzabrutinib, and then a 4-week safety follow-up period or entry into the LTE. At the end of 12 weeks of blinded treatment (Week 13) participants were assessed for achieving a platelet response defined as a) platelet count of ≥50,000/μL OR a platelet count of between ≥30,000/μL and <50,000/μL and at least doubled from baseline at any time during the first 12 weeks and b) absence of rescue medication in the 4 weeks prior to the elevated platelet count that met platelet response criteria. The decision process for assessing response at week 13 is presented below. Baseline is defined as the average of the participant's predose platelet counts (Screening and Study Day 1).

• Participants who met this definition of response were to continue the blinded treatment period for a total of 24 weeks before entering the OL period.

• Participants who did not meet this definition of response (including participants who receive rescue medication after 8 weeks of treatment) could discontinue from the study or enter the 28-week OL period at the end of 12 weeks of blinded treatment (Week 13 per the schedule of assessments in the protocol), receiving treatment with rilzabrutinib 400 mg BID. Initial study medication assignment remained blinded.

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

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



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

At the end of 12 weeks of treatment, (ie, at the Week 13 visit) participants were assessed for a platelet response. Participants who met the criteria for response, continued in the blinded treatment period for a total of 24 weeks before entering the open-label period. Participants who did not meet the criteria for response, could discontinue from the study or enter the open-label period at the end of 12 weeks of treatment (ie, at the Week 13 visit).

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

Figure 16: Study design PRN1008-018

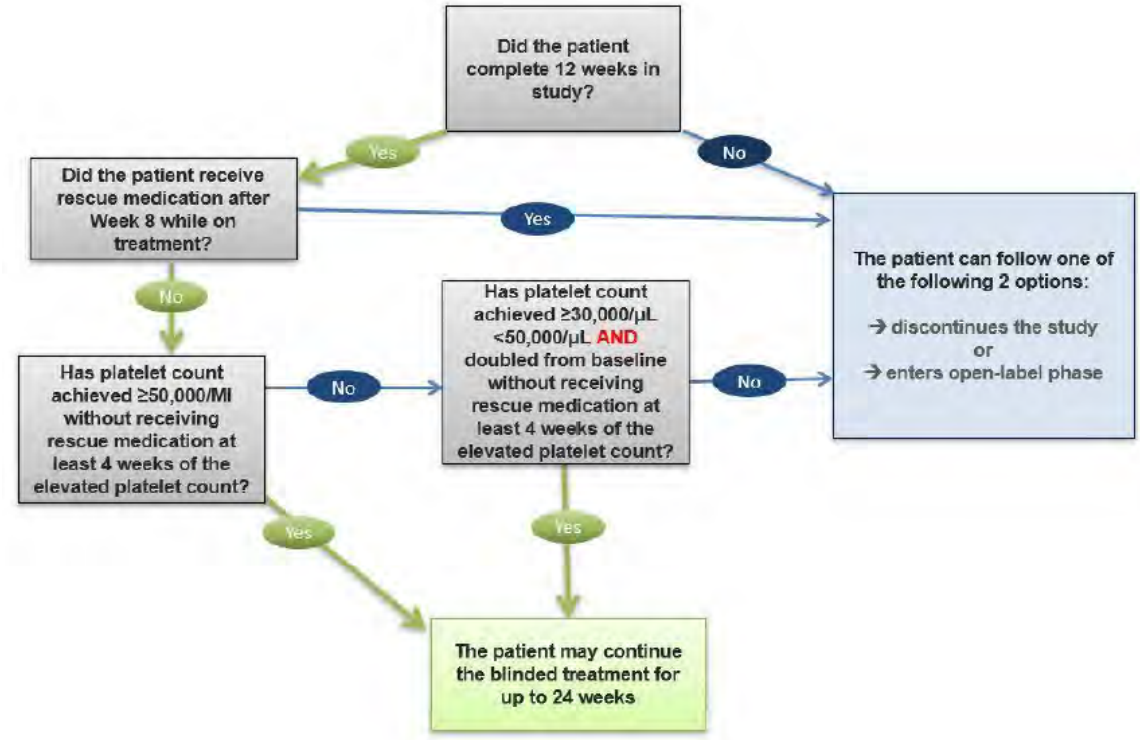


Figure 17: Decision tree for assessing response at week 13

- **Study Participants**

Major 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 paediatric participants aged 12 to <18 years (paediatric participants aged 10 to <12 years will be enrolled in the EU [EEA countries] only) and duration of >3 months in adults aged ⩾18 years

2. Participants who had a response (achievement of platelet count ≥50,000/ μ 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/µL during the screening period and no single platelet count >35,000/µL, within 14 days prior to the first dose of study drug. Paediatric participants must additionally be determined to need treatment for ITP as per clinical assessment by the Investigator (EU [EEA countries] specific criteria were applied)

4. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ⩾1.5 × 109/L, AST/ALT ⩽1.5 × upper limit of normal (ULN), albumin ⩾3 g/dL, total bilirubin ⩽1.5 × ULN [unless the participant has documented Gilbert syndrome], estimated glomerular filtration rate (GFR) >50 [Cockcroft and Gault method])

5. Haemoglobin >9 g/dL within 1 week prior to Study Day 1

6. All contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (further details not shown here).

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

Major 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

Participants with electrocardiogram (ECG) findings :

- Aged ≥10 and <16 years: QTcF >449 msec (males) or >457 msec (females)

- Aged ≥16 and <18 years: QTcF >450 msec (males) or >460 msec (females)

- Aged ≥18 years, of QTcF >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic participants or a ventricular rate above 100 beats/min on ECG), or other clinically significant abnormalities

4. History (within 5 years of Study Day 1) or current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the study, with the exception of non-melanoma skin cancer

5. Transfusion with blood, blood products, plasmapheresis, or use of any other rescue medications with intent to increase platelet count within 14 days before Study Day 1

6. Change in CS and/or TPO-RA dose within 14 days prior to Study Day 1 (more than 10% variation from current doses)

7. Immunosuppressant drugs other than CSs within 5 times the elimination half-life of the drug or 14 days of Study Day 1, whichever is longer

8. Treatment with rituximab or splenectomy within the 3 months prior to Study Day 1. Participants treated with rituximab will have normal B-cell counts prior to enrolment

9. Ongoing need for the use of proton pump inhibitor drugs such as omeprazole and esomeprazole (it is acceptable to change participant to H2 receptor blocking drugs prior to Study Day 1)

10. Use of known strong-to-moderate inducers or inhibitors of CYP3A within 14 days or 5 half-lives (whichever is longer) of Study Day 1 and until the end of the active treatment period

11. Planned or concomitant use of any anticoagulants and platelet aggregation inhibiting drugs such as aspirin (except for low dose aspirin up to 100 mg per day), nonsteroidal anti-inflammatory drugs, and/or thienopyridines within 14 days of Study Day 1 and until the end of the active treatment period

12. Has received any investigational drug within the 30 days before receiving the first dose of study medication, or at least 5 times elimination half-life of the drug (whichever is longer); participant should not be using an investigational device at the time of dosing

- Participants who previously received treatment with BTK inhibitors (except rilzabrutinib) within 30 days before the first dose of study drug are not eligible

- Participants who previously received rilzabrutinib at any time are not eligible

13. Current drug or alcohol abuse

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

15. History of solid organ transplant

16. Positive at Screening for HIV, HBV (surface and core antibodies unrelated to vaccination), or HCV (anti-HCV antibody confirmed with Hep C RNA)

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

- Participants who are HBsAg negative and HBV core antigen antibody (HBcAb) positive will be tested for HBV surface antibody (HBsAb) and HBV DNA. If HBV DNA is negative and HBsAb titer is ≥100 IU/L, participants may be enrolled. Monthly HBV DNA monitoring will be required while on treatment and for 6 months after the last dose of the study drug. Positive HBV DNA results will be managed appropriately as per local standard of care

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

17. Positive QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus (QFT Plus) at Screening unless all of the following 3 conditions are true:

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

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

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

i. Oral daily Isoniazid for 6 months or

ii. Oral daily Rifampin for 4 months or

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

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

18. History of recurring (2 or more) serious infections requiring intravenous antibiotic, antivirals or antifungals therapy within the last 3 months before Study Day 1 or active serious or moderate infection ongoing on the day of randomization

19. Myelodysplastic syndrome

20. Live vaccine within 28 days prior to Study Day 1 or plan to receive one during the study

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

22. Any other clinically significant disease, condition, known allergy to any of the study medication, their analogues, or excipients in the various formulations of any agent, or medical history that, in the opinion of the Investigator or Sponsor’s medical monitor, would interfere with participant safety, study evaluations, and/or study procedures

23. Positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) molecular test (if COVID-19 testing required per local guidelines to be determined for each site)

24. The COVID-19 vaccine within 14 days prior to Study Day 1 or planned during the last 12 weeks of blinded treatment period

- **Treatments**

Table 9: Overview of study intervention administered

Intervention name	Rilzabrutinib	Placebo
Type	Drug	Drug
Dose formulation	Tablet	Tablet
Unit dose strength(s)	400 mg	0 mg
Dosage level(s)	400 mg (1 tablet) BID	1 tablet BID
Route of administration	Oral	Oral
Use	Experimental	Placebo
IMP	IMP	IMP
Packaging and labeling	Rilzabrutinib tablets are supplied in white plastic bottles with child-resistant induction-sealed caps	Matching placebo tablets are supplied in white plastic bottles with child-resistant induction-sealed caps
Current/Former names or aliases	PRN1008 or SAR444671	Not applicable

Abbreviations: BID = twice daily; IMP = investigational medicinal product.

Prohibited Medications

The study prohibits the use of concomitant immunosuppressant medications other than corticosteroids, as outlined in the protocol. Participants who need other immunosuppressant therapy during the study must be withdrawn - see Exclusion# 7 for washout periods. Concomitant use of strong-to-moderate inducers or inhibitors of cytochrome P450 (CYP) 3A - see Exclusion # 10 for washout periods. Proton pump inhibitors were prohibited because they were shown to reduce rilzabrutinib exposureby approximately 50%, presumably due to the effects of a lack of an acidic environment on tablet dissolution; participants should switch to H2 receptor blockers if possible - see Exclusion # 9. Rescue medications other than one of IVIg, high-dose CSs, platelet infusion, or anti-D immunoglobulin infusion intended to increase platelet counts or prevent bleeding when platelet counts are less than 20×10^9/L, or for bleeding or wet purpura, are not permitted. Additionally, the use of COVID-19 vaccines during the last 12 weeks of the blinded treatment period and live vaccines throughout the study was not permitted.

Permissible Medications

Participants could continue using oral corticosteroids (CS) and/or thrombopoietin receptor agonists (TPO-RAs) authorized for treating ITP, provided the doses remain stable from 14 days before Study Day 1 until the last dose of study medication. Dose adjustments were only allowed for safety reasons. Corticosteroids and TPO-RAs should be administered according to their updated SmPCs. Tapering was permitted during the long-term extension (LTE) period if a durable platelet response was achieved, following a standard tapering scheme with biweekly platelet monitoring. If platelet counts drop below 50,000/μL on two consecutive measurements, corticosteroid doses could be increased. IVIg, high-dose CS, platelet infusion, or anti-D immunoglobulin infusion were allowed as rescue medications. Clinically relevant drugs that are substrates of CYP3A, including those considered to be sensitive CYP3A substrates. Appropriate caution should be used when co-administering sensitive CYP3A substrates with rilzabrutinib, including an assessment of medical risk-benefit for each medication. Consideration should also be given to avoidance of high doses, dose reduction, or replacement of sensitive CYP3A substrate drugs. H2 receptor blockers like ranitidine or famotidine, as well as antacids, were permitted if administered at least two hours after rilzabrutinib or placebo.

- **Objectives and endpoints**

Table 10: Primary Objective and Endpoints

Objectives	Endpoints
Primary Efficacy (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	• Durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for ≥ two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/μL during the last 6 weeks of the 24-week blinded treatment period (Definition 1) • Durable platelet response defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy (Definition 2) (Country specific definition for EU [EEA countries] and UK)

Table 11: Key Secondary Objectives and Endpoints

Objectives	Endpoints
Key Secondary Efficacy (Blinded Treatment Period)	
• To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline, over the 24-week blinded treatment period in the absence of rescue therapy	• Number of weeks with platelet count ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy.
• To evaluate the effect of rilzabrutinib versus placebo on the number of weeks with platelet counts ≥30,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy	• Number of weeks with platelet counts ≥30,000/μL and at least doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy
• To evaluate the effect of rilzabrutinib versus placebo on the time to first platelet count of ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and at least doubled from baseline	• Time to first platelet count of ≥50,000/μL OR between ≥30,000/μL and <50,000/μL and doubled from baseline
• To evaluate the effect of rilzabrutinib versus placebo on the proportion of participants requiring rescue therapy	• Proportion of participants requiring rescue therapy during the 24-week blinded treatment period
• To evaluate the effect of rilzabrutinib versus placebo on the change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (≥18 years) at Week 13	• Change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) in adult participants (≥18 years) at Week 13
• To evaluate the change from baseline in ITP Bleeding Scale (IBLS) (Applicable to countries within the EU [EEA countries] and UK)	• Change from baseline in IBLS assessment at Week 25 (Applicable to countries within the EU [EEA countries] and UK)

Abbreviations: BTK = Bruton's tyrosine kinase; CS = corticosteroid; ECG = electrocardiogram; EEA = European Economic Area; EU = European Union; Euroqol-5D-5L = Euroqol-5 Dimensions-5 Level; IBLS = ITP Bleeding Scale; Ig = immunoglobulin; ITP = immune thrombocytopenia; ITP-KIT = Kids' ITP Tools; ITP-PAQ = ITP-Patient Assessment Questionnaire; LTE = long-term extension; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics; QoL = quality of life; TPO = thrombopoietin; TPO-RA = thrombopoietin receptor agonist; TEAE = treatment-emergent adverse event; UK = United Kingdom

- **Sample size**

The adult sample size chosen for this study was selected to achieve enrolment of 129 adult participants (≥18 years) on rilzabrutinib and 65 adult participants on placebo. A sample size of approximately 194 (129 versus 65 adult participants in the rilzabrutinib versus placebo arms, respectively) would provide 95% power to detect a 20% difference in response rates as defined in the primary endpoint between

the 2 arms (25% vs 5%, in the rilzabrutinib versus placebo arms, respectively), using the Fisher's Exact test with a 0.05 two-sided significance level. The assumption of a 25% response rate in the rilzabrutinib group was based on the Phase 1/2 study PRN1008-010 Part A (DFI17124 Part A) (durable response [8 out of the last 12 weeks with platelet count at or above 50,000/μL in the absence of rescue medication]) and the 5% response rate was estimated based on the observed placebo response in previous randomized controlled trials of ITP medications (Bussel 2018). The participants who are not evaluable for primary efficacy due to dropout or missing data were considered as non-responders.

The paediatric 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 paediatric participants. With a sample size of 20 paediatric participants on rilzabrutinib the maximum width of an exact 90% CI on response rate would be 40%.

- **Randomisation and Blinding (masking)**

Stratified permuted block randomization was implemented. The factors used for stratification were splenectomy status (yes/no), and by severity of thrombocytopenia (Inclusion Criteria #3 platelet counts <15,000/μL or ≥15,000/μL).

After randomization, participants started a blinded treatment period of up to 25 weeks followed by an open-label period of 28 weeks during which all participants received rilzabrutinib, and then a 4-week safety follow-up period or long-term extension.

- **Statistical methods**

The primary endpoint of the study was durable platelet response. Two definitions of endpoint and estimand were presented, of which Definition 2 applies to European countries. Only the analysis method for Definition 2 is presented below.

Table 12: Summary of primary estimands for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint [a]	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Primary objective: To demonstrate the efficacy of rilzabrutinib versus placebo in participants with refractory/relapsed ITP, based on the durability of platelet response during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy				
Primary endpoint (Composite estimand)	Durable platelet response is defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for ≥two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/μL during the last 6 weeks of the 24-week blinded treatment period (Definition 1) [b] Country-specific definition [c]: Durable platelet response is defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy (Definition 2)	ITT	1) Rescue medication: participants will be considered as non-responders if taking rescue medication after 8 weeks of double-blind treatment and before Week 25 (or last IMP intake, whichever earlier) (composite strategy). 2) Discontinuation of study intervention before Week 25 due to lack of response or related adverse events per eCRF: participants will be considered as non-responders (composite strategy). 3) Discontinuation of study intervention before Week 25 due to reasons other than the aforementioned: data during the double-blind on-treatment period will be included in the analysis. Post-treatment data will be considered to have had no platelet response (composite strategy)	Adults: p-value from Cochran-Mantel-Haenszel (CMH) test adjusted by randomization stratification factors [d]. Mantel- Haenszel common risk difference and 95% CI based on Mantel-Haenszel stratum weights (1) and the Sato variance estimator (2). Pediatrics: Descriptive. For Definition 2, Missing data due to Covid-19 (per eCRF) are assumed missing at random and will be imputed using the participant's median value of available (a minimum of 3 available required) weekly platelet counts during the last 12 weeks of double-blind on-treatment period. Otherwise, missing data will be considered as no response.

To qualify for a durable responder (Definition 2, Section 1.2.2.1), a participant must have met ALL of the following criteria:

- Platelet counts ≥50,000/μL for at least 8 out of the last 12 weeks [Week 14 (Day 92) to Week 25 (Day 169)] during the 24-week double-blind treatment period, and
- Not rescued after 8 weeks of treatment and before Week 25 (or last IMP intake, whichever

earlier). A participant who is rescued during this period was considered as a non-responder, and,

- Not discontinued before Week 25 due to related TEAE (per investigator's assessment) or lack of response. A participant who discontinued before Week 25 and the reason for discontinuation was treatment related AE or lack of response was considered as a non-responder.

The primary analysis was planned to compare the proportion of participants in the adult ITT population who achieve durable platelet response defined as platelet counts at or above 50,000/μL for ≥8 out of the 12 scheduled observations in the last 12 weeks of the 24-week blinded treatment period in the absence of rescue medication between rilzabrutinib and placebo with a Cochran-Mantel-Haenszel test using the two stratification factors (splenectomy status, severity of thrombocytopenia) at a 2-sided alpha level of 0.05. Participants who did not respond in the first 12 weeks and enter the open label period were planned to be treated as non-responders in the primary analysis. Participants who discontinued the study due to a rilzabrutinib-related AE, lack of efficacy or receive rescue medication (including an increase in allowed concomitant ITP medications dose) were planned to be considered as non-responders.

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

Missing data

For durable platelet response missing data was handled as follows,

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

Sensitivity analyses for the primary endpoint

Several sensitivity analyses are described (Definition 1 does not apply to Europe):

Table 13: Missing data handling for primary efficacy endpoint

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

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

All efficacy analyses based on ITT, unless otherwise specified.

a Definition 1. Durable platelet response defined as a proportion of participants able to achieve platelet counts at or above 50,000/µL for ≥two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/µL during the last 6 weeks of the 24-week blinded treatment period. Definition 1 not applicable to countries within the EU (EEA countries) and UK.

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

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

Sensitivity analyses for primary endpoint (relevant for EU):

1. *(alternative assumption of missing data)* all missing weekly platelet count regardless of reason for missingness: handled as non-responder (assuming MAR)
2. *(alternative assumption of missing data)* all missing weekly platelet count regardless of reason for missingness: if they stayed on IMP beyond Week 13, missing data was imputed via multiple imputation, assuming MAR and multivariate log-normally distributed platelet values:
    - Data was imputed using data from participants who were not rescued and stay on IMP beyond week 13 and have available data
    - Treatment group, randomization stratification factors and geographic region were included as classified variables and baseline value was included as covariate
    - Imputed data was analysed as per main analytical approach and combined using Rubin's rule
    - Two scenarios were considered: 1) no missing data in placebo participants 2) missing data in the placebo group, but there are non-missing data from at least three participants who have not received rescue medication
3. *(alternative assumption of missing data)* two-dimensional tipping point analysis for missing data (See also table below): given (p0, p1) as the response rate among those participants with missing durable response status for the placebo and the rilzabrutinib group respectively, p0 and p1 could systematically vary starting from 0% and ending at 100% by every 10%. Given a set of (p0, p1), a participant with missing response was randomly assigned as a responder or a non-responder using binomial distribution to generate multiple imputed datasets. Data was analysed according to the main analytical approach and combined using Rubin's rule (see table below).

4. *(modified primary estimand)* the main analysis was carried out on an alternative population:
    - mITT, i.e. ITT participants who have received at least one dose of the IMP
    - 24-week completers
    - Participants not receiving Covid-19 vaccine

Table 14: Tipping point Analysis: Durable Platelet Response Status

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

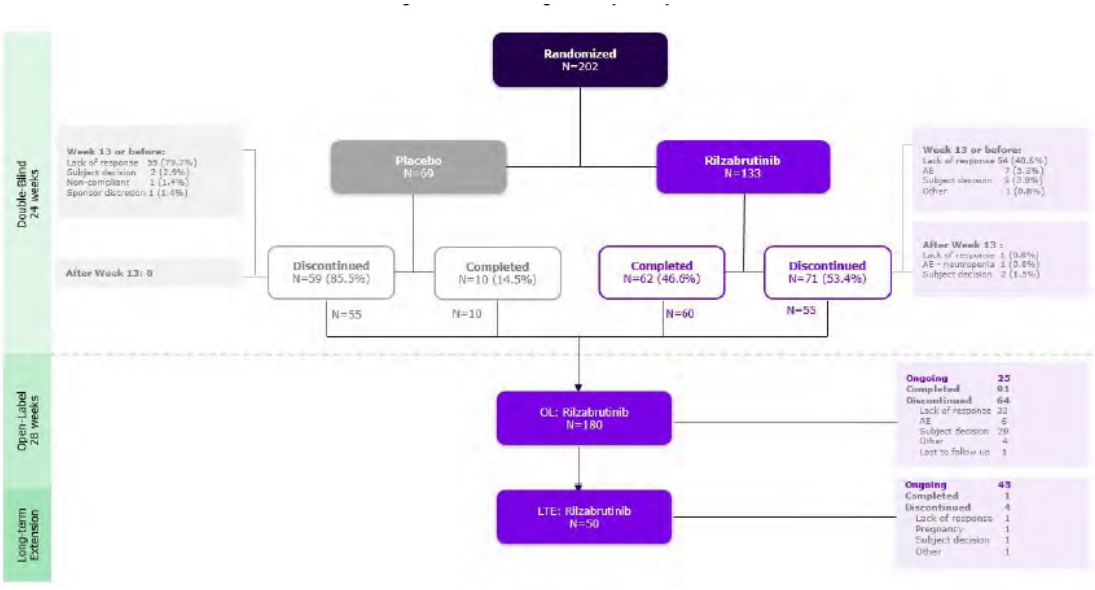
a Definition 1. Durable platelet response defined as a proportion of participants able to achieve platelet counts at or above 50,000/μL for ≥two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/μL during the last 6 weeks of the 24-week blinded treatment period. Definition 1 not appliable to countries within the EU (EEA countries) and UK.

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

TEAE = treatment emergent adverse event.

Results

- **Participant flow**



Abbreviations: AE = adverse event; LTE = long term extension; OL = open label.

- **Recruitment**

Table 15: Participant disposition – Adults screened

n (%)	Placebo (N=69)	Rilzabrutinib 400 mg BID (N=133)	All screened (N=393)
All screened			393
Screened but not randomized			191
Exposed and not randomized			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 double-blind period	10 (14.5)	62 (46.6)	72 (35.6)
Discontinued the 24-week double-blind period	59 (85.5)	71 (53.4)	130 (64.4)
Reason for discontinuation			
Subject decision	2 (2.9)	7 (5.3)	9 (4.5)
Adverse event	0	8 (6.0)	8 (4.0)
Subject is noncompliant to study requirements	1 (1.4)	0	1 (0.5)
Subject did not meet eligibility requirements	0	0	0
Pregnancy	0	0	0
Subject lost to follow-up	0	0	0
Lack of response	55 (79.7)	55 (41.4)	110 (54.5)
Sponsor discretion	1 (1.4)	0	1 (0.5)
Other	0	1 (0.8)	1 (0.5)

Completed the 12-week double-blind period	66 (95.7)	121 (91.0)	187 (92.6)
Discontinued at Week 13 or earlier[a]	59 (85.5)	67 (50.4)	126 (62.4)
Reason for discontinuation			
Subject decision	2 (2.9)	5 (3.8)	7 (3.5)
Adverse event	0	7 (5.3)	7 (3.5)
Subject is noncompliant to study requirements	1 (1.4)	0	1 (0.5)
Subject did not meet eligibility requirements	0	0	0
Pregnancy	0	0	0
Subject lost to follow-up	0	0	0
Lack of response	55 (79.7)	54 (40.6)	109 (54.0)
Sponsor discretion	1 (1.4)	0	1 (0.5)
Other	0	1 (0.8)	1 (0.5)
Entered the 28-week open-label period	65 (94.2)	115 (86.5)	180 (89.1)
Completed the 24-week double-blind period	10 (14.5)	60 (45.1)	70 (34.7)
Discontinued the 24-week double-blind period	55 (79.7)	55 (41.4)	110 (54.5)
On-going	5 (7.2)	20 (15.0)	25 (12.4)
Completed the 28-week open-label period	36 (52.2)	55 (41.4)	91 (45.0)
Discontinued the 28-week open-label period	24 (34.8)	40 (30.1)	64 (31.7)
Reason for discontinuation			
Subject decision	7 (10.1)	13 (9.8)	20 (9.9)
Adverse event	3 (4.3)	3 (2.3)	6 (3.0)
Subject is noncompliant to study requirements	0	0	0
Subject did not meet eligibility requirements	0	0	0
Pregnancy	0	0	0
Subject lost to follow-up	0	1 (0.8)	1 (0.5)
Lack of response	13 (18.8)	20 (15.0)	33 (16.3)
Sponsor discretion	0	0	0
Other	1 (1.4)	3 (2.3)	4 (2.0)
Entered long-term extension period	17 (24.6)	33 (24.8)	50 (24.8)
On-going	17 (24.6)	28 (21.1)	45 (22.3)
Completed LTE period	0	1 (0.8)	1 (0.5)
Discontinued the LTE period	0	4 (3.0)	4 (2.0)
Reason for discontinuation			
Subject decision	0	1 (0.8)	1 (0.5)
Adverse event	0	0	0
Subject is noncompliant to study requirements	0	0	0
Subject did not meet eligibility requirements	0	0	0
Pregnancy	0	1 (0.8)	1 (0.5)
Subject lost to follow-up	0	0	0
Lack of response	0	1 (0.8)	1 (0.5)
Sponsor discretion	0	0	0
Other	0	1 (0.8)	1 (0.5)
Status at last contact	69 (100)	133 (100)	202 (100)
Alive	69 (100)	132 (99.2)	201 (99.5)
Dead	0	1 (0.8)	1 (0.5)

LTE: Long-term extension

Percentages are calculated using the number of adult randomized participants (i.e., adult ITT population) as denominator

a Derived based on scheduled visits and early withdrawal visits recorded in eCRF, including participants who had no scheduled visits beyond Week 13 where Week 13 could be recorded as a Week 25 visit per protocol or an early withdrawal visit regardless of visit window

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- **Conduct of the study**

Table 16: Key changes to the study conduct

Protocol Version & Date	Key Changes
Version 1.1 - 06 Aug 2020	Removed inclusion criterion #6, adolescent weight requirement.
Version 1.2 Germany - 28 Oct 2020	Incorporated Germany specific requirements
Version 1.2 Canada - 03 Nov 2020	Incorporated Canada specific requirements
Version 1.3 Canada - 06 Nov 2020	Incorporated Canada specific requirements
Version 1.2 UK - 09 Nov 2020	Incorporated United Kingdom specific requirements
Version 1.2 Austria - 03 Dec 2020	Incorporated Austria specific requirements
Version 1.2 France - 04 Dec 2020	Incorporated France specific requirements
Version 1.2 Norway - 15 Dec 2020	Incorporated Norway specific requirements
Version 1.3 France - 02 Jan 2021	Incorporated France specific requirements
Version 1.2 Turkey - 06 Jan 2021	Incorporated Turkey specific requirements
Version 1.2 Ukraine - 21 Jan 2021	Incorporated Ukraine specific requirements
Version 2.0 - 19 Feb 2021	Incorporated feedback from health authorities as well as other clarifications deemed necessary by the Sponsor
Protocol 02 - 21 Jul 2021	Incorporated feedback from health authorities as well as other clarifications deemed necessary by the Sponsor Implemented new clinical safety results and measures based on updated Investigator's Brochure. Added the exploratory endpoint in order to evaluate the impact of the investigational medicinal product (IMP) on vaccine responses. Added other exploratory efficacy endpoints to enable comparison between studies and projects.
Protocol 03 - 11 Aug 2022	Modified the primary endpoint and objective to specify participants having platelet counts at or above 50,000/µL for ≥ two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/µL during the last 6 weeks of the 24-week blinded treatment period. This change does not apply to the EU (EEA countries) and the UK. Required conducting platelet count testing at local laboratories. Provided guidelines for temporary discontinuation of study medication. Moved the Idiopathic Thrombocytopenic Purpura Bleeding Scale (IBLS) assessment from the Secondary to the Exploratory endpoints (not applicable for the EU [EEA countries] and UK). Introduced a fatigue assessment using Item 10 of the ITP-PAQ, as a Key Secondary endpoint. Provided new instructions for the long-term extension duration and study visit schedule. Added efficacy objectives and endpoints to the open label and long-term extension periods.
Protocol 04 - 09 June 2023	Modified the Cochran- Mantel-Haenszel test stratification factors two-sided alpha level and the Fisher's Exact test two-sided significance level from 0.01 to 0.05. Clarified the distinct durations of participation in the long-term extension for the adult and pediatric populations.

Abbreviations: FDA = Food and Drug Administration.

- **Baseline data**

Demographic data

Table 17: Demographics and participant characteristics at baseline – Adult randomized

	Placebo (N=69)	Rilzabrutinib 400 mg BID (N=133)	All (N=202)
Age (years)			
Number	69	133	202
Mean (SD)	47.1 (18.0)	46.8 (17.1)	46.9 (17.4)
Median	46.0	47.0	47.0
Min ; Max	19 ; 79	18 ; 80	18 ; 80
Age group 1 [n (%)]			
Number	69	133	202
< 65 years	54 (78.3)	112 (84.2)	166 (82.2)
≥65 years	15 (21.7)	21 (15.8)	36 (17.8)

Age group 2 [n (%)]			
Number	69	133	202
< 65 years	54 (78.3)	112 (84.2)	166 (82.2)
65 to <75 years	12 (17.4)	15 (11.3)	27 (13.4)
75 to <85 years	3 (4.3)	6 (4.5)	9 (4.5)
≥85 years	0	0	0
Sex [n (%)]			
Number	69	133	202
Male	20 (29.0)	55 (41.4)	75 (37.1)
Female	49 (71.0)	78 (58.6)	127 (62.9)
Post-menopausal	20 (29.0)	34 (25.6)	54 (26.7)
Race [n (%)]			
Number	69	133	202
White	40 (58.0)	85 (63.9)	125 (61.9)
Black or African American	0	1 (0.8)	1 (0.5)
Asian	24 (34.8)	40 (30.1)	64 (31.7)
Chinese	15 (21.7)	17 (12.8)	32 (15.8)
Japanese	1 (1.4)	8 (6.0)	9 (4.5)
Other Asian	8 (11.6)	15 (11.3)	23 (11.4)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	1 (1.4)	3 (2.3)	4 (2.0)
Other	2 (2.9)	3 (2.3)	5 (2.5)
Not Reported	2 (2.9)	1 (0.8)	3 (1.5)
Ethnicity [n (%)]			
Number	69	133	202
Hispanic or Latino	13 (18.8)	28 (21.1)	41 (20.3)
Not Hispanic or Latino	53 (76.8)	103 (77.4)	156 (77.2)
Not Reported	3 (4.3)	2 (1.5)	5 (2.5)
Weight (kg) at screening			
Number	69	133	202
Mean (SD)	71.08 (17.12)	78.49 (20.67)	75.96 (19.80)
Median	71.60	76.00	73.95
Min ; Max	43.5 ; 111.6	44.0 ; 139.5	43.5 ; 139.5
BMI (kg/m^2) at screening			
Number	69	131	200
Mean (SD)	26.226 (5.509)	28.233 (6.364)	27.541 (6.144)
Median	25.433	27.511	27.062
Min ; Max	16.58 ; 41.08	16.53 ; 54.06	16.53 ; 54.06
Geographic region [n (%)]			
Number	69	133	202
Asia/Pacific	26 (37.7)	44 (33.1)	70 (34.7)
West Europe	16 (23.2)	33 (24.8)	49 (24.3)
East Europe	13 (18.8)	19 (14.3)	32 (15.8)
North America	3 (4.3)	13 (9.8)	16 (7.9)
South America	11 (15.9)	24 (18.0)	35 (17.3)

BMI: Body mass index

Baseline disease characteristics

Table 18: ITP disease history - Adult randomized population

	Placebo (N=69)	Rilzabrutinib 400 mg BID (N=133)	All (N=202)
Duration of ITP (years)			
Number	69	133	202
Mean (SD)	9.80 (9.12)	11.45 (11.00)	10.89 (10.40)
Median	6.17	8.12	7.69
Min ; Max	0.3 ; 35.8	0.3 ; 52.2	0.3 ; 52.2
Duration of ITP [n (%)]			
Number	69	133	202
≤1 year	5 (7.2)	10 (7.5)	15 (7.4)
>1 year to ≤3 years	14 (20.3)	21 (15.8)	35 (17.3)
>3 years	50 (72.5)	102 (76.7)	152 (75.2)
Average of two qualifying platelet counts at screening per eCRF ($x10^3$/uL)			
Number	69	133	202
Mean (SD)	15.0 (8.1)	14.5 (7.8)	14.7 (7.9)
Median	15.5	14.5	14.5
Min ; Max	1 ; 30	0 ; 30	0 ; 30
Baseline platelet count[a] ($x10^3$/uL)			
Number	69	133	202
Mean (SD)	15.7 (9.7)	14.7 (7.9)	15.0 (8.5)
Median	15.3	15.3	15.3
Min ; Max	1 ; 54	1 ; 32	1 ; 54
Baseline platelet counts by category [n (%)]			
Number	69	133	202
<15,000/uL	32 (46.4)	65 (48.9)	97 (48.0)
>=15,000/uL	37 (53.6)	68 (51.1)	105 (52.0)
Randomization strata of severity of thrombocytopenia[b] [n (%)]			
Number	69	133	202
<15,000/uL	37 (53.6)	69 (51.9)	106 (52.5)
>=15,000/uL	32 (46.4)	64 (48.1)	96 (47.5)
Randomization strata of splenectomy [n (%)]			
Number	69	133	202
Yes	19 (27.5)	36 (27.1)	55 (27.2)
No	50 (72.5)	97 (72.9)	147 (72.8)
Splenectomy as recorded in eCRF [n (%)]			
Number	69	133	202
Yes	19 (27.5)	37 (27.8)	56 (27.7)
No	50 (72.5)	96 (72.2)	146 (72.3)
Prior ITP medication category			
Number	69	133	202
Corticosteroids	66 (95.7)	127 (95.5)	193 (95.5)
TPO-RA	51 (73.9)	88 (66.2)	139 (68.8)
IVIg	39 (56.5)	70 (52.6)	109 (54.0)
Anti-D immunoglobulin	3 (4.3)	6 (4.5)	9 (4.5)
Anti-CD20 monoclonal antibody/Rituximab	29 (42.0)	42 (31.6)	71 (35.1)
Fostamatinib	7 (10.1)	17 (12.8)	24 (11.9)
Immunosuppressants and other immunomodulatory agents (incl. Cyclophosphamide)	42 (60.9)	67 (50.4)	109 (54.0)
Dapsone	4 (5.8)	13 (9.8)	17 (8.4)
Danazol	7 (10.1)	12 (9.0)	19 (9.4)
Investigational ITP medications	6 (8.7)	7 (5.3)	13 (6.4)
Other	20 (29.0)	26 (19.5)	46 (22.8)

Prior corticosteroids and/or TPO-RAs [n (%)]			
Number	69	133	202
Corticosteroids	18 (26.1)	42 (31.6)	60 (29.7)
TPO-RAs	3 (4.3)	3 (2.3)	6 (3.0)
Both Corticosteroids and TPO-RAs	48 (69.6)	85 (63.9)	133 (65.8)
Neither Corticosteroids nor TPO-RAs	0	3 (2.3)	3 (1.5)
Number of prior ITP therapy (by type)[c] (incl. splenectomy)			
Number	69	133	202
Mean (SD)	4.4 (1.9)	3.9 (2.2)	4.1 (2.2)
Median	4.0	4.0	4.0
Min ; Max	1 ; 9	1 ; 11	1 ; 11
Number of prior ITP therapy (by type)[c] (incl. splenectomy) [n (%)]			
Number	69	133	202
1 to 2	14 (20.3)	43 (32.3)	57 (28.2)
3 to 4	22 (31.9)	40 (30.1)	62 (30.7)
>=5	33 (47.8)	50 (37.6)	83 (41.1)
Number of prior unique ITP therapy[d] (incl. splenectomy)			
Number	69	133	202
Mean (SD)	5.0 (2.6)	4.4 (2.9)	4.6 (2.8)
Median	5.0	4.0	4.0
Min ; Max	1 ; 12	1 ; 15	1 ; 15
Number of prior unique ITP therapy[d] (incl. splenectomy) [n (%)]			
Number	69	133	202
1 to 2	15 (21.7)	43 (32.3)	58 (28.7)
3 to 4	18 (26.1)	33 (24.8)	51 (25.2)
>=5	36 (52.2)	57 (42.9)	93 (46.0)
Number of prior ITP therapy (by record identifier)[e] (incl. splenectomy)			
Number	69	133	202
Mean (SD)	20.7 (24.9)	16.2 (23.6)	17.7 (24.1)
Median	13.0	10.0	11.0
Min ; Max	1 ; 125	1 ; 177	1 ; 177
Number of prior ITP therapy (by record identifier)[e] (incl. splenectomy) [n (%)]			
Number	69	133	202
1 to 2	7 (10.1)	14 (10.5)	21 (10.4)
3 to 4	6 (8.7)	20 (15.0)	26 (12.9)
>=5	56 (81.2)	99 (74.4)	155 (76.7)

Prior corticosteroids [n (%)]			
Number	69	133	202
Yes	66 (95.7)	127 (95.5)	193 (95.5)
Responded[f]	47 (68.1)	93 (69.9)	140 (69.3)
Not responded	19 (27.5)	33 (24.8)	52 (25.7)
No	3 (4.3)	6 (4.5)	9 (4.5)
Prior TPO-RA [n (%)]			
Number	69	133	202
Yes	51 (73.9)	88 (66.2)	139 (68.8)
Responded[f]	32 (46.4)	55 (41.4)	87 (43.1)
Not responded	19 (27.5)	33 (24.8)	52 (25.7)
No	18 (26.1)	45 (33.8)	63 (31.2)
Prior anti-CD20 monoclonal antibody/Rituximab [n (%)]			
Number	69	133	202
Yes	29 (42.0)	42 (31.6)	71 (35.1)
Responded[f]	12 (17.4)	11 (8.3)	23 (11.4)
Not responded	17 (24.6)	30 (22.6)	47 (23.3)
No	40 (58.0)	91 (68.4)	131 (64.9)
Prior fostamatinib [n (%)]			
Number	69	133	202
Yes	7 (10.1)	17 (12.8)	24 (11.9)
Responded[f]	3 (4.3)	4 (3.0)	7 (3.5)
Not responded	4 (5.8)	12 (9.0)	16 (7.9)
No	62 (89.9)	116 (87.2)	178 (88.1)
Prior IVIg/Anti-D immunoglobulin [n (%)]			
Number	69	133	202
Yes	40 (58.0)	72 (54.1)	112 (55.4)
Responded[f]	31 (44.9)	55 (41.4)	86 (42.6)
Not responded	9 (13.0)	16 (12.0)	25 (12.4)
No	29 (42.0)	61 (45.9)	90 (44.6)

ITP: Immune thrombocytopenia, TPO-RA: Thrombopoietin receptor agonist, IVIg: Intravenous immunoglobulin

Prior (ITP) medications are those the participant used prior to first IMP intake. Prior (ITP) medications can be discontinued before first administration or can be ongoing during treatment period; Prior ITP medications include prior ITP medications for rescue purpose as well

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

b Average of two qualifying screening platelet counts as recorded in IRT

c Type categorized by ITP medications presented in the "Prior ITP medication category" section. Each category will be counted as 1 type except for the "Other" category where each standardized medication name will be counted as 1 type

d Unique ITP therapy is identified using standard medication term AND different corticosteroids counted as one therapy

e Identified by eCRF entry records

f Responded is defined as "resulted in platelet count >=50,000/μL" per eCRF

- **Numbers analysed**

The ITT population and safety population were defined and were used for efficacy and safety analyses, respectively. All 202 randomized participants were included in the ITT population and safety population. A total of 202 participants were included in the PK population.

As of the cutoff date, 180 participants were in the OL population, and 50 participants were in the LTE population. A total of 198 participants were in the rilzabrutinib safety population, ie, have taken rilzabrutinib during the course of the study (cumulatively across periods).

Table 19: Analysis populations - Adult randomized population

n (%)	Placebo (N=69)	Rilzabrutinib 400 mg BID (N=133)	All (N=202)
Randomized population	69 (100)	133 (100)	202 (100)
Efficacy population			
Intent-to Treat (ITT)	69 (100)	133 (100)	202 (100)
Modified Intent-to Treat (mITT)	69 (100)	133 (100)	202 (100)
Pharmacokinetic population	69 (100)	133 (100)	202 (100)
Safety population (double-blind)	69 (100)	133 (100)	202 (100)
Open-Label population	65 (94.2)	115 (86.5)	180 (89.1)
Long-term-extension population	17 (24.6)	33 (24.8)	50 (24.8)
Rilzabrutinib safety population (cumulatively across periods)	65 (94.2)	133 (100)	198 (98.0)
Population without trial impact (disruption) due to COVID-19	69 (100)	123 (92.5)	192 (95.0)

- **Outcomes and estimation**

Table 20: Summary of the primary and key secondary efficacy endpoints in the statistical hierarchical testing procedure - Adult ITT population

		Placebo (N=69)	Rilzabrutinib 400 mg BID (N=133)
Primary endpoint			
Durable platelet response*	n (%)	0 (0.0)	31 (23.3)
	95% CI[1a]	0.00 , 0.00	16.12 , 30.49
	Risk difference (95% CI) vs. placebo[1b]		23.1 (15.95 , 30.31)
	p-value[1c]		<.0001
Durable platelet response (EU and UK)**	n (%)	0 (0.0)	31 (23.3)
	95% CI[1a]	0.00 , 0.00	16.12 , 30.49
	Risk difference (95% CI) vs. placebo[1b]		23.1 (15.95 , 30.31)
	p-value[1c]		<.0001
Key secondary endpoints			
Number of weeks with platelet response*	LS Mean (SE)[2a]	0.72 (0.350)	7.18 (0.747)
	LS Mean difference (SE) vs. placebo[2a]		6.46 (0.782)
	95% CI[2a]		4.923 , 7.990
	p-value[2a]		<.0001
Number of weeks with platelet response[#]	LS Mean (SE)[2a]	0.64 (0.337)	6.95 (0.749)
	LS Mean difference (SE) vs. placebo[2a]		6.31 (0.776)
	95% CI[2a]		4.787 , 7.831
	p-value[2a]		<.0001
Time to first platelet response *	Time (days) to first response (95% CI)		
	1st quartile (25th percentile)	65.0 (36.00 , NA)	10.0 (8.00 , 15.00)
	Median (50th percentile)	NA (NA , NA)	36.0 (22.00 , 44.00)
	Hazard ratio (95% CI) vs. placebo[3a]		3.10 (1.948 , 4.934)
	p-value[3b]		<.0001
% participants requiring rescue therapy	n (%)	40 (58.0)	44 (33.1)
	Time (days) to first rescue (95% CI)		
	1st quartile (25th percentile)	16.0 (8.00 , 36.00)	29.0 (17.00 , 86.00)
	Median (50th percentile)	56.0 (36.00 , NA)	NA (NA , NA)
	Hazard ratio (95% CI) vs. placebo[3a]		0.48 (0.309 , 0.733)
	p-value[3b]		0.0007

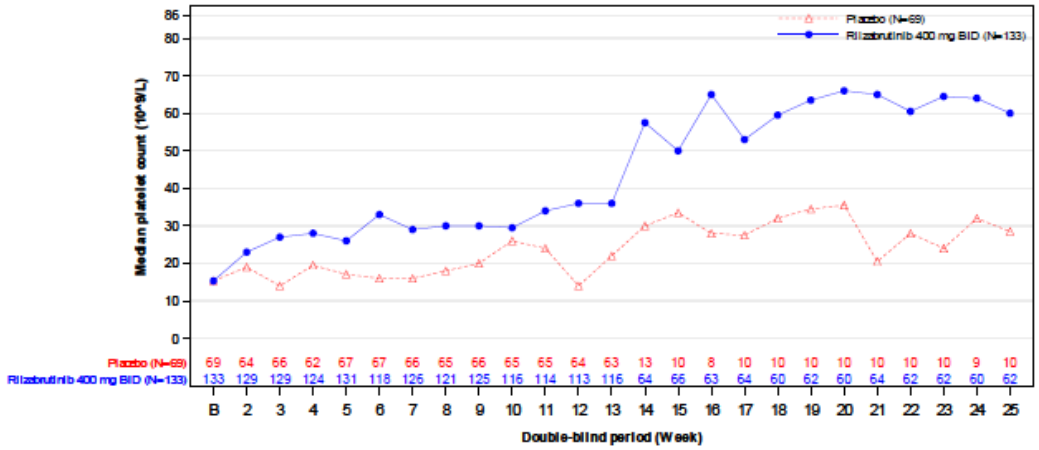
Change from baseline on Item 10 of the ITP-PAQ (ie, physical fatigue) at Week 13	LS Mean (SE)[4a]	-0.13 (2.861)	7.95 (2.132)
	LS Mean difference (SE) vs. placebo[4a]		8.08 (3.194)
	95% CI[4a]		1.818 , 14.337
	p-value[4a]		0.0114
Change from baseline on IBLS at Week 25 (EU and UK)	LS Mean (SE)[4a]	0.047 (0.0226)	-0.040 (0.0169)
	LS Mean difference (SE) vs. placebo[4a]		-0.087 (0.0251)
	95% CI[4a]		-0.1358 , -0.0373
	p-value[4a]		0.0006

* Durable platelet response is defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for >=two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/μL during the last 6 weeks of the 24-week blinded treatment period.
** Durable platelet response (EU and UK) is defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for at least 8 out of the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy. Missing data due to Covid-19 was imputed using the participant's median value of available weekly platelet counts during the last 12 weeks of double-blind period.
* Platelet count >=50,000/μL or between 30,000μL and <50,000/μL and at least doubled from baseline.
# Platelet count >=30,000/μL and at least doubled from baseline.
1a Asymptotic confidence interval.
1b Mantel-Haenszel estimate based on Mantel-Haenszel stratum weights and the Sato variance estimator.
1c Cochran-Mantel-Haenszel test adjusted by stratification factors.
2a 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.
3a Cox regression model with treatment group and stratification factors as covariates.
3b Log-rank test adjusted by stratification factors.
4a Analysis of covariance (ANCOVA) model with the treatment group, stratification factors and geographic region as fixed effects and baseline score as a covariate. Missing score at Week 13 for ITP PAQ (Week 25 for IBLS) will be imputed via worst observation carried forward (WOCF) for the participants who were rescued after 8-week of double-blind treatment or discontinued before Week 13 (Week 25 for IBLS) due to lack of efficacy or related adverse events, OR via multiple imputation otherwise. This will result in multiple sets of complete data. Each complete dataset will be analyzed by fitting an ANCOVA model. Statistical inference obtained from all imputed data will be combined using Rubin's rule. 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)

Table 21: Initial platelet response (≥50,000/μL OR ≥30,000/μL and doubled from baseline in absence of rescue therapy) after 12 weeks of double-blind treatment – Adults ITT population

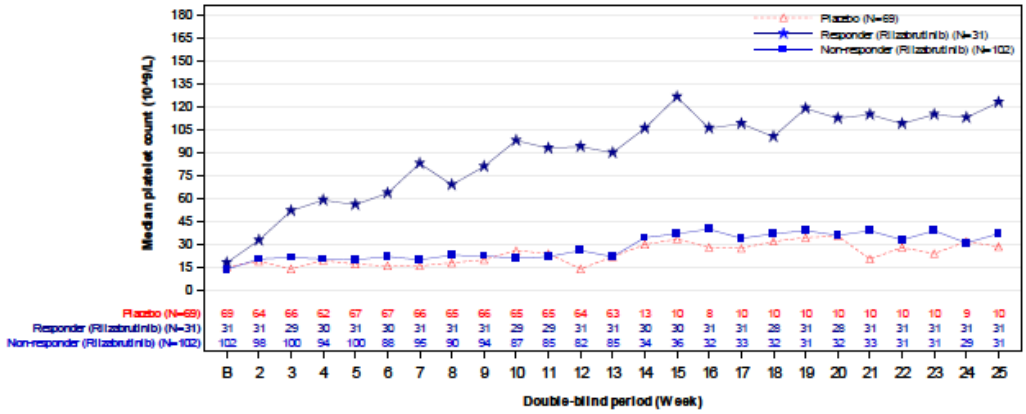
	Placebo (N=69)	**Rilzabrutinib 400 mg BID (N=133)**
Initial platelet response		
n (%)	22 (31.9)	85 (63.9)
95% CI[a]	20.89 , 42.88	55.75 , 72.07
Cochran-Mantel-Haenszel test		
Risk difference (95% CI) vs. placebo[b]		31.7 (18.70 , 44.70)
p-value[c]		<.0001

BID: twice daily, CI: confidence interval, ITT: intention-to-treat
Initial platelet response: a) platelet count of ≥50,000/μL OR a platelet count between ≥30,000/μL and <50,000/μL and at least doubled from baseline at any time during the first 12 weeks (ie, at Week 13 or earlier) and b) absence of rescue medication in the 4 weeks prior to the elevated platelet count that meets platelet response criteria
[a] Asymptotic confidence interval
[b] Mantel-Haenszel estimate based on Mantel-Haenszel stratum weights and the Sato variance estimator
[c] Cochran-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)



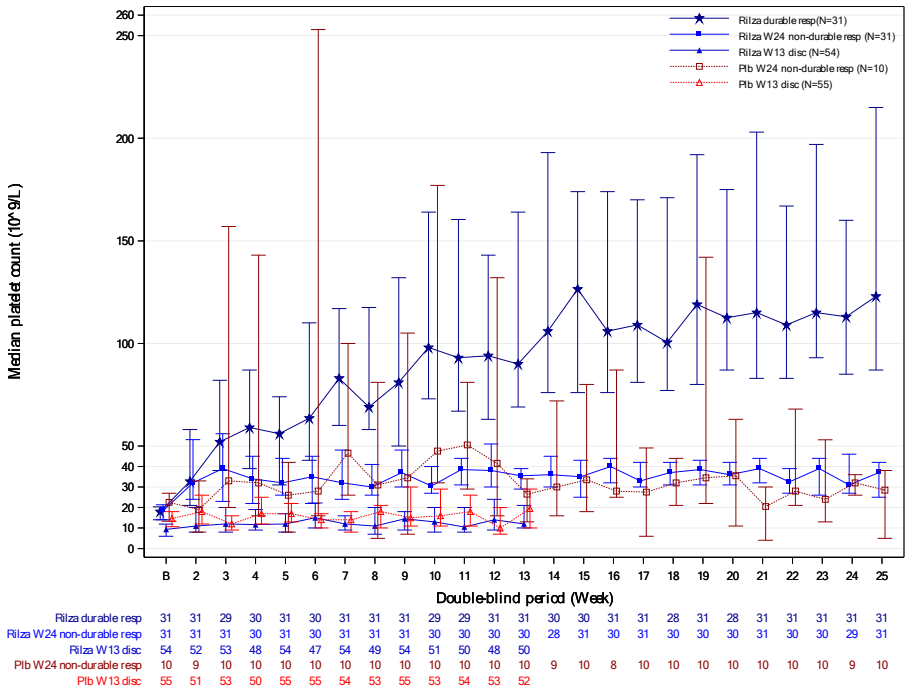
B: Baseline
Baseline platelet count is defined as average of 1st , 2nd qualifying screening platelet counts, and Week 1 (Study day 1) platelet count
Based on all available platelet counts

Figure 18: Plot of median platelet count by visit during the 24-week double-blind treatment period - Adult ITT population



B: Baseline
Baseline platelet count is defined as average of 1st, 2nd qualifying screening platelet counts, and Week 1 (Study day 1) platelet count
Durable platelet response is defined as the proportion of participants able to achieve platelet counts at or above 50,000/µL for >=two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/µL during the last 6 weeks of the 24-week blinded treatment period
Based on all available platelet counts

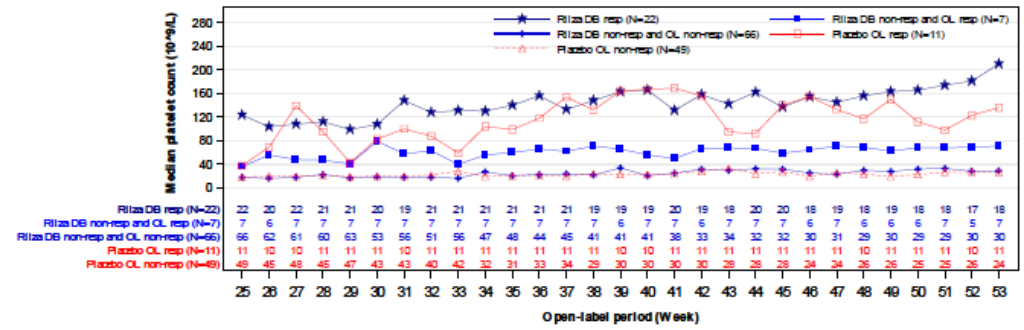
Figure 19: Plot of median platelet count by visit and by durable platelet response status during the 24-week double-blind treatment period - Adult ITT population



B: Baseline, BID: twice daily, CI: confidence interval, ITT: intention-to-treat
Durable platelet response is defined as 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
Initial platelet response: a) platelet count of ⩾50,000/µL OR a platelet count between ⩾30,000/µL and <50,000/µL and at least doubled from baseline at any time during the first 12 weeks (ie, at Week 13 or earlier) and b) absence of rescue medication in the 4 weeks prior to the elevated platelet count that meets platelet response criteria
Based on all available platelet counts regardless of rescue therapy. Median and confidence interval are not presented for visits with ⩽ 5 participants in a group.
Treatment groups labels: 1. Rilza durable resp = durable platelet responder in the rilzabrutinib 400 mg BID group (all initial platelet responders). 2. Rilza W24 non-durable resp = participants continued until week 24 without durable response in the rilzabrutinib 400 mg BID group (all initial platelet responders). 3. Rilza W13 disc = participants discontinued at week 13 due to "lack of response" in the rilzabrutinib 400 mg BID group. 4. Plb W24 non-durable resp = participants continued until week 24 without durable response in the placebo group (all initial platelet responders). 5. Plb W13 disc = participants discontinued at week 13 due to "lack of response" in the placebo group.

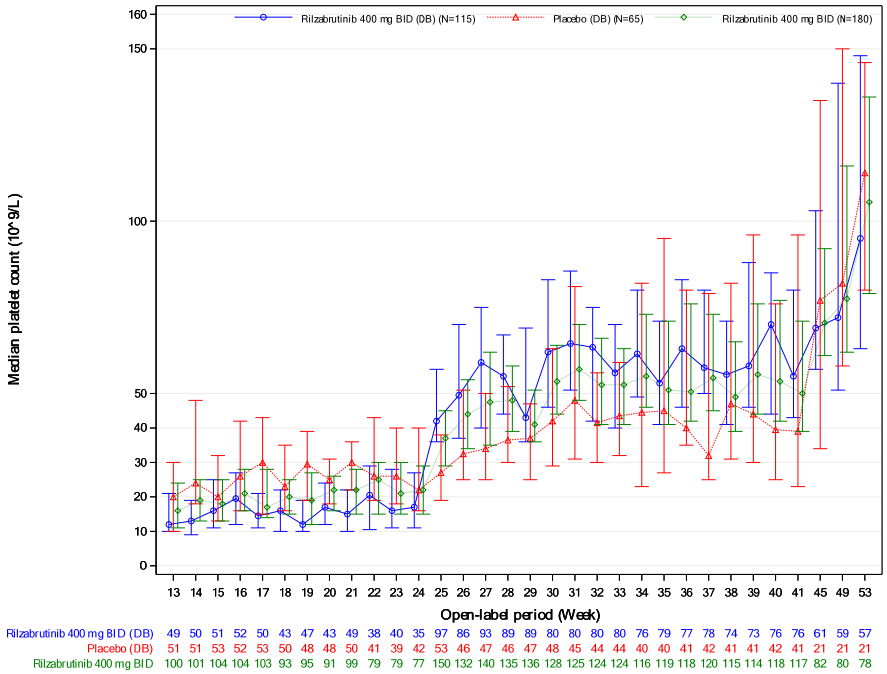
Figure 20: Plot of median platelet counts (95% CI) by groups of interest during the double-blind treatment period - Adults ITT population

Open-label period



DB: Double-blind, OL: Open-label, Resp: Responder
Presented are participant's platelet counts during the open-label period. Rilza/Placebo refers to participants were randomized as Rilzabrutinib 400 mg BID/Placebo group during the double-blind treatment period, note all participants received Rilzabrutinib 400 mg BID during open-label treatment period
DB responder refers to durable responder in double-blind period. Durable platelet response is defined as the proportion of participants able to achieve platelet counts at or above 50,000/μL for >=two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/μL during the last 6 weeks of the 24-week blinded treatment period
OL responder refers to durable responder in open-label period. Durable platelet response is defined as platelet counts at or above 50,000/μL for >= two-thirds of at least 10 non missing weekly scheduled platelet measurements during the last 16 weeks of the 28 of the open label period in the absence of rescue therapy, provided that at least 3 non-missing weekly scheduled platelet measurements are at or above 50,000/μL during the last 8 weeks of the 28-week open label period

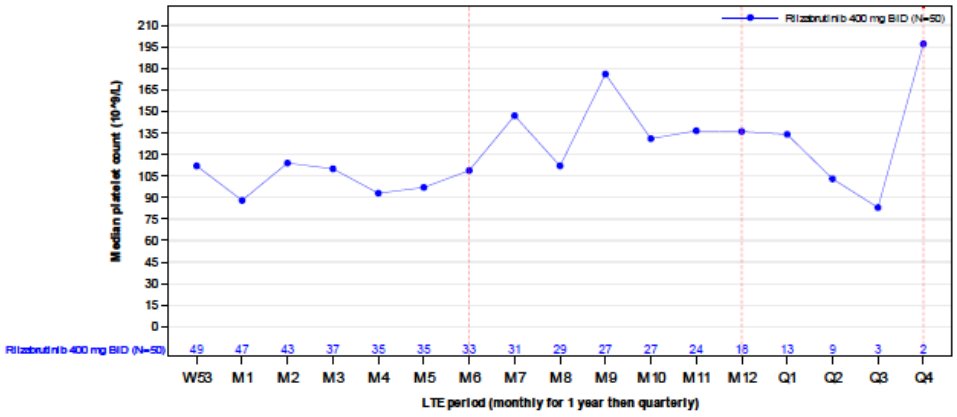
Figure 21: Plot of median platelet count by visit and by durable platelet response status during the 28-week open-label treatment period - Adult OL population who completed or discontinued OL



Data cutoff: 15 Oct 2024
OL: Open-label; LTE: Long-term extension
Median is based on all available platelet counts regardless of the use of rescue therapy
For continuality purpose, LTE data are presented starting from week 41 for participants who entered OL at week 13.

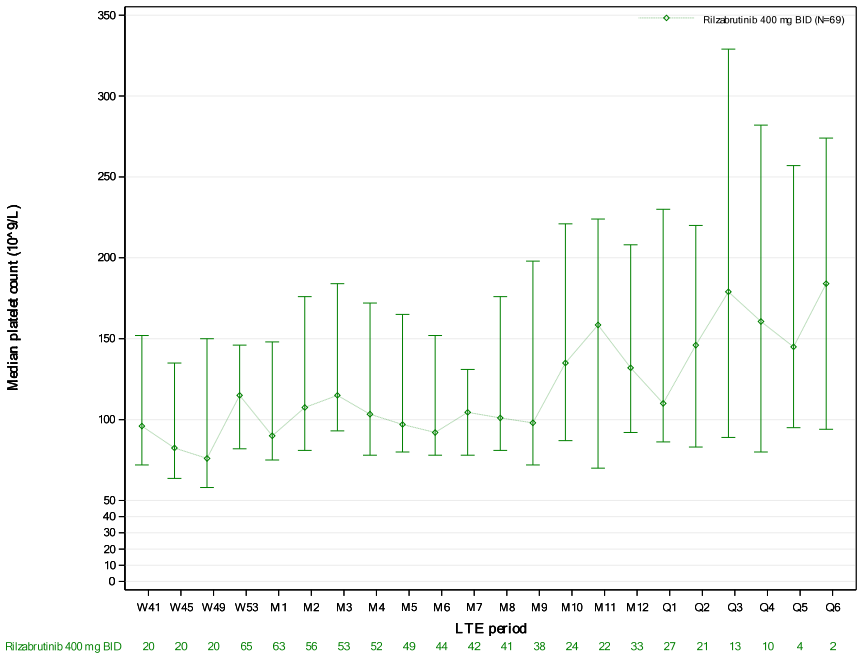
Figure 22: Median platelet counts (95% CI) during the open-label period by actual visit – Adult OL population

Long-term extension



LTE: Long-term extension, W: week, M: month, Q: quarter
Based on all available platelet counts

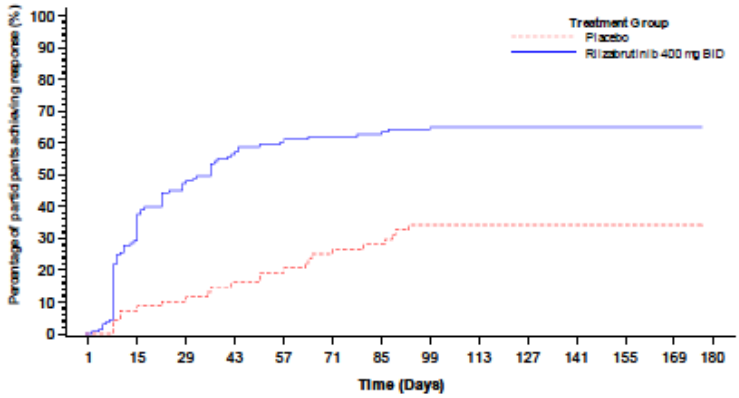
Figure 23: Plot of median platelet count by visit during the long-term extension treatment period - Adult LTE population



Data cutoff: 15 Oct 2024
W: week, M: month, Q: quarter, LTE: Long-term extension
Median is based on all available platelet counts regardless of the use of rescue therapy

Figure 24: Median platelet counts (95% CI) during the LTE period by actual visit – Adult LTE population

Further secondary endpoints

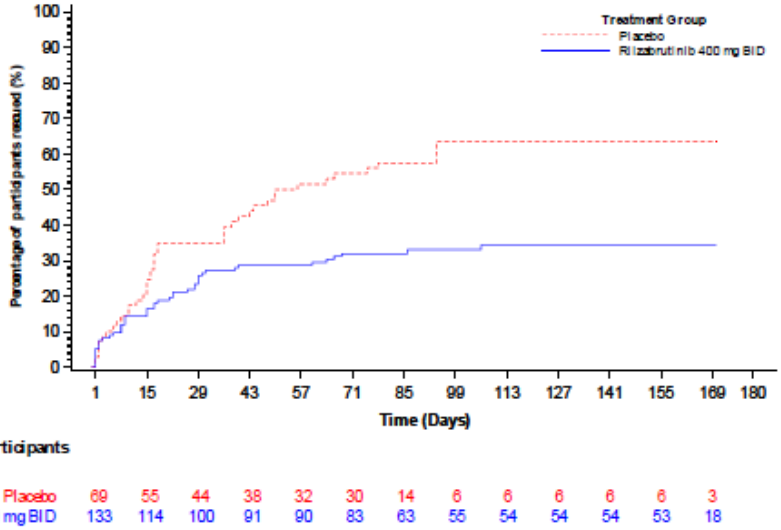


Participants who have not achieved the platelet response will be censored either at 1 week after the protocol scheduled Week 25 (Day 169) visit for those who prematurely discontinued the 24-week treatment period due to related AE or lack of response, or, at the last assessment during the double-blind on-treatment period

Primary estimand = Hypothetical + composite estimand

(>=50,000/µL OR >=30,000/µL and at least doubled from baseline) is the same as (>=50,000/µL OR >=30,000/µL and <50,000/µL and at least doubled from baseline)

Figure 25: Kaplan-Meier plot of time to 1st platelet count ≥50,000/uL OR ≥30,000/uL and doubled from baseline during the 24-week double-blind period - Primary estimand - Adult ITT population



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

Primary estimand = While on-treatment estimand

Figure 26: Kaplan-Meier plot for time to first use of rescue therapy during the 24-week double-blind treatment period - Primary estimand - Adult ITT population

- **Ancillary analyses**

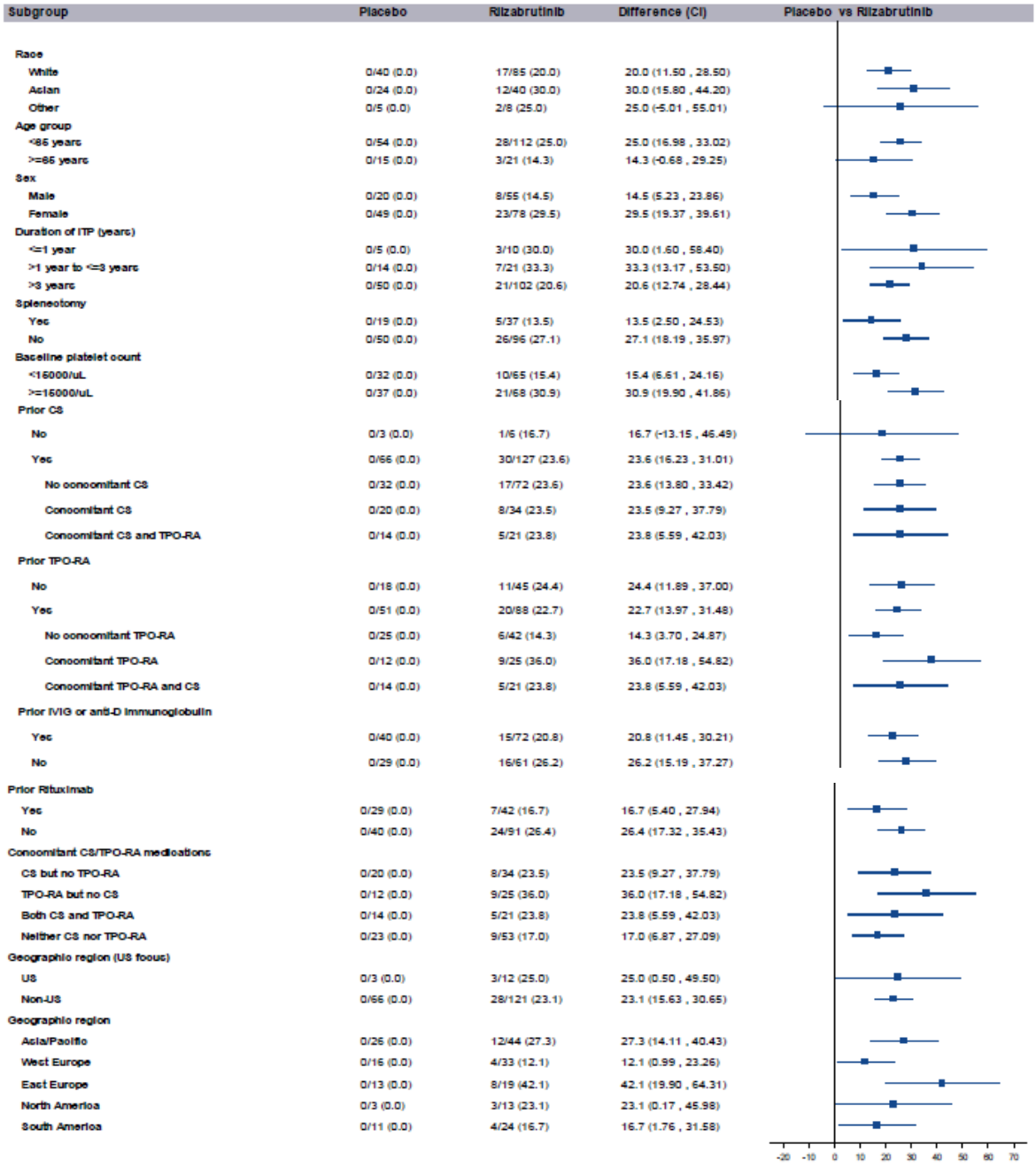


Figure 27: Forest plot of subgroup analysis of durable platelet response during the 24-week double-blind treatment period - Adult ITT population

Table 22: Subgroup analysis (prior and/or concomitant ITP medications excluding rescue therapy) on primary endpoint durable platelet response - Adult ITT population

	Placebo (N=69)			Rilzabrutinib 400 mg BID (N=133)			vs. Placebo	
Subset, n (%)	**N**	**n (%)**	**95% CI[a]**	**N**	**n (%)**	**95% CI[a]**	**Difference[b]**	**95% CI[b]**
Concomitant CS/TPO-RA medications								
CS but no TPO-RA	20	0 (0.0)	0.00 , 0.00	34	8 (23.5)	9.27 , 37.79	23.5	9.27 , 37.79
TPO-RA but no CS	12	0 (0.0)	0.00 , 0.00	25	9 (36.0)	17.18 , 54.82	36.0	17.18 , 54.82
Both CS and TPO-RA	14	0 (0.0)	0.00 , 0.00	21	5 (23.8)	5.59 , 42.03	23.8	5.59 , 42.03
Neither CS nor TPO-RA**	23	0 (0.0)	0.00 , 0.00	53	9 (17.0)	6.87 , 27.09	17.0	6.87 , 27.09

Table 23: Concomitant CS and/or TPO-RA (excluding rescue therapy) during the 24-week double-blind treatment period - Adult ITT population

CS or TPO-RA, n (%)	Placebo (N=69)	Rilzabrutinib 400 mg BID (N=133)
Participants on concomitant CS or TPO-RA	46 (66.7)	80 (60.2)
Maintained/stopped/initiated concomitant CS or TPO-RA	37 (53.6)	62 (46.6)
Maintained	31 (44.9)	53 (39.8)
Maintained CS and maintained TPO-RA	8 (11.6)	13 (9.8)
Maintained CS only	13 (18.8)	23 (17.3)
Maintained TPO-RA only	10 (14.5)	17 (12.8)
Stopped	5 (7.2)	9 (6.8)
Stopped CS and maintained TPO-RA	1 (1.4)	2 (1.5)
Stopped TPO-RA and maintained CS	1 (1.4)	1 (0.8)
Stopped CS only	1 (1.4)	3 (2.3)
Stopped TPO-RA only	2 (2.9)	3 (2.3)
Initiated		
Initiated[a] CS and decrease in TPO-RA	1 (1.4)	0
Changed dose (increase, decrease) of concomitant CS or TPO-RA	4 (5.8)	14 (10.5)
Increase	1 (1.4)	0
Increase in CS	1 (1.4)	0
Decrease	3 (4.3)	14 (10.5)
Decrease in CS	2 (2.9)	7 (5.3)
Decrease in CS and maintained TPO-RA	1 (1.4)	1 (0.8)
Decrease in CS and stopped TPO-RA	0	1 (0.8)
Decrease in TPO-RA	0	6 (4.5)
Altered concomitant CS or TPO-RA	5 (7.2)	4 (3.0)
Altered[b] CS	3 (4.3)	2 (1.5)
Altered[b] CS and maintained TPO-RA	2 (2.9)	1 (0.8)
Altered[b] CS and decrease in TPO-RA	0	1 (0.8)

BID: twice daily, ITT: intention-to-treat, CS: corticosteroid; TPO-RA: thrombopoietin receptor agonist.
Percentage is based on adult ITT population.
[a] Participants who were not on CS (TPO-RA) and newly initiated a CS (TPO-RA).
[b] Participants who were on a CS (TPO-RA) which was replaced with a higher dose CS (TPO-RA) as a rescue therapy or a different type of CS (TPO-RA).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24: Summary of Efficacy for trial PRN1008-018 (EFC17093)

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)
Study identifier	PRN1008-018 (EFC17093) EudraCT: 2020-002063-60
Design	Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Double-blind 24 weeks Not applicable Open-label 28 weeks, followed by long-term extension
Hypothesis	Superiority		
Treatments groups	Rilzabrutinib 400 mg BID		24 weeks n=133
	Placebo		24 weeks n=69
Endpoints and definitions	Primary endpoint	Durable platelet response	% participants achieving platelet counts ≥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 endpoint	# weeks with platelet response (Threshold 1)	Number of weeks with platelet counts ≥50,000/μL OR between ≥30,000/μL and ≤50,000/μL and doubled from baseline during the 24-week blinded treatment period in the absence of rescue therapy
	Secondary endpoint	# weeks with platelet response (Threshold 2)	Number of weeks with platelet counts ≥30,000/μL and doubled from baseline during the 24-week blinded treatment period in the absence of rescue therapy
	Secondary endpoint	Time to platelet response (Threshold 1)	Time to first platelet count of ≥50,000/μL OR between ≥30,000/μL and ≤50,000/μL and doubled from baseline during the 24-week blinded treatment period in the absence of rescue therapy
	Secondary endpoint	% participants requiring rescue therapy	% participants requiring rescue therapy during the 24-week blinded treatment period
	Secondary endpoint	Change from baseline in physical fatigue score at Week 13	Change from baseline on Item 10 of the ITP purpura patient assessment questionnaire (ITP-PAQ) (ie, physical fatigue) in adult participants (≥18 years) at Week 13
	Secondary endpoint	Change from baseline in IBLS score at Week 25	Change from baseline on ITP purpura bleeding scale (IBLS) score at Week 25
Database lock	16 Apr 2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat: randomized at the end of 24-week double-blind treatment period		

	Treatment group	Placebo	Rilzabrutinib 400 mg BID
	Number of subjects	69	133

Descriptive statistics and estimate variability	Durable platelet response n (%)	0 (0%)	31 (23.3%)
	95% confidence interval	0.00, 0.00	16.12, 30.49
	#weeks with platelet response (Threshold 1) (Estimated mean)	0.72	7.18
	Standard error	0.350	0.747
	#weeks with platelet response (Threshold 2) (Estimated mean)	0.64	6.95
	Standard error	0.337	0.749
	Time to platelet response (Threshold 1) (Median in days)	Not reached	36
	95% confidence interval	Not reached	22, 44
	% participants requiring rescue therapy (Median in days of time to rescue therapy)	56	Not reached
	95% confidence interval	36, Not calculated	Not reached
	Change from baseline in physical fatigue score at Week 13 (Estimated mean)	-0.13	7.95
	Standard error	2.861	2,132
	Change from baseline in IBLS score at Week 25	0.047	-0.040
	Standard error	0.0226	0.0169
Effect estimate per comparison	Primary endpoint: Durable platelet response	Comparison groups	Rilzabrutinib 400 mg BID versus Placebo
		Risk difference between groups	23.1%
		Confidence interval	15.95, 30.31
		Cochran-Mantel-Haenszel test p-value	<0.0001
	Secondary endpoint: #weeks with platelet response (Threshold 1)	Comparison groups	Rilzabrutinib 400 mg BID versus Placebo
		Mean difference between groups	6.46
		95% confidence interval	4.923, 7.990
		Mixed-effect model with repeated measures (MMRM) via generalized estimating equations (GEE) p-value	<0.0001

	Secondary endpoint: #weeks with platelet response (Threshold 2)	Comparison groups	Rilzabrutinib 400 mg BID versus Placebo
		Mean difference between groups	6.31
		95% confidence interval	4.787, 7.831
		MMRM via GEE p-value	<0.0001
	Secondary endpoint: Time to platelet response (Threshold 1)	Comparison groups	Rilzabrutinib 400 mg BID versus Placebo
		Hazard ratio	3.10
		95% confidence interval	1.948, 4.934
		Log-rank test p-value	<0.0001
	Secondary endpoint: % participants requiring rescue therapy	Comparison groups	Rilzabrutinib 400 mg BID versus Placebo
		Hazard ratio	0.48
		95% confidence interval	0.309, 0.733
		Log-rank test p-value	0.0007
	Secondary endpoint: Change from baseline in physical fatigue score at Week 13	Comparison groups	Rilzabrutinib 400 mg BID versus Placebo
		Mean difference between groups	8.08
		95% confidence interval	1.818, 14.337
		Analysis of covariance (ANCOVA) P-value	0.0114
	Secondary endpoint: Change from baseline in IBLS score at Week 25	Comparison groups	Rilzabrutinib 400 mg BID versus Placebo
		Mean difference between groups	-0.087
		95% confidence interval	-0.1358, -0.0373
		ANCOVA p-value	0.0006

2.6.5.3. Clinical studies in special populations

Table 25: Clinical studies in special populations

	Controlled Trials [a]		**Non-controlled trials [b] (N=86)**
	Placebo (N=69)	**Rilzabrutinib (N=133)**	
Renal impairment* patients (Subjects number /total number)	0/69	0/133	0/86
Hepatic impairment** patients (Subjects number /total number)	0/69	2/133	2/86
Paediatric*** patients <18 years (Subjects number /total number)	0	0	0
Age 65-74 (Subjects number /total number)	12/69	15/133	13/86

	Controlled Trials [a]		Non-controlled trials [b] (N=86)
	Placebo (N=69)	Rilzabrutinib (N=133)	
Age 75-84 (Subjects number /total number)	3/69	6/133	2/86
Age 85+ (Subjects number /total number)	0/69	0/133	0/86
Other (Subjects number /total number)	54/69	112/133	71/86
Paediatric*** patients <18 years (Subjects number /total number)	Blinded: 30		

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition) at baseline
** Hepatic impairment is defined as having Child-Pugh score B or C at baseline (ascites and encephalopathy by medical history). Two participants in rilzabrutinib group in PRN1008-018 were classified as Child-Pugh score B due to missing hepatomegaly severity and hepatic cirrhosis severity, respectively, in medical history. One participant in PRN1008-010 part A was classified as Child-Pugh score B due to missing Albumin assessment at baseline
*** Paediatric participants were not included in the total of 202 participants in the controlled trial in the header. Thirty paediatric participants remained blinded at the time of registration application submission
[a] Controlled trials include Phase 3 PRN1008-018 during the double-blind treatment period
[b] Non-controlled trials include Phase 1/2 PRN1008-010 (part A, part B) during the entire treatment period

2.6.5.4. Supportive study(ies)

See study PRN1008-010 above.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The claimed indication is the treatment of persistent or chronic immune thrombocytopenia (ITP) in adult patients who are refractory to a previous treatment. While adolescent from 10 years old were enrolled in the Phase 3 study, only adult population is targeted in this MAA.

For the assessment of efficacy, the applicant conducted one open-label, adaptive phase 1/2 trial (PRN1008-010, referred to as study 010) and a single confirmatory phase 3 trial (PRN1008-018, referred to as study 018). It is critically noted that only a **single pivotal trial** was conducted to estimate the efficacy of rilzabrutinib in ITP patients. Even though this is in principle possible and can be understood considering the epidemiology of the condition, as per the respective guideline (CPMP/EWP/2330/99) such a single pivotal trial has to provide particularly compelling results.

Study 010 was an adaptive, dose-finding study conducted in patients with refractory or relapsed immune thrombocytopenia (ITP). It tested 4 different starting doses of rilzabrutinib: 200mg QD, 400mg QD, 300mg BID and 400mg BID. The study allowed intra-patient dose escalation every 28 days if no platelet response was observed up to a maximum of 400 mg BID. If a response was achieved, the dose was maintained. Most patients who started on doses lower than 400 mg BID escalated to higher doses (11 out of 15), and the majority of participants overall (45 out of 60) began and remained on the 400 mg BID dose. Due to the small number of patients starting on lower doses (only 15 in total, n=9 for 200mg QD, n=1 for 400mg QD and n=5 for 300mg BID), and the lack of a dose-reduction option, the data collected were limited in helping determine the optimal dosing regimen.A total of 78 patients have been exposed to the intended dose of 400mg BID (n=45 as starting dose in part A, n=8 escalating doses from lower starting doses in part A and n=26 in part B). Ultimately, the 400 mg BID dose was selected for the confirmatory trial. This decision was supported by efficacy data from Study 010 parts A and B, where over 30% of patients on 400 mg BID achieved a platelet response, compared to less than 30% in all lower-dose groups in part A. This is acceptable.

In **Study 018**, 133 patients were treated with the intended dose of 400 mg rilzabrutinib twice daily. The study included parallel treatment arms for rilzabrutinib and placebo, with a 2:1 randomization, and a double-blind treatment period lasting until the primary endpoint analysis at week 24. Following this,

all patients transitioned into a 28-week open-label phase where they received rilzabrutinib, which was considered acceptable. The study also included a long-term extension to further evaluate efficacy in responders from the open-label phase, which is acknowledged.

A key feature of the study was an **early responder analysis** conducted at week 12 during the blinded phase. Patients were considered responders if they achieved a *platelet count of ≥50,000/μL OR a platelet count of between ≥30,000/μL and <50,000/μL and at least doubled from baseline at any time during the first 12 weeks AND absence of rescue medication in the 4 weeks prior to the elevated platelet count*. Only those who met these criteria were allowed to continue in the blinded treatment period. However, the primary endpoint was defined based on platelet counts between weeks 13 and 24, without acknowledging that only early responders were included in this analysis. This pre-selection likely excluded a significant number of placebo-treated patients, who were less likely to meet the early response criteria, thereby introducing bias. It must have been expected that substantially more subjects will fail to meet the responder requirement after 12 weeks on treatment with placebo, compared to the active treatment with rilzabrutinib. The study design therefore compromises the validity of conclusions drawn from the blinded phase beyond week 12, as the endpoints do not account for the early responder filtering. Indeed, the measured primary endpoint seems to reflect a combination of early and durable response, rather than just durability. Despite this limitation, the overall study duration and assessments were considered sufficient to identify durable responders and evaluate the maintenance of treatment effect, with procedures aligned across both treatment groups. This is further discussed below.

Population

Trial 018 included both paediatric and adult participants, but only data from adult patients were submitted, with paediatric data planned for a separate submission. The submitted data cover adult male and female patients diagnosed with immune thrombocytopenia (ITP), either in the persistent phase (3–12 months since diagnosis) or chronic phase (more than 12 months since diagnosis). This patient population aligns with the proposed indication, although the number of patients with a diagnosis under 12 months appears to be limited. The inclusion and exclusion criteria used in the trial are considered appropriate for evaluating efficacy. The randomization scheme, which assigned patients to rilzabrutinib or placebo in a 2:1 ratio, and the stratification factors—splenectomy status and severity of thrombocytopenia—are deemed acceptable. However, it is noted that stratification based on concomitant therapy was not implemented, despite being recommended in regulatory guidelines (EMA/CHMP/153191/2013). Additionally, patients were not stratified on persistent or chronic status, which could be relevant. Despite these concerns, the randomization appears to have resulted in well-balanced treatment groups. The placebo control was designed to be visually identical to the active treatment, which supports the integrity of the blinded study design.

Rescue and concomitant medication

In Trial 018, **rescue medication** was limited to intravenous immunoglobulin (IVIg), high-dose corticosteroids (CSs), platelet infusion, or anti-D immunoglobulin infusion, with no other rescue treatments permitted. This selection is considered acceptable. The protocol specified that rescue medication could be administered if platelet counts dropped below 20,000/μL, or if bleeding or wet purpura occurred. The applicant justified this threshold by referencing international ITP guidelines, which recommend maintaining platelet levels above 20,000–30,000/μL in symptomatic patients (Provan et al., 2019). However, the clinical assessment of bleeding was left to the investigator's judgment, which introduces variability and limits the clarity of how bleeding was defined and managed.

Oral corticosteroids and thrombopoietin receptor agonists (TPO-RAs), both approved for ITP treatment, were allowed as **concomitant medications** if their doses were stable for at least 14 days before

study inclusion. This allowance is considered acceptable, especially for patients in the placebo group who might otherwise be inadequately treated. It also aligns with EMA guidelines. However, the use of concomitant treatment should have been a stratification factor which was not the case. Although dose adjustments were permitted during the study, these were restricted to safety concerns or the long-term extension phase. It is acknowledged that CSs and TPO-RAs typically increase platelet counts within the first two weeks of treatment, but their continued effect beyond this period could influence trial endpoints. As a result, it is difficult to attribute platelet responses solely to rilzabrutinib in patients who also received these concomitant treatments. This concern is underscored by the fact that a majority of participants in both the placebo (46 of 69) and rilzabrutinib (80 of 133) groups received permitted concomitant medications. The extent to which these treatments affected efficacy and safety outcomes remains unclear. Lastly, the prohibition of proton pump inhibitors and CYP3A inhibitors in the study is considered appropriate.

Primary objectives and endpoint definition

Objectives and endpoints are supported for the evaluation of efficacy upon treatment with rilzabrutinib. However, as discussed above and below, it is noted that the primary endpoint does not appear to be eligible with the applied study design. There are two definitions of the primary endpoint depending on the regulatory region. Indeed, in the Scientific Advice EMA/SA/0000090350, the CHMP had strongly discouraged the applicant to use the alternative definitions applied in other regions. However, the analysis for both endpoint definition was presented and resulted in the same estimate (and variability).

For EMA, the primary endpoint is defined as a "durable platelet response," meaning the proportion of participants achieving platelet counts of at least 50,000/μL for at least 8 out of the final 12 weeks of the blinded treatment period, without rescue therapy. However, only patients who met the week 12 response criteria were allowed to continue into this final 12-week period. The week 12 response was defined as either a platelet count ≥50,000/μL or a count between ≥30,000/μL and <50,000/μL that had at least doubled from baseline, along with no rescue medication in the preceding four weeks (see also above). As a result, the actual primary endpoint effectively combines two components: the initial week 12 response and the subsequent durable response. The applicant's presentation of the endpoint as solely focused on the latter is considered misleading. This dual-component structure complicates interpretation, as it blends short-term and long-term efficacy measures.

Upon request, the applicant provided analyses of key secondary endpoints excluding data after week 12. These results were consistent with those at week 25, suggesting some reliability. However, since data from patients who did not continue past week 12 were imputed as non-responders or set to missing, it remains difficult to separate short-term effects from longer-term outcomes. While early treatment effects in all key secondary endpoints lend credibility to longer-term results, it cannot be ruled out that the observed effects at week 25 are at least partially driven by early responses. This uncertainty limits the ability to isolate and interpret the long-term effect of treatment on key secondary endpoints.

Primary endpoint analyses

The trial aimed at comparing the effect of rilzabrutinib vs. placebo in the management of ITP. The main outcome for comparison was durable platelet response. The study protocol and SAP were overall well presented and statistical methods were in general described with sufficient clarity. Primary and key secondary analyses were performed in the ITT population, which included all randomised patients. Acknowledging the difficulties of interpretation due to the two-part study design as discussed above and below, the statistical methods themselves and their adjustment for randomisation stratification factors are generally deemed appropriate.

The early responder analysis is particularly critical, since it introduces a bias in the population in which the primary endpoint is actually measured at 24 weeks. The defined response during the first 12 weeks, which refers to a single platelet measure above the define threshold, could be attributed not only to the drug itself, but also to random fluctuations in the platelet counts (for both arms, but especially for "placebo responders"). Participants who were considered "non-responders" after 12 weeks of treatment did not have the chance to have their endpoint measured at week 24, and thus possible "late responders" could not be evaluated, but were still included in the numerator when 'proportions of participants'-endpoints were calculated. Furthermore, the number of patients achieving week 12 response according to the protocol criteria was not summarised by the applicant. It may be implied by the number of patients not entering the open-label period after week 12 from the patient disposition table, but it is currently unclear whether these numbers actually match the frequency of week 12 responders. Overall, this design feature has made it more difficult to interpret the results (see further comments below).

As requested, the applicant provided a summary table of patients achieving week 12 response according to pre-defined protocol criteria (a: platelet count of ≥50,000/μL OR a platelet count of between ≥30,000/μL and <50,000/μL and at least doubled from baseline at any time during the first 12 weeks and b: absence of rescue medication in the 4 weeks prior to the elevated platelet count that met platelet response criteria). The risk difference (95% CI) was 31.7% (18.70% to 44.70%) in favour of rilzabrutinib. The analysis was repeated when response was defined regardless of rescue therapy. The risk difference was 15.5% (95% CI 2.34% to 28.74%), also in favour of rilzabrutinib. It is acknowledged that the smaller effect can be expected due to the higher percentage of placebo patients receiving rescue therapy. It is noted that the risk difference observed in the pre-defined protocol response criteria at week 12 is rather large in comparison with the risk difference in durable platelet response (23.1%). It is therefore reasonable to assume that the effect observed on short-term response is the main driver of the treatment effect observed on durable platelet response.

Due to week 12 non-responders either joining the OL part or discontinuing from trial after week 12, there is no double-blind nor comparator data available for non-responders past week 12. It is therefore not possible to derive the proportion of patients achieving durable response regardless of their week 12 response (which could be considered the second component of the primary endpoint). In other words, the estimand targeting the effect on durable response regardless of week 12 efficacy is not supported by study data. It is further noted that each component of the primary endpoint (week 12 response and durable response) are not aligned with regard to the platelet count thresholds used in their definition. This situation further complicates the interpretation of efficacy data. A composite strategy (imputation as non-response) has been followed to handle the following intercurrent events (ICE): a) initiation of rescue medication after 8 weeks of double-blind treatment and before Week 25 (or last IMP intake, whichever earlier), b) discontinuation of study intervention before Week 25 due to lack of response or related AE. It is acknowledged that both ICEs are likely indicative of non-response, and as such, a composite strategy appears reasonable for the primary estimand.

For discontinuation of study intervention before Week 25 due to other reasons, all available on-treatment measurements are included in the analysis, and post-treatment values imputed as non-response. The applicant refers to this approach as a composite strategy, whereas this might have been better described as a while on-treatment strategy (EMA/CHMP/ICH/436221/2017), considering that patients can still be considered durable responders based on available on-treatment measurements (as long as the durable response criteria are met).

It would have been of regulatory interest to additionally investigate an alternative estimand targeting the effect of treatment on durable response regardless of treatment discontinuation and regardless of rescue medication. Due to week 12 non-responders discontinuing from the double-blind treatment period after week 12, this alternative estimand is not adequately supported by study data either.

Nevertheless, the applicant was requested to provide an additional analysis when applying a treatment policy strategy for all intercurrent events in the double-blind period. Results were generally consistent.

The strategy to handle **missing data** in the primary endpoint was generally conservative: if a platelet count was missing for a week, the participant was set as non-responder for that week. This also seemed to be the case e.g. in case of technical issues with the platelet measurement, although no such statement could be explicitly found in the protocol or SAP. While data missing due to Covid-19 were imputed using the median value of available weekly platelet counts, other missing measurements were imputed as non-response. Although not objected to in principle, it is unclear whether the primary approach to missing data is necessarily conservative, depending on missing data patterns and associated reasons.

However, the applicant has presented several (subgroup and) sensitivity analyses for the primary endpoint, targeting both the population and the assumptions for missing data. Most strategies are well understood and endorsed; some aspects are not fully clear (e.g. scenarios for missing data in sensitivity analysis 2), but given the consistency of the results, they are not considered critical. The study included (for Europe) five key secondary endpoints, and type 1 error control was achieved via hierarchical strategy. The methods were overall understandable, but a few questions were raised (see below). Most importantly, the fact that week 12 non-responders could not continue in the last 12-week blinded period also complicated the interpretation of all key secondary endpoints. Indeed, all patients who did not continue in the last 12-week blinded period (based on their platelet count at week 12) have their week 13-week 24 data imputed as non-response (for binary response and time to event endpoints) or data set to missing and assumed MAR (for change from baseline in IBLS). It would have been highly preferable to study all key secondary endpoints regardless of week 12 platelet response. However, as for the primary endpoint, any estimands targeting the effect of treatment on key secondary endpoints regardless of week 12 platelet response are unfortunately not supported by study data. As a consequence, it is difficult to differentiate the short-term effect of treatment on platelet counts (at week 12) from its effect on other longer-term efficacy measurements. This situation challenged the interpretability as well as the clinical relevance of secondary endpoints. The handling of ICEs for secondary endpoints generally assumes that rescue therapy indicates non-response (for a period of 4 weeks for repeated binary response data or from rescue administration for continuous endpoints), with a composite strategy. Similarly, data following treatment discontinuation have been handled either with a composite strategy (for repeated binary response data), or with a combination of composite and hypothetical strategies depending on the reason for missingness (for continuous endpoints). While these approaches can be understood in principle, the applicant was requested to investigate alternative estimands targeting the effect of treatment on key secondary endpoints regardless of treatment discontinuation and regardless of rescue medication, as for the primary endpoint. Results were generally consistent with the main primary and key secondary results.

Key secondary endpoints definition and analysis

For all key secondary endpoints related to platelet count, missing data were imputed or assumed to represent non-response. However, the interpretation is complicated by week 12 non-responders discontinuing from the double-blind period per study design. The current results for the key secondary analyses comparing the number of weeks with a response assume (i.e. impute) a 'no response' status in weeks 13-25 for all subjects who have discontinued blinded treatment for not having an initial response. Likewise, the analysis for the time to first response appears to assume that subjects without an initial response cannot have a response in weeks 13-25. Given the large imbalance in subjects discontinuing at week 13, it can be expected that this strategy yields an anti-conservative impact on the treatment effect estimate. For all key secondary endpoints at week 24, the applicant provided further clarification on the handling of missing data as well as additional sensitivity analyses, whose results were in line with the main analyses results.

Regarding the endpoint "% participants requiring rescue therapy", it was stated that the endpoint was planned to be compared "via the time to event analysis due to the expected high rate of treatment discontinuation". Hence, this endpoint should have been renamed "time to first rescue therapy". In the CSR, both the time-to-event analysis and a comparison of the % of participants requiring rescue therapy were presented, however only one of the endpoints was included in the hierarchical strategy. The p-value for the % comparison (the one not included in the hierarchical strategy) was hence only interpreted exploratively. Finally, criticism to the endpoint "Change from baseline in physical fatigue (Item 10 of the ITP-PAQ) in adults at Week 13" was raised. First, the endpoint had been criticized in the past (EMA/SA/0000090350) since only the whole questionnaire and not the single items are validated, and the applicant was asked to discuss the relevance of using the single item 10. Second, it was not understood why all other key secondary endpoints were evaluated at the end of the double-blind period (week 25, as the primary endpoint and all other key secondary endpoints), while only this one was already evaluated at Week 13. Third, since MMRM is being used, it is not really change "at" Week 13, but rather change "until" Week 13, which affects the interpretation of the endpoint. The applicant clarified that missing data were imputed via WOCF, if they were missing before week 13 (in case of rescuing after the first 8 week or discontinuation due to lack of response or AEs), or MI if only week 13 was missing. Furthermore, four sensitivity analyses (two pre-specified, two arising from Assessor's comments) were presented which confirm the robustness of the results for this key secondary endpoint.

Further methodological aspects

In principle, the sample size was sufficiently motivated and could be replicated based on the provided information. Nevertheless, it should be noted that response rate assumptions in the protocol were based on clinical trials that did not involve the discontinuation of week 12 non-responders from the following 12-week period of assessment (phase 2 study PRN1008-010 Part A for the rilzabrutinib arm, and RCTs reported by Bussel et al, 2018, for the placebo arm). No discussion on the clinical relevance of the expected difference could be found.

In total four **protocol amendments** were conducted. Two amendments affected the statistical analysis. The substantial protocol amendment of July 2021 included an amendment of sample size, increasing the study power from 80% to 86% to detect a 20% difference in response rates between the 2 study arms (alpha = 0.01). The amendment to increase the power from 80% to 86% seems unnecessary, considering that neither the expected difference nor the global alpha level were amended. Furthermore, the protocol was substantially amended on July 2023 and it included an increase of the global alpha from 0.01 to 0.05. The applicant justified the change by stating that this was done "to align with health authority common standard, in response to the feedback received from health authority". The change was stated to be implemented in response to an FDA comment reminding the applicant that "the FDA's common standard for the significance level is 0.05 two-sided". Given the single pivotal trial, such a statement seems anti-conservative and the change in the alpha level had not been further discussed with EMA. Furthermore, the amendment happened late in the trial, when it was known how many participants had discontinued the blinded portion of the trial at week 12, which might have informed the probability of success of the trial. However, an analysis of the primary and key secondary endpoints as per initial protocol (including only the first 164 randomised patients and using an alpha level of 0.01), presented upon request, minimised these concerns, as the results were fully aligned with those of the final analysis.

The proportion of **major protocol deviations** was similar between the two arms (43.5% for rilzabrutinib vs. 43.6% for placebo). Deviations related to a prohibited concomitant medication were observed for 10.5% and 15.9% of the participants in the rilzabrutinib and placebo groups, respectively. However, prohibited rescue medications was found in 3.0 % and 11.6 % of the participants in the

rilzabrutinib and placebo groups, respectively. It is observed that respectively 5.3% and 10.1% of major deviation related to primary and key secondary endpoint data. 12 participants deviated due to errors in randomization stratification (5 [3.8%] in the rilzabrutinib group and 7 [10.1%] in the placebo group), and the remaining 2 (1.5%) participants in the rilzabrutinib group deviated from the protocol due to missing assessments in ITP-PAQ Item 10 (physical fatigue). To assess the impact on the results, a sensitivity analysis was provided and results were consistent with the main findings.

Patient flow and numbers

Among 393 participants screened, 202 adult participants were randomized: 191 patients (48.6%) failed at screening, 91 (23.2%) failed to meet the required platelet count for inclusion, which is understood as the most frequent reason. Patient numbers reported for randomization and drug exposure in both treatment arms (i.e. n=69 in placebo and n=133 in rilzabrutinib) are in line with the proposed sample size and the randomization scheme (2:1). The majority of participants discontinued the 24-week double-blind period (85.5% in placebo and 53.4% in rilzabrutinib) and the driving reason for discontinuation was lack of response. All of these participants, except for one in the rilzabrutinib arm, actually have discontinued at week 13 or earlier due to lack of response. The vast majority of those patients that have discontinued the blinded period, have subsequently entered the open-label period (55/59 in placebo and 55/71 in rilzabrutinib). These data indicate a possible desire to switch from an unknown (blinded) treatment without experienced effect (on individual level) to the active treatment as given in the open-label period. It can be interpreted, that a number of patients treated with rilzabrutinib (>50%) experience a lack of effect that might also trigger a desire/need to change treatment.

Baseline data

Whereas the median age appears balanced between both treatment groups (46 in placebo and 47 in rilzabrutinib), it is noted that a limited number of patients ≥65 years were included in the study (n=15 in placebo and n=21 in rilzabrutinib). Still, this can be acceptable, considering the rarity of the disease. An imbalance is evident for the inclusion of male and female participants (37.1% male and 62.9% female) and this imbalance appears more pronounced in the placebo treatment arm (29% male and 71% female) compared to the rilzabrutinib treatment arm (41.4% male and 58.6% female). Considering the observed tendency that female participants might respond mildly better to the treatment with rilzabrutinib (14.5% of males and 20.5% of females with durable platelet response) and taking into account that participants treated with placebo had generally no longer lasting effect on platelet counts, this imbalance does not appear to critically affect the interpretation of study results. Imbalance at baseline in subjects older than 65 years (15.8 % for the rilzabrutinib group and 21.7 % for the placebo group) was also observed, which was of concern given that elderly may have a higher ITP-related morbidity (Michel at al., 2011, American Journal of Haematology). However, in answer to the D120 LoQ, analyses of primary and key secondary endpoints were repeated by including gender and age group (respectively) as stratification factor (or a covariate) in the statistical models; results were overall consistent with initial findings. It is to note that almost 40% of the patients were recruited in Europe, which appears acceptable to generalise the results to the European population. Baseline data on race, ethnicity, weight, BMI and geographic region do not give rise to concern.

Regarding disease characteristics, the reported duration of ITP seems around two years higher in the rilzabrutinib group (mean of 9.8 and 11.45 years from diagnosis), which appears mostly driven by a few more participants included that had their diagnosis >3 years before randomization (72.5% and 76.7%). No critical impact on study results is expected from this mild imbalance. A lower number of patients was included with duration of ITP <1 year (n=10 treated with rilzabrutinib). A time since diagnosis of ITP <1 year is referred to as persistent ITP, whereas a duration ≥1 year is referred to as chronic ITP. The applicant intends to license rilzabrutinib for both, persistent and chronic ITP. The proportion of patients meeting the primary endpoint of durable response is roughly comparable

between the overall population (23.3% of patients with persistent and chronic ITP) and the subgroup of patients with persistent ITP (30% of patients with persistent ITP). No patient treated with placebo has achieved this aim. The results are acknowledged, but it should be noted that interpretability is limited as patient numbers of the persistent ITP subgroup are low (n=10). Still, the dividing factor between persistent and chronic ITP is based solely on the time since diagnosis, but the underlying disease pathophysiology principally does not differ between patients of this categorization. In line with this, it was stressed by the European Haematology Association in the scope of a "CHMP early dialogue with healthcare professionals" that the terms "persistent" and "chronic" ITP are of interest for epidemiological characterisation of patients, but do not describe clinical therapeutic needs. Thus, even though current regulatory EMA guidance (EMA/CHMP/153191/2013) specifically addressed chronic ITP, patients with persistent or chronic ITP could principally both benefit from novel ITP medications. It is also important to consider that rilzabrutinib is intended to be used as a late line treatment option after at least two other treatments have failed and that patients without response are to discontinue the treatment to reduce unnecessary treatment burden (see SmPC 4.2). Therefore, no specification of persistent or chronic ITP is required for the indication as no therapeutic benefit seems given by this separation.

The vast majority of participants had more than 2 prior ITP therapies (around 90% as identified by eCRF entry records, around 70% if different corticosteroids are counted as one therapy). Thus, the indication was amended upon request to *adult patients who are refractory to previous treatments* and a reference to section 5.1 was added. The applicant has clarified that 24 participants (3 participant in the placebo arm (4.3%) and 21 participants in rilzabrutinib arm (15.8%)) had received a single prior ITP therapy, which includes splenectomy. Platelet counts at screening and baseline as well as status of splenectomy appear comparable between treatment groups, which is in line with the intended stratification of these factors.

Considering reported numbers on prior CS and TPO-RAs, these two treatment options appear to be the first choice of treatment. Overall, there is no critical imbalance on treatment history across the two arms, 95 % of the subjects had prior corticosteroids with almost 69 % of responders and 69 % of the subjects had prior TPO-RA with almost 43 % of responders. Importantly, concomitant use of CS and/or TPO-RAs was permitted in the study and the majority of included patients had been taken permitted concomitant medication in either study group (n=46 of 69 patients in placebo and n=80 of 133 patients treated with rilzabrutinib). Rilzabrutinib as ITP monotherapy (i.e. without concomitant ITPO medication) was given in 39.8% of patients in the rilzabrutinib group, whereas 33.3% of patients in the placebo group (n=23) had received rilzabrutinib as ITP monotherapy during the study. Among those patients that have received concomitant CS and/or TPO-RA therapy vs. patients without either of the two concomitant therapies on top of rilzabrutinib durable platelet response was achieved in 27.5% vs. 17%, initial platelet response (i.e. week 12 assessment) was achieved by 70% vs. 54.7% and among those that have achieved the week 12 responder assessment durable platelet response was achieved by 48.9% vs. 42.9% of patients, respectively. Notably, 95% CIs are largely overlapping for all subgroups (certainly also related to the very small sample sizes of subgroups) and, importantly, also the monotherapy group seems to have a clearly better effect on the primary measure compared to patients treated only with placebo (difference vs. placebo in rate with durable response was 17%, 95%CI: 6.87, 27.09). Also, the platelet response within the first 12 weeks of treatment in patients treated only with placebo and without concomitant medication was clearly lower compared to those only on rilzabrutinib (achieved by 31.9% and 54.7%, respectively). The majority of patients on concomitant ITP therapy had maintained the background therapy group (67.4% on placebo and 66.2% on rilzabrutinib), but a dose decrease of concomitant medication was recorded for 4.3% of patients treated with placebo and 10.5% of patients on rilzabrutinib with concomitant ITP medication. Initiation or increased dosing of any concomitant therapy was not recorded for patients on rilzabrutinib during the study (but was also rare in placebo patients with n=1 patient). In conclusion, the treatment with

rilzabrutinib as monotherapy (i.e. without concomitant ITP therapy) seems principally justified, but expected durable platelet responder rates are below the overall population.

Efficacy data and additional analyses

The defined **primary endpoint** addressing durable platelet response (i.e. 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*) was met and all key secondary endpoints were also reported with statistically significant results. In total, 31 participants (23.3% with 95% CI: 16.12%, 30.49%) had durable platelet response as defined for the primary endpoint during treatment with rilzabrutinib, whereas no patient managed to succeed in the placebo treatment group (risk difference of 23.1 % with 95% CI: 15.95, 30.31; Cochran-Mantel-Haenszel test p-value <0.0001). However, it is important to note that the conducted responder analysis after 12 weeks led to the exclusion of a substantial number of participants from the time of data collection that waere relevant for the primary endpoint (weeks 13-24) and for secondary endpoints that have referred to the entire blinded treatment period. Early response was achieved by 85 (63.9%) patients and 22 (31.9%) patients in the rilzabrutinib group and placebo group, respectively. However, lack of response at or before week 13 was reported for 55 (79.7%) and 55 (41.4%), respectively (only 64 and 13 patients have continued in both treatment groups from week 13). It must have been expected that substantially more subjects would have failed to meet the responder requirement after 12 weeks on treatment with placebo, compared to the active treatment with rilzabrutinib. Therefore, it was rather critical to count these patients as failure also for the primary analysis, without referencing this analysis in the primary endpoint. In fact, the early responder analysis appears to have a bigger influence on the primary endpoint result than the data from the actual study period relevant for the primary analysis (only around 38% of patients were still included from week 13). The procedure to discontinue treatment in patients without platelet response is principally acknowledged from a clinical perspective (discontinuation of an ineffective treatment), but from a methodological point of view the applied approach cannot be followed. The early analysis should have been an integrated part of the primary (and also some of the secondary) endpoints. Thus, the study seems not well planned for the intended primary endpoint and the comparison to placebo seems compromised. Considering that platelet counts is a rather objective measure and with respect to the actual results on platelet counts (i.e. no durable response in placebo evident, but clear response in a subgroup of patients on rilzabrutinib), the above outlined critique nevertheless appears not overly critical for the conclusion on efficacy of rilzabrutinib.

Plotted **median platelet counts** by visit until week 24 indicate a mild benefit regarding platelet numbers for patients treated with rilzabrutinib. Median platelet counts in the rilzabrutinib group appear to rise modestly until week 12 to around 30-40,000 platelets per µl, whereas platelet counts in the placebo group rise to 20-30,000 platelets/µl (both groups starting with baseline at around 15,000 platelets/µl). Due to the early responder analysis conducted after week 12, the study population that was further followed in the blinded study part is largely reduced (from 63 to 13 and from 116 to 64 participants before and after the week 12 responder assessment/selection in the placebo and rilzabrutinib group, respectively). As a consequence of this responder selection, also the reported median platelet counts increased in both study groups (to around 30,000 platelets/µl in placebo and >50,000 platelets/µl in the rilzabrutinib groups), reflecting that subjects with weakest platelet counts were excluded from further reporting. Those subjects treated with rilzabrutinib and that have continued the blinded study period until week 24, have remained at a median count of 50-70,000 platelets/µl from week 13 to week 24 on treatment, whereas median platelet counts in the placebo group remained at around 30,000 platelets/µl in the same time period. This clearly indicates the beneficial effect of the responder analysis (and respective participant exclusion) after 12 weeks on reported median platelet results. Notably, plots of longitudinal data (notably of platelet count) provided

by durable platelet response status are considered largely misleading as these are non-randomised comparisons. Indeed, durable response is a post-baseline outcome, and highly correlated to the longitudinal outcome measures themselves (durable responders are per definition expected to show higher level of platelet counts). Figures that allow for adequate treatment comparisons are those presented by treatment arms, without further separation by durable response. As for summary tables, the interpretation of figures is further complicated by week 12 non-responders not contributing to week 12-week 24 double-blind treatment period.

Notably, within the study group treated with rilzabrutinib, two distinct **responder groups** can be identified based on median platelet counts. One group (of 102 participants starting at baseline) did not demonstrate any substantial increase in median platelets until week 12, with a mild increase after the first responder analysis that is comparable to the increase observed for the placebo group (as described above, probably reflecting that subjects with weakest platelet counts were excluded from further reporting). However, those patients that have met the primary endpoint as reported (n=31 participants) demonstrated a steady increase of median platelet counts to around 100,000 platelets/µl after 9 weeks of treatment and >100,000 platelets/µl from 13 weeks on treatment, which was maintained until treatment week 24. Particularly this study group seems to benefit from the treatment with rilzabrutinib. It is of crucial importance to discontinue treatment in patients that do not benefit from treatment, as the risks might otherwise dominate effect profile. A late response during the OL period was reported only for a few patients that were randomised to rilzabrutinib (n=10, 11.9% compared to 21.5% of those randomised to placebo with rilzabrutinib treatment starting with the OL period). The benefit-risk balance for these patients remains unclear, as potential unwanted effects might dominate the extended time without response and regarding the suggested benefit, no analysis was pre-specified to allow for a robust statement on late responses. In this context, a prospectively planned exploration of potential predictive factors for response/non-response would have been of interest.

In line with the very distinct platelet response profile, also discontinuations from the blinded study period appear to be reported only for the subset of patients that did not have a substantial increase in platelet counts (from n=102 participants at baseline to n=85 at week 12, n=34 after the week 12 responder analysis and n=31 at week 24), whereas the group with solid increase in platelet counts remained constant throughout the blinded study period (n=31 at baseline and at week 24). The discontinuation of patients in the placebo group was even more substantial (from n=69 participants at baseline to n=35 after 12 weeks of treatment, n=11 after the week 12 responder analysis and n=7 at week 24). As discussed above, the vast majority of participants has discontinued the blinded study period due to lack of response, in either study group. Most of these subjects have then continued in the **open-label period** (n=149 DB non-responders have entered the OL period, n=65 and n=84 that were initially randomized to placebo and rilzabrutinib, respectively). During the open-label period, all patients have received rilzabrutinib treatment. Thus, all patients randomized to placebo treatment during the double-blind period have initiated rilzabrutinib treatment in the open-label period. Of those subjects that have initiated rilzabrutinib treatment in the OL period (n=65), 21.5% were regarded as durable treatment responders. This rate appears comparable to the rate concluded from patients randomised to rilzabrutinib in the blinded period. Platelet responders of the double-blind period also seem to maintain the high platelet count throughout the additional 28 week open-label treatment period. Interestingly, also 10 (11.9%) of the non-responders from the rilzabrutinib group during the double-blind period (from a total of n=84 DB non-responders that have entered the OL period) seem to have responded to treatment in the OL period, even though nothing has changed in their treatment. It can be speculated that those are late (and only mild) treatment responder that were excluded after 12 weeks of treatment due to the early responder analysis. The applicant has provided an overview of a baseline demographic data and disease characteristics among the late responders as identified during the open-label study period. However, no obvious factor seems apparent that could explain the

delayed onset of efficacy and no pattern among these patients seems evident that would facilitate an earlier identification of these late responders.

Importantly, data provided for the long-term extension study also demonstrate that the median platelet count of included patients is >75,000/µl throughout the entire 2-year period reported. Altogether, plots of median platelet counts demonstrate a very robust response that is maintained throughout a long treatment period (several years) but appears only for the specific fraction of patients that do respond to the treatment with rilzabrutinib. This view is also supported by data from the phase 1/2 study (see data and discussion below). The benefit for these responder patients seems compelling. Also, all provided **secondary endpoints** do support the conclusion that rilzabrutinib treatment does have a positive effect on platelets, required rescue medication, level of fatigue in patients and the IBLS bleeding score. Key secondary endpoints were all statistically significant. However, results in bleeding show a difference in mean change from baseline on IBLS at Week 25 -0.087 (95%CI -0.1358, -0.0373). This appears limited. About fatigue, the difference in mean change from baseline at Week 13 in ITP-PAQ item 10 was 8.08 (95%CI 1.818, 14.337). However, the validity of using a single item from the ITP-PAQ was questioned. In answer to the D120 LoQ, a validation exercise was provided. However, while the approach appears theoretically reasonable, there are true concerns that the data set to validate are the Phase 3 data. It is particularly important that the validity of an endpoint is established before the confirmatory trial, or at least on another data set, especially given that a single item was used to assess a multidimensional concept such as fatigue. The treatment effect seems also supported by submitted patient-reported outcomes (EQ-5D-5L for quality-of-life, Patient Global Impression of Severity and ITP-PAQ domains beyond the fatigue score). However, it appears of crucial importance to reliably identify the responder patient population and discontinue treatment in patients that do not benefit from the treatment as early as possible, in order to avoid ineffective treatment and respective safety risks.

Overall, all **subgroup analyses** on the primary endpoint show a favourable effect for rilzabrutinib. The provided forest plot demonstrates a comparable level throughout all presented subgroups and indicates that rilzabrutinib is beneficial over placebo treatment for all of these subgroups. Variable responses can be seen for gender (with female having a slightly better response compared to male with 29.5% vs. 14.5%), age (25% for subjects <65 years and 14.3% for subjects ≥65 years), splenectomy status (with splenectomy 13.5% vs. 27.1% without), baseline platelet count (15.4% for <15,000/µl vs. 30.9% for ≥15,000/µl), prior TPO-RA therapy (without concomitant TPO-RA 14.3% vs. with concomitant TPO-RA 36%), concomitant ITP therapy (no concomitant therapy: 17%, TPO-RA and/or CS: 27.5%), as well as study groups treated in West Europe and East Europe (12.1% vs. 42.1%). However, CIs are overlapping for all the mentioned subgroups and, due to the low number of subjects, are very wide, rendering the interpretation difficult. No evident concerns arise from the response in reported subgroups.

Healthcare provider engagement

Feedback from healthcare providers was received by EURORDIS and the European Haematology Association in the scope of a "CHMP early dialogue with healthcare professionals". This feedback was appreciated. Both expert groups highlighted that it might be beneficial for patients that are not well controlled with available therapies to have other options with products targeting different pathways. The experts from the European Haematology Association further stressed that the terms "persistent" and "chronic" ITP are of interest for epidemiological characterisation of patients, but do not describe clinical therapeutic needs. Thus, even though current regulatory EMA guidance (EMA/CHMP/153191/2013) specifically addressed chronic ITP, patients with persistent or chronic ITP could principally both benefit from novel ITP medications. This view was followed for the assessment and resulted in an indication that is independent of the time since diagnosis, despite low patient numbers in the group with persistent ITP included in the main clinical study.

2.6.7. Conclusions on the clinical efficacy

The applicant provided a randomized, parallel, placebo-controlled, double blind single pivotal study to evaluate efficacy in patients with persistent and chronic ITP (PRN1008-018). Further efficacy data are available from the open-label dose-finding study (PRN1008-010).

The principal study design, including objectives and endpoints, of study 018 is acceptable. All provided results indicate a benefit for the treatment with rilzabrutinib compared to the treatment with placebo. The effect is specifically driven by a patient group that responded with increasing platelet counts early and persistently (stable, high platelet counts also throughout the open-label period) to the treatment with rilzabrutinib, whereas other patients appear as clear non-responders (with platelet counts rather comparable to participants treated with placebo). Thus, it is relevant to define the responder group as early as possible and at the latest within 12 weeks of treatment, in order to avoid unnecessary risks by ineffective treatment and safety risks for non-responding patients (see SmPC section 4.2). Furthermore, concomitant use of CS and/or TPO-RAs was permitted and was used by the majority of patients during the study, which resulted in a higher rate of platelet response compare to those without concomitant medication.

Based on these results, rilzabrutinib seems to provide a possible treatment benefit in at least some patients, regardless if used as monotherapy and/or as add-on therapy concomitantly with CS and TPO-RAs. Efficacy results from the single pivotal trial are principally supported by results from trial 010.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

ITP patient safety data were presented by the applicant with a data cut-off date of 15 Oct 2024, with a primary focus on the pivotal Study PRN1008-018 comparing the rilzabrutinib-treated group to the placebo group during the DB period. Data from the OL and LTE periods provide confirmatory evidence for longer-term rilzabrutinib safety and tolerability. Also presented as part of the analyses are data from the ITP Phase 1/2 Study PRN1008-010 Parts A and B and LTE. The data are supported by pooled analyses from Study PRN1008-018 (all treatment periods) and Study PRN1008-010 (Parts A and B main treatment and LTE periods) comprising all rilzabrutinib doses up to the dossier cutoff date (15 Oct 2024). The pooled analyses denoted as 'ITP rilzabrutinib pool' include safety data in 284 adult participants treated with any dose of rilzabrutinib including 278 participants treated with the 400 mg BID dose.

In this report, where applicable, data are presented for the double-blind period of study PRN1008-018, as well as for the any dose rilzabrutinib pooled patient group.

Study PRN1008-018

The ITP pivotal study comprised 202 participants randomized to either rilzabrutinib 400 mg BID (133 participants) or placebo (69 participants) and treated during the PRN1008-018 DB period. All participants randomized were exposed to study drug and included in the safety analyses.

Double-blind period

During the DB period, 112 (84.2%) participants were exposed to rilzabrutinib 400 mg BID and 54 (78.3%) participants were exposed to placebo for 12 weeks or longer. Cumulative duration of treatment exposure in the rilzabrutinib group exceeded that of the placebo group: 44.3 participant-years versus 17.9 participant-years, respectively (Table 26).

Table 26: Extent of exposure to investigational medicinal product during the 24-week double-blind treatment period - Adult safety population

	Placebo (N=69)	Rilzabrutinib 400 mg BID (N=133)
Cumulative duration to treatment exposure (participant-years[a])	17.9	44.3
Duration of IMP exposure (days)[b]		
Number	69	133
Mean (SD)	94.7 (32.7)	121.5 (46.9)
Median	84.0	98.0
Min ; Max	17 ; 173	22 ; 182
Duration of IMP exposure by period [n (%)]		
≥0 to <4 weeks	1 (1.4)	2 (1.5)
≥4 to <8 weeks	1 (1.4)	6 (4.5)
≥8 to <12 weeks	13 (18.8)	13 (9.8)
≥12 to <16 weeks	44 (63.8)	47 (35.3)
≥16 to <20 weeks	0	1 (0.8)
≥20 to <24 weeks	1 (1.4)	14 (10.5)
≥24 weeks	9 (13.0)	50 (37.6)

IMP: Investigational medicinal product
Percentages are calculated using the number of participants in the adult safety population with a non-missing duration of exposure as denominator
[a]Participant-years = the cumulative duration of observation period in days /365.25
[b]Duration of IMP exposure (days) = (Date of last dose - Date of first dose) + 1, regardless of unplanned intermittent interruption
PGM=PRODOPS/SAR444671/EFC17093/CSR_01/REPORT/PGM/cdc_exposure_db_s_t.sas
OUT=REPORT/OUTPUT/cdc_exposure_db_s_t_i.rtf (14JUN2024 16:09)

Open-label period and long-term extension

As of the data cutoff date, 180 participants received rilzabrutinib 400 mg BID during the OL period for a median 196.0 days (range 14 to 215 days) with a cumulative duration of exposure of 75.6 participant-years. In total 96 participants were exposed to rilzabrutinib 400 mg BID in the LTE period for a median 331.0 days (range 20 to 910 days); cumulative duration of exposure was 69.3 participant-years.

ITP rilzabrutinib pool

The 284 adult participants exposed to any dose of rilzabrutinib (including 278 participants treated with the 400 mg BID dose) had a median duration of exposure of 197.0 days (range 4 to 2124 days) and cumulative duration of exposure of 290.6 participant-years. The majority (187 of 284 participants) were exposed for ≥24 weeks and 98 participants were exposed for ≥52 weeks. The longer exposure in this pool reflects the longer duration of study participation when considering all parts of both ITP studies (PRN1008-018 and PRN1008-010) and all doses evaluated.

Healthy participants

13 Phase 1 studies were conducted in healthy participants. By the data cutoff date (14 March 2024), rilzabrutinib had been administered orally to 310 healthy adult participants in the 13 completed Phase 1 studies.

2.6.8.2. Adverse events

Table 27: Number (%) of participants with TEAE(s) by primary SOC and PT - Adult safety population

	ITP placebo-controlled pool[a]		ITP rilzabrutinib pool[b]
PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	**Placebo (N=69)**	**Rilzabrutinib 400 mg BID (N=133)**	**Rilzabrutinib any dose (N=284)**
Any event	52 (75.4)	111 (83.5)	246 (86.6)
INFECTIONS AND INFESTATIONS	14 (20.3)	44 (33.1)	131 (46.1)
COVID-19	3 (4.3)	18 (13.5)	42 (14.8)
Nasopharyngitis	2 (2.9)	9 (6.8)	31 (10.9)
Upper respiratory tract infection	3 (4.3)	5 (3.8)	31 (10.9)
Influenza	0	4 (3.0)	7 (2.5)
Pneumonia	0	2 (1.5)	4 (1.4)
Skin infection	0	2 (1.5)	2 (0.7)
Urinary tract infection	1 (1.4)	2 (1.5)	17 (6.0)
Bronchitis	1 (1.4)	1 (0.8)	4 (1.4)
Chronic sinusitis	0	1 (0.8)	1 (0.4)
Chronic tonsillitis	0	1 (0.8)	1 (0.4)
Conjunctivitis	0	1 (0.8)	2 (0.7)
Cystitis	0	1 (0.8)	1 (0.4)
Gastroenteritis	1 (1.4)	1 (0.8)	3 (1.1)
Oropharyngeal candidiasis	0	1 (0.8)	1 (0.4)
Otitis media acute	0	1 (0.8)	2 (0.7)
Pelvic inflammatory disease	0	1 (0.8)	1 (0.4)
Pharyngitis	0	1 (0.8)	2 (0.7)
Renal abscess	0	1 (0.8)	1 (0.4)
Rhinitis	0	1 (0.8)	2 (0.7)
Sepsis	0	1 (0.8)	2 (0.7)
Tonsillitis	0	1 (0.8)	2 (0.7)
Tooth infection	0	1 (0.8)	1 (0.4)
Viral infection	1 (1.4)	1 (0.8)	2 (0.7)
Wound infection	0	1 (0.8)	2 (0.7)
Acute sinusitis	0	0	2 (0.7)
Antibiotic associated colitis	0	0	1 (0.4)
Body tinea	0	0	1 (0.4)
Bronchopulmonary aspergillosis	0	0	1 (0.4)
COVID-19 pneumonia	0	0	1 (0.4)
Candida infection	0	0	1 (0.4)
Cytomegalovirus viraemia	0	0	1 (0.4)
Erysipelas	0	0	1 (0.4)
Fungal skin infection	0	0	1 (0.4)
Gastroenteritis viral	0	0	2 (0.7)
Gingivitis	1 (1.4)	0	0
Haematoma infection	0	0	1 (0.4)
Hepatitis B reactivation	0	0	1 (0.4)
Hepatitis E	0	0	1 (0.4)
Herpes zoster	0	0	1 (0.4)
Infected skin ulcer	0	0	1 (0.4)
Localised infection	0	0	1 (0.4)
Lower respiratory tract infection	0	0	2 (0.7)
Meningitis aseptic	0	0	1 (0.4)
Onychomycosis	0	0	1 (0.4)
Oral herpes	1 (1.4)	0	3 (1.1)
Osteomyelitis	0	0	1 (0.4)
Pharyngitis streptococcal	0	0	1 (0.4)
Pulpitis dental	2 (2.9)	0	0
Pyelonephritis	0	0	1 (0.4)
Pyuria	1 (1.4)	0	0
Respiratory syncytial virus infection	0	0	1 (0.4)
Respiratory tract infection	0	0	3 (1.1)
Respiratory tract infection viral	0	0	1 (0.4)
Sinusitis	0	0	3 (1.1)
Subcutaneous abscess	0	0	1 (0.4)
Tinea infection	0	0	1 (0.4)
Tinea pedis	0	0	1 (0.4)
Urosepsis	0	0	1 (0.4)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	ITP placebo-controlled pool[a] Placebo (N=69)	 Rilzabrutinib 400 mg BID (N=133)	ITP rilzabrutinib pool[b] Rilzabrutinib any dose (N=284)
Vaginal infection	0	0	1 (0.4)
Varicella zoster virus infection	0	0	1 (0.4)
Viral upper respiratory tract infection	0	0	2 (0.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	8 (2.8)
Bowen's disease	0	0	1 (0.4)
Marrow hyperplasia	0	0	1 (0.4)
Metastatic malignant melanoma	0	0	1 (0.4)
Myelofibrosis	0	0	1 (0.4)
Neoplasm skin	0	0	1 (0.4)
Ovarian clear cell carcinoma	0	0	1 (0.4)
Paraproteinaemia	0	0	1 (0.4)
Seborrhoeic keratosis	0	0	1 (0.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	12 (17.4)	11 (8.3)	44 (15.5)
Anaemia	4 (5.8)	5 (3.8)	18 (6.3)
Hypochromic anaemia	0	1 (0.8)	1 (0.4)
Immune thrombocytopenia	1 (1.4)	1 (0.8)	3 (1.1)
Iron deficiency anaemia	3 (4.3)	1 (0.8)	3 (1.1)
Neutropenia	0	1 (0.8)	2 (0.7)
Neutrophilia	1 (1.4)	1 (0.8)	1 (0.4)
Thrombocytopenia	2 (2.9)	1 (0.8)	12 (4.2)
Antiphospholipid syndrome	0	0	1 (0.4)
Autoimmune haemolytic anaemia	0	0	1 (0.4)
Coagulopathy	1 (1.4)	0	1 (0.4)
Eosinophilia	0	0	1 (0.4)
Evans syndrome	0	0	1 (0.4)
Haemorrhagic diathesis	1 (1.4)	0	1 (0.4)
Idiopathic neutropenia	0	0	1 (0.4)
Leukocytosis	1 (1.4)	0	2 (0.7)
Leukopenia	0	0	1 (0.4)
Lymphadenitis	0	0	1 (0.4)
Normochromic normocytic anaemia	1 (1.4)	0	0
Nucleated red cells	0	0	1 (0.4)
Thrombocytosis	0	0	3 (1.1)
IMMUNE SYSTEM DISORDERS	0	1 (0.8)	9 (3.2)
Seasonal allergy	0	1 (0.8)	3 (1.1)
Allergy to chemicals	0	0	1 (0.4)
Food allergy	0	0	1 (0.4)
Hypersensitivity	0	0	3 (1.1)
Sarcoidosis	0	0	1 (0.4)
ENDOCRINE DISORDERS	0	1 (0.8)	5 (1.8)
Hypothyroidism	0	1 (0.8)	1 (0.4)
Autoimmune thyroiditis	0	0	1 (0.4)
Cushingoid	0	0	2 (0.7)
Glucocorticoid deficiency	0	0	1 (0.4)
METABOLISM AND NUTRITION DISORDERS	2 (2.9)	6 (4.5)	22 (7.7)
Hypokalaemia	1 (1.4)	3 (2.3)	6 (2.1)
Hyperglycaemia	0	2 (1.5)	2 (0.7)
Decreased appetite	0	1 (0.8)	4 (1.4)
Abnormal loss of weight	0	0	1 (0.4)
Dehydration	0	0	2 (0.7)
Diabetes mellitus	0	0	2 (0.7)
Fluid retention	0	0	1 (0.4)
Folate deficiency	0	0	1 (0.4)
Gout	0	0	1 (0.4)
Hypercholesterolaemia	0	0	1 (0.4)
Hyperlipidaemia	0	0	1 (0.4)
Hypertriglyceridaemia	0	0	1 (0.4)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	ITP placebo-controlled pool[a] Placebo (N=69)	 Rilzabrutinib 400 mg BID (N=133)	ITP rilzabrutinib pool[b] Rilzabrutinib any dose (N=284)
Hyperuricaemia	0	0	2 (0.7)
Hypophosphataemia	0	0	2 (0.7)
Iron deficiency	0	0	2 (0.7)
Type 2 diabetes mellitus	0	0	1 (0.4)
Vitamin D deficiency	1 (1.4)	0	0
PSYCHIATRIC DISORDERS	1 (1.4)	6 (4.5)	16 (5.6)
Insomnia	1 (1.4)	3 (2.3)	7 (2.5)
Depression	0	2 (1.5)	5 (1.8)
Initial insomnia	0	1 (0.8)	1 (0.4)
Irritability	0	1 (0.8)	1 (0.4)
Abnormal dreams	0	0	1 (0.4)
Anxiety	0	0	2 (0.7)
Depressed mood	0	0	1 (0.4)
Panic attack	0	0	1 (0.4)
NERVOUS SYSTEM DISORDERS	8 (11.6)	32 (24.1)	73 (25.7)
Headache	5 (7.2)	24 (18.0)	52 (18.3)
Dizziness	1 (1.4)	11 (8.3)	18 (6.3)
Neuropathy peripheral	0	2 (1.5)	2 (0.7)
Facial paralysis	0	1 (0.8)	2 (0.7)
Hypoaesthesia	0	1 (0.8)	2 (0.7)
Presyncope	0	1 (0.8)	3 (1.1)
Sciatica	0	1 (0.8)	3 (1.1)
Akathisia	0	0	1 (0.4)
Amnesia	0	0	1 (0.4)
Bell's palsy	0	0	1 (0.4)
Brain fog	0	0	1 (0.4)
Carpal tunnel syndrome	0	0	2 (0.7)
Cerebral microhaemorrhage	0	0	1 (0.4)
Dementia with Lewy bodies	0	0	1 (0.4)
Disturbance in attention	0	0	1 (0.4)
Head discomfort	0	0	1 (0.4)
Hemianopia	0	0	1 (0.4)
Lethargy	0	0	1 (0.4)
Migraine	0	0	2 (0.7)
Myoclonus	0	0	1 (0.4)
Neuralgia	0	0	1 (0.4)
Paraesthesia	0	0	3 (1.1)
Parosmia	0	0	1 (0.4)
Peripheral motor neuropathy	0	0	1 (0.4)
Peripheral sensory neuropathy	0	0	1 (0.4)
Restless legs syndrome	0	0	1 (0.4)
Sleep deficit	0	0	1 (0.4)
Somnolence	0	0	1 (0.4)
Syncope	1 (1.4)	0	1 (0.4)
Transient ischaemic attack	0	0	1 (0.4)
Tremor	1 (1.4)	0	2 (0.7)
Ulnar neuritis	0	0	1 (0.4)
EYE DISORDERS	2 (2.9)	5 (3.8)	19 (6.7)
Blepharitis	0	1 (0.8)	1 (0.4)
Dry eye	0	1 (0.8)	2 (0.7)
Ocular discomfort	0	1 (0.8)	1 (0.4)
Swelling of eyelid	0	1 (0.8)	1 (0.4)
Visual field defect	0	1 (0.8)	1 (0.4)
Cataract	1 (1.4)	0	0
Conjunctival haemorrhage	1 (1.4)	0	6 (2.1)
Episcleritis	0	0	1 (0.4)
Eye pain	0	0	1 (0.4)
Eyelid cyst	0	0	1 (0.4)
Eyelid ptosis	0	0	1 (0.4)
Iridocyclitis	0	0	1 (0.4)
Photophobia	0	0	1 (0.4)
Vision blurred	0	0	1 (0.4)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	ITP placebo-controlled pool[a] Placebo (N=69)	 Rilzabrutinib 400 mg BID (N=133)	ITP rilzabrutinib pool[b] Rilzabrutinib any dose (N=284)
EAR AND LABYRINTH DISORDERS	0	2 (1.5)	8 (2.8)
Ear pain	0	1 (0.8)	1 (0.4)
Motion sickness	0	1 (0.8)	1 (0.4)
Otorrhoea	0	1 (0.8)	1 (0.4)
Ear pruritus	0	0	1 (0.4)
Tinnitus	0	0	1 (0.4)
Vertigo	0	0	3 (1.1)
Vertigo positional	0	0	2 (0.7)
CARDIAC DISORDERS	2 (2.9)	2 (1.5)	7 (2.5)
Arrhythmia	0	1 (0.8)	1 (0.4)
Extrasystoles	0	1 (0.8)	1 (0.4)
Myocardial injury	0	1 (0.8)	1 (0.4)
Tachycardia	0	1 (0.8)	2 (0.7)
Atrial fibrillation	0	0	2 (0.7)
Bradycardia	0	0	1 (0.4)
Bundle branch block right	1 (1.4)	0	0
Palpitations	1 (1.4)	0	3 (1.1)
Pericarditis	0	0	1 (0.4)
VASCULAR DISORDERS	4 (5.8)	1 (0.8)	15 (5.3)
Peripheral embolism	0	1 (0.8)	1 (0.4)
Aortic stenosis	0	0	1 (0.4)
Deep vein thrombosis	0	0	1 (0.4)
Haematoma	0	0	2 (0.7)
Haemorrhage	0	0	1 (0.4)
Hot flush	0	0	1 (0.4)
Hypertension	3 (4.3)	0	6 (2.1)
Orthostatic hypotension	0	0	1 (0.4)
Peripheral venous disease	1 (1.4)	0	0
Varicose vein	0	0	1 (0.4)
Vasculitis	0	0	1 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (4.3)	15 (11.3)	46 (16.2)
Cough	0	6 (4.5)	13 (4.6)
Oropharyngeal pain	1 (1.4)	3 (2.3)	7 (2.5)
Dysphonia	0	1 (0.8)	1 (0.4)
Dyspnoea	0	1 (0.8)	6 (2.1)
Epistaxis	0	1 (0.8)	10 (3.5)
Nasal congestion	0	1 (0.8)	3 (1.1)
Productive cough	0	1 (0.8)	2 (0.7)
Pulmonary mass	0	1 (0.8)	1 (0.4)
Respiratory tract congestion	0	1 (0.8)	1 (0.4)
Vocal cord polyp	0	1 (0.8)	1 (0.4)
Asthma	0	0	1 (0.4)
Bronchitis chronic	1 (1.4)	0	0
Dyspnoea exertional	0	0	3 (1.1)
Interstitial lung disease	0	0	1 (0.4)
Obstructive sleep apnoea syndrome	0	0	1 (0.4)
Pulmonary embolism	0	0	2 (0.7)
Reflux laryngitis	0	0	1 (0.4)
Rhinitis allergic	1 (1.4)	0	0
Rhinorrhoea	0	0	1 (0.4)
Upper respiratory tract inflammation	0	0	1 (0.4)
Upper-airway cough syndrome	0	0	1 (0.4)
GASTROINTESTINAL DISORDERS	16 (23.2)	71 (53.4)	156 (54.9)
Diarrhoea	7 (10.1)	43 (32.3)	97 (34.2)
Nausea	4 (5.8)	27 (20.3)	72 (25.4)
Abdominal pain	1 (1.4)	10 (7.5)	18 (6.3)
Vomiting	1 (1.4)	9 (6.8)	21 (7.4)
Abdominal pain upper	0	7 (5.3)	20 (7.0)
Dyspepsia	0	7 (5.3)	17 (6.0)
Abdominal discomfort	0	4 (3.0)	9 (3.2)
Abdominal distension	0	3 (2.3)	9 (3.2)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	ITP placebo-controlled pool[a] Placebo (N=69)	 Rilzabrutinib 400 mg BID (N=133)	ITP rilzabrutinib pool[b] Rilzabrutinib any dose (N=284)
Gastritis	0	3 (2.3)	7 (2.5)
Constipation	1 (1.4)	2 (1.5)	6 (2.1)
Oral pain	0	2 (1.5)	2 (0.7)
Dental caries	0	1 (0.8)	1 (0.4)
Dry mouth	0	1 (0.8)	2 (0.7)
Duodenitis	0	1 (0.8)	1 (0.4)
Enterocolitis	0	1 (0.8)	1 (0.4)
Faeces soft	0	1 (0.8)	2 (0.7)
Gastrointestinal disorder	1 (1.4)	1 (0.8)	2 (0.7)
Gastrointestinal pain	0	1 (0.8)	1 (0.4)
Gastrooesophageal reflux disease	2 (2.9)	1 (0.8)	10 (3.5)
Inguinal hernia	0	1 (0.8)	2 (0.7)
Odynophagia	0	1 (0.8)	1 (0.4)
Oesophageal varices haemorrhage	0	1 (0.8)	1 (0.4)
Oesophagitis	0	1 (0.8)	1 (0.4)
Toothache	0	1 (0.8)	5 (1.8)
Abdominal pain lower	0	0	3 (1.1)
Aphthous ulcer	0	0	1 (0.4)
Coeliac disease	0	0	1 (0.4)
Defaecation urgency	0	0	1 (0.4)
Enteritis	0	0	1 (0.4)
Epigastric discomfort	0	0	1 (0.4)
Flatulence	0	0	1 (0.4)
Food poisoning	0	0	2 (0.7)
Frequent bowel movements	0	0	1 (0.4)
Gastrointestinal haemorrhage	0	0	2 (0.7)
Gingival bleeding	1 (1.4)	0	5 (1.8)
Gingival pain	0	0	1 (0.4)
Haematemesis	1 (1.4)	0	0
Haematochezia	0	0	1 (0.4)
Haemorrhoidal haemorrhage	0	0	1 (0.4)
Haemorrhoids	0	0	1 (0.4)
Hiatus hernia	0	0	2 (0.7)
Irritable bowel syndrome	0	0	1 (0.4)
Loose tooth	0	0	1 (0.4)
Mouth haemorrhage	1 (1.4)	0	0
Mouth ulceration	0	0	2 (0.7)
Noninfective sialoadenitis	0	0	1 (0.4)
Oral blood blister	0	0	2 (0.7)
Pancreatic disorder	1 (1.4)	0	1 (0.4)
Rectal haemorrhage	0	0	1 (0.4)
Tongue haematoma	0	0	1 (0.4)
HEPATOBILIARY DISORDERS	0	2 (1.5)	4 (1.4)
Hepatic cirrhosis	0	1 (0.8)	1 (0.4)
Hepatic function abnormal	0	1 (0.8)	1 (0.4)
Hepatic steatosis	0	1 (0.8)	1 (0.4)
Biliary colic	0	0	1 (0.4)
Biliary cyst	0	0	1 (0.4)
Cholelithiasis	0	0	1 (0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8 (11.6)	15 (11.3)	61 (21.5)
Rash	1 (1.4)	5 (3.8)	15 (5.3)
Eczema	1 (1.4)	2 (1.5)	3 (1.1)
Acne	0	1 (0.8)	2 (0.7)
Alopecia	0	1 (0.8)	6 (2.1)
Dermatitis	1 (1.4)	1 (0.8)	3 (1.1)
Dermatitis contact	0	1 (0.8)	1 (0.4)
Erythema nodosum	0	1 (0.8)	2 (0.7)
Photosensitivity reaction	0	1 (0.8)	1 (0.4)
Pruritus	1 (1.4)	1 (0.8)	8 (2.8)
Rash maculo-papular	0	1 (0.8)	5 (1.8)
Rash pruritic	0	1 (0.8)	2 (0.7)
Urticaria	1 (1.4)	1 (0.8)	1 (0.4)
Actinic keratosis	0	0	1 (0.4)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	ITP placebo-controlled pool[a] Placebo (N=69)	 Rilzabrutinib 400 mg BID (N=133)	ITP rilzabrutinib pool[b] Rilzabrutinib any dose (N=284)
Blood blister	0	0	2 (0.7)
Butterfly rash	0	0	1 (0.4)
Cutaneous lupus erythematosus	0	0	1 (0.4)
Decubitus ulcer	0	0	1 (0.4)
Dermatitis acneiform	1 (1.4)	0	1 (0.4)
Dermatitis allergic	0	0	1 (0.4)
Dry skin	0	0	1 (0.4)
Erythema	1 (1.4)	0	1 (0.4)
Hand dermatitis	0	0	2 (0.7)
Pain of skin	0	0	1 (0.4)
Panniculitis	0	0	1 (0.4)
Papule	0	0	1 (0.4)
Petechiae	0	0	8 (2.8)
Psoriasis	0	0	1 (0.4)
Purpura	2 (2.9)	0	2 (0.7)
Rash erythematous	0	0	1 (0.4)
Rash papular	0	0	1 (0.4)
Scab	0	0	1 (0.4)
Skin discolouration	0	0	1 (0.4)
Skin exfoliation	0	0	1 (0.4)
Skin lesion	0	0	2 (0.7)
Skin mass	0	0	1 (0.4)
Skin odour abnormal	0	0	1 (0.4)
Skin striae	0	0	1 (0.4)
Skin warm	0	0	1 (0.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (11.6)	27 (20.3)	79 (27.8)
Arthralgia	3 (4.3)	12 (9.0)	32 (11.3)
Back pain	2 (2.9)	4 (3.0)	19 (6.7)
Pain in extremity	2 (2.9)	4 (3.0)	11 (3.9)
Myalgia	1 (1.4)	3 (2.3)	8 (2.8)
Musculoskeletal pain	0	2 (1.5)	5 (1.8)
Neck pain	0	2 (1.5)	4 (1.4)
Intervertebral disc protrusion	0	1 (0.8)	1 (0.4)
Joint swelling	0	1 (0.8)	3 (1.1)
Muscle spasms	0	1 (0.8)	9 (3.2)
Muscle tightness	0	1 (0.8)	1 (0.4)
Osteonecrosis	0	1 (0.8)	2 (0.7)
Arthritis	0	0	1 (0.4)
Bone lesion	0	0	1 (0.4)
Bone pain	0	0	2 (0.7)
Bursitis	1 (1.4)	0	0
Costochondritis	0	0	3 (1.1)
Flank pain	0	0	1 (0.4)
Intervertebral disc degeneration	0	0	1 (0.4)
Joint stiffness	0	0	1 (0.4)
Lumbar spinal stenosis	0	0	1 (0.4)
Muscle contracture	0	0	1 (0.4)
Musculoskeletal chest pain	0	0	3 (1.1)
Musculoskeletal stiffness	1 (1.4)	0	0
Osteoporosis	0	0	1 (0.4)
Pain in jaw	0	0	1 (0.4)
Scoliosis	0	0	1 (0.4)
Spondyloarthropathy	0	0	1 (0.4)
Spondylolisthesis	0	0	1 (0.4)
Synovitis	0	0	1 (0.4)
RENAL AND URINARY DISORDERS	1 (1.4)	2 (1.5)	10 (3.5)
Bladder stenosis	0	1 (0.8)	1 (0.4)
Nocturia	0	1 (0.8)	1 (0.4)
Chronic kidney disease	0	0	1 (0.4)
Dysuria	0	0	1 (0.4)
Haematuria	0	0	1 (0.4)
Micturition urgency	0	0	1 (0.4)
Proteinuria	0	0	2 (0.7)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	ITP placebo-controlled pool[a] Placebo (N=69)	 Rilzabrutinib 400 mg BID (N=133)	ITP rilzabrutinib pool[b] Rilzabrutinib any dose (N=284)
Stress urinary incontinence	1 (1.4)	0	0
Urinary incontinence	0	0	1 (0.4)
Urine flow decreased	0	0	1 (0.4)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	2 (0.7)
Pregnancy	0	0	2 (0.7)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (2.9)	4 (3.0)	12 (4.2)
Dysmenorrhoea	0	1 (0.8)	2 (0.7)
Erectile dysfunction	0	1 (0.8)	1 (0.4)
Intermenstrual bleeding	0	1 (0.8)	1 (0.4)
Menopausal symptoms	0	1 (0.8)	1 (0.4)
Vaginal haemorrhage	0	1 (0.8)	2 (0.7)
Breast cyst	0	0	1 (0.4)
Cervical dysplasia	0	0	1 (0.4)
Heavy menstrual bleeding	2 (2.9)	0	5 (1.8)
Vulvovaginal dryness	0	0	1 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9 (13.0)	20 (15.0)	66 (23.2)
Asthenia	2 (2.9)	6 (4.5)	8 (2.8)
Pyrexia	0	5 (3.8)	14 (4.9)
Fatigue	4 (5.8)	4 (3.0)	28 (9.9)
Influenza like illness	2 (2.9)	2 (1.5)	8 (2.8)
Face oedema	0	1 (0.8)	2 (0.7)
Illness	0	1 (0.8)	1 (0.4)
Malaise	0	1 (0.8)	7 (2.5)
Oedema peripheral	0	1 (0.8)	5 (1.8)
Thirst	0	1 (0.8)	1 (0.4)
Chest pain	0	0	3 (1.1)
Chills	0	0	2 (0.7)
Facial pain	0	0	1 (0.4)
Gait disturbance	0	0	1 (0.4)
Generalised oedema	0	0	1 (0.4)
Non-cardiac chest pain	0	0	2 (0.7)
Oedema	0	0	3 (1.1)
Pain	0	0	1 (0.4)
Peripheral swelling	0	0	4 (1.4)
Swelling face	1 (1.4)	0	0
Temperature regulation disorder	0	0	1 (0.4)
Vessel puncture site bruise	0	0	1 (0.4)
Vessel puncture site discharge	0	0	1 (0.4)
INVESTIGATIONS	6 (8.7)	12 (9.0)	42 (14.8)
Alanine aminotransferase increased	2 (2.9)	3 (2.3)	9 (3.2)
Aspartate aminotransferase increased	2 (2.9)	3 (2.3)	9 (3.2)
Coombs test positive	0	2 (1.5)	2 (0.7)
Hepatic enzyme increased	1 (1.4)	1 (0.8)	2 (0.7)
Platelet count decreased	0	1 (0.8)	2 (0.7)
Platelet count increased	0	1 (0.8)	2 (0.7)
Serum ferritin decreased	0	1 (0.8)	1 (0.4)
Transaminases increased	0	1 (0.8)	1 (0.4)
Weight decreased	1 (1.4)	1 (0.8)	3 (1.1)
Adenovirus test positive	0	0	1 (0.4)
Alanine aminotransferase abnormal	0	0	1 (0.4)
Aspartate aminotransferase abnormal	0	0	1 (0.4)
Blood alkaline phosphatase abnormal	0	0	1 (0.4)
Blood alkaline phosphatase increased	0	0	2 (0.7)
Blood bilirubin increased	0	0	3 (1.1)
Blood creatine phosphokinase increased	0	0	2 (0.7)
Blood creatinine increased	0	0	1 (0.4)
Blood fibrinogen increased	0	0	1 (0.4)
Blood glucose abnormal	0	0	1 (0.4)
Blood iron decreased	0	0	2 (0.7)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	ITP placebo-controlled pool[a] Placebo (N=69)	ITP placebo-controlled pool[a] Rilzabrutinib 400 mg BID (N=133)	ITP rilzabrutinib pool[b] Rilzabrutinib any dose (N=284)
Blood lactate dehydrogenase increased	0	0	1 (0.4)
Blood pressure increased	0	0	2 (0.7)
Blood urine present	0	0	1 (0.4)
Fibrin D dimer increased	0	0	1 (0.4)
Gamma-glutamyltransferase abnormal	0	0	1 (0.4)
Gamma-glutamyltransferase increased	0	0	3 (1.1)
Heart rate irregular	0	0	1 (0.4)
Lymphocyte count decreased	1 (1.4)	0	1 (0.4)
Lymphocyte count increased	0	0	1 (0.4)
Neutrophil count decreased	0	0	1 (0.4)
SARS-CoV-2 test positive	0	0	3 (1.1)
Vitamin D decreased	0	0	1 (0.4)
Weight increased	1 (1.4)	0	3 (1.1)
White blood cell count increased	0	0	1 (0.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (5.8)	11 (8.3)	49 (17.3)
Contusion	0	2 (1.5)	24 (8.5)
Ligament sprain	0	2 (1.5)	3 (1.1)
Accident at work	0	1 (0.8)	1 (0.4)
Fall	1 (1.4)	1 (0.8)	5 (1.8)
Infusion related reaction	0	1 (0.8)	1 (0.4)
Joint injury	0	1 (0.8)	2 (0.7)
Limb injury	1 (1.4)	1 (0.8)	4 (1.4)
Periorbital haematoma	0	1 (0.8)	1 (0.4)
Skin abrasion	0	1 (0.8)	2 (0.7)
Skin laceration	0	1 (0.8)	1 (0.4)
Animal bite	0	0	1 (0.4)
Arthropod bite	0	0	3 (1.1)
Bone contusion	0	0	1 (0.4)
Eye contusion	0	0	1 (0.4)
Head injury	0	0	1 (0.4)
Humerus fracture	0	0	1 (0.4)
Inappropriate schedule of product administration	0	0	1 (0.4)
Ligament injury	0	0	1 (0.4)
Lumbar vertebral fracture	0	0	1 (0.4)
Meniscus injury	1 (1.4)	0	0
Scratch	0	0	1 (0.4)
Seroma	0	0	1 (0.4)
Skin injury	0	0	1 (0.4)
Spinal compression fracture	0	0	1 (0.4)
Splenosis	1 (1.4)	0	0
Subdural haematoma	0	0	1 (0.4)
Tendon rupture	0	0	1 (0.4)
Thermal burn	0	0	1 (0.4)
Traumatic haematoma	0	0	2 (0.7)

Abbreviations: BID = twice daily; COVID-19 = coronavirus disease 2019; DB = double-blind; ITP = immune thrombocytopenia; LTE = long term extension; MedDRA = medical dictionary for regulatory activities; OL = open-label; PT = preferred term;SOC = system organ class; TEAE = treatment-emergent adverse event.
MedDRA dictionary version 26.1.

a ITP placebo-controlled pool (iSAF1) includes Phase 3 PRN1008-018 during the double-blind treatment period.

b ITP Rilzabrutinib pool (iSAF2) includes Phase 1/2 PRN1008-010 and Phase 3 PRN1008-018 during the entire treatment period (Main/DB, OL, LTE, if applicable, cumulatively).

Table sorted by SOC internationally agreed order and by decreasing frequency of PT based on any TEAE in the Rilzabrutinib 400 mg BID group.

Severity of TEAEs

Study PRN1008-018

Double-blind period

In the rilzabrutinib group, there were 47 (35.3%) participants with a TEAE of Grade 1, 49 (36.8%) participants with a TEAE of Grade 2, 10 (7.5%) participants with a TEAE of Grade 3, 4 (3.0%) participants with a TEAE of Grade 4, and 1 (0.8) participant with a TEAE of Grade 5 intensity. The Grade 3 TEAEs by PT were anaemia, asthenia, COVID-19, epistaxis, facial paralysis, hepatic cirrhosis, hyperglycaemia, ITP, hepatic enzyme increased, intermenstrual bleeding, otitis media acute, pelvic inflammatory disease, periorbital hematoma, peripheral embolism, renal abscess, sepsis, swelling of eyelid, urinary tract infection, and vaginal haemorrhage in 1 (0.8%) participant each. There were 4 (3.0%) participants with a Grade 4 TEAE, which included neutropenia, thrombocytopenia, oesophageal varices haemorrhage (in a participant with pre-existing cirrhosis), and platelet count decreased in 1 [0.8%] participants each, and 1 (0.8%) participant with a Grade 5 TEAE, which was pneumonia.

In the placebo group, there were 17 (24.6%) participants with a TEAE of Grade 1, 25 (36.2%) participants with a TEAE of Grade 2, 8 (11.6%) participants with a TEAE of Grade 3, 2 (2.9%) participants with a TEAE of Grade 4, and no participants with a TEAE of Grade 5. Grade 3 TEAEs were reported in 8 (11.6%) participants, which included conjunctival haemorrhage, heavy menstrual bleeding, hematemesis, hypertension, ITP, mouth haemorrhage, purpura, and syncope in 1 (1.4%) participant each. There were 2 Grade 4 TEAEs, which were thrombocytopenia in 2 (2.9%) participants.

ITP rilzabrutinib pool

In the rilzabrutinib any dose group, there were 61 (21.5) participants with a TEAE of Grade 1, 127 (44.7%) participants with a TEAE of Grade 2, 41 (14.4%) participants with a TEAE of Grade 3, 20 (7.0%) participants with a TEAE of Grade 4, and 1 (0.4%) participant with a TEAE of Grade 5 intensity.

Among the 20 (7.0%) participants with a Grade 4 TEAE, PTs were thrombocytopenia in 11 (3.9%) participants; platelet count decreased in 2 (0.7%) participants; and COVID-19 pneumonia, neutropenia, Evans syndrome, oesophageal varices haemorrhage, haematuria, heavy menstrual bleeding, and subdural hematoma in 1 (0.4%) participant each.

In the rilzabrutinib any dose group, there were 62 (21.8%) participants in the rilzabrutinib any dose group with a Grade ≥3 TEAE. The most frequent SOCs (≥5%) with Grade ≥3 TEAEs were Blood and lymphatic system disorders (22 [7.7%] participants) and Infections and infestations (15 [5.3%] participants).

Treatment-Related AEs

Study PRN1008-018

Double-blind period

A higher percentage of participants in the rilzabrutinib group experienced TEAEs that were considered related to treatment compared with the placebo group (68 [51.1%] versus 12 [17.4%] participants, respectively). Treatment-related TEAE was most frequently (≥20% participants) in the SOC of GI disorders (52 [39.1%] participants for the rilzabrutinib group.

The most frequently reported treatment-related TEAEs by PT (≥5%) in the rilzabrutinib group diarrhea (30 [22.6%] participants), nausea (23 [17.3%] participants), headache (10 [7.5%] participants), abdominal pain (8 [6.0%] participants), and vomiting (7 [5.3%] participants).

ITP rilzabrutinib pool

In the rilzabrutinib any dose group, there were 148 (52.1%) participants with a TEAE considered by the Investigator as related to study drug. The most frequent SOC (≥20%) was GI disorders (116 [40.8%] participants). The most frequent PTs (≥10%) were diarrhea (74 [26.1%] participants) and nausea (61 [21.5%] participants).

The primary assessment for adverse drug reactions was initially conducted on the safety population from the DB period of study PRN1008-018, which was comprised of all adult participants who received at least 1 dose of study drug (rilzabrutinib 400 mg BID [n=133] and placebo [n=69]).

Identification of potential ADRs was based on the following criteria:

- The PTs or cluster of PTs (identified based on medical concept consisting of similar medical terms at PT and HLT levels in the pooled safety population) with incidence of n≥5 participants or ≥3.8% in the rilzabrutinib group were reviewed for potential causal relationship taking into consideration modified Bradford-Hill criteria including biologic plausibility, presence of potential confounders and/or alternative explanation, and plausible exposure relationship.
- Less frequent PTs, AESI, and important potential risks were also evaluated to determine if any PT qualified as an ADR based on pathobiological mechanisms or medical judgment.

Additional analyses were provided upon request and included ADR characterization based on pooled safety data from ITP population and available data from other indications, including single events (without a threshold) and Investigator causality assessments of reported treatment emergent adverse event (TEAE) with respect to rilzabrutinib and concomitant ITP therapy(ies) (including corticosteroids [CS] and/or thrombopoietin receptor agonists [TPO-RA]). Important potential risks of rilzabrutinib, risks of concomitant ITP therapies and other BTK inhibitors, preclinical findings and the natural course of ITP were taken into consideration in the adverse drug reaction (ADR) process, including review of individual participant underlying conditions and concomitant medications for potential confounders.

The applicant has assessed the ADRs for rilzabrutinib in ITP as shown below for inclusion in Section 4.8 of the SmPC.

- Infections and Infestations: *Very Common*: COVID-19, Nasopharyngitis; *Common:* Pneumonia
- Nervous System Disorders: *Very Common*: Headache; *Common*: Dizziness
- Respiratory, Thoracic, and Mediastinal Disorders: Common: Cough
- Gastrointestinal Disorders: *Very Common*: Diarrhoea, Nausea, Abdominal pain; *Common*: Vomiting, Dyspepsia
- Musculoskeletal and Connective Tissue Disorder: *Very Common*: Arthralgia
- Skin and Subcutaneous Tissue Disorder: *Common*: Rash

2.6.8.3. Serious adverse event/deaths/other significant events

AESIs

Adverse events of special interest, based on the important potential risks, included ALT >3× ULN, infection Grade 4 or 5 where the participant is hospitalized ≥24 hours and/or requires emergency care and/or requires IV antibiotics, as well as events of pregnancy and symptomatic overdose.

Increase in ALT >3× ULN

Liver enzyme increase is an important potential risk of rilzabrutinib based on preclinical and clinical data.

In the double-blind period of Study PRN1008-018 there were 4 (3.0%) participants in the rilzabrutinib group and 1 (1.4%) participant in the placebo group who had an AESI of ALT increase >3× ULN in Study PRN1008-018. In the rilzabrutinib group, the ALT increase >3× ULN category included the TEAEs of ALT increased (2 [1.5%] participants), hepatic enzyme increased (1 [0.8%] participant), and hepatic function abnormal (1 [0.8%] participant). In the placebo group, the ALT increase >3× ULN category included the TEAE hepatic enzyme increased in 1 (1.4%) participant.

For liver function test increase events, regardless of Grade, there were 5.3% of participants in the rilzabrutinib group versus 4.3% of participants in the placebo group. They were mainly Grades 1 to 2. They include TEAEs in the rilzabrutinib group of ALT increased and aspartate aminotransferase (AST) increased in 3 (2.3%) participants and hepatic enzyme increased and transaminase increased 1 (0.8%) participant each. In placebo group, there were TEAEs of ALT and AST increased in 2 (2.9%) participants and hepatic enzyme increased in 1 (1.4%) participant. Participants generally recovered without change to IMP. There were no participants who met the criteria of Hy's law.

Three participants experienced ALT or AST >3× ULN and bilirubin >2× ULN. One participant was treated with rilzabrutinib and another participant was dosed with placebo in study PRN1008-018; the third participant was treated with rilzabrutinib in study PRN1008-010 Part B. The descriptions of the 2 rilzabrutinib-treated participants are described below:

This case (from Study PRN1008-018) involves a participant who experienced bleeding oesophageal varices (Grade 4), decompensated cirrhosis (Grade 3), and increase in liver enzyme while treated with rilzabrutinib during the DB portion of Study PRN1008-018. His medical history includes cirrhosis due to non-alcoholic steatosis, which was assessed as mild and compensated with normal AST, ALT, and albumin prior to commencing the study. He also had a history of variceal bleeding (s/p variceal ligation). Hepatitis B surface antigen and hepatitis B core antibody were negative at screening. Twenty-eight days following the first dose of IMP administration, the participant was hospitalized for serious variceal bleeding and event cirrhosis decompensated, as well as nonserious Grade 2 hypokalaemia. Liver enzyme increased peaked at ALT was at 411 U/L and AST was at 297 U/L, both ≥3× ULN, with bilirubin at ≥2× ULN. Rilzabrutinib was withdrawn; the participant recovered. The Investigator assessed the events as not related to rilzabrutinib, but rather to poorly treated hepatic cirrhosis. The majority of a panel of 3 independent hepatic experts assessed the event as unlikely related.

Study PRN1008-010 Part B enrolled a participant with ITP and remote prior history of hepatitis B, hepatitis A, and recent stable liver function test results. He experienced hepatitis E on study Day 177. Peak liver function test results include ALT 571 U/L (12.7× ULN, Grade 3), AST 483 U/L (12× ULN, Grade 3), and bilirubin 77 µmol/L (3.7× ULN, Grade 3). Hepatitis E was confirmed on study Day 177. Rilzabrutinib and other medications such as statins were interrupted, participant recovered, and rilzabrutinib was restarted. The events were assessed as not related by the Investigator. A panel of 3 independent hepatic experts assessed the event as unlikely related.

ITP rilzabrutinib pool

For increased liver function tests, regardless of Grade of increase over ULN, 16 (5.6%) experienced an LFT increased event (SMQ Liver Related Investigations, Signs, and symptoms, narrow). Of these, there were 9 (3.2%) participants in the rilzabrutinib any dose group who had a TEAE of ALT increased, 9 (3.2%) participants with AST increased, 3 (1.1%) participants with blood bilirubin increased, 3 (1.1%) participants with gamma-glutamyltransferase increased, 2 (0.7%) participants with hepatic enzyme increased, and 1 (0.4%) participant each for transaminases increased, ALT abnormal, AST abnormal, gamma-glutamyl transferase abnormal, and hepatic function abnormal.

Infection

Treatment-emergent serious infections

Grade 3 or higher infections in adult ITP participants, based on the SOC Infections and infestations, are presented below for each of the studies, as well as the pooled data.

Study PRN1008-018

Double-blind period

In general, TEAEs of infection regardless of Grade, were Grade 1 and 2 and occurred more frequently in the rilzabrutinib group compared with the placebo group (infections overall 33.1% in the rilzabruininb group versus 20.3% in the placebo group). Most infections recovered without change to IMP treatment.

In the rilzabrutinib group, 5 (3.8%) participants experienced a TEAE of infections Grade ≥3, which were considered an SAE for 3 (2.3%) participants. One (0.8%) participant had a TEAE of infection of Grade ≥3 (pneumonia) that led to death and permanent study discontinuation. The remainder of the participants recovered, rilzabrutinib treatment was not changed or interrupted and none of the events were assessed as related to rilzabrutinib by the Investigator. Five participants experienced Grade ≥3 infections, with 1 (0.8%) participant experiencing each infections PT, ie, COVID-19, pneumonia, urinary tract infection, otitis media acute, pelvic inflammatory disease, and renal abscess and sepsis (in the same participant). Four of the 5 participants recovered with dose interruption or no change to rilzabrutinib dose. Four participants reported SAEs of infection, which were all Grade ≥3, except 1 participant who experienced a Grade 2 SAE, wound infection (of the wrist), who recovered; rilzabrutinib treatment was not changed; and the event was assessed as not related to IMP by the Investigator.

In the placebo group, there were no participants with a treatment emergent infection of Grade ≥3.

ITP rilzabrutinib pool

There were 15 (5.3%) participants in the rilzabrutinib any dose group with a TEAE of infection Grade ≥3. Among them, 9 (3.2%) participants experienced a TEAE of infection Grade ≥3 that was considered an SAE, the total number of participants with SAEs of infection (all Grades) was 11 (3.9%). There was 1 (0.4%) participant who had a TEAE with fatal outcome in this group (Grade 5 pneumonia). Four (1.4%) participants in the rilzabrutinib any dose group were discontinued due to a TEAE of infection Grade ≥3 (1 participant each with pneumonia [Grade 3], pneumonia [Grade 5], subcutaneous abscess [Grade 3], and urosepsis [Grade 3], all of which were considered not related). Two (0.7%) participants experienced a TEAE of infection Grade ≥3 that was considered by the Investigator as related to IMP. The most common infections were COVID-19 in 3 (1.1%) participants and pneumonia, sepsis, and urinary tract infection in 2 (0.7%) participants each.

Grade 4 and 5 infections (AESI)

In Study PRN1008-018 (and the ITP placebo-controlled pool), 1 (0.8%) participant in the rilzabrutinib group experienced pneumonia (Grade 5 intensity), which met AESI criteria. No participant in the placebo group had a Grade 4 or 5 infection.

In the ITP rilzabrutinib pool (rilzabrutinib any dose group), there was 1 (0.4%) participant each with a Grade 4 infection (COVID-19 pneumonia; pneumonia [Grade 4] in 1 [6.3%] participant in Study PRN1008-010 Part A, which resulted in permanent IMP discontinuation) and a Grade 5 infection (see above) reported.

SAEs

Study PRN1008-018

Double-blind period

A total of 12 (9.0%) participants in the rilzabrutinib group and 8 (11.6%) participants in the placebo group experienced an SAE during the DB period. In the rilzabrutinib group, SOCs (≥1%) with the most participants who experienced an SAE were Infections and infestations (4 [3.0%] participants and 0 participants, respectively), GI disorders (1 [0.8%] and 2 [2.9%] participants, respectively), Blood and lymphatic system disorders (2 [1.5%] participants and 3 [4.3%] participants, respectively), and

Investigations (2 [1.5%] participants and 0 participants, respectively). In the rilzabrutinib group, no treatment-emergent SAE (by PT) was reported in more than 1 participant, and in the placebo group, thrombocytopenia was the only SAE that occurred in more than 1 participant (2 [2.9%] participants in total). All participants with SAEs recovered, except for 1 participant with an SAE of pneumonia, which had a fatal outcome and is described section "Deaths". One (0.8%) participant in the rilzabrutinib group had an SAE that was considered related to rilzabrutinib by the Investigator (peripheral embolism), and none of the SAEs in the placebo group were considered treatment-related.

ITP rilzabrutinib pool

There were 48 (16.9%) participants in the rilzabrutinib any dose group who experienced a treatment-emergent SAE. The SOCs with the most participants who experienced an SAE were Blood and lymphatic system disorders (14 [4.9%] participants) and Infections and infestations (11 [3.9%] participants) in the rilzabrutinib any dose group. In the rilzabrutinib any dose group, there were 3 (1.1%) participants with an SAE considered related to IMP by the Investigator. The PTs for these SAEs were bronchopulmonary aspergillosis and cytomegalovirus viremia in the same participant (1 [0.4%] participant), peripheral embolism (1 [0.4%] participant), and interstitial lung disease (1 [0.4%] participant).

Deaths

Overall, there were 2 participants in the rilzabrutinib any dose group who had a TEAE that led to death: 1 participant in Study PRN1008-018 in the rilzabrutinib group had an SAE of pneumonia that led to death; and 1 participant in Study PRN1008-010 Part A with Evans syndrome following study withdrawal.

Brief overview of the event in the DB period of Study PRN1008-018:

A participant≥75-year-old with history of ITP, splenectomy, subarachnoid haemorrhage) and upper limb fracture, as well as a fall during the study (4 days prior to pneumonia) experienced a fatal pneumonia. Medications included prednisolone 32 mg QD (prior and concomitant), eltrombopag (prior and concomitant), and levetiracetam (concomitant).

The hospital admission for pneumonia was 1 month 28 days after the first administration and 3 days after the last dose of IMP. The participant did not have neutropenia. The type of organisms were nocardia spp. Bronchoscopy confirmed pneumonia (aspergillus fumigatus, candida albicans). Rilzabrutinib was withdrawn. Fifteen days after hospital admission, the participant died. The cause of death was reported as cardiac and respiratory arrest due to pneumosepsis. There was no information regarding autopsy. The Investigator assessed the event as not related to IMP. The Sponsor assessed the event as not reportable (not related).

One additional TEAE that led to death was reported in the ITP rilzabrutinib pool from study PRN1008-010 Part A. No participants died during the active (ongoing) part of PRN1008-010 Part A, however, 1 participant had a Grade 4 SAE of Evans syndrome, which was recognized on Day 8 after study drug initiation. Rilzabrutinib treatment (400 mg BID) was discontinued as the participant did not meet the entry criteria of the study (participant was diagnosed with Evan's syndrome instead of ITP) and use of rescue medication, which was not permitted. IMP was discontinued and the participant was withdrawn from the study 4 days later. The participant was hospitalized and had a fatal outcome reported at approximately 100 days (which was beyond the routine follow-up period) and after the participant had discontinued from the study due to sequalae of the underlying conditions. The event was assessed as not related to IMP.

Other AEs of interest

Treatment-emergent thromboembolic events

Study PRN1008-018

The incidence of thromboembolic events in the DB period was low. One (0.8%) participant experienced a thromboembolic event, which was peripheral embolism (reported as Grade 3, serious [hospitalization] and related to study drug per the Investigator; participant recovered). This participant had prior significant risk factors including a history of peripheral arterial occlusive disease and vascular bypass surgery at the same anatomical site of the thrombosis. Additional prior significant risk-factors for thromboembolism included eltrombopag 75 mg/day, smoker, hypercholesterolemia, and hypertension.

No participants in the placebo group experienced a thromboembolic event.

ITP rilzabrutinib pool

In the rilzabrutinib any dose group, there were 5 (1.8%) participants with a thromboembolic event. These events included 2 (0.7%) participants with pulmonary embolism and 1 (0.4%) participant each with peripheral embolism, antiphospholipid syndrome, deep vein thrombosis, and transient ischemic attack.

Table 28: Number (%) of participants experiencing treatment emergent neutropenia, anemia or thromboembolic events by PT - Adult safety population

	ITP placebo-controlled pool[a]		ITP rilzabrutinib pool[b]
AE category Preferred Term n(%)	**Placebo (N=69)**	**Rilzabrutinib 400 mg BID (N=133)**	**Rilzabrutinib any dose (N=284)**
Neutropenia[c]	0	1 (0.8)	3 (1.1)
Neutropenia	0	1 (0.8)	2 (0.7)
Idiopathic neutropenia	0	0	1 (0.4)
Leukopenia	0	0	1 (0.4)
Neutrophil count decreased	0	0	1 (0.4)
Anaemia[d]	5 (7.2)	5 (3.8)	18 (6.3)
Anaemia	4 (5.8)	5 (3.8)	18 (6.3)
Normochromic normocytic anaemia	1 (1.4)	0	0
Thromboembolic eventse	0	1 (0.8)	5 (1.8)
Peripheral embolism	0	1 (0.8)	1 (0.4)
Antiphospholipid syndrome	0	0	1 (0.4)
Deep vein thrombosis	0	0	1 (0.4)
Pulmonary embolism	0	0	2 (0.7)
Transient ischaemic attack	0	0	1 (0.4)

Abbreviations: DB = double-blind; ITP = immune thrombocytopenia; LTE = long term extension; MedDRA = medical dictionary for regulatory activities; OL = open-label; PT = preferred term; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event;.
MedDRA dictionary version 26.1.
Percentage is based on adult safety population.
a ITP placebo-controlled pool (iSAF1) includes Phase 3 PRN1008-018 during the double-blind treatment period.
b ITP Rilzabrutinib pool (iSAF2) includes Phase 1/2 PRN1008-010 and Phase 3 PRN1008-018 during the entire treatment period (Main/DB, OL, LTE, if applicable, cumulatively).
c Neutropenia identified by CMQ10801.
d Anemia identified by SMQ ="Haematopoietic erythropenia", #20000029, broad and narrow search.
e Thromboembolic events identified by SMQ ="Embolic and thrombotic events", #20000081, broad and narrow search..
Table sorted by decreasing frequency of PT within each AE category in the Rilzabrutinib 400 mg BID group

BTKi-associated events - Cytopenias

Treatment-emergent cytopenia (neutropenia and anemia)

Study PRN1008-018

The incidence of neutropenia in the DB period was low. One (0.8%) participant in the rilzabrutinib group experienced a treatment-emergent neutropenia. This event was assessed as Grade 4 severity, and it was considered as related to rilzabrutinib by the Investigator; rilzabrutinib was discontinued, and the participant recovered. No participants in the placebo group experienced treatment emergent neutropenia.

The percentage of participants who experienced treatment-emergent anemia was lower in the rilzabrutinib group (5 [3.8%] participants, generally Grades 1 to 2 with 1 nonserious Grade 3; all participants recovered) compared with the placebo group (5 [7.2%] participants; all recovered).

ITP rilzabrutinib pool

In the rilzabrutinib any dose group, there were 3 (1.1%) participants with neutropenia, which included 2 (0.7%) participants with neutropenia (nonserious, Grade 4, related, drug withdrawn, recovered; and nonserious, Grade 3, not related, recovered), 1 (0.4%) participant with leukopenia (nonserious, Grade 1, recovered), 1 (0.4%) participant with idiopathic neutropenia (nonserious, Grade 2, recovered), and 1 (0.4%) participant with a reported lab abnormality of neutrophil count decreased (nonserious, Grade 3, not related, recovered).

There were 20 (7.0%) participants with anaemia in the rilzabrutinib any dose group. Several had a history of anaemia prior to study enrolment.

BTKi-associated events – Bleeding events, severity

Grade ≥3 bleeding events

Study PRN1008-018

Overall, in the ITP placebo-controlled pool, there were 5 (3.8%) participants in the rilzabrutinib group who experienced a TESAE of bleeding event Grade ≥3. None of these TEAEs of bleeding event Grade ≥3 led to death. There was 1 (0.8%) participant who discontinued the study due to a TEAE of bleeding event Grade ≥3 in the rilzabrutinib group. No participants had a TEAE of bleeding event Grade ≥3 that was considered by the Investigator as related to IMP. The SAE PTs in participants in the rilzabrutinib group were all reported in 1 (0.8%) participant each.

There were 6 (8.7%) participants in the placebo group who experienced a TEAE of bleeding event Grade ≥3, 5 of which were considered SAEs. No participant in the placebo group died or permanently discontinued the study drug due to a TEAE of bleeding event Grade ≥3. One (1.4%) participant in the placebo group had a TEAE of bleeding event Grade ≥3 that was considered by the Investigator as related to IMP. The SAE PTs in participants in the placebo group were all reported in 1 (1.4%) participant each.

ITP rilzabrutinib pool

Overall, there were 19 (6.7%) participants in the rilzabrutinib any dose group who experienced a TEAE of bleeding event Grade ≥3, of which 17 (6.0%) participants were considered to be SAEs. No TEAEs of bleeding event Grade ≥3 led to death. There were 5 (1.8%) participants in the rilzabrutinib any dose group who permanently discontinued rilzabrutinib due to a TEAE of bleeding event Grade ≥3. One (0.4%) participant had a TEAE of bleeding event Grade ≥3 that was considered by

the Investigator as related to IMP. The SAE PT of ITP was reported in 3 (1.1%) participants, and all other PTs were reported in ≤2 (<1.0%) participants each.

Atrial fibrillation/cardiac arrhythmias

Study PRN1008-018

During the DB period, 2 (1.5%) participants in the rilzabrutinib group reported single cases of treatment-emergent arrythmias. The TEAEs were arrhythmia in 1 (0.8%) participant, while a second participant had both extrasystoles and tachycardia (1 [0.8%] participant).

In the placebo group, 3 (4.3%) participants reported single cases of palpitation, syncope, and unspecified right bundle branch block (1 [1.4%] participant each). No case of atrial fibrillation was reported.

ITP rilzabrutinib pool

There were 8 (2.8%) participants in the rilzabrutinib any dose group with a cardiac arrhythmia. Most of these TEAEs were Grade 1 or 2 and included palpitations (3 [1.1%] participants), tachycardia (2 [0.7%] participants), atrial fibrillation (2 [0.7%] participants), arrhythmia (1 [0.4%] participant), extrasystoles (1 [0.4%] participant), bradycardia (1 [0.4%] participant), heart rate irregular (1 [0.4%] participants), and syncope (1 [0.4%] participant; Grade 3)

The 2 cases of atrial fibrillation in study PRN1008-010 Part B (based on the pooled data cutoff date) are described as follows:

- A participant (<65 years old), with medical history of rheumatic fever, mitral valve prolapse and Lyme disease, experienced Grade 2 atrial fibrillation. The treatment with IMP was not changed. He was prescribed aspirin and apixaban for atrial fibrillation and he recovered. The Investigator assessed the event as nonserious and not related to IMP.
- A participant (>65 years old), with a medical history of paroxysmal atrial fibrillation (ongoing), hypertension, ischemic heart disease, s/p coronary artery bypass surgery, and mild atrial valve regurgitation, experienced Grade 2 nonserious atrial fibrillation from study Day 381. The dose of IMP was not changed; participant recovered. The Investigator assessed the atrial fibrillation as not related to IMP.

Malignancy

There were 5 (1.8%) participants with treatment -emergent malignancy in the rilzabrutinib any dose rilzabrutinib group. These TEAEs included Bowen's disease, lung adenocarcinoma, metastatic malignant melanoma, as well as neoplasm skin and ovarian clear cell carcinoma in 1 (0.4%) participant each, none of which were considered to be related to treatment by the Investigator. The Grade 3 event of metastatic melanoma was reported as an SAE and the participant discontinued the study due to this SAE.

2.6.8.4. Laboratory findings

Clinical laboratory evaluations

Results of clinical laboratory evaluations are presented for the double-blind period of the placebo-controlled ITP pool.

Hematology

RBC

In the rilzabrutinib group, during the DB period, the erythrocyte count was high in 3 (2.3%) participants and showed a shift from normal/missing to high in 2 (1.5%) participants. During DB period, haemoglobin was low in 7 (5.3%) participants and showed a decrease from baseline in 9 (6.9%) participants, while haematocrit was low in 19 of 132 (14.4%) of participants and showed a shift from normal to low in 11 (9.1%) participants.

In the placebo group, during the DB period, the erythrocyte count was high in 3 (4.4%) participants and showed a shift from normal/missing to high in 3 (4.4%) participants. During the DB period, the haemoglobin was low in 5 (7.4%) participants and showed a decrease from baseline in 8 (11.8%) participants, while haematocrit was low in 9 (13.2%) participants and high in 1 (1.5%) participant.

WBC

In the rilzabrutinib group, during the DB period, the WBC count was low in 8 (6.1%) participants and high in 11 (8.3%) participants. There was a shift in WBCs from normal/missing to low in 8 (6.3%) participants and from normal/missing to high in 5 (4.0%) participants. During the DB period, neutrophils were low in 5 (3.8%) participants and shifted from normal/missing to low in 5 (3.8%) participants, while lymphocytes were high in 19 (14.4%) participants and shifted from normal/missing to high in 15 (11.7%) participants, and monocytes were high in 61 (46.2%) participants and shifted from normal/missing to high in 39 (37.1%) participants. In addition, during the DB period, basophils were high in 32 (24.2%) participants and shifted from normal/missing to high in 27 (21.6%) participants, and eosinophils were high in 4 (3.0%) participants and shifted from normal/missing to high in 4 (3.1%) participants.

In the placebo group, during DB period, the WBC count was not low in any participants and was high in 8 (11.8%) participants. There was a shift in WBCs from normal/missing to high in 4 (6.3%) participants. During the DB period, neutrophils were low in 2 (2.9%) participants and shifted from normal/missing to low in 2 (2.9%) participants, lymphocytes were high in 13 (19.1%) participants and shifted from normal/missing to high in 10 (15.4%) participants, and monocytes were high in 31 (45.6%) participants and shifted from normal/missing to high in 23 (40.4%) participants. In addition, during the DB period, basophils were high in 14 (20.6%) participants and shifted from normal/missing to high in 11 (17.5%) participants, and eosinophils were high in 2 (2.9%) participants and shifted from normal/missing to high in 2 (3.0%) participants.

Coagulation

In the rilzabrutinib group, during the DB period, 8 (6.2%) participants had total prothrombin time shorter than the lower limit of normal (LLN) and 58 (45.0%) participants had a total prothrombin time longer than the ULN. There were 7 (7.3%) participants with a shift in total prothrombin time from normal to shorter than the LLN and 35 (36.5%) participants with a shift from normal to ULN. There was 1 (3.1%) participant with a shift from longer than the ULN to shorter than the LLN. During the DB period, for the prothrombin international normalized ratio (INR), no participants had a result below the LLN and 29 (22.5%) participants had a result above the ULN. There were 22 (18.5%) participants with a result that shifted from normal to above the ULN. There were no other shifts in the INR. During the DB period, for the activated partial thromboplastin time (aPTT), there were 13 (10.1%) participants with a result shorter than the LLN and 12 (9.3%) participants with a result longer than the ULN. Eleven (9.8%) participants had a shift from normal to shorter than the LLN and 2 (1.8%) participants had a shift from normal to longer than the ULN. There were no other shifts in the aPTT.

In the placebo group, during the DB period, 5 (7.4%) participants had total prothrombin time shorter than the LLN and 22 (32.4%) participants had a total prothrombin time longer than the ULN. There were 5 (10.2%) participants with a shift in total prothrombin time from normal to shorter than the LLN and 10 (20.4%) participants with a shift from normal to longer than the ULN. There was 1 (100%) participant with a shift from shorter than the LLN to above the ULN. During the DB period, for the prothrombin INR, 1 (1.5%) participant had a result below the LLN and 11 (16.2%) participants had a result above the ULN. There was 1 (1.6%) participant with a shift from normal to below the LLN and 8 (13.1%) participants with a result that shifted from normal to above the ULN. There were no other shifts in the INR. During the DB period, for the aPTT, there were 7 (10.3%) participants with a result shorter than the LLN and 6 (8.8%) participants with a result longer than the ULN. Six (9.4%) participants had a shift from normal to shorter than the LLN and 3 (4.7%) participants had a shift from normal to longer than the ULN. There were no other shifts in the aPTT.

Chemistry

Liver function parameters

During the DB period, the incidence of participants with at least one PCSA in liver function was low and similar between treatment groups. All PCSAs in liver function occurred with an incidence <5% (regardless of baseline status). Among the participants with a PCSA in ALT, most were at least a Grade 1 (>3× ULN) increase (4/131 [3.1%] and 1/68 [1.5%] in the rilzabrutinib and placebo groups, respectively). Grade 2 (>5× ULN) ALT PCSAs occurred in 1/131 (0.8%) participants and 1/68 (1.5%) participants, respectively. Grade 3 (>10× ULN) ALT PCSAs occurred in 1/131 (0.8%) participants in the rilzabrutinib group and 0 in the placebo group. Among the participants with a PCSA in total bilirubin, most were at least a Grade 1 increase (2/131 [1.5%] and 3/68 [4.4%] in the rilzabrutinib and placebo groups, respectively). Grade 2 total bilirubin PCSAs occurred in 1/131 (0.8%) participants and 1/68 (1.5%) participants, respectively. One (0.8%) participant in the rilzabrutinib group and 1 (1.5%) participant in the placebo group had an ALT >3× ULN and total bilirubin >2× ULN during the DB period. No liver function test abnormalities met the criteria of Hy's law.

Renal function parameters

There were no clinically meaningful changes over time in mean renal function parameters observed throughout the course of the study. In the rilzabrutinib group, no participants had high creatinine levels. During the DB period, 10 (7.6%) participants had an increase in creatinine from baseline to at least Grade 1, and no participant had an increase in creatinine from baseline to at least Grade 2. There were no participants with high urea nitrogen.

In the placebo group, no participants had high creatinine levels. During the DB period, 1 (1.5%) participant had an increase in creatinine from baseline to at least Grade 1, and no participant had an increase in creatinine from baseline to at least Grade 2. There were no participants with high urea nitrogen.

Vital signs, physical findings and other observations related to safety

Vital signs

In the rilzabrutinib group, 2 (1.5%) participants had systolic blood pressure that was low and decreased from baseline from baseline, while 4 (3.0%) participants had systolic blood pressure that was high and increased from baseline. One (0.8%) participant had diastolic blood pressure that was high and increased from baseline. One (0.8%) participant had pulse rate that was high and increased from baseline. Sixteen (12.1%) participants had weight that decreased from baseline and 16 (12.1%) participants had weight that increased from baseline.

In the placebo group, 2 (2.9%) participants had systolic blood pressure that was low and decreased from baseline, while 2 (2.9%) participants had systolic blood pressure that was high and increased from baseline. No participants had diastolic blood pressure that was high and increased from baseline or pulse rate that was high and increased from baseline. Four (5.9%) participants had weight that decreased from baseline and 9 (13.2%) participants had weight that increased from baseline.

Electrocardiogram

ECG variables included heart rate, PR interval, QRS duration, QT interval, QTc (Fridericia's formula, QTcF), and RR interval.

In the rilzabrutinib group, the most frequent PCSA in heart rate was >90 beats/min (10 [8.3%] participants). One (0.8%) participant had a heart rate >100 beats/min, which was also increased ≥20 msec from baseline. There were no participants with a heart rate >120 beats/min. The PR interval was >200 msec in 8 (6.8%) participants, the QRS duration was >110 msec in 7 (5.8%) participants, and the QT interval was >500 msec in 2 (1.7%) participants. The QTcF interval was >450 msec in 8 (7.0%) participants and >500 msec in 2 (1.7%) participants. An increase from baseline in the QTcF interval of 30 to 60 msec was observed in 10 (8.7%) participants and >60 msec from baseline in 2 (1.7%) participants.

In the placebo group, 1 (1.8%) participant had a PCSA heart rate of >90 beats/min. No participants had a heart rate >100 beats/min. The PR interval was >200 msec in 2 (3.6%) participants and >220 msec in 2 (3.6%) participants. A QRS duration of >110 msec was observed in 3 (5.5%) participants, with 1 (1.8%) of these participants having an increase from baseline ≥25%. One (1.8%) participant had a QRS duration of >120 msec, with an increase from baseline of ≥25%. No participants had a QT interval that was >500 msec. There were no QTcF intervals >450 msec. An increase in the QTcF interval of 30 to 60 msec was observed in 5 (9.3%) participants, and no participant had an increase in the QTcF interval >60 msec from baseline. Of note regarding relevant TEAEs, there was 1 participant with syncope in the placebo group and none in the rilzabrutinib group. There were no cases of Torsade des pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, or seizure.

In the rilzabrutinib group, 1 (1.1%) participant had a shift in ECG from normal to abnormal-clinically significant, as well as AEs of arrhythmia and myocardial injury. No participants had a shift from abnormal-not clinically significant to abnormal-clinically significant or from abnormal-clinically significant to abnormal-clinically significant.

In the placebo group, there were no abnormal clinically significant ECG results or shifts in ECG results from normal, abnormal-not clinically significant, or abnormal-clinically significant to abnormal-clinically significant.

2.6.8.5. Safety in special populations

The following intrinsic factors were considered in the ITP placebo-controlled pool and the ITP rilzabrutinib pool for TEAEs, treatment-emergent SAEs, TEAEs leading to study drug discontinuation, infection (Grade ≥3) and GI events.

Specific subgroup analyses were conducted according to sex, race, age group, concomitant ITP medications and splenectomy status.

TEAEs by age group 1

As of the cutoff date (02 August 2024), in the rilzabrutinib any dose group, there were 233 of 284 participants who were <65 years old and 51 of 284 participants who were ≥65 years old. In the <65 years group, there were 203 (87.1%) participants who had a TEAE. The most frequent SOCs (≥20% participants) were GI disorders (128 [54.9%] participants), Infections and infestations (120 [51.5%] participants), Musculoskeletal and connective tissue disorders (62 [26.6%] participants), Nervous system disorders (61 [26.2%] participants), General disorders and administration site conditions (54 [23.2%] participants), and Skin and subcutaneous tissue disorders (56 [24.0%] participants). The most frequent TEAE PTs (≥10% participants) were diarrhoea (81 [34.8%] participant), nausea (62 [26.6%] participants), headache (43 [18.5%] participants), COVID-19 (37 [15.9%] participants), upper respiratory tract infection (34 [14.6%] participants), nasopharyngitis (29 [12.4%] participants), and arthralgia (25 [10.7%] participants).

In the rilzabrutinib any dose group, there were 47 (92.2%) participants who had a TEAE in the ≥65 years group. The most frequent SOCs (≥20% participants) were GI disorders (31 [60.8%] participants), Infections and infestations (23 [45.1%] participants), and Musculoskeletal and connective tissue disorders (19 [37.3%] participants); General disorders and administration site conditions (12 [23.5%] participants); Nervous system disorders (12 [23.5%] participants); Injury, poisoning, and procedural complications (11 [21.6%] participants); and Respiratory, thoracic, and mediastinal disorders (11 [21.6%] participants). The most frequent TEAE PTs (≥10% participants) were diarrhoea (17 [33.3%] participants), nausea (10 [19.6%] participants), headache (9 [17.6%] participants), fatigue (8 [15.7%] participants), arthralgia (7 [13.7%] participants), COVID 19 (7 [13.7%] participants), urinary tract infection (7 [13.7%] participants), and pain in extremity (6 [11.8%] participants).

Permanent discontinuation by age group 1

In the rilzabrutinib any dose group, there were 20 (8.6%) participants who were <65 years old and 11 (21.6%) participants who were ≥65 years old who had a TEAE that led to permanent IMP discontinuation. The TEAEs in participants in the <65 years group that led to permanent discontinuation included the PTs thrombocytopenia in 3 (1.3%) participants, diarrhoea and pregnancy in 2 (0.9%) participants each, and all other PTs (pneumonia, urosepsis, metastatic malignant melanoma, neutropenia, Evans syndrome, migraine, pulmonary embolism, nausea, abdominal pain, abdominal discomfort, gastritis, gastroesophageal reflux disease, defecation urgency, flatulence, frequent bowel movements, rectal haemorrhage, erythema nodosum, cutaneous lupus erythematosus, vaginal haemorrhage, fatigue, subdural hematoma, thrombocytosis and heavy menstrual bleeding) were reported in 1 (0.4%) participants each. The TEAEs in participants in the ≥65 years group that led to permanent discontinuation included the PTs of headache (2 [3.9%] participants), and pneumonia, hepatitis B reactivation, headache, interstitial lung disease, nausea, dyspepsia, oesophageal varices haemorrhage, GI haemorrhage, arthralgia, pain in extremity, hepatic enzyme increased subcutaneous abscess, and peripheral embolism were reported in 1 (2.0%) participant each.

TEAEs by age group 2

An additional analysis by age group was performed, taking into account age groups <65 years, 65 to <75 years, 75to <85 years, or ≥85 years. In the rilzabrutinib any dose group, there were 233 of 284 participants who were <65 years old, 40 of 284 participants who were 65 to <75 years old, and 11 of 284 participants who were 75 to <85 years old. No participants were ≥85 years old.

In the rilzabrutinib any dose group, there were 37 (92.5%) participants who had a TEAE in the 65 to <75 years group. The most frequent SOCs (≥20% participants) were GI disorders (23 [57.5%] participants), Infections and infestations (17 [42.5%] participants), Musculoskeletal and connective tissue disorders (13 [32.5%] participants), General disorders and administration site conditions (10 [25.0%] participants), Respiratory, thoracic, and mediastinal disorders (9 [22.5%] participants), and

Skin and subcutaneous tissue disorders (8 [20.0%] participants). The most frequent TEAE PTs (≥10% participants) were diarrhoea (13 [32.5%] participants), nausea (7 [17.5%] participants), fatigue (7 [17.5%] participants), urinary tract infection (6 [15.0%] participants), headache, COVID-19, and arthralgia (5 [12.5%] participants each), abdominal pain upper, back pain (4 [10.0%] participants each).

In the rilzabrutinib any dose group, there were 10 (90.9%) participants who had a TEAE in the 75 to <85 years group. The most frequent SOCs (≥20% participants) were GI disorders (8 [72.7%] participants), Infections and infestations (6 [54.5%] participants), Nervous system disorders (5 [45.5%] participants), Musculoskeletal and connective tissue disorders (6 [54.5%] participants), Investigations (5 [45.5%] participants), and Injury, poisoning, and procedural complications (4 [36.4%] participants). The most frequent TEAE PTs (≥10% participants) were headache, gastroesophageal reflux disease, and diarrhoea (4 [36.4%] participants each), and nausea and fall (3 [27.3%] participants each), and arthralgia, pain in extremity, contusion, COVID-19, vertigo positional, palpitations, and vomiting (2 [18.2%] participants).

Permanent discontinuation by age group 2

Regarding TEAEs leading to permanent discontinuation, in the rilzabrutinib any dose group, there were 20 (8.6%) participants who were <65 years old, 6 (15.0%) participants who were 65 to <75 years old, 5 (45.5%) participants who were 75 to <85 years old, and no participants who were ≥85 years old. The TEAEs in participants in the 65 to <75 years group that led to permanent discontinuation included subcutaneous abscess, peripheral embolism, nausea, oesophageal varices haemorrhage, GI haemorrhage, arthralgia, and hepatic enzyme increased in 1 (2.5%) participants each, and those in the 75 to <85 years group included pneumonia, hepatitis B reactivation, headache, interstitial lung disease, dyspepsia, and pain in extremity in 1 (9.1%) participants each.

Sex (Male, Female)

As of the cutoff date (02 August 2024), in the rilzabrutinib any dose group, there were 156 (90.2%) female participants and 94 (84.7%) male participants with a TEAE. The most frequent SOCs (≥20% participants) were GI disorders (105 [60.7%] female participants and 54 [48.6%] male participants), Infections and infestations (91 [52.6%] female participants and 52 [46.8%] male participants), Musculoskeletal and connective tissue disorders (52 [30.1%] female participants and 29 [26.1%] male participants), Nervous system disorders (49 [28.3%] female participants and 24 [21.6%] male participants), Skin and subcutaneous tissue disorders (46 [26.6%] female participants and 20 [18.0%] male participants), and General disorders and administration site conditions (39 [22.5%] female participants and 27 [24.3%] male participants).

The most frequent PTs (≥10% participants) were diarrhoea (62 [35.8%] female participants and 36 [32.4%] male participants), nausea (51 [29.5%] female participants and 21 [18.9%] male participants), headache (36 [20.8%] female participants and 16 [14.4%] male participants), COVID 19 (28 [16.2%] female participants and 16 [14.4%] male participants), arthralgia (24 [13.9%] female participants and 8 [7.2%] male participants), nasopharyngitis (22 [12.7%] female participants and 10 [9.0%] male participants), vomiting (21 [12.1%] female participants and 1 [0.9%] male participants), upper respiratory tract infection (23 [13.3%] female participants and 13 [11.7%] male participants), and fatigue (18 [10.4%] female participants and 10 [9.0%] male participants).

Differences between female and male participants (≥5% participants) were as follows: anemia (female: 16 [9.2%] participants versus male: 3 [2.7%] participants), headache (female: 36 [20.8%] participants versus male: 16 [14.4%] participants), nausea (female: 51 [29.5%] participants versus male: 21 [18.9%] participants), vomiting (female: 21 [12.1%] participants versus male: 1 [0.9%] participants), and arthralgia (female: 24 [13.9%] participants versus male: 8 [7.2%] participants).

Concomitant ITP medications

The TEAEs in study participants were analysed for the pooled safety population by concomitant ITP medications (CS + TPO-RA, CS alone, TPO-RA alone, or neither CS nor TPO-RA). See table below.

Table 29: Number (%) of participants with TEAE(s) by primary SOC and PT by concomitant ITP medications - Adult safety population

	ITP placebo-controlled pool[a]								ITP rilzabrutinib pool[b]			
	Placebo (N=69)				Rilzabrutinib 400 mg BID (N=133)				Rilzabrutinib any dose (N=284)			
PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	CS + TPO-RA (N=14)	CS alone (N=20)	TPO-RA alone (N=12)	Neither CS nor TPO-RA (N=23)	CS + TPO-RA (N=21)	CS alone (N=34)	TPO-RA alone (N=25)	Neither CS nor TPO-RA (N=53)	CS + TPO-RA (N=41)	CS alone (N=71)	TPO-RA alone (N=63)	Neither CS nor TPO-RA (N=109)
Any event	13 (92.9)	15 (75.0)	8 (66.7)	16 (69.6)	20 (95.2)	27 (79.4)	22 (88.0)	42 (79.2)	39 (95.1)	64 (90.1)	59 (93.7)	84 (77.1)
INFECTIONS AND INFESTATIONS	4 (28.6)	4 (20.0)	1 (8.3)	5 (21.7)	7 (33.3)	12 (35.3)	8 (32.0)	17 (32.1)	21 (51.2)	39 (54.9)	29 (46.0)	42 (38.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	0	0	0	1 (2.4)	1 (1.4)	2 (3.2)	4 (3.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (21.4)	5 (25.0)	1 (8.3)	3 (13.0)	1 (4.8)	1 (2.9)	4 (16.0)	5 (9.4)	7 (17.1)	9 (12.7)	13 (20.6)	15 (13.8)
IMMUNE SYSTEM DISORDERS	0	0	0	0	0	1 (2.9)	0	0	1 (2.4)	4 (5.6)	1 (1.6)	3 (2.8)
ENDOCRINE DISORDERS	0	0	0	0	0	1 (2.9)	0	0	2 (4.9)	1 (1.4)	1 (1.6)	1 (0.9)
METABOLISM AND NUTRITION DISORDERS	1 (7.1)	0	1 (8.3)	0	2 (9.5)	2 (5.9)	0	2 (3.8)	6 (14.6)	9 (12.7)	4 (6.3)	3 (2.8)
PSYCHIATRIC DISORDERS	0	0	0	1 (4.3)	0	3 (8.8)	1 (4.0)	2 (3.8)	3 (7.3)	7 (9.9)	2 (3.2)	4 (3.7)
NERVOUS SYSTEM DISORDERS	3 (21.4)	4 (20.0)	0	1 (4.3)	5 (23.8)	8 (23.5)	7 (28.0)	12 (22.6)	16 (39.0)	17 (23.9)	18 (28.6)	22 (20.2)
EYE DISORDERS	1 (7.1)	0	0	1 (4.3)	2 (9.5)	2 (5.9)	1 (4.0)	0	7 (17.1)	3 (4.2)	4 (6.3)	5 (4.6)
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	1 (4.0)	1 (1.9)	1 (2.4)	3 (4.2)	2 (3.2)	2 (1.8)
CARDIAC DISORDERS	0	0	2 (16.7)	0	0	1 (2.9)	0	1 (1.9)	1 (2.4)	4 (5.6)	0	2 (1.8)
VASCULAR DISORDERS	1 (7.1)	2 (10.0)	0	1 (4.3)	0	0	1 (4.0)	0	3 (7.3)	5 (7.0)	4 (6.3)	3 (2.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (5.0)	1 (8.3)	1 (4.3)	2 (9.5)	4 (11.8)	5 (20.0)	4 (7.5)	9 (22.0)	14 (19.7)	9 (14.3)	14 (12.8)
GASTROINTESTINAL DISORDERS	5 (35.7)	5 (25.0)	2 (16.7)	4 (17.4)	14 (66.7)	18 (52.9)	14 (56.0)	25 (47.2)	26 (63.4)	40 (56.3)	38 (60.3)	52 (47.7)
HEPATOBILIARY DISORDERS	0	0	0	0	2 (9.5)	0	0	0	2 (4.9)	1 (1.4)	1 (1.6)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (21.4)	3 (15.0)	0	2 (8.7)	1 (4.8)	3 (8.8)	3 (12.0)	8 (15.1)	8 (19.5)	17 (23.9)	10 (15.9)	26 (23.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (21.4)	2 (10.0)	2 (16.7)	1 (4.3)	2 (9.5)	8 (23.5)	7 (28.0)	10 (18.9)	13 (31.7)	20 (28.2)	20 (31.7)	26 (23.9)
RENAL AND URINARY DISORDERS	0	0	1 (8.3)	0	1 (4.8)	1 (2.9)	0	0	2 (4.9)	4 (5.6)	0	4 (3.7)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	0	0	0	0	0	0	0	0	2 (1.8)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (7.1)	1 (5.0)	0	0	1 (4.8)	1 (2.9)	1 (4.0)	1 (1.9)	2 (4.9)	5 (7.0)	3 (4.8)	2 (1.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (14.3)	3 (15.0)	0	4 (17.4)	5 (23.8)	9 (26.5)	2 (8.0)	4 (7.5)	16 (39.0)	19 (26.8)	18 (28.6)	13 (11.9)
INVESTIGATIONS	3 (21.4)	1 (5.0)	1 (8.3)	1 (4.3)	5 (23.8)	1 (2.9)	1 (4.0)	5 (9.4)	10 (24.4)	11 (15.5)	8 (12.7)	13 (11.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (14.3)	1 (5.0)	0	1 (4.3)	3 (14.3)	3 (8.8)	2 (8.0)	3 (5.7)	8 (19.5)	15 (21.1)	9 (14.3)	17 (15.6)

Splenectomy status

As of the cutoff date (02 August 2024), in the rilzabrutinib any dose group, there were 72 (88.9%) participants with splenectomy and 178 (87.7%) participants with no splenectomy who had a TEAE. The most frequent SOCs were GI disorders (47 [58.0%] participants with splenectomy and 112 [55.2%] participants with no splenectomy), Infections and infestations (44 [54.3%] participants with splenectomy and 99 [48.8%] participants with no splenectomy), Musculoskeletal and connective tissue disorders (24 [29.6%] participants with splenectomy and 57 [28.1%] participants with no splenectomy), Nervous system disorders (26 [32.1%] participants with splenectomy and 47 [23.2%] participants with no splenectomy), General disorders and administration site conditions (24 [29.6%] participants with splenectomy and 42 [20.7%] participants with no splenectomy), Respiratory, thoracic, and mediastinal disorders (17 [21.0%] participants with splenectomy and 29 [14.3%]

participants with no splenectomy), and Skin and subcutaneous tissue disorders (22 [27.2%] participants with splenectomy and 44 [21.7%] participants with no splenectomy).

The most frequent PTs were diarrhoea (33 [40.7%] participants with splenectomy and 65 [32.0%] participants with no splenectomy), nausea (26 [32.1%] participants with splenectomy and 46 [22.7%] participants with no splenectomy), headache (18 [22.2%] participants with splenectomy and 34 [16.7%] participants with no splenectomy), COVID 19 (16 [19.8%] participants with splenectomy and 28 [13.8%] participants with no splenectomy), nasopharyngitis (8 [9.9%] participants with splenectomy and 24 [11.8%] participants with no splenectomy), arthralgia (9 [11.1%] participants with splenectomy and 23 [11.3%] participants with no splenectomy), and fatigue (9 [11.1%] participants with splenectomy and 19 [9.4%] participants with no splenectomy).

Elderly

Results summarized in table below.

Table 30: PRN1008-018 TEAE(s) by age range during the double-blind treatment emergent period - Adult safety population

	Rilzabrutinib 400 mg BID (N=133)				Placebo (N=69)			
MedDRA Terms	Age <65 n(%) (N=112)	Age 65-74 n(%) (N=15)	Age 75-84 n(%) (N=6)	Age 85+ n(%) (N=0)	Age <65 n(%) (N=54)	Age 65-74 n(%) (N=12)	Age 75-84 n(%) (N=3)	Age 85+ n(%) (N=0)
Total AEs	92 (82.1)	13 (86.7)	6 (100)	0	39 (72.2)	10 (83.3)	3 (100)	0
Serious AEs - Total	6 (5.4)	5 (33.3)	1 (16.7)	0	6 (11.1)	2 (16.7)	0	0
- Fatal	0	0	1 (16.7)	0	0	0	0	0
- Hospitalization/prolong existing hospitalization	6 (5.4)	4 (26.7)	1 (16.7)	0	6 (11.1)	2 (16.7)	0	0
- Life-threatening	0	1 (6.7)	0	0	0	0	0	0
- Disability/incapacity	1 (0.9)	0	0	0	0	0	0	0
- Other (medically significant)	0	1 (6.7)	0	0	0	0	0	0
AE leading to drop-out	3 (2.7)	3 (20.0)	2 (33.3)	0	0	0	0	0
Psychiatric disorders *	6 (5.4)	0	0	0	1 (1.9)	0	0	0
Nervous system disorders *	29 (25.9)	1 (6.7)	2 (33.3)	0	7 (13.0)	1 (8.3)	0	0
Accidents and injuries **	0	0	1 (16.7)	0	1 (1.9)	0	0	0
Cardiac disorders *	2 (1.8)	0	0	0	2 (3.7)	0	0	0
Vascular disorders *	0	1 (6.7)	0	0	4 (7.4)	0	0	0
Cerebrovascular disorders **	0	0	0	0	0	0	0	0
Infections and infestations *	40 (35.7)	2 (13.3)	2 (33.3)	0	12 (22.2)	2 (16.7)	0	0
Anticholinergic syndrome **	0	0	0	0	0	0	0	0
Quality of life decreased #	28 (25.0)	6 (40.0)	3 (50.0)	0	23 (42.6)	6 (50.0)	1 (33.3)	0
Quality of life decreased ##	17 (15.2)	2 (13.3)	3 (50.0)	0	13 (24.1)	4 (33.3)	1 (33.3)	0
Quality of life decreased ###	15 (13.4)	2 (13.3)	3 (50.0)	0	12 (22.2)	4 (33.3)	0	0
Sum of orthostatic hypotension, fall, Loss of consciousness, syncope, dizziness, ataxia, fracture ***	9 (8.0)	1 (6.7)	2 (33.3)	0	1 (1.9)	2 (16.7)	0	0
Other PTs								
- Diarrhoea	36 (32.1)	5 (33.3)	2 (33.3)	0	4 (7.4)	2 (16.7)	1 (33.3)	0
- Nausea	25 (22.3)	0	2 (33.3)	0	2 (3.7)	1 (8.3)	1 (33.3)	0
- Headache	22 (19.6)	1 (6.7)	1 (16.7)	0	5 (9.3)	0	0	0

AE: adverse event, BID: twice daily, PT: preferred term, TEAE: treatment emergent adverse event
MedDRA dictionary version 26.1
* Based on system organ class (SOC).
** Based on standardized MedDRA queries (SMQ).
*** Based on preferred term (PT).
# Quality of life decreased: change from baseline <0 at last double-blind on-treatment assessment in ITP-PAQ overall QoL (5 items, Items 26 to 30). Two participants with missing baseline ITP-PAQ overall QoL were excluded in the analysis.
Quality of life decreased: change from baseline <=-8 at last double-blind on-treatment assessment in ITP-PAQ overall QoL (5 items, Items 26 to 30). Two participants with missing baseline ITP-PAQ overall QoL were excluded in the analysis.
Quality of life decreased: change from baseline <=-12 at last double-blind on-treatment assessment in ITP-PAQ overall QoL (5 items, Items 26 to 30). Two participants with missing baseline ITP-PAQ overall QoL were excluded in the analysis.

Hepatic and renal Impairment

Results summarized in table below.

Table 31: PRN1008-018 TEAE(s) by special population during the double-blind treatment period - Adult safety population

MedDRA Terms	Rilzabrutinib 400 mg BID (N=133)				Placebo (N=69)			
	Hepatically impaired* n(%) (N=2)	Renally impaired** n(%) (N=0)	Pregnant n(%) (N=0)	Other*** n(%) (N=131)	Hepatically impaired* n(%) (N=0)	Renally impaired** n(%) (N=0)	Pregnant n(%) (N=0)	Other*** n(%) (N=69)
Total AEs	2 (100)	0	0	109 (83.2)	0	0	0	52 (75.4)
Serious AEs - Total	2 (100)	0	0	10 (7.6)	0	0	0	8 (11.6)
- Fatal	0	0	0	1 (0.8)	0	0	0	0
- Hospitalization/prolong existing hospitalization	2 (100)	0	0	9 (6.9)	0	0	0	8 (11.6)
- Life-threatening	1 (50.0)	0	0	0	0	0	0	0
- Disability/incapacity	0	0	0	1 (0.8)	0	0	0	0
- Other (medically significant)	0	0	0	1 (0.8)	0	0	0	0
AE leading to drop-out	2 (100)	0	0	6 (4.6)	0	0	0	0
PTs								
- Pneumonia	0	0	0	2 (1.5)	0	0	0	0
- Diarrhoea	0	0	0	43 (32.8)	0	0	0	7 (10.1)
- Nausea	0	0	0	27 (20.6)	0	0	0	4 (5.8)
- PTs related to Liver function test #	1 (50.0)	0	0	6 (4.6)	0	0	0	3 (4.3)

AE: adverse event, BID: twice daily, CKD:PT: preferred term, TEAE: treatment emergent adverse event
MedDRA dictionary version 26.1
* Hepatic impairment is defined as having Child-Pugh score B or C at baseline (ascites and encephalopathy by medical history). Two participants in rilzabrutinib group in PRN1008-018 were classified as Child-Pugh score B due to missing hepatomegaly severity and hepatic cirrhosis severity, respectively, in medical history.
** Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition) at baseline

*** Other: not hepatic impaired, not renally impaired and not pregnant

Include "Alanine aminotransferase increased", "Aspartate aminotransferase increased", "Hepatic enzyme increased", "Transaminases increased", "Hepatic function abnormal".

2.6.8.6. Immunological events

NA

2.6.8.7. Safety related to drug-drug interactions and other interactions

Drug-drug interactions are presented in the clinical pharmacology section.

2.6.8.8. Discontinuation due to adverse events

In the DB period of Study PRN1008-018, 8 (6.0%) participants in the rilzabrutinib group and no participants in the placebo group had TEAEs leading to permanent IMP discontinuation from the DB period. No TEAE (by PT) leading to IMP discontinuation was reported in more than 1 participant. The TEAEs that led to IMP discontinuation were pneumonia, neutropenia, headache, peripheral embolism, diarrhoea, nausea, dyspepsia, abdominal discomfort, oesophageal varices haemorrhage, erythema nodosum, arthralgia, pain in extremity, and hepatic enzyme increased, and each of these TEAEs occurred in 1 (0.8%) participant each. Of note, there were 3 participants who discontinued for GI TEAEs and one each for infection (fatal pneumonia), hepatic enzyme increased, and neutropenia. Most TEAEs leading to IMP discontinuation were considered related to IMP.

In the rilzabrutinib any dose group, there were 31 (10.9%) participants with a TEAE leading to permanent study drug discontinuation. The SOCs with the highest frequency (≥2% participants) were GI disorders (9 [3.2%] participants) and Blood and lymphatic system disorders (6 [2.1%] participants). All TEAEs that led to permanent study discontinuation had a frequency of <1% except thrombocytopenia (3 [1.1%] participants).

2.6.8.9. Post marketing experience

NA

2.6.9. Discussion on clinical safety

ITP patient safety data are available from the pivotal study PRN1008-018, as well as parts A and B of study PRN1008-010. The applicant provided different datasets for safety evaluation. These include separate analyses for the safety data generated during the double-blind period of the pivotal study, its open-label and long term extension periods, separate analyses for part A and part B of study PRN1008-010, as well as a pooled overall rilzabrutinib any dose group consisting of data from study PRN1008-018 and PRN1008-010A+B. Supportive safety data were provided from HV studies. Overall, 284 ITP patients were exposed to rilzabrutinib. Additionally, 310 healthy adult participants were exposed to different strengths of mostly single dose rilzabrutinib in pharmacology studies. The overall extent of the available safety database is limited and smaller than what was anticipated from the SA procedure. Further, upon request, available data from the clinical programmes of other indications currently under development by the applicant were provided to support the available safety data from ITP patients.

At submission, overall long-term data were also very limited, with a total of 74 patients treated with rilzabrutinib for a minimum duration of 52 weeks (as a reference, 164 ITP patients exposed to rilzabrutinib at target doses for >52 weeks were anticipated by the applicant during the SA procedure). Given the established BTKi class safety profile from authorised BTK inhibitors (which includes delayed onset ADRs, e.g. malignancies), this limited data regarding long-term safety raised major concerns initially. Upon request, the applicant provided additional data from new data cut-offs (PRN1008-018 new cut-off: 15 Oct 2024, PRN1008-010 new cut-off: 2 Aug 2024) to expand the available safety database. With this update, a total of 98 patients treated at target dose for at least 52 weeks have become available. Of these, 48 ITP patients were treated ≥2 years and 16 ITP patients were treated ≥3 years. The cumulative duration of rilzabrutinib treatment exposure increased from 235.6 patient years to 290.6 patient years. The extent of the available long-term safety data package largely complies with minimum long-term safety database requirements and was considered acceptable. Regarding TEAEs, the newly provided safety data package was in line with previously available data and TEAE frequencies remained largely comparable with the old cut-off of 14 Mar 2024. Based on the newly provided data, the issues were resolved.

An important deficiency of the clinical safety database from ITP patients based on the study design of the placebo-controlled pivotal study is noted. During the double-blind period of pivotal study PRN1008-018, a large proportion of rilzabrutinib treated patients discontinued the study, most of whom due to lack of response: of the 133 participants entering the 24-week double-blind period, 67 (50.4%) participants discontinued before week 13, and ultimately only 62 (46.6%) completed the double-blind period. While 66 of the 69 placebo participants who entered the double-blind period completed the first 12 weeks of the double-blind period, 59 participants (85.5%) discontinued before week 13, and only 10 participants (14.5%) completed the full duration of the 24-week double-blind period. Therefore, the presented placebo comparison is severely hampered due to differences in exposure duration between

the rilzabrutinib and the placebo arms during the second half of the double-blind period of the study, and a meaningful comparison to placebo background can only be drawn for (very) short-term (12 weeks).

This was further complicated by the allowed use of background standard of care concomitant medication, including CS and TPO-RA. While subgroup analyses based on concomitant medication were provided, only small numbers per subgroups are available to discern the unique rilzabrutinib safety profile.

From the data provided, overall in the placebo-controlled pool, TEAEs were more frequently reported from rilzabrutinib treated patients. In the rilzabrutinib treatment arm, 83.5% (111/133) of patients reported TEAEs, compared to 75.4% (52/69) in the placebo group (88.0% in the rilzabrutinib any dose pool). Substantial increases were reported in the system organ classes of Gastrointestinal disorders (53.4% rilzabrutinib vs 23.2% placebo), infections and infestations (33.1% rilzabrutinib vs 20.3% placebo), nervous system disorders (24.1% rilzabrutinib vs 11.6% placebo), musculoskeletal and connective tissue disorders (20.3% rilzabrutinib vs 11.6% placebo), and thoracic and mediastinal disorders (11.3% rilzabrutinib vs 4.3% placebo). Most TEAEs were assessed as grade 1 or grade 2 in both treatment groups, and overall fewer TEAEs with grade ≥3 were reported in rilzabrutinib treated patients compared to placebo (11.3% vs 14.5%). However, more grade ≥3 TEAEs were reported in rilzabrutinib patients from the SOC infections and infestations, 3.8% (5/133), compared to 0 events on placebo. In the double-blind period, related TEAEs were reported from 51.1% (68/133) rilzabrutinib patients compared to 17.4% (12/69) placebo patients. Similarly, 52.1% of patients in the pooled any dose group reported ADRs. The most commonly reported rilzabrutinib related AE was diarrhoea (22.6% rilzabrutinib, 4.3% placebo), followed by nausea, headache, abdominal pain, and vomiting. The most commonly reported related AEs in the rilzabrutinib any dose pool were diarrhoea and nausea.

SAEs: In the double-blind period, SAEs occurred in 9.0% of rilzabrutinib and 11.6% of placebo patients, mainly in infections, GI, blood, and investigations SOCs. Only one SAE (peripheral embolism) was considered related to rilzabrutinib. In the ITP pool, 16.9% had SAEs, mostly thrombocytopenia and infections. Bleeding events were fewer with rilzabrutinib than placebo, but some led to discontinuation. In the overall any dose rilzabrutinib patient pool four SAEs were considered related to rilzabrutinib, prompting updates to SmPC sections 4.4 regarding serious infections (including bacterial, viral, or fungal). The applicant included pneumonia (due to aspergillosis in 2 cases) into the list of ADRs in SmPC section 4.8.

Deaths: Two deaths occurred in the rilzabrutinib safety pool, both deemed unrelated to the drug. One case raised questions due to fatal pneumonia in an elderly patient with multiple risk factors. A warning regarding serious infections is reflected in SmPC section 4.4. Three SAEs were considered related to rilzabrutinib, but no deaths were attributed to it.

Discontinuations: In study PRN1008-018, 6.0% discontinued due to TEAEs; in the overall rilzabrutinib group, it was 10.9%. GI, blood and lymphatic disorders and infections were the most common causes. Further AEs leading to discontinuation include hepatitis B reactivation, pulmonary embolism, and subdural hematoma. 4.2% had TEAEs considered related to rilzabrutinib. Temporary discontinuations were mainly due to infections and GI issues.

Rebound effects: only very limited information regarding the investigation of possible rebound effects were provided in the dossier at submission. In the pooled rilzabrutinib population 2 (1.0%) participants with thrombocytopenia and 1 (0.5%) participant with platelet count decreased were reported. Upon request, the applicant provided further ad-hoc evaluations regarding possible rebound effects in 9 patients, which did not raise concerns.

Effect on ability to drive or use tools: As with other BTK inhibitors, fatigue, dizziness, and asthenia were reported to be common adverse events. These adverse events can affect the patients ability to drive or use any tools or machines, and rewording of section 4.7 of the SmPC was therefore requested in order to harmonise with other authorised BTK inhibitors. The applicant agreed to include dizziness into section 4.7.

Safety in special populations: Older patients (≥65) had slightly more TEAEs and significantly more SAEs, especially infections. Discontinuations due to AEs were more frequent with age, peaking in those >75. An increase was also seen in an analysis of serious ADRs analysed per age group, provided by the applicant upon request. In the any dose rilzabrutinib pool, such events were reported from 1.3% (3/233) of patients <65 yoa compared to 3.9% (2/51) of patients ≥65 yoa. Respective information was included in SmPC section 4.8. More female than male study participants reported more TEAEs overall (90.2% vs 84.7%), notably in GI and blood disorders. SAEs were similar across sexes. TEAEs increased with concomitant ITP medications and splenectomy, especially in nervous and respiratory disorders. Splenectomised patients also had more SAEs, mainly infections.

Irritation of the upper GI tract was observed in the preclinical and clinical studies. Diarrhoea, nausea, abdominal pain, vomiting and dyspepsia are listed as ADRs in 4.8 of the SmPC. These events were mainly observed in the first two weeks of treatment and were mostly restored within some weeks. Nevertheless, gastritis, gastrooesophageal reflux and gastrointestinal haemorrhage were further observed in the any dose rilzabrutinib safety pool, gastritis also in the RCT in 2.3% vs 0% with placebo. The applicant discussed, that in Phase 1 studies, the frequency of GI disorders, including bleedings, were reduced from about 58% to 17% when rilzabrutinib was administered following a high fat meal. Therefore, the statement that patients with GI symptoms may take rilzabrutinib with food is included in SmPC 4.2. GI bleeding events will additionally be monitored in the PSURs.

Hepatic impairment: In study PRN1008-020 which recruited participants with mild (Child-Pugh class A, n=8) and moderate (Child Pugh class B, n=8) hepatic impairment, as well as healthy volunteers (n=13), increased GI ADR rates were reported in participants with hepatic impairment compared to the healthy control group. Section 4.2 of the SmPC mentions it should not be administered to patients with moderate or severe hepatic impairment.

AESIs

- Liver enzyme elevations (ALT/AST) were slightly more frequent with rilzabrutinib but mostly mild and manageable; Routine pharmacovigilance was deemed sufficient to monitor liver enzyme elevation and section 4.4 of the SmPC were updated accordingly.
- Infections were more common and severe with rilzabrutinib, including one fatal pneumonia case (see also below). Following an in-depth analysis of infection-related TEAE and based on the mechanism of action of rilzabrutinib (inhibition of human B-cell activation and antibody mediated activation of immune cells via Fc receptor signalling), the applicant has provided more comprehensive information on infections and an associated warning recommending close monitoring in the product information (see section 4.4). Serious infections: As only a low number of serious infections were reported in the ITP studies and supportive safety data of rilzabrutinib in other indications, serious infections are classification as important potential risk. Based on a provided literature review (Sandvad et al, 2021), adult patients with ITP have a 4.5-fold increased adjusted 1-year relative risk of severe and fatal infections compared to the general population. A respective information to monitor patients for symptoms of infection is added to SmPC section 4.4. Infections with increased frequency are listed in the SmPC as ADRs. A specific ADR follow-up form for serious infections is now implemented. A recategorization will be evaluated in upcoming PSURs.

- GI events were frequent but mild; in the double-blind period one, in the overall rilzabrutinib treatment pool three events led to discontinuation. A subgroup analysis conducted by the applicant (age group, concomitant ITP medication) did not bring notable information.
- Thromboembolic events occurred only in the rilzabrutinib group but considering the existence of confounding factors including medical history and/or concomitant thrombopoietin receptor agonists known for increasing the risk of thromboembolic events, no further discussion was considered needed.
- Cardiac arrhythmias were rare but are a class effect for BTKi and therefore atrial fibrillation and cardiac arrhythmias will be closely monitored in the PSURs. An observation of shortening in QTc interval proportional to concentration was observed in a thorough QT study of rilzabrutinib. The issue is sufficiently reflected in the SmPC section 4.4 and 5.1.
- Bleeding events were less frequent than with placebo treatment but remain a concern in non-responders. Therefore a recommendation is provided in Section 4.2 of the SmPC in order to mitigate serious bleeding in non-responders to rilzabrutinib.
- Two cases of pregnancy led to study withdrawal. Based on reproductive and developmental toxicity studies performed in animals and in line with guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005), a warning in section 4.4 and a recommendation in section 4.6 of the SmPC are provided to avoid use of rilzabrutinib during pregnancy and to use contraception during treatment with rilzabrutinib and for 1 month after treatment cessation. While no further justification based on PK data was provided for the duration of contraception, the wording is in line with other products and is acceptable. A patient card as additional measure is implemented.
- One uveitis case was deemed unrelated by the investigators however based on cases of uveitis reported in other indications by the applicant, uveitis is taken as important potential risk in the RMP.

Safety data from other indications

Upon request, available rilzabrutinib safety data from other indications under development by the applicant were provided. While extrapolation of the reported safety profiles between indications and studies may not be straight forward, the provided information was considered supportive in nature and endorsed. Particularly TEAE data available from placebo-controlled studies are considered an important supportive addition to the limited placebo controlled comparison available from the clinical ITP rilzabrutinib programme. Across studies and indications serious adverse events (SAEs) were rare, with no deaths reported. Some cases of ALT increase, uveitis, and bleeding (mainly bruising) were noted and led to discontinuation. GI events were common but mostly mild. No increased risk of serious infections or cytopenias was observed. Overall, no new safety concerns emerged from lab findings.

Isolated cases of SAEs transaminases increases leading to permanent discontinuation were reported. Further TEAEs leading to permanent discontinuation reported across studies included nausea, diarrhoea, pancreatic pseudocyst, pneumonitis, Grade 2 chest pain, cellulitis, septic shock, meningitis bacterial, renal neoplasm, abdominal pain, and gastroenteritis. Isolated events of ALT increases >3x ULN were reported. Additionally, events of ALT increased not according to this definition were reported from various studies. While not observed at high frequencies, some of these events were assessed as related to rilzabrutinib treatment and led to permanent treatment discontinuation. In placebo-controlled studies a higher frequency of events ALT increase were reported from rilzabrutinib treatment arms compared to placebo.

Events of uveitis were reported, including cases considered related to rilzabrutinib by the investigator and leading to permanent treatment discontinuation.

In line with data available from the ITP patient population, high rates of GI events, to a large part of mild intensity, were reported across all studies, which included nausea, diarrhoea, vomiting, abdominal pain. However, also more severe cases were reported, including cases of e.g. gastroenteritis, gastritis, and diarrhoea which led to permanent IMP discontinuation.

No signs for increases in cytopenias in rilzabrutinib treatment arms were noted across studies in other indications.

In one study, significantly increased frequencies of bleeding related events were reported from the rilzabrutinib arm (400mg BID) compared to the placebo arm, 32.3% (21/65) vs 16.7% (11/66) on placebo. This difference seemed to be driven by a significantly increased frequency reported for bruising, 24.6% vs 10.6%. No increased reporting of bleeding related events were noted from the remaining placebo controlled studies.

Overall, no clear increases in cardiac arrythmia relevant TEAEs were reported from rilzabrutinib treatment arms across indications. However, in one study, more TEAEs cardiac arrhythmias were reported from the rilzabrutinib 400mg BID treatment arm compared to placebo, 6.2% (4/65) vs 1.5% (1/66), respectively. The events reported from rilzabrutinib treated patients included cardiac arrest, flutter, tachycardia, and ventricular extrasystoles. In the open-label extension and LTE, one event of atrial fibrillation and one event tachycardia was reported, both considered not related to IMP by the investigator. Overall, no clear safety signals were noted in the provided data from other indications regarding cardiac arrhythmias.

Taken together, some of the potential safety signals identified in the ITP safety database were also reported from other indications, including the placebo-controlled studies. These include: ALT increase, uveitis, bleeding events (bruising). Reassuringly, no signs for increases in serious infection and cytopenias were noted in the provided new data sets.

In conclusion, rilzabrutinib presents itself with a safety profile of high frequencies of GI adverse events and significantly increased risk for infections in patients with ITP. Overall, the safety profile of rilzabrutinib in ITP is considered to be adequately reflected in the SmPC.

2.6.10. Conclusions on the clinical safety

The available safety database for rilzabrutinib in ITP patients presents a safety profile characterised by high frequencies of GI adverse events and a significantly increased risk for infections. Overall, the safety profile is considered acceptable and adequately reflected in the SmPC.

The submission of the results of studies PRN1008-018 and PRN1008-010 in the context of additional pharmacovigilance (category 3 measures) is agreed in order to evaluate the safety and tolerability of rilzabrutinib. An additional study is also agreed to assess the effect of multiple doses of rilzabrutinib on plasma exposure of oral contraceptives (see RMP).

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 32: Safety concerns

Important identified risk	None
Important potential risks	Serious infections
	Uveitis
	Embryo-fetal toxicity
Missing information	None

Pharmacovigilance plan

Table 33: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
PRN1008-018 (EFC17093) – LUNA 3 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). *Ongoing*	To evaluate the safety and tolerability of rilzabrutinib in pediatric participants (≥10 - ≤17 years) and in adult participants (≥18 years) with refractory/relapsed ITP.	Serious infections Uveitis	**Adult LTE Part** Clinical Study Report	*Planned date:* 20-Mar-2026
PRN1008-010 (DFI17124) – LUNA 2 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. *Ongoing*	To characterize the safety and tolerability of 400 mg BID dose of rilzabrutinib in patients with ITP.	Serious infections Uveitis	**Long-Term Extension part** Clinical Study Report	*Planned date:* 27-May-2026
Clinical interaction study with oral contraceptives A drug-drug interaction study in healthy female	Assess effect of multiple doses of rilzabrutinib on plasma	Embryo-fetal toxicity	Final protocol Final CSR	Q2 2026 Sep-2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
participants to investigate the effect of multiple doses of rilzabrutinib on combined hormonal oral contraceptive. *Planned*	exposure of oral contraceptives.			

BID: Twice Daily; BTK: Bruton's Tyrosine Kinase; CSR: Clinical Study Report; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; Q: Quarter.

2.7.2. Risk minimisation measures

Table 34: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.4 and 4.8. • SmPC section 4.4 (monitoring of patients for signs and symptoms of infection). Legal status: Prescription only medication. Treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of hematological diseases. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire for serious infections. **Additional pharmacovigilance activities:** • PRN1008-018 (EFC17093), LTE. • PRN1008-010 (DFI17124), LTE.
Uveitis	**Routine risk minimization measures:** SmPC and PL: Not labeled. Legal status: Prescription only medication. Treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of hematological diseases. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire for uveitis. **Additional pharmacovigilance activities:** • PRN1008-018 (EFC17093), LTE. • PRN1008-010 (DFI17124), LTE.
Embryo-fetal toxicity	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.6 and 5.3. • PL: Labeled in section 2. • SmPC sections 4.4 and 4.6 (pregnancy testing before initiation of treatment). Legal status: Prescription only medication. Treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of hematological diseases. **Additional risk minimization measures:** Patient card (part of the Labeling and Package Leaflet, Annex III)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Clinical interaction study with oral contraceptives

Safety concern	Risk minimization measures	Pharmacovigilance activities

LTE: Long-Term Extension; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

2.7.3. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

The applicant confirmed that serious infections, atrial fibrillation and cardiac arrhythmias, haemorrhages (bleeding events) grade ⩾3, GI bleeding, serious hepatotoxicity and malignancy will be subject to a close monitoring in the PSURs.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 19.06.2025. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, WAYRILZ (Rilzabrutinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The therapeutic indication for rilzabrutinib is:

> WAYRILZ is indicated for the treatment of persistent or chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1).

3.1.2. Available therapies and unmet medical need

Treatment goals for ITP primarily focus on the prevention of bleeding by elevating patient's platelet count. The standard therapy for adult patients with newly diagnosed ITP consists of corticosteroids (CS), such as oral high-dose dexamethasone or oral prednisone/prednisolone, but their prolonged use should be avoided due to associated adverse event (AE) burden. Although most patients respond to initial CS therapy, responses are typically not durable, are associated with significant toxicities, and have a low rate of lasting remission. First-line therapies also include intravenous immunoglobulins (IVIG) and anti-D immunoglobulin.

Recommended second-line treatments include rituximab, thrombopoietin-receptor agonists (TPO-RA) and splenectomy. Splenectomy is an effective treatment choice with durable off-treatment remission rates of 60%-70%; however, splenectomy might be associated with short-term surgery-related complications, infections and thromboembolisms. While rituximab and TPO-RAs have shown initial response rates of >60% in randomized clinical trials (RCTs) high percentages of patients relapse after variable duration of treatment. In addition, infections, thromboembolisms and other severe side effects have been associated with available treatments. Fostamatinib is also approved for patients with ITP who are refractory to other treatments with placebo adjusted durable response rates of 15%.

Despite the availability of current therapies, patients with ITP continue to endure burden from their disease. New therapies able to provide sustained remission with a favourable safety profile are needed.

3.1.3. Main clinical studies

The main evidence of efficacy and safety derives from a single Phase 3, multicenter, randomised, double-blind, placebo-controlled study with an OLE (PRN1008-018) in adults and adolescents with persistent or chronic Immune Thrombocytopenia (ITP). Only data from the adult patient population were available for review during this MAA.

3.2. Favourable effects

The proportion of subjects achieving the primary efficacy endpoint of durable platelet response (i.e. defined as *platelet counts ≥50,000/µl on at least 8 out of the last 12 weeks of the 24-week treatment in the absence of rescue therapy*) was 23.3% for patients treated with rilzabrutinib, whereas no patient achieved the endpoint in the placebo group.

Median platelet counts by study visit suggest an early and persistent platelet response (>50,000 platelets/µl after 2 weeks of treatment) in the subset of patients that has met the primary endpoint, which is clearly separated from placebo control (but also the non-responding population) without clear change from median baseline counts.

The responding population from the double-blind period (i.e. those that have met the primary endpoint) appears to maintain the established high median platelet count throughout the open-label phase and long-term extension (at least for those patients that are reported).

Beneficial efficacy compared to placebo is supported by all other reported endpoints (including weeks with response, time-to response, time-to as well as % of patients requiring rescue medication and the IBLS bleeding scale).

The difference to placebo in durable platelet response (see primary endpoint definition above) appears consistent throughout presented subgroups.

All provided sensitivity analyses (including no imputation on missing data, tipping point analysis of durable platelet response, multiple imputation, composite strategy) support the conclusion of the primary endpoint analysis.

3.3. Uncertainties and limitations about favourable effects

The pivotal clinical study 018 has included very few patients with persistent ITP (n=15, n=10 treated with rilzabrutinib).

Concomitant CS and/or TPO-RAs were allowed as standard of care ITP therapy and were used by (n=46 of 69 patients in placebo and n=80 of 133 patients treated with rilzabrutinib) patients. The proportion of patients that have achieved durable platelet response was clearly higher for those with concomitant therapy compared to those without (27.5% vs. 17%, respectively). The rate was still higher for those on rilzabrutinib compared to patients on placebo (none has achieved durable platelet response with or without concomitant therapy).

Only a subset of patients responded to the rilzabrutinib treatment with durable platelet response. Reasons for response/non-response are unclear, but guidance for non-responders is provided in the PI (i.e. discontinuation of treatment for those patients without expected benefit within 12 weeks of treatment).

The majority of patients were excluded from the primary analysis due to an early responder analysis (i.e. *platelet count of ≥50,000/µL OR a platelet count of between ≥30,000/µL and <50,000/µL and at least doubled from baseline at any time during the first 12 weeks AND absence of rescue medication in the 4 weeks prior to the elevated platelet count*) before start of the period relevant for the primary endpoint (week 13 – 24), but no reference to this pre-selection is included in the primary endpoint. Due to week 12 non-responders either joining the OL part or discontinuing from trial after week 12, it is not possible to derive the proportion of patients achieving durable response regardless of their week 12 response. Interpretability of the primary and secondary endpoints was therefore severely challenged. A large proportion in each study arm (85.5% in placebo and 53.4% in rilzabrutinib) has discontinued the blinded treatment phase, mostly due to lack of response. It cannot be fully excluded that the effect at week 25 may be (at least partially) driven by the short-term effect observed in the first 12 weeks, and it is challenging to isolate the longer-term effect on key secondary endpoints in the absence of data from week 12 non-responders. This uncertainty remains.

The fatigue item of the ITP-PAQ has an unclear validity and reliability as an isolated item (i.e. not as integrated part of the full ITP-PAQ PRO), as applied here as secondary endpoint.

3.4. Unfavourable effects

The most common AEs observed across studies were related to gastrointestinal events, such as diarrhoea, nausea, abdominal pain, and vomiting. In the double-blind placebo-controlled part of the pivotal study in ITP patients GI adverse events were reported in 53.4% of rilzabrutinib treated patients compared to 23.2% of placebo patients. The most common GI AEs were diarrhoea (32.3% vs 10.1% placebo), nausea (20.3% vs 5.8% placebo), abdominal pain (7.5% vs 1.4% placebo), and vomiting (6.8% vs 1.4% placebo).

Increased rates of infections were reported from patients treated with rilzabrutinib. In the double-blind placebo-controlled part of the pivotal study 33.1% of rilzabrutinib and 20.3% of placebo patients experienced infection AEs. The most commonly reported AE relating to the SOC was COVID-19 (13.5% vs 4.3% placebo), followed by nasopharyngitis, upper respiratory tract infection, influenza, and pneumonia.

In the DB period of the pivotal study, 12 (9.0%) of rilzabrutinib patients and 8 (11.6%) of placebo patients experienced SAEs.

SAEs were markedly increased in the older patient stratum (14.2% in patients <65y vs 29.4% in patients ≥65y), with a significant increase in serious infections in these patients (2.1% vs 11.8%).

In the double-blind period, related TEAEs were reported from 51.1% (68/133) rilzabrutinib patients compared to 17.4% (12/69) placebo patients.

3.5. Uncertainties and limitations about unfavourable effects

The available comparative data from the double-blind placebo-controlled period of the pivotal study are difficult to interpret due to a high rate of discontinuations in both arms, with particularly high numbers of placebo patients discontinuing before week 13 of the study and only 10 placebo patients completing the double-blind period.

Concomitant background standard of care medication was allowed during the study and were used by more than 60% of participants in both, which further complicates the characterisation of the unique rilzabrutinib safety profile. While subgroup analyses regarding concomitant medications were provided, sizes of subgroups were small, particularly in the placebo arm.

3.6. Effects table

Table 35: Effects table for Wayrilz for the treatment of ITP (DLP 15 Oct 2024)

Effect	Short Description	Unit	Treatment	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Durable platelet count	Primary Endpoint, platelet counts ≥50,000/µl on at least 8 out of the last 12 weeks of the 24-week treatment in the absence of rescue therapy	n (%); 95% CI	31 (23.3%); 16.12, 30.39	0 (0%); 0, 0	Early responder selection after 12 weeks of treatment not referenced in the primary endpoint. Cochran-Mantel-Haenszel test adjusted by stratification factors p-value: <0.0001	CSR 018
Time to first platelet response	Secondary EP, platelet count ≥50,000/µL or between 30,000µL and <50,000/µL and at least doubled from baseline	Days to first response (95% CI)	25th percentile: 10 (8, 15) 50th percentile: 36 (22,44)	25th percentile 65 (36, NA) 50th percentile: NA (NA, NA)	Log-rank test p-value: <0.0001 Analysis compromised due to patient exclusion based on response within 12 weeks of treatment (higher impact on placebo group)	CSR 018

Time to rescue medication	Secondary EP, use of rescue treatment indicates lack of efficacy	Days to first rescue (95% CI)	25th percentile: 29 (17, 86) 50th percentile: NA (NA, NA)	25th percentile: 16 (8, 36) 50th percentile: 56 (36, NA)	Log-rank test p-value: <0.0001 Analysis compromised due to patient exclusion based on response within 12 weeks of treatment (higher impact on placebo group)	CSR 018
Change from baseline on IBLS at Week 25	ITP Bleeding Scale	Mean (SE)	-0.04 (0.017)	0.047 (0.0226)	ANCOVA p-value: 0.0006	CSR 018
Unfavourable Effects (data from the double-blind placebo-controlled part of pivotal study PRN1008-018)						
Overall Gastro-intestinal AEs		%	53.4	23.2		
Overall infections AEs		%	33.1	20.3		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A single pivotal phase 3 trial was submitted to support licensure of rilzabrutinib for the treatment of ITP patients. The pivotal study design is principally appropriate, but the exclusion of non-responders based on the 12 week platelet analysis undermines primary and key secondary endpoint validity, even though the discontinuation of patients without expectable response can be followed from clinical perspective. Despite this, rilzabrutinib showed clear benefit over placebo. The reported primary endpoint as well as all secondary endpoints that were controlled for the alpha risk indicate that the treatment with rilzabrutinib has a beneficial effect compared to placebo treatment. This is also confirmed by the concluded durable response for presented subgroups, which however is limited in interpretability due to low numbers in each subgroup. Importantly, median platelet counts plotted per visit indicate a clear treatment responder group, with early (>50,000 platelets/µl after 2 weeks of treatment) and persistent (maintained throughout reporting period, including open-label and LTE phases) platelet response in a subset of patients treated with rilzabrutinib, whereas the remaining subjects treated with rilzabrutinib show a comparable response to the group treated with placebo, both without any clear change from median baseline counts. Lack of response in that patient subset is also reflected in the large discontinuation rate during the blinded treatment (85.5% in placebo and 53.4% in rilzabrutinib). Less than one quarter of the participants treated by rilzabrutinib were considered as responders (23.3%). Consequently, the responding subset of patients should be identified as early as possible after treatment initiation and non-responders should discontinue the treatment. This can prevent an inefficient treatment with non-negligible safety risks. Concomitant ITP therapy was permitted during the study (CS and/or TPO-RAs) and was used by the majority of patients (n=46 of 69 patients on placebo and n=80 of 133 patients treated with rilzabrutinib). Even though the proportion of patients that has achieved durable platelet response was clearly higher for those with concomitant therapy compared to those without (27.5% vs. 17%, respectively), the rate was still higher for those on rilzabrutinib compared to patients on placebo (none has achieved durable platelet response with or without concomitant therapy). The single confirmatory trial appears principally acceptable, as all results support the conclusion of robust efficacy in a subset of patients (also in line with platelet results from the phase 1/2 study 010).

The interpretation of safety events is generally compromised by the high rate of discontinuations from the blinded study period in both treatment arms (only 10 subjects completed the 24 weeks on placebo). The safety database is rather limited but largely complies with minimum long-term safety database requirements and is considered acceptable in this orphan setting. Reported adverse events

indicate especially increased rates in GI disorders (53.4% of rilzabrutinib treated patients compared to 23.2% of placebo patients) and infections (33.1% of rilzabrutinib and 20.3% of placebo patients) but appear principally manageable. Related cardiac events and malignancies seem not reported from clinical studies, but one serious thrombotic event was related to treatment (peripheral embolism). Generally, the safety profile of rilzabrutinib in ITP patients is considered to be adequately reflected in the SmPC.

3.7.2. Balance of benefits and risks

The clinical pharmacology of rilzabrutinib appears well characterised and the provided evidence on clinical efficacy for rilzabrutinib seems sufficiently convincing to conclude that the treatment does support an early and durable increase in platelet counts in a subset of ITP patients that had more than one prior therapy. Still, it should be noted that the proportion of the targeted population which may benefit of the treatment will be limited. Importantly, the responding subset of patients should be identified as early as possible after treatment initiation and non-responders should discontinue the treatment (see SmPC 4.2). The positive conclusion on efficacy is supported also by secondary endpoints beyond platelet counts (use of rescue, ITP-PAQ, IBLS, QoL) in the pivotal trial and by platelet results provided for the supportive phase 1/2 trial. Furthermore, it should be anticipated that patients using concomitant ITP medications (CS and/or TPO-RAs) might have a higher chance to experience a durable platelet response as measured by the primary endpoint in trial 018 compared to those using rilzabrutinib as monotherapy.

The safety profile of rilzabrutinib in ITP patients is considered to be adequately reflected in the SmPC.

In conclusion, efficacy of rilzabrutinib on platelet numbers is demonstrated and outweighs the concluded risk of rilzabrutinib treatment. The benefit/risk balance is therefore positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of WAYRILZ is positive, subject to the conditions stated in section 'Recommendations'

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of WAYRILZ is favourable in the following indication(s):

WAYRILZ is indicated for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where WAYRILZ is marketed, all patients who are expected to use WAYRILZ have access to/are provided with the following educational material:

- Patient Card (included in each pack, together with the patient leaflet)

1. Patient educational material:

1.1. Patient card:

The patient card is aligned with the product labelling and includes the following key elements:

● Rilzabrutinib should not be used by pregnant women.

● Language describing how to reduce the potential risk of exposure during pregnancy based on the following:

o A pregnancy test should be performed before start of treatment with rilzabrutinib.

o Women of childbearing potential have to use highly effective contraception method during treatment with rilzabrutinib and up to at least 1 month after the last dose.

o Rilzabrutinib may reduce the efficacy of hormonal contraceptives. Therefore, a non-hormonal contraceptive method should be used or have their male partner use a barrier method.

o If a pregnancy occurs during treatment with rilzabrutinib contact your treating physician immediately.

• Contact details of the rilzabrutinib prescriber.

• Women of childbearing potential should be instructed to talk to their healthcare professional about contraception while taking rilzabrutinib.

• Instruct patient to refer to PIL for additional information about the safety of rilzabrutinib.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that rilzabrutinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.