EU-RISK MANAGEMENT PLAN FOR WAYRILZ® (RILZABRUTINIB)

Data Lock Point (DLP)	15-OCT-2024
Risk Management Plan (RMP) Version number	Version 1.0
Date of final sign-off	10-OCT-2025

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Risk Management Plan document updated in the frame of procedure EMEA/H/C/006425 and as response to D233 Committee for Medicinal Products for Human Use (CHMP)/Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteurs Updated Joint Assessment Report and related List of Outstanding Issues issued on 09-Oct-2025.
Summary of significant changes in this RMP	The following Parts have been updated: • Part II Module SIV and Part II Module SVII • Part III • Part V • Annexes 4 (final version), 6 and 8

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	Not applicable
Approved with procedure	Not applicable
Date of approval (opinion date)	Not applicable

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

AE:	Adverse Event
AESI:	Adverse Event of Special Interest
ALT:	Alanine Aminotransferase
anti-D:	anti-RhD Immune Globulin
ASH:	American Society of Hematology
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under the Plasma Concentration-Time Curve
AUClast:	Area Under the Plasma Concentration-Time Curve From Time 0 to Last Measurable Concentration
BID:	Twice Daily
BTK:	Bruton's Tyrosine Kinase
CD20:	Cluster of Differentiation 20
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CNS:	Central Nervous System
COVID-19:	Coronavirus Disease-2019
CSR:	Clinical Study Report
CTD:	Common Technical Document
CYP:	Cytochrome P450
DALA:	Drug-Abuse Liability Assessment
DB:	Double-Blind
DLP:	Data Lock Point
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EMEA/EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
EU:	European Union
Fc:	Fragment Crystallizable
FCγR:	Fc-Gamma Receptor
GVP:	Good Pharmacovigilance Practices
HBV:	Hepatitis B Virus
HCP:	Healthcare Professional
HCV:	Hepatitis C Virus
hERG:	Human Ether-a-go-go-Related Gene
HLA-B27:	Human Leukocyte Antigen-B27
IBA-1:	Ionized Calcium-Binding Adaptor Protein-1
IC50:	Half Maximal Inhibitory Concentration
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP:	Investigational Medicinal Product
INN:	International Nonproprietary Name

IQR:	Interquartile Range
iSAF1:	ITP Safety Pool 1
iSAF2:	ITP Safety Pool 2
ITP:	Immune Thrombocytopenia
IV:	Intravenous
IVIG:	Intravenous Immunoglobulin
LTE:	Long-Term Extension
Max:	Maximum
MedDRA:	Medical Dictionary for Regulatory Activities
Min:	Minimum
n:	Number of Patient
N:	Total Number of Patient
NCPRR:	Nordic Country Patient Registry for Romiplostim
NHS:	National Health Service
NOAEL:	No-Observed-Adverse-Effect Level
OL:	Open-Label
PBPK:	Physiological Based Pharmacokinetic
PEG:	Polyethylene Glycol
PK:	Pharmacokinetics
PL:	Package Leaflet
PND:	Post-Natal Development
PPND:	Pre-/Post-Natal Development
PRAC:	Pharmacovigilance Risk Assessment Committee
PT:	Preferred term
Q:	Quarter
QPPV:	Qualified Person Responsible for Pharmacovigilance
QTc:	Corrected QT Interval
RMP:	Risk Management Plan
SAE:	Serious Adverse Event
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query
SPM:	Second Primary Malignancy
TCH:	Texas Children’s Hospital
TEAE:	Treatment-Emergent Adverse Event
TPO-RA:	Thrombopoietin Receptor Agonist
UGT:	Uridine Diphosphate Glucuronosyltransferase
UK:	United Kingdom
ULN:	Upper Limit of Normal
US:	United States
UTI:	Urinary Tract Infection
UV-A:	Ultraviolet-A
VKHD:	Vogt-Koyanagi-Harada Disease

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance (International Nonproprietary Name [INN] or common name)	Rilzabrutinib
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	B02BX (TBC)
Marketing Authorization Applicant	Sanofi B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Wayrilz®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Bruton Agammaglobulinemia Tyrosine Kinase inhibitor
	Summary of mode action: *Rilzabrutinib is a selective, covalent, reversible inhibitor of Bruton tyrosine kinase (BTK), with a tailored residence time at BTK to reduce off-target effects. In ITP, rilzabrutinib mediates its therapeutic effect through multi-immune modulation by inhibiting B cell activation, interruption of FcγR mediated phagocytosis, and potentially amelioration of chronic inflammation associated with ITP.*
	Important information about its composition: Not applicable
Hyperlink to the product information	Refer to Electronic Common Technical Document (e-CTD) sequence 0004, Module 1.3.1 English proposed Product Information.
Indication in the EEA	Current: Not applicable
	Proposed: *Rilzabrutinib is indicated for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.*
Dosage in the EEA	Current: Not applicable
	Proposed: *The recommended dose of rilzabrutinib is 400 mg twice daily.*
Pharmaceutical form and strength	Current: Not applicable
	Proposed: *Rilzabrutinib 400 mg film-coated tablet.*

Is/will the product (be) subject to additional monitoring in the European Union (EU)?	Yes

ATC: Anatomical Therapeutic Chemical; BTK: Bruton's Tyrosine Kinase; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; FCγR: Fc-Gamma Receptor; INN: International Nonproprietary Name; ITP: Immune Thrombocytopenia; RMP: Risk Management Plan.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

The rilzabrutinib proposed indication is for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

The epidemiology of the disease is summarized in the following table.

Table 6 - Epidemiology of Immune thrombocytopenia (ITP)

Indication	Immune thrombocytopenia (ITP)
Incidence	Immune thrombocytopenia is a rare autoimmune disease. Its incidence in adults is approximately 3 per 100 000 person-years. (1) The Nordic Country Patient Registry for Romiplostim (NCPRR) database (2009-2016) is a cohort study that encompasses all adult patients aged 18 years and older in Denmark, Sweden, and Norway who have chronic ITP. The incidence rates of chronic ITP per 100 000 person-years were 2.8 (with a 95% Confidence Interval (CI): 2.6-3.0) in Denmark, 1.8 (with a 95% CI: 1.7-1.9) in Sweden, and 2.1 (with a 95% CI: 1.9-2.2) in Norway. (2) Older studies reported comparable incidences in Europe: 3.9 per 100 000 (with a 95% CI: 3.7-4.1) in the United Kingdom (UK) using Clinical Practice Research Datalink to identify patients diagnosed with ITP between 1990 and 2005, (3) and 2.9 per 100 000 (with a 95% CI: 2.8-3.1) for ITP requiring treatment or hospitalization in France between 2009 and 2011. (4) In a 2021 retrospective Korean study, the incidence of ITP was 13.39 per 100 000 persons. (5) In a comprehensive overview of the clinical epidemiology, treatment outcomes, and mortality rates among ITP patients receiving care at a tertiary multicenter hematology facility in Malaysia, the incidence of ITP is reported in 1.5 to 5 per 100 000 persons in the general population for both adults and children. (6)
Prevalence	In an observational study conducted in six European countries (Germany, Spain, France, Italy, Netherlands, UK) in 2020, the prevalence of ITP was estimated between 9 and 10 per 100 000 adults, apart from Spain (12.6) and Netherlands (18.1), supporting the European consensus of national ITP association estimated prevalence of 9.7 per 100 000 adults. (7) In a retrospective observational research study, the information from the Korean National Health Insurance Service Claims Database, which is overseen by the Korea Health Insurance Research and Assessment Service, the prevalence of ITP was 24.53 per 100 000 persons. (5)
Demographics of the population in the authorized or proposed indication	**Age** A primary ITP cohort (International Classification of Diseases, Tenth Revision code D693) was identified from National Health Service (NHS) (England) digital records encompassing both inpatient and outpatient data. In summary, 25 805 adults were identified with primary ITP between 2003 and 2014, where the mean age was 59.0 years (Standard Deviation [SD]: 0.1), with a median age of 62.8 years (Interquartile Range [IQR]: 40.3, 76.7). (8) Among males, the mean age was 63.0 years (SD: 0.2), and the median age was 67.0 years (IQR: 50.4, 77.9), while for females, the mean age was 56.1 years (SD: 0.2), and the median age was 57.8 years (IQR: 35.3, 75.5). (8) In a French cohort of 113 incident ITP patients included from 2013 to 2014, the median age was 65 years (range: 18-95) and 57 patients (50.4%) were female. The incidence increased after 60-year-old and was higher in 75 years. (9) In Nordic European countries, using the NCPRR data from 2009 to 2016, 30.2% of prevalent or incident included chronic ITP patients were aged 70 years or more. (2)

Indication	Immune thrombocytopenia (ITP)
	Using nationwide Danish health registries (1980-2016), 1762 patients diagnosed with chronic primary ITP were identified and had a median age of 58 years (IQR: 37-73). (10) **Gender** There is a significant preponderance of females diagnosed with primary ITP (57.8%, probability <0.001). In the aforementioned study conducted in England among all sex-specific age groups, the incidence rates significantly increased over time, except in 18-29 year-old males. The greatest increase was among females aged 30-39 (Average Annual Percent Change: 8.7%). Following a stratified analysis across different age groups, it was observed that this gender difference was not consistently maintained. (8) Similar proportions of women were also observed in the NCPRR data (58%) (2) and in the Danish health registries (60%). (10) In the French cohort, there was a female predominance in younger patients and a clear male predominance in older patients. (9) **Ethnicity/Race** In an observational study published in 2022 involving 25 805 patients identified between 2003 and 2014 completed in England using NHS Digital inpatient and outpatient data, most ITP patients (76%) were of European ancestry, followed by Asian (5.1%) and African/Caribbean (3.1%) ancestries. (8) In an examination of the occurrence of ITP among children at two prominent tertiary care facilities in the United States (US), findings reveal that Black children had a lower likelihood of developing ITP. This was a retrospective analysis evaluating race and ethnicity of all children with ITP treated at Texas Children's Hospital (TCH), (Houston, Texas) from Jan-2015 to Jul-2019, and compared to both the Houston metropolitan area and the TCH Cancer Center 2018 race and ethnicity data. Those who developed ITP were more prone to developing chronic conditions compared to individuals of other races. The demographic data regarding race and ethnicity at the two institutions closely aligned with the surrounding metropolitan areas, implying that the noted distinctions are not attributable to disparities in care or access. (11) **Mortality** The median survival in adult patients with chronic primary immune thrombocytopenia using the nationwide Danish Health registries was 22.1 years (95% CI: 18.1-26.2). The 5-year survival increased from 69% (95% CI: 59-78) in 1980 to 1989 to 80% (95% CI: 75-83) in 2010 to 2016. (10) The cumulative incidences (%, [95% CI]) for causes of deaths in Danish chronic ITP patients at 1, 5 and 10 years were as follows: (10) • For bleeding: 0.92 (0.55-1.46), 2.32 (1.65-3.17) and 3.18 (2.34-4.21). • For hematological cancer: 0.88 (0.52-1.42), 2.82 (2.07-3.75), and 3.83 (2.88-4.96). • For solid cancer: 1.35 (0.88-1.98), 3.70 (2.83-4.75) and 5.36 (4.22-6.68). • For cardiovascular events: 1.88 (1.32-2.62), 5.15 (4.10-6.35) and 7.03 (5.71-8.52). • For infections: 0.58 (0.30-1.03), 1.72 (1.15-2.48) and 2.69 (1.88-3.71). Characteristics such as individual demographics, length of hospital stays, hospitalization expenses, and in-hospital mortality were examined in the context of hospitalizations related to ITP within the US National Inpatient Sample from 2006 to 2012. The reported in-hospital mortality was 3.08 (95% CI: 2.93-3.23), and the standardized mortality ratio: 1.22 (95% CI: 1.19-1.24). (12)
Main existing treatment options	**Initial Treatment (or first-line treatments)** In adults with newly diagnosed ITP, international guidelines (including American Society of Hematology [ASH]) (13) and expert consensus (14) suggest a short course of corticosteroids (<6 weeks), either prednisone (0.5-2.0 mg/kg/day) or dexamethasone (40 mg/day for 4 days)

Indication	Immune thrombocytopenia (ITP)
	and/or intravenous immunoglobulins (IVIG) or intravenous (IV) anti-RhD immune globulin (anti-D) (in appropriate patients) if corticosteroids are contraindicated. **Subsequent Treatment (or advanced treatments or second line treatment and beyond)** International guidelines (including ASH) (13) and expert consensus (14) recommend for adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the following options: • Thrombopoietin Receptor Agonist (TPO-RA): romiplostim, eltrombopag, avatrombopag; • Rituximab (anti-cluster of differentiation 20 [CD20] monoclonal antibody); • Fostamatinib (Spleen Tyrosine Kinase inhibitor). Other treatments mentioned in guidelines (13) without robust evidence are: • Mycophenolate mofetil, Azathioprine, Cyclosporin A, Cyclophosphamide, Danazol, Dapsone; • Splenectomy can be considered for patients with ITP lasting ≥12 months for patients who are unresponsive/ineligible for other treatments.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Among adult patients, roughly 70% enter the persistent phase of the disease, lasting more than 3 months, while approximately 60% progress into the chronic phase, which persists for ≥12 months. Unlike in children, there is limited understanding of the factors that can forecast the development of persistence or chronicity. Based on data from two prospective cohorts, it appears that a more severe disease presentation, including mucosal or visceral bleeding at the onset of ITP, is associated with an acute disease course. (1)
Important co-morbidities	Comorbidities frequently reported for adults with ITP: • Hematological malignancies • Thrombotic/Thromboembolic events (arterial and venous) • Cardiovascular risk factors: hypertension and diabetes mellitus • Anxiety and depression • Cognitive impairment • Osteoporosis and osteoporosis-related fractures • Infections • Other autoimmune conditions: autoimmune thyroiditis, primary Sjogren's syndrome, Rheumatoid Arthritis. (15)(16)(17) Immune thrombotic thrombocytopenic purpura patients referred to the French Reference Center for Thrombotic Microangiopathies from 2000 to 2016 were studied separately according to their age (under 60 years of age, or 60 years of age or older). As one can expect the comorbidities were less frequent in the youngest patients than in the oldest one: Diabetes mellitus (4% versus 21%), Coronary heart disease (2% versus 13%), Dyslipidemia (9% versus 44%); Hypertension (12% versus 65%), Chronic kidney disease (2% versus 10%), Transient stroke/stroke (4% versus 10%). (18) A nationwide Danish health registries 1980-2016 identified 1762 patients with chronic primary ITP (median age: 58 years, women: 60.0%). The most frequent comorbidities were tumors (solid and hematological) 13.6%, connective tissue disease 9.4%, chronic pulmonary disease 8.1% and liver disease 5.2%. (10)

anti-D: anti-RhD Immune Globulin; ASH: American Society of Hematology; CD20: Cluster of Differentiation 20; CI: Confidence Interval; IQR: Interquartile Range; ITP: Immune Thrombocytopenia; IV: Intravenous; IVIG: Intravenous Immunoglobulin; NCPRR: Nordic Country Patient Registry for Romiplostim; NHS: National Health Service; SD: Standard Deviation; TCH: Texas Children's Hospital; TPO-RA: Thrombopoietin Receptor Agonist; UK: United Kingdom; US: United States.

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

This section presents a summary of non-clinical data in rodents and non-rodents for rilzabrutinib.

The non-clinical safety profile of rilzabrutinib was evaluated in the following in vivo and ex vivo studies:

- Core battery of safety pharmacology studies as defined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S7A and S7B guidelines was performed, systems evaluated included the central nervous system (CNS), cardiovascular (in vitro human ether-a-go-go-related gene [hERG]; telemetered dog), and respiratory systems.
- Single-dose study in rats and dogs
- Repeat-dose general toxicity studies up to 1-month duration in RasH2 (wild-type) mice, up to 6-month in rats, and up to 39-week 9-month in dogs using the oral route
- Genotoxicity battery (2 in vitro; 1 in vivo)
- Carcinogenicity studies: 6-month study in TgRasH2 mice and 2-year study in rats
- Fertility study in adult male and female rats
- Embryo-fetal developmental toxicity studies in rats and rabbits
- Pre-/post-natal development (PPND) toxicity study in rats
- Exploratory juvenile toxicity study in rats
- In vitro phototoxicity

The key rilzabrutinib-related non-clinical findings are described below and in Table 7.

Safety pharmacology studies showed that rilzabrutinib had a half maximal inhibitory concentration (IC_{50}) of 3.5 μM in the hERG assay. In a telemetered dog study, no rilzabrutinib-related effect on cardiac electrophysiology was observed. In a function observation battery and locomotor activity study in rats, no rilzabrutinib-related gross behavioral, physiological, or neurological changes were observed. No adverse rilzabrutinib-related changes to respiratory parameters were observed.

In toxicology studies performed in mice, rats, and dogs, the adrenal gland (rat), bone marrow (rat), brain (rat), gastrointestinal tract (rat/dog), cervical/mesenteric lymph nodes (rat/dog), liver (rat/dog), lung (rat), ovaries (rat), Peyer's patches (dog), spleen (rat), thymus (rat/dog), uterus (rat), and vagina (rat) were identified as primary target organs of toxicity. An increase in ionized calcium-binding adaptor protein-1 (IBA-1) expression (suggestive of an increase in the number of microglia cells) was observed in the lateral, third and fourth ventricles and near the optic chiasm. No evidence of neurodegeneration or cellular alteration in the brain was observed.

Rilzabrutinib was well-tolerated in rats and dog studies of up to 6- and 9-month duration, respectively. In a 6-month oral repeat-dose rat study, the no-observed-adverse-effect level

(NOAEL) for female rats was 50 mg/kg/day (Area under the plasma concentration-time curve from time 0 to last measurable concentration [AUC_{last}] 5760 hr.ng/mL) and 150 mg/kg/day in males (AUC_{last} 6860 hr.ng/mL), based on lethality, decreased body weight gain, macroscopic and microscopic changes in the gastrointestinal tract, and neutrophilic inflammation in the brain. In a 9-month oral repeat-dose dog study, the NOAEL was 30 mg/kg/day (AUC_{last} 689 hr.ng/mL), based on body weight loss and the euthanasia of 1 male dog at 50 mg/kg/day.

Rilzabrutinib was not mutagenic or clastogenic.

Rilzabrutinib was not carcinogenic in a 6-month transgenic mouse study at doses up to 300 mg/kg/day. In a 2-year rat carcinogenicity study, rilzabrutinib-related thyroid adenomas and carcinomas were observed for male rats at 100 mg/kg/day; the non-carcinogenic dose was considered to be 30 mg/kg/day for males and 50 mg/kg/day for females. An assessment of available toxicology and literature data conducted by an external expert concluded that the thyroid tumor induction in rats was consistent with impairment of thyroid hormone balance by induction of Phase II uridine diphosphate glucuronosyltransferase (UGT) enzymes in the liver. This is a nongenotoxic mechanism of cancer in rats that is not considered relevant to humans.

No rilzabrutinib-related effects on fertility and reproductive performance were observed and the parental and reproductive/developmental NOAELs were 150 and 300 mg/kg/day, respectively.

Embryo-fetal development was evaluated in rats and rabbits. In an exploratory rat embryo-fetal range-finding study, rilzabrutinib increased post-implantation loss and incidence of early resorptions and decreased fetal weight at 500 mg/kg/day. Fetal external (anasarca), visceral (urogenital), and skeletal (delayed ossification) changes were observed at 500 mg/kg/day. In an exploratory rabbit embryo-fetal range-finding study, a slight increase in the incidence of early resorptions, was noted at 150 mg/kg/day. Fetal visceral changes were observed at 150 mg/kg/day (area under the plasma concentration-time curve [AUC] exposure margin of 5.6-fold).

In definitive rat and rabbit embryo-fetal toxicity studies, no rilzabrutinib-related external, visceral, or skeletal malformations were observed. The NOAELs for embryo-fetal development were 300 and 100 mg/kg/day in rats and rabbits, respectively.

In the rat PPND toxicity study NOAELs were 50 mg/kg/day (F0 maternal systemic toxicity), 150 mg/kg/day (F1 neonatal/developmental toxicity) and 300 mg/kg/day (F1 systemic and parental toxicity, and F2 embryonic toxicity).

In an exploratory juvenile toxicity study, rats were dosed from post-natal development (PND) 10 to PND 34. Rilzabrutinib-related mortality and clinical signs were observed at ≥100 mg/kg/day. The NOAEL was considered to be 30 mg/kg/day.

No phototoxic potential was observed in 3T3 cells exposed to rilzabrutinib with or without ultraviolet-A (UV-A) irradiation. No rilzabrutinib-related changes in hematology and immunophenotyping were observed in repeat-dose rat and dog studies. Reversible test article-related microscopic findings were noted in rat lymphoid tissues (cervical lymph nodes, thymus) and dog lymphoid and hematopoietic (thymus, Peyer's patches, lymph nodes, bone marrow) tissues. Rilzabrutinib and its major metabolite, thiocyanate[redacted], demonstrated no signal of dependence and abuse potential or similarities to known drugs of abuse according to

chemical structure, physiochemical properties, pharmacology, and mechanism of action. Evaluation of animal and human metabolites revealed that the metabolic pathways among various species including rat, dog, and human were qualitatively similar. Collectively, these data demonstrated that the significant circulating metabolites in humans were also observed in preclinical species.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • In repeat-dose toxicity studies performed in mice, rats, and dogs, the adrenal gland (rat), bone marrow (rat), brain (rat), gastrointestinal tract (rat/dog), cervical/mesenteric lymph nodes (rat/dog), liver (rat/dog), lung (rat), ovaries (rat), Peyer's patches (dog), spleen (rat), thymus (rat/dog), uterus (rat), and vagina (rat) were identified as primary target organs of toxicity. An increase in IBA-1 expression (suggestive of an increase in the number of microglia cells) was observed in the lateral, third and fourth ventricles and near the optic chiasm. No evidence of neurodegeneration or cellular alteration in the brain was observed.	Gastrointestinal adverse events (AEs) have been reported in humans during clinical studies.
Genotoxicity • No rilzabrutinib-related genotoxicity was observed in a battery of 2 in vitro (bacterial reverse mutation assay; mammalian chromosome aberration test in human lymphocytes) and 1 in vivo (bone marrow micronucleus test in rats) studies.	No relevance. No safety issues in humans based upon negative results in the in vitro and in vivo genotoxicity studies.
Carcinogenicity • No rilzabrutinib-related effects on survival or incidence of neoplasms were observed in a 6-month carcinogenicity study in TgHRas mice. In a 2-year carcinogenicity study in Wistar Han rats an increase in the incidence of thyroid (follicular cell adenoma/carcinoma) and pancreas (islet cell adenoma) tumors was noted for 100 mg/kg/day males. It was concluded that rilzabrutinib was not carcinogenic in rats at $\leq$30 mg/kg/day in males and 50 mg/kg/day in females	No relevance. While rilzabrutinib-related thyroid tumors (adenoma; carcinoma) were observed in males in the 2-year rat study, an assessment of available toxicology and literature data conducted by an external expert concluded that the thyroid tumor induction was consistent with the impairment of thyroid hormone balance by induction of Phase II UGT enzymes in the liver. This is a nongenotoxic mechanism of cancer in rats that is not considered relevant to humans. (19) Pancreatic adenomas are common spontaneous age-related tumors in rats; the incidence observed did not exceed the available historical controls and there were no other findings supporting a proliferative effect of rilzabrutinib on islet cells.
Reproductive/developmental toxicity • Fertility/early development: No rilzabrutinib-related effects on rat fertility, reproductive performance, and early embryonic development were observed. The NOAEL was 300 mg/kg/day, the highest dose evaluated.	The effect of rilzabrutinib on pregnancy is not known; therefore, protocols include pregnancy testing for women of childbearing potential and specify acceptable means of contraception consistent with local regulations. The concentration of rilzabrutinib in human milk is not known; therefore, breastfeeding is not permitted during the clinical trials.

Key Safety Findings	Relevance to human usage
• Embryo-fetal development: Reproductive and developmental toxicity studies have been performed in rats and rabbits. - In an exploratory rat embryo-fetal range-finding study, increased post-implantation loss and incidence of early resorptions, and decreased fetal weight were recorded at 500 mg/kg/day. Fetal external, visceral, and skeletal malformations were observed at 500 mg/kg/day. No malformations were noted at ≤150 mg/kg/day. - In an exploratory rabbit embryo-fetal range-finding study, a slight increase in the incidence of early resorptions, possibly associated with the observed maternal toxicity, was noted at 150 mg/kg/day. Fetal visceral changes were observed at 150 mg/kg/day (AUC exposure margin of 5.6-fold), however, any test article-related association was considered to be equivocal since the incidence of the abnormalities did not increase in a dose-dependent manner. - In definitive rat and rabbit embryonic development studies, there were no rilzabrutinib related fetal development changes and no fetal development external, visceral, or skeletal morphology changes observed. Therefore, the embryo-fetal development NOAEL was 300 and 100 mg/kg/day in rats and rabbits, respectively.	Embryo-fetal toxicity is considered an important potential risk in the RMP.
• Pre-/postnatal development toxicity: No rilzabrutinib-related effects on mean gestation lengths or the process of parturition, macroscopic observations, numbers of former implantation sites and unaccounted for sites were noted for F0 rats. No rilzabrutinib-related effects on survival, post-weaning developmental landmarks, neurobehavioral assessments, or reproductive performance, mean estrous cycle lengths, and pre-coital intervals were noted for F1 pups. No test article-related changes in mean numbers of corpora lutea and implantation sites were noted for F1 females; rilzabrutinib-related decrease in mean F1 pup body weight and body weight gains were observed during the pre- and post-weaning periods. No rilzabrutinib-related change in the intrauterine survival of F2 embryos was noted.	No relevance. No safety issues in humans in association with reproductive parameters and neurobehavioral development. Unknown relevance body weight. It is not known what the potential risk is from a rilzabrutinib-related decrease in F1 pup body weight and body weight gain.
• Exploratory juvenile toxicity study: Rilzabrutinib-related mortality and clinical signs were observed at >100 mg/kg/day.	Unknown relevance. Purpose of this study was to identify the maximum tolerated dose for the planned definitive juvenile toxicity study.
Safety pharmacology	
• Cardiovascular system: No rilzabrutinib-related effect on cardiac electrophysiology, including potential effect on the QT interval was observed. Increased systolic and pulse pressure at ≥150 mg/kg and increased	Preclinical cardiovascular-related changes in heart rate and blood pressure were observed at doses considerably higher than the therapeutic dose for the treatment of ITP (400 mg twice daily [BID]).

Key Safety Findings	Relevance to human usage
heart rate and blood pressure (diastolic; mean arterial) at 500 mg/kg were observed in dogs (study DVR0177).	The findings in the DVR0177 Study, demonstrate that the rilzabrutinib-related cardiovascular effects at 500 mg/kg (increased heart rate and blood pressure) were observed at an exposure (AUC) in dogs that was 13.1-fold higher than the therapeutic AUC in ITP patients who receive rilzabrutinib 400 mg BID (as per pivotal study PRN1008-018 [EFC17093]). In the "Thorough QT Study," co-administration of 400 mg rilzabrutinib and the cytochrome P450 (CYP) 3A inhibitor (ritonavir) resulted in plasma exposure 8 times higher than rilzabrutinib alone. Under these conditions, there was no prolongation of the mean corrected QT interval (QTc) interval to any clinically relevant effect. In this same study, a concentration dependent shortening in the QTc interval was observed (-10.2 ms [90% CI: -12.24, -8.16]) following the supratherapeutic dose (combination of rilzabrutinib and ritonavir 100 mg). The shortening was smaller (-7.3 ms [90% CI: -9.33, -5.19]) at the rilzabrutinib 400 mg BID dose. In the clinical trials with ITP patients, there were no clinically meaningful QTc interval changes. A warning has been added to the Summary of Product Characteristics (SmPC) for clinicians to use clinical judgment when assessing whether to prescribe rilzabrutinib to patients at risk from further shortening their QTc duration (eg, Congenital Short QT Syndrome or patients with a family history of such a syndrome).
• Central nervous system: No rilzabrutinib-related gross behavioral, physiological, or neurological changes were observed in rats (study DVR0176). • Respiratory system: No adverse rilzabrutinib-related changes in respiratory parameters were observed in dog (study DVR0177).	No relevance. No safety issues in humans based on the absence of rilzabrutinib-related CNS findings. No relevance. No safety issues in humans based on the absence of rilzabrutinib-related respiratory findings.
Other toxicity-related information or data • Rilzabrutinib did not show any phototoxicity potential in an in vitro 3T3 neutral red uptake phototoxicity test. • No rilzabrutinib-related immunotoxicity was observed. • Rilzabrutinib and its major metabolite, thiocyanate [redacted], demonstrated no signal of dependence and abuse potential. • Evaluation of animal and human metabolites revealed that the metabolic pathways among various species including rat, dog, and human were qualitatively similar and that the significant circulating metabolites in humans were also observed in preclinical species.	No relevance. No safety issues in humans based upon absence of rilzabrutinib-related phototoxicity.

AE: Adverse Event; AUC: Area Under the Plasma Concentration-Time Curve; BID: Twice Daily; CI: Confidence Interval; CNS: Central Nervous System; CYP: Cytochrome P450; IBA-1: Ionized Calcium Binding Adaptor Protein-1; ITP: Immune Thrombocytopenia; NOAEL: No-Observed-Adverse-Effect Level; QTc: Corrected QT Interval; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics; UGT: Uridine Diphosphate Glucuronosyltransferase.

No additional non-clinical safety studies have been performed to evaluate the safety of rilzabrutinib in any special populations.

RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

This overview of safety with a cut-off date 15 October 2024 primarily focuses on the ITP placebo-controlled results from the pivotal Phase 3 Study PRN1008-018 (EFC17093) comparing the rilzabrutinib-treated arm to the placebo arm during the completed double-blind (DB) treatment period, and include the results from the completed open-label (OL) treatment period, and ongoing long-term extension (LTE) period that provide additional evidence for longer-term rilzabrutinib safety and tolerability in patients with ITP.

The data are supported by integrated analyses from ITP Studies PRN1008-010 (DFI17124), a Phase 1/2 study, and PRN1008-018 (EFC17093), the Phase 3 study, during all treatment periods up to the dossier cut-off date and including all rilzabrutinib doses (ITP rilzabrutinib pool). The ITP rilzabrutinib pool includes safety data in 284 participants treated with any dose of rilzabrutinib.

Safety findings are supported by data from individual studies in ITP (PRN1008-010 and PRN1008-018).

The safety population includes all participants allocated to an intervention (PRN1008-010) or randomized intervention (PRN1008-018) who received at least one dose of study drug. The pooling strategy defined the following 3 data pools for analysis:

- **ITP placebo-controlled pool** containing participant data from Study PRN1008-018, DB treatment period.
- **ITP open-label pool** containing participant data from Study PRN1008-018, completed OL treatment period and ongoing LTE period.
- **ITP rilzabrutinib pool** consisting of safety data integrated from Studies PRN1008-010 (Parts A and B) and PRN1008-018 during the entire treatment period (DB, OL and LTE).

Table 8 - Cumulative exposure to IMP by duration - 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)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Duration of exposure (weeks)	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
≥0 weeks	69	17.9	133	44.3	284	290.6	278	286.9
≥4 weeks	68	17.8	131	44.1	276	290.3	269	286.5
≥12 weeks	54	14.9	112	40.8	238	285.1	233	281.5
≥24 weeks	9	4.2	50	23.2	187	267.8	185	265.0
≥52 weeks					98	213.2	98	211.7
≥104 weeks					48	147.9	48	146.3
≥156 weeks					16	67.6	16	66.1
Total	69	17.9	133	44.3	284	290.6	278	286.9

Data cutoff: 15-Oct-2024 for PRN1008-018 and 02-Aug-2024 for PRN1008-010.

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 Participant received rilzabrutinib 400 mg BID any time.

d Participant-years = the cumulative duration of observation period in days /365.25.

PGM=PRODOPS/SAR444671/OVERALL/ITP_EMA_02/REPORT/PGM/cdc_exp_cum_dur_rmp_pool_s_t.sas OUT=REPORT/OUTPUT/cdc_exp_cum_dur_rmp_pool_s_t_x.rtf (21JUL2025 5:40)

BID: Twice Daily; DB: Double-Blind; IMP: Investigational Medicinal Product; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; N: Total Number of Patient; OL: Open-Label.

Table 9 - Cumulative exposure to IMP by sex - 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)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Sex	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
Male	20	5.3	55	18.0	111	109.9	107	108.2
Female	49	12.6	78	26.3	173	180.8	171	178.7
Total	69	17.9	133	44.3	284	290.6	278	286.9

Data cutoff: 15-Oct-2024 for PRN1008-018 and 02-Aug-2024 for PRN1008-010.

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 Participant received rilzabrutinib 400 mg BID any time.

d Participant-years = the cumulative duration of observation period in days /365.25.

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BID: Twice Daily; DB: Double-Blind; IMP: Investigational Medicinal Product; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; N: Total Number of Patient; OL: Open-Label.

Table 10 - Cumulative exposure to IMP by age group - 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)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Age group	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
<65 years	54	13.7	112	38.2	233	240.5	227	237.7
65 to <75 years	12	3.3	15	4.4	40	40.1	40	39.2

	ITP placebo-controlled pool[a]				ITP rilzabrutinib pool[b]			
	Placebo (N = 69)		Rilzabrutinib 400 mg BID (N = 133)		Rilzabrutinib any dose (N = 284)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Age group	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
75 to <85 years	3	0.9	6	1.7	11	10.0	11	10.0
≥85 years	0	0	0	0	0	0	0	0
Total	69	17.9	133	44.3	284	290.6	278	286.9

Data cutoff: 15-Oct-2024 for PRN1008-018 and 02-Aug-2024 for PRN1008-010.

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 Participant received rilzabrutinib 400 mg BID any time.

d Participant-years = the cumulative duration of observation period in days /365.25.

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BID: Twice Daily; DB: Double-Blind; IMP: Investigational Medicinal Product; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; N: Total Number of Patient; OL: Open-Label.

Table 11 - Cumulative exposure to IMP by sex and age group - 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)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Sex	Age group	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
Male	<65 years	17	4.4	46	15.2	93	95.3	89	93.7
	65 to <75 years	2	0.5	4	1.3	11	7.7	11	7.7
	75 to <85 years	1	0.5	5	1.5	7	6.9	7	6.9

		ITP placebo-controlled pool[a]				ITP rilzabrutinib pool[b]			
		Placebo (N = 69)		Rilzabrutinib 400 mg BID (N = 133)		Rilzabrutinib any dose (N = 284)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Sex	Age group	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
	≥85 years	0	0	0	0	0	0	0	0
Female	<65 years	37	9.3	66	22.9	140	145.2	138	144.0
	65 to <75 years	10	2.8	11	3.2	29	32.4	29	31.5
	75 to <85 years	2	0.5	1	0.2	4	3.1	4	3.1
	≥85 years	0	0	0	0	0	0	0	0

Data cutoff: 15-Oct-2024 for PRN1008-018 and 02-Aug-2024 for PRN1008-010.

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 Participant received rilzabrutinib 400 mg BID any time.

d Participant-years = the cumulative duration of observation period in days /365.25.

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BID: Twice Daily; DB: Double-Blind; IMP: Investigational Medicinal Product; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; N: Total Number of Patient; OL: Open-Label.

Table 12 - Cumulative exposure to IMP by race - 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)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Race	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
White	40	10.9	85	28.1	198	215.9	192	212.2

	ITP placebo-controlled pool[a]				ITP rilzabrutinib pool[b]			
	Placebo (N = 69)		Rilzabrutinib 400 mg BID (N = 133)		Rilzabrutinib any dose (N = 284)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Race	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
Black or African American	0	0	1	0.5	1	1.0	1	1.0
Asian	24	5.8	40	13.6	68	60.2	68	60.2
American Indian or Alaska Native	1	0.2	3	1.2	4	4.8	4	4.8
Native Hawaiian or Other Pacific Islander	0	0	0	0	1	0.2	1	0.2
Other	2	0.5	3	0.7	9	8.0	9	8.0
Not Reported	2	0.5	1	0.2	3	0.5	3	0.5
Total	69	17.9	133	44.3	284	290.6	278	286.9

Data cutoff: 15-Oct-2024 for PRN1008-018 and 02-Aug-2024 for PRN1008-010.

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 Participant received rilzabrutinib 400 mg BID any time.

d Participant-years = the cumulative duration of observation period in days /365.25.

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BID: Twice Daily; DB: Double-Blind; IMP: Investigational Medicinal Product; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; N: Total Number of Patient; OL: Open-Label.

Table 13 - Cumulative exposure to IMP by ethnicity - 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)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Ethnicity	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
Hispanic or Latino	13	3.7	28	9.6	45	52.8	44	52.7
Not Hispanic or Latino	53	13.5	103	34.2	234	236.6	229	233.0
Not Reported	3	0.7	2	0.5	5	1.2	5	1.2
Total	69	17.9	133	44.3	284	290.6	278	286.9

Data cutoff: 15-Oct-2024 for PRN1008-018 and 02-Aug-2024 for PRN1008-010.

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 Participant received rilzabrutinib 400 mg BID any time.

d Participant-years = the cumulative duration of observation period in days /365.25.

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BID: Twice Daily; DB: Double-Blind; IMP: Investigational Medicinal Product; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; N: Total Number of Patient; OL: Open-Label.

Table 14 - Extent of exposure to investigational medicinal product - 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)	Rilzabrutinib 400 mg BID[c] (N = 278)
Cumulative duration to treatment exposure (participant-years)[d]	17.9	44.3	290.6	286.9

	ITP placebo-controlled pool[a]		ITP rilzabrutinib pool[b]	
	Placebo (N = 69)	**Rilzabrutinib 400 mg BID (N = 133)**	**Rilzabrutinib any dose (N = 284)**	**Rilzabrutinib 400 mg BID[c] (N = 278)**
Duration of IMP exposure (days)[e]				
Number	69	133	284	278
Mean (SD)	94.7 (32.7)	121.5 (46.9)	373.8 (398.6)	377.0 (393.3)
Median	84.0	98.0	197.0	197.0
Min ; Max	17 ; 173	22 ; 182	4 ; 2124	7 ; 1905
Duration of IMP exposure by intervals [n (%)]				
≥0 to <4 weeks	1 (1.4)	2 (1.5)	8 (2.8)	9 (3.2)
≥4 to <8 weeks	1 (1.4)	6 (4.5)	20 (7.0)	18 (6.5)
≥8 to <12 weeks	13 (18.8)	13 (9.8)	18 (6.3)	18 (6.5)
≥12 to <16 weeks	44 (63.8)	47 (35.3)	16 (5.6)	14 (5.0)
≥16 to <20 weeks	0	1 (0.8)	15 (5.3)	14 (5.0)
≥20 to <24 weeks	1 (1.4)	14 (10.5)	20 (7.0)	20 (7.2)
≥24 weeks	9 (13.0)	50 (37.6)		
≥24 to <52 weeks			89 (31.3)	87 (31.3)
≥52 to <78 weeks			39 (13.7)	39 (14.0)
≥78 to <104 weeks			11 (3.9)	11 (4.0)
≥104 to <130 weeks			17 (6.0)	17 (6.1)
≥130 to <156 weeks			15 (5.3)	15 (5.4)
≥156 weeks			16 (5.6)	16 (5.8)

Data cutoff: 15-Oct-2024 for PRN1008-018 and 02-Aug-2024 for PRN1008-010.

	ITP placebo-controlled pool[a]		ITP rilzabrutinib pool[b]	
	Placebo (N = 69)	**Rilzabrutinib 400 mg BID (N = 133)**	**Rilzabrutinib any dose (N = 284)**	**Rilzabrutinib 400 mg BID[c] (N = 278)**

Percentages are calculated using the number of participants in the adult safety population with a non-missing duration of exposure as denominator.

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 Participant received rilzabrutinib 400 mg BID any time.

d Participant-years = the cumulative duration of observation period in days /365.25.

e Duration of IMP exposure (days) = (Date of last dose - Date of first dose) + 1, regardless of unplanned intermittent interruption.

PGM=PRODOPS/SAR444671/OVERALL/ITP_EMA_02/REPORT/PGM/cdc_exp_extent_rmp_pool_s_t.sas OUT=REPORT/OUTPUT/cdc_exp_extent_rmp_pool_s_t_x.rtf (21JUL2025 5:40)

BID: Twice Daily; DB: Double-Blind; IMP: Investigational Medicinal Product; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; Max: Maximum; Min: Minimum; N: Total Number of Patient; OL: Open-Label; SD: Standard Deviation.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 15 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnancy and lactation, females who breastfeed or females who intend to become pregnant during the participation in the study.	These exclusion criteria were considered due to methodological considerations, to prevent any potential direct or indirect harmful effects on pregnancy, embryo-fetal development, birth, or postnatal development in the absence of information on the use of rilzabrutinib during pregnancy or lactation in humans.	No	Rilzabrutinib should not be used during pregnancy and in women of childbearing potential not using contraception. A decision must be made whether to discontinue rilzabrutinib therapy or discontinue breast-feeding taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother.
Pediatrics (0-17 years of age).	Children (0 to ≤9) were not involved in the clinical development of rilzabrutinib as they are not the intended target population at this time. Adolescent (≥10 to 17) are not included at this time, as their clinical development is still ongoing. Only adult data is available at first development of this RMP.	No	Pediatric population is not targeted at the initial submission. The absence of clinical data is reflected in the claimed indication for “adult use only” at this time.
Patients with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5x upper limit of normal (ULN) and/or total bilirubin >1.5 x ULN, except for known Gilbert Syndrome).	Based on the labeling from other BTK inhibitors patients with ALT and/or AST >1.5 x ULN and/or total bilirubin >1.5 x ULN were excluded from the clinical studies supporting the already approved hematologic oncologic indications given the potential risk of elevations of liver transaminases or other liver parameters.	No	Rilzabrutinib should not be administered in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Renal impairment: Patients with a glomerular filtration rate <50 mL/Min/1.73m^2 (Cockcroft and Gault method)	Impairment of the renal function does not play a major role in rilzabrutinib excretion; however, a sufficient renal function is an international requirement for conducting clinical trials. Subsequently, to these international requirements this exclusion criterion was considered for methodological reasons as well, to prevent biases on the safety endpoints evaluation as a decline in renal function may be associated with increases of AEs and/or reporting of AEs.	No	Rilzabrutinib pharmacokinetic (PK) has not been investigated in humans with renal impairment. Since renal excretion of rilzabrutinib is very low (approximately 0.03% of dose was recovered as unchanged drug in urine), the likely impact of renal impairment on rilzabrutinib PK is anticipated to be minimal and not clinically relevant. This was further confirmed by in silico physiological based pharmacokinetic (PBPK) prediction showing that a minimal increase by 1.1- to 1.4-fold in rilzabrutinib exposure, with less impact in mild renal impairment compared to moderate and severe renal impairment for which the results were similar (Study PBS0230). Also, the population PK analysis showed no impact of the creatinine clearance, with (the lowest value being 46 mL/min in the dataset).
Immunocompromised patients: Positive at screening for human immunodeficiency virus, Hepatitis B Virus (HBV) (surface and core antibodies unrelated to vaccination), or Hepatitis C Virus (HCV) (anti-HCV antibody confirmed with Hepatitis C Ribonucleic Acid)	It is unknown if impairment of the immune function plays a role in rilzabrutinib mechanism of action; however, a sufficient immune function is an international requirement for conducting clinical trials.	No	The absence of safety data in this patient population does not constitute a safety concern, rilzabrutinib safety data does not indicate an imbalance of events associated with HBV or HCV or immunocompromised state. Rilzabrutinib was not studied in patients with known or suspected immunodeficiency, including organ transplant

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			patients. No specific safety issues are foreseen in this population.

AE: Adverse Event; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BTK: Bruton's Tyrosine Kinase; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; PBPK: Physiological Based Pharmacokinetic; PK: Pharmacokinetics; RMP: Risk Management Plan; ULN: Upper Limit of Normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program may not detect certain types of adverse reactions such as rare or very rare adverse reactions.

The overall size of the rilzabrutinib safety population is commensurate with the size of the target population. As of 15 October 2024, 284 participants have received rilzabrutinib in the clinical development program for ITP comprised of Phase 1 to Phase 3 clinical trials. While the number of participants is adequate to evaluate common adverse reactions, uncommon and rare adverse reactions may not be reliably detected based on the sample size. Among the 284 participants exposed to rilzabrutinib, 98 participants have been exposed for ≥52 weeks, 48 participants for ≥104 weeks, and 16 participants for ≥156 weeks (these include 8 participants exposed for more than 5 years) (Table 14).

Cumulative effects are not anticipated due to the short half-life of rilzabrutinib and extensive metabolism (PRN1008-001 Part B). In the absorption, metabolism, and excretion study (PRN1008-015), the prevalence of metabolites in feces indicate that metabolism is the major mechanism of elimination of rilzabrutinib in humans. After multiple dosing, the mean apparent terminal half-life ranged from 3.82 to 4.50 hours for all cohorts on Day 10 and did not appear to change with varying dose regimens in study PRN1008-001.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 16 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. There are no available data on rilzabrutinib use in pregnant women. During the conduct of the pivotal Phase 3 trial DB period PRN1008-018 (EFC17093) no pregnancies were reported. In the ITP rilzabrutinib pool (N = 284), overall n = 2 (0.7%) participants had become pregnant and have been exposed to rilzabrutinib. There were no untoward events reported for the pregnancies. One participant[redacted], who reported pregnancy on Day 394 (LTE part of PRN1008-010). The participant underwent elective termination of pregnancy.

Type of special population	Exposure
	Another participant [redacted], who reported a pregnancy on Day 410 (LTE part of PRN1008-018). The outcome of the pregnancy was reported as unknown. Both participants were discontinued from study and IMP.
Breastfeeding women	There are no available data on the presence of rilzabrutinib or its metabolites in human milk, effects on milk production, or the breastfed infant. During the conduct of PRN1008-018 (EFC17093) no female participants were confirmed to be breastfeeding (n = 0). No additional information is available concerning this special population.
Patients with relevant comorbidities. • Patients with history of hepatic impairment	During the Phase 3 pivotal study (N = 202) 43 (21.3%) participants with a medical history of hepatic impairment have been randomized and treated with rilzabrutinib or placebo (32 treated with rilzabrutinib). In the ITP rilzabrutinib pool (N = 284), overall n = 52 (18.3%) participants with a medical history of hepatic impairment have been randomized and treated with rilzabrutinib. Rilzabrutinib was not studied in participants with severe hepatic impairment. The cumulative exposure of patients with history of hepatic impairment in the ITP placebo pool and the ITP rilzabrutinib pool is provided in Table 17 below.
• Patients with renal impairment	Participants with mild to severe renal impairment have not been excluded from rilzabrutinib clinical trial participation. Impairment of the renal function does not play a major role in rilzabrutinib excretion; however, a sufficient renal function is an international requirement for conducting clinical trials. Rilzabrutinib PK has not been investigated in humans with renal impairment. Since renal excretion of rilzabrutinib is very low (approximately 0.03% of dose was recovered as unchanged drug in urine), the likely impact of renal impairment on rilzabrutinib PK is anticipated to be minimal and not clinically relevant. Therefore, renal impairment is not considered missing information. During the Phase 3 pivotal study (N = 202) 6 (3.0%) participants with a medical history of renal impairment have been randomized and treated with rilzabrutinib or placebo (5 treated with rilzabrutinib). In the ITP rilzabrutinib pool (N = 284), overall n = 9 (3.2%) participants with a medical history of renal impairment have been randomized and treated with rilzabrutinib. The cumulative exposure of patients with history of renal impairment in the ITP placebo pool and the ITP rilzabrutinib pool is provided in Table 17 below.
• Patients with cardiovascular impairment	Patients with cardiovascular impairment: Participants with cardiovascular impairment have not been excluded from rilzabrutinib clinical trial participation. Overall, in PRN1008-018 (EFC17093) (ITP placebo-controlled pool) 36 participants ≥65 years of age have been included, and all together in the ITP rilzabrutinib pool 51 participants ≥65 years of age have been included. Of these participants, during the Phase 3 pivotal study [N = 202] 6 (3.0%) participants with a medical history of cardiovascular impairment have been randomized and treated with rilzabrutinib or placebo (3 treated with rilzabrutinib). In the ITP rilzabrutinib pool (N = 284), overall n = 14 (4.9%) participants with a medical history of cardiovascular impairment have been randomized and treated with rilzabrutinib. The cumulative exposure of patients with history of cardiovascular impairment in the ITP placebo pool and the ITP rilzabrutinib pool is provided in Table 17 below.

Type of special population	Exposure
• Immunocompromised patients	Immunocompromised patients: Rilzabrutinib was not studied in patients with known or suspected immunodeficiency, including organ transplant patients. No specific safety issues are foreseen in this population. No participant with a known immunocompromised state has been randomized. It is unknown if impairment of the immune function plays a role in rilzabrutinib mechanism of action; however, a sufficient immune function is an international requirement for conducting clinical trials. The absence of safety data in this patient population does not constitute a safety concern, rilzabrutinib safety data does not indicate an imbalance of events associated with HBV or HCV or immunocompromised state.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable, as all severity types of chronic ITP are included in the clinical trial population. Excluded from clinical trial participation are patients with secondary ITP, as this is not an indication that is pursued.
Populations with relevant different race and/or ethnic origin	To date, there is no information to suggest that patients of specific racial or ethnic origins are adversely affected by rilzabrutinib. As per Table 12 in the ITP placebo-controlled pool, which includes the Phase 3 PRN1008-018 (EFC17093) study, during the DB treatment period there have been 74 (36.6%) participants of non-Caucasian race randomized in the Phase 3 pivotal trial from a total of 202 participants (of which 3 participants did not have their race reported).
Subpopulations carrying known and relevant genetic polymorphisms	Not relevant. To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of rilzabrutinib in the currently proposed indication.
Other	Not applicable

DB: Double-Blind; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; IMP: Investigational Medicinal Product; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; n: Number of Patient; N: Total Number of Patient; PK: Pharmacokinetic.

Table 17 - Cumulative exposure to IMP by special population - 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)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Special population	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]
Participants with history of hepatic impairment[e]	11	2.8	32	9.8	52	48.7	51	48.4
Participants with history of renal impairment[f]	1	0.5	5	2.1	9	9.2	9	8.9
Participants with history of cardiovascular impairment[g]	3	0.9	3	1.0	14	14.3	14	14.0
Participants with history of risk factors for thromboembolic events[h]	10	2.3	18	5.3	44	45.4	44	45.1

Data cutoff: 15-Oct-2024 for PRN1008-018 and 02-Aug-2024 for PRN1008-010.

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

b TP 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 Participant received rilzabrutinib 400 mg BID any time.

d Participant-years = the cumulative duration of observation period in days /365.25.

e History of hepatic impairment identified based on SMQ = “Biliary disorders”, #20000118 and SMQ = “Hepatic disorders”, #20000005, broad and narrow search.

f History of renal impairment identified based on SMQ = “Acute renal failure”, # 20000003 and SMQ = “Tubulointerstitial diseases”, #20000221, broad and narrow search.

	ITP placebo-controlled pool[a]				ITP rilzabrutinib pool[b]			
	Placebo (N = 69)		Rilzabrutinib 400 mg BID (N = 133)		Rilzabrutinib any dose (N = 284)		Rilzabrutinib 400 mg BID[c] (N = 278)	
Special population	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]	Participant	Participant-years[d]

g History of cardiovascular impairment identified based on SMQ = “Cardiac failure”, #20000004 and SMQ = “Cardiomyopathy”, #20000150, broad and narrow search.

h History of risk factors for thromboembolic events identified based on SMQ = “Cardiac arrhythmias”, #20000049, broad and narrow search, SMQ = “Embolic and thrombotic events”, #20000081, narrow search, SMQ = “Ischaemic heart disease”, #20000043, broad and narrow search, and SMQ = “Thrombophlebitis”, #20000115, broad and narrow search.

PGM=PRODOPS/SAR444671/OVERALL/ITP_EMA_02/REPORT/PGM/cdc_exp_cum_spe_rmp_pool_s_t.sas OUT=REPORT/OUTPUT/cdc_exp_cum_spe_rmp_pool_s_t_x.rtf (21JUL2025 5:40)

BID: Twice Daily; DB: Double-Blind; IMP: Investigational Medicinal Product; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; N: Total Number of Patient; OL: Open-Label; SMQ: Standardized MedDRA Query.

Rilzabrutinib should not be used during pregnancy and in women of childbearing potential not using contraception.

Rilzabrutinib should not be administered in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

As participants with renal impairment have been randomized in ITP clinical trials, this population is not considered missing information, neither is there a specific safety concern associated with the use of rilzabrutinib in this specific patient population.

As participants with cardiovascular impairment have been randomized in ITP clinical trials, this population is not considered missing information, neither is there a specific safety concern associated with the use of rilzabrutinib in this specific patient population.

Rilzabrutinib was not studied in patients with known or suspected immunodeficiency, including organ transplant patients. While efficacy may or may not be compromised in this population, no specific safety issue is foreseen. Therefore, this population is not considered missing information, neither is there a specific safety concern associated with the use of rilzabrutinib in this specific patient population.

To date, there is no information to suggest that patients of specific racial or ethnic origins are adversely affected by rilzabrutinib. Therefore, the use in this population of different racial or ethnic origins is not considered missing information, neither is there a specific safety concern associated with the use of rilzabrutinib in diverse racial or ethnic patient populations.

To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of rilzabrutinib in the currently proposed indication(s). Therefore, this population is not considered missing information, neither is there a specific safety concern associated with the use of rilzabrutinib in this specific patient population.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

Because this is the initial submission of the RMP for rilzabrutinib and the drug is not yet registered in any market worldwide, this module is “not applicable”.

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The available data from non-clinical and completed clinical studies, as well as an evaluation of its chemical structure, physiochemical properties, pharmacology and mechanism of action, the absence of preclinical/clinical signs and/or symptoms associated with abuse supports the conclusion that rilzabrutinib's potential for abuse is negligible.

The molecular structure, non-clinical pharmacology, non-clinical PK, and toxicology study data, and clinical PK of rilzabrutinib and its main metabolite thiocyanate do not predispose them to become a source of drug abuse or dependence.

The Sponsor conducted a search of treatment-emergent adverse event (TEAE) data from the ongoing PRN1008-018 and PRN1008-010 studies (DLP of 15 October 2024) using the search criteria in accordance with the "Assessment of Abuse Potential of Drugs" guidance document (Food and Drug Administration, 2017).

The available safety data from PRN1008-010 and PRN1008-018 clinical studies on a total of 284 participants did not result in events raising a concern of drug dependence or abuse, see Table 18 below. No overdoses occurred during the studies. Although "Dizziness" is listed under euphoria-related terms, this AE is not by itself indicative of abuse potential.

Table 18 - Number (%) of participants with drug abuse related TEAE by PT - Adult safety population

	ITP placebo-controlled pool[a]		ITP rilzabrutinib pool[b]
CATEGORY **Preferred Term n(%)**	**Placebo** **(N = 69)**	**Rilzabrutinib 400 mg BID** **(N = 133)**	**Rilzabrutinib any dose** **(N = 284)**
Any event	1 (1.4)	12 (9.0)	20 (7.0)
EUPHORIA-RELATED TERMS	1 (1.4)	11 (8.3)	18 (6.3)
Dizziness	1 (1.4)	11 (8.3)	18 (6.3)
TERMS INDICATIVE OF IMPAIRED ATTENTION, COGNITION, AND MOOD	0	1 (0.8)	2 (0.7)
Irritability	0	1 (0.8)	1 (0.4)
Somnolence	0	0	1 (0.4)

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 decreasing frequency of PT based on any TEAE in the Rilzabrutinib 400 mg BID group.

PGM=PRODOPS/SAR444671/OVERALL/ITP_ISS_2024/REPORT/PGM/ae_dgabpt_s_t.sas
OUT=REPORT/OUTPUT/ae_dgabpt_s_t_i.rtf (06MAY2024 15:06)

BID: Twice Daily; DB: Double-Blind; iSAF1: ITP Safety Pool 1; iSAF2: ITP Safety Pool 2; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; MedDRA; Medical Dictionary for Regulatory Activities; n: Number of Patient; N: Total Number of Patient; OL: Open-Label; PT: Preferred Term; TEAE: Treatment-Emergent Adverse Event.

The relevant data to support the drug-abuse liability assessment (DALA) are found in the non-clinical module of the Common Technical Document (CTD).

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety topics were assessed as either not relevant to rilzabrutinib RMP based on the currently available clinical evidence or not benefiting from additional pharmacovigilance or additional risk minimization activities.

The safety topics evaluated in Section SVII.1.1 as not important for inclusion in the list of safety concerns in the RMP, are the following:

- Atrial fibrillation/Cardiac Arrythmias
- Cytopenia, including neutropenia, thrombocytopenia, and anemia,
- Hemorrhage (bleeding)
- Recurrent Malignancy or Second Primary Malignancy (SPM)
- Drug-drug interactions

The following safety topics were considered important for inclusion in the list of safety concerns in the initial RMP. They are discussed in Section SVII.1.2:

- **Important identified risk**:
  - None
- **Important potential risks**:
  - Serious infections
  - Uveitis
  - Embryo-fetal toxicity
- **Missing information**:
  - None

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

Risks known to be associated with other approved drugs of the same therapeutic class (BTK inhibitors), however assessed as not relevant to rilzabrutinib and its benefit/risk balance, based on the currently available evidence or which would not benefit from additional risk minimization activities or from further evaluation:

Rilzabrutinib has characteristics that may solve many of the selectivity- and reversibility-related concerns accompanying currently available BTK inhibitors. (20) Rilzabrutinib binds in a covalent manner, increasing selectivity by forming a chemical bond to a specific cysteine residue present in

BTK. This durable covalent engagement allows for maximal efficacy. However, rilzabrutinib's unique binding mechanism provides the opportunity for a tailored residence time while reducing safety concerns associated with irreversible inhibitors such as ibrutinib and acalabrutinib. In addition, there are important differences between the background safety risk profiles of chronic autoimmune and/or inflammatory disease populations versus the oncologic population (where these events have been observed). By taking into consideration the above-mentioned unique characteristics of rilzabrutinib and the observed safety profile to date, "BTK inhibitor Class" adverse events could be relatively lower or may not be relevant compared to other BTK inhibitors.

Events evaluated known to be assessed as important identified or potential risks for other BTK inhibitors in other indications but not relevant to rilzabrutinib are described below:

- **Atrial fibrillation/Cardiac Arrythmias**
  - Through the development program, no events of atrial fibrillation related to the mechanism of action of rilzabrutinib have been reported.
  - During the ITP clinical development, no events of clinical relevance were observed for cardiac arrythmias, as most events were Grade 1/mild, and all recovered and assessed as not related to rilzabrutinib per Investigator assessment. The exposure adjusted incidence rate for cardiac arrythmia's was higher in the placebo arm with 17.17 compared to the rilzabrutinib arm with 4.54. In the pivotal Phase 3 trial PRN1008-018 (EFC17093) no imbalance was seen for cardiac arrythmia's between rilzabrutinib arm (2 [1.5%] participants) and placebo arm (3 [4.3%] participants).
  - Also, it is important to note that, in contrast to other BTK inhibitors, rilzabrutinib is not indicated in oncological diseases which may expose to a higher risk of atrial fibrillation or cardiac arrythmias. For the ITP indication there is no known increased risk of atrial fibrillation or cardiac arrythmia's. During the conduct of the ITP development program participants were not exposed to anti-cancer therapies which could have increased the risk of atrial fibrillation or cardiac arrythmias as well.
  - In a thorough QT study, rilzabrutinib produced a shortening in QTc interval proportional to concentration (see Table 7). Although the underlying mechanism and safety relevance of this finding is not known, a warning is added in the SmPC for clinicians who should use clinical judgment when assessing whether to prescribe rilzabrutinib to patients at risk from further shortening their QTc duration (eg, Congenital Short QT Syndrome or patients with a family history of such a syndrome).
  - The risk is not considered as an important risk for the RMP.

- **Cytopenia**
  - Cytopenia has been divided in neutropenia, thrombocytopenia, and anemia.
  - Neutropenia: One (0.8%) participant from the pivotal Phase 3 trial PRN1008-018 (EFC17093) DB period reported neutropenia which was Grade 4 and assessed as related to rilzabrutinib, however no clear mechanism of action has been determined and no imbalance between the two arms of the pivotal trial PRN1008-018 (EFC17093) have been observed (1 event in rilzabrutinib versus no event in placebo).
  - Thrombocytopenia: One (0.8%) participant from the pivotal Phase 3 trial PRN1008-018 (EFC17093) DB period reported an event of thrombocytopenia Grade 4 not related to

rilzabrutinib, and 2 (2.9%) participants reported events of thrombocytopenia Grade 4 not related to placebo in the pivotal trial PRN1008-018 (EFC17093). Less events were reported in the rilzabrutinib arm compared to the placebo arm.

- Anemia: from the pivotal Phase 3 trial PRN1008-018 (EFC17093) DB period, 5 events of anemia were reported in 5 (5.3%) participants in the rilzabrutinib arm (Grades 1 to 2 with one non-serious Grade 3; not related; all participants recovered), and 4 events of anemia were reported in 4 (5.8%) participants in the placebo arm (Grade 1 to 2; not related; all participants recovered). No imbalance was observed between the arms.
- Also, it is important to note that rilzabrutinib is not indicated in oncological diseases (hematological malignancies), which may have a higher risk of developing neutropenia. For the ITP indication there is no known increased risk of neutropenia. The other characteristics of thrombocytopenia and anemia are known events to occur due to the background disease of ITP and its management in the target population is well understood, and it would not benefit from additional pharmacovigilance or risk minimization activities besides routine measures.
- The risk is not considered as an important risk for the RMP.

- **Hemorrhage (bleeding)**
  - No events of hemorrhage related to rilzabrutinib were reported in the pivotal Phase 3 trial PRN1008-018 (EFC17093). Hemorrhagic events are part of the ITP background disease due to the patient's low platelet count, especially before and at treatment initiation. No imbalance in bleeding events were seen between rilzabrutinib and placebo arms in the pivotal Phase 3 trial PRN1008-018 (EFC17093). The evaluation of ≥Grade 3 bleeding events has shown: 5 (3.8%) participants in the rilzabrutinib arm (of which 1 event [0.8%] lead to treatment discontinuation) compared to 6 (8.7%) participants in the placebo arm (of which 5 (7.2%) events were serious adverse events [SAEs]). No participants had a TEAE of bleeding event Grade ≥3 that was considered by the Investigator as related to rilzabrutinib. Whereas 1 (1.4%) participant in the placebo group had a TEAE of bleeding event Grade ≥3 that was considered by the Investigator as related to placebo.
  - In addition, Rilzabrutinib has been shown to increase platelet counts in individuals with ITP, thereby decreasing the risk of bleeding in that setting as supported by the data in the pivotal Phase 3 Trial. Although other BTK inhibitors identify bleeding as a risk factor, this is primarily in the setting of oncologic disorders which contribute to bleeding risk.
  - The risk is not considered as an important risk for the RMP.

- **Recurrent Malignancy or Second Primary Malignancy (SPM)**
  - No imbalance has been observed, between the two arms of the pivotal trial PRN1008-018 (EFC17093). No events of neoplasms benign or malignant have been reported in the Phase 3 trial DB placebo-controlled period. During the OL part of the Phase 3 trial one event of Grade 1 ovarian clear cell carcinoma was reported in a participant with a history of ovarian chocolate cyst (rilzabrutinib treatment was not changed or interrupted), and one case of Grade 3 lung adenocarcinoma was reported during the LTE period and led to withdrawn. The events were assessed as not related to

rilzabrutinib by the Investigator. Therefore, no imbalance is observed between the two treatment arms.

- In general, it should be mentioned that for rilzabrutinib:
  - The primary indication is not oncologic, which carries on its own an increased risk of new-onset or recurrent malignancies or SPM,
  - Treatment therapies used to treat primary malignancies (chemotherapy, radiation therapy or alkylating agents), as indicated for other BTK inhibitors, carry a risk of secondary malignancy (and are considered risk factors for these BTK inhibitors). These are not applicable to patients with ITP. Treatment for ITP does not include any other agent that has the capacity to induce radiation or be alkylating, as a pre-treatment prior to initiating rilzabrutinib as treatment for ITP, hence the pre-exposure risk to malignancies or SPM is low in ITP patients.
- The risk of recurrent malignancy or SPM will be closely assessed and further characterized via routine pharmacovigilance activities. No additional pharmacovigilance and/or risk minimization activities is proposed for the risk of recurrent malignancy or SPM. Recurrent malignancy or SPM is not included in the list of safety concerns in the RMP, consistent with the European Guideline on Good Pharmacovigilance Practices (GVP), Module V Rev. 2.

Other risks considered as no important for inclusion in the RMP:

- **Drug-drug interactions:**
  - Given the in vitro characterizations and completed clinical interactions studies, it is confirmed that drug-drug interactions with rilzabrutinib would not lead to an important risk that would require additional pharmacovigilance activities or risk minimization activities besides routine measures. As such it is not listed as a safety concern in the RMP.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table 19 - Important potential risk considered for inclusion in the list of safety concerns: Serious infections

Serious infections	
Scientific evidence that has led to the inclusion	Serious infections are assessed as an important potential risk based on rilzabrutinib's mechanism of action and were considered adverse event of special interest (AESI) in the studies. Rilzabrutinib may increase the risk of infection due to inhibition of human B-cell activation and antibody mediated activation of immune cells via Fragment crystallizable (Fc) receptor signaling. **Non-clinical:** No observations. **Clinical:** **ITP placebo-controlled pool:** *(Phase 3 pivotal trial PRN1008-018 [EFC17093])* Infections occurred more frequently in the rilzabrutinib-treated participants than in the placebo arm (33.1% versus 20.3%). However, most were Grade 1-2 with participants recovered without change to rilzabrutinib treatment. Treatment-emergent infections of

Serious infections	
	Grade ≥2 occurred in 23 (17.3%) in the rilzabrutinib group and in 10 (14.5%) in the placebo group. Serious adverse events of infection occurred in 3.0% of rilzabrutinib-treated participants in the Phase 3 DB period versus 0% in placebo. Five (3.8%) rilzabrutinib versus no (0%) placebo participants experienced one or more TEAE of infections Grade ≥3. The infections events were coronavirus disease-2019 (COVID-19), pneumonia, urinary tract infection (UTI), otitis media acute, pelvic inflammatory disease, renal abscess and sepsis. One (0.8%) participant had a Grade 5 pneumonia that led to permanent study discontinuation of rilzabrutinib and death (see details below). 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. • A [redacted] female with history of ITP, splenectomy, subarachnoid hemorrhage, 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 once daily (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 rilzabrutinib. 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 rilzabrutinib. During the Phase 3 DB period, infections were lower in the ≥65-year-old participants than those <65 years (19.0% versus 35.7%). Grade ≥3 infections were slightly higher in the ≥65-year-old cohort than in the younger population (4.8% versus 3.6%) as were SAEs (9.8% versus 1.8%), although the numbers are small. Infections were similar in participants status post-splenectomy than with those who did not undergo splenectomy (32.4% versus 33.3%, respectively). Grade ≥3 infections occurred more frequently in participants without splenectomy compared to participants who were status post-splenectomy. Frequency of infections in participants taking concomitant medication of corticosteroids were comparable. Participants in the rilzabrutinib arm taking corticosteroids had infections in 12 (35.3%) participants versus placebo 4 (20%). Those taking corticosteroids and TPO-RA had infections in 7 (33%) versus 4 (28.6%) in placebo. **ITP rilzabrutinib pool:** *(Phase 3 pivotal trial PRN1008-018 (EFC17093) and Phase 2 PRN1008-010A/B [DFI17124 Part A/B])* 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. 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 to rilzabrutinib treatment). Two (0.7%) participants experienced a TEAE of infection Grade ≥3 that was considered by the Investigator as related to rilzabrutinib. The most common infections were COVID-19 in 3 (1.1%) participants and pneumonia, sepsis, and UTI in 2 (0.7%) participants each.

Serious infections	
Risk-benefit impact	Benefit/Risk impact on the patient level, is dependent on the type of infection and the inter-patient variables, such as age, medical history of concurrent diseases (such as diabetes mellitus type 2), smoking, use of concomitant medications (IVIG) or immunosuppressants (corticosteroid or rituximab). Although serious infections have been reported in the rilzabrutinib clinical development program, the incidence was low. The overall benefit-risk profile remains favorable.

AESI: Adverse Event of Special Interest; COVID-19: Coronavirus Disease-2019; DB: Double-Blind; Fc: Fragment Crystallizable; ITP: Immune Thrombocytopenia; IVIG: Intravenous Immunoglobulin; SAE: Serious Adverse Event; TEAE: Treatment-Emergent Adverse Event; TPO-RA: Thrombopoietin Receptor Agonist; UTI: Urinary Tract Infection.

Table 20 - Important potential risk considered for inclusion in the list of safety concerns: Uveitis

Uveitis	
Scientific evidence that has led to the inclusion	**Class-effect:** The currently available literature does not describe any class effect for uveitis with BTK inhibitors. (21) However, based on the experience with other BTK inhibitors, particularly ibrutinib (first in class), events of uveitis have been reported in the postmarketing setting of ibrutinib. Uveitis has been reported as an adverse reaction to other kinase inhibitors (non-BTK inhibitors). In particular, vemurafenib, dabrafenib, and trametinib have been linked with uveitis. Uveal inflammation in mitogen-activated protein kinase inhibitors, such as trametinib, has been postulated to be linked to dysregulation of tight junctions of the endothelial cells in the ciliary body. Though, the mechanisms of other kinase inhibitors in relationship to uveitis remain unclear. (21) **Literature:** Literature presented 6 cases of uveitis with ibrutinib. (21) (22) (23) (24) (25) **Non-clinical:** No observations. The mechanism of onset of (non-infectious) uveitis with rilzabrutinib remains unclear. **Clinical:** **ITP placebo-controlled pool:** *(Phase 3 pivotal trial PRN1008-018 [EFC17093])* No events of uveitis were reported in in the rilzabrutinib and placebo arms of the ITP pivotal trial PRN1008-018 (EFC17093). No imbalance was determined in the data evaluated. **ITP rilzabrutinib pool:** *(Phase 3 pivotal trial PRN1008-018 [EFC17093] and Phase 2 PRN1008-010A/B [DFI17124 Part A/B])* There was one participant with Grade 2 uveitis (bilateral iridocyclitis) in the Phase 2 study (Part A), which was assessed as related to ulcerative colitis and autoimmune predisposition and not related to rilzabrutinib by the Investigator and an independent ophthalmologist. The participant elected to discontinue from the study while the event was recovering (Grade 1). No imbalance was determined in the data evaluated. The reported event in the ITP rilzabrutinib pool falls within the general background rate of occurrence seen with drug-induced uveitis, accounting for around 0.3-0.5% of all cases. (22) Of note, the 1 (0.5%) event reported is confirmed to be not drug induced, general background rate provided for illustrative purposes.

Uveitis	
Risk-benefit impact	Benefit/Risk impact on the patient level, is dependent on the severity of the uveitis (potentially serious leading to vision loss if not treated adequately and on time) and the etiology of the uveitis (infectious, autoimmune, traumatic, or idiopathic causes), use of concomitant medications or immunosuppressants (immune-checkpoint inhibitors). The impact is assessed as low, due to the rare nature of this event.

BTK: Bruton's Tyrosine Kinase; ITP: Immune Thrombocytopenia.

Table 21 - Important potential risk considered for inclusion in the list of safety concerns: Embryo-fetal toxicity

Embryo-fetal toxicity	
Scientific evidence that has led to the inclusion	**Non-clinical:** In an exploratory rat embryo-fetal range-finding study, increased post-implantation loss and incidence of early resorptions, and decreased fetal weight were recorded at 500 mg/kg/day. Fetal external, visceral, and skeletal malformations were observed at 500 mg/kg/day. In an exploratory rabbit embryo-fetal range-finding study, a slight increase in the incidence of early resorptions, possibly associated with the observed maternal toxicity, was noted at 150 mg/kg/day. Fetal visceral changes were observed at 150 mg/kg/day (AUC exposure margin of 5.6-fold), however, any test article-related association was considered to be equivocal since the incidence of the abnormalities did not increase in a dose-dependent manner.
Risk-benefit impact	Rilzabrutinib should not be used during pregnancy and in women of childbearing potential not using contraception.The risk-benefit is favorable for the indicated population.

AUC: Area Under the Plasma Concentration-Time Curve.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable since first RMP.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for rilzabrutinib:

- Important identified risk:
  - None
- Important potential risks:
  - Serious infections
  - Uveitis
  - Embryo-fetal toxicity
- Missing information:
  - None

SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified risks for rilzabrutinib.

Important potential risks are defined below in Table 22 to Table 24.

Table 22 - Potential risk: Serious infections

Potential risk	Serious infections
Potential mechanism	The BTK enzyme plays an important role in immune modulation. Inhibition of the BTK pathway modulates B-cell function, however, does not deplete B-cells or impact existing plasma cells. It also aids in reducing inflammation through actions on macrophages and neutrophils, however, has no direct action on T-cells that are instrumental to the body's immune system. Rilzabrutinib may increase the risk of infection due to inhibition of human B-cell activation and antibody mediated activation of immune cells via Fc receptor signaling.
Evidence source(s) and strength of evidence	Mechanism of action, clinical data.
Characterization of the risk	**ITP placebo-controlled pool:** *(Phase 3 pivotal trial PRN1008-018 [EFC17093])* Infections occurred more frequently in the rilzabrutinib-treated participants than in the placebo arm (33.1% versus 20.3%). However, most were Grade 1-2 with participants recovered without change to rilzabrutinib treatment. Treatment-emergent infections of Grade ≥2 occurred in 23 (17.3%) in the rilzabrutinib group and in 10 (14.5%) in the placebo group. Serious adverse events of infection occurred in 3.0% of rilzabrutinib-treated participants in the Phase 3 DB period versus 0% in placebo. Five (3.8%) rilzabrutinib (reported in 4 participants) versus no (0%) placebo participants experienced one or more TEAE of infections Grade ≥3. The infections events were COVID-19, pneumonia, UTI, otitis media acute, pelvic inflammatory disease, renal abscess and sepsis. • One (0.8%) participant had a Grade 5 pneumonia that led to permanent study discontinuation of rilzabrutinib and death (see details below). 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. - A [redacted] female with history of ITP, splenectomy, subarachnoid hemorrhage, 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 once daily (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 rilzabrutinib. The participant did not have neutropenia. The type of organisms were *Nocardia spp*. Bronchoscopy confirmed pneumonia (*A. fumigatus*, *C. 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 rilzabrutinib. • One (0.8%) participant was hospitalized for 4 days for a serious event (criteria: hospitalization) of Grade 3 COVID-19 infection and recovered without sequalae; the event was assessed as not related by Investigator, as the event onset was not reasonably associated with the IMP. The reason for hospitalization was mentioned by the Investigator as low platelet count, most likely due to the infection. The participant did not interrupt their treatment and recovered while under rilzabrutinib treatment.

Potential risk	Serious infections
	• One (0.8%) participant reported 2 serious events Grade 3 UTI and Grade 3 renal abscess. The initial serious event (criteria: hospitalization) of Grade 3 UTI, was assessed as not related by the Investigator. The participant recovered after a 4 day hospitalization and treatment with antibiotics, the study drug was temporarily interrupted, and thereafter resumed. The same participant reported after 22 days Grade 3 renal abscess. The participant recovered after 11 days hospitalization and renal drainage; the Investigator assessed as not related to rilzabrutinib. After temporary interruption of study treatment the participant continued on rilzabrutinib and continued in the trial without recurrence of any UTI. • One (0.8%) participant reported a serious event (criteria: hospitalization) of Grade 2 wound infection, which was assessed as not related by the Investigator as the participant was known with a medical history of chronic wound due to a cat bite approximately 4 months prior to onset of new infection (participant had an acute new infection of a slow-healing wound of the left wrist). The participant had a skin graft approximately 1 month prior to onset of new infection of known wound infection. The participant was hospitalized for 1 day and recovered after 7 days. The participant was treated and continued rilzabrutinib dosing without interruption. During the Phase 3 DB period, infections were lower in the ≥65-year-old participants than those <65 years (19.0% versus 35.7%). Grade ≥3 infections were slightly higher in the ≥65-year-old cohort than in the younger population (4.8% versus 3.6%) as were SAEs (9.8% versus-1.8%), although the numbers are small. Infections were similar in participants status post-splenectomy than with those who did not undergo splenectomy (32.4% versus 33.3%, respectively). Grade ≥3 infections occurred more frequently in participants without splenectomy compared to participants who were status post-splenectomy. Frequency of infections in participants taking concomitant medication of corticosteroids were comparable. Participants in the rilzabrutinib arm taking corticosteroids had infections in 12 (35.3%) participants versus placebo 4 (20%). Those taking corticosteroids and TPO-RA had infections in 7 (33%) versus 4 (28.6%) in placebo. **ITP rilzabrutinib pool:** (*Phase 3 pivotal trial PRN1008-018 [EFC17093] and Phase 2 PRN1008-010A/B [DFI17124 Part A/B]*) The rate of serious infections reported in the overall ITP rilzabrutinib pool (3.5%) is below the expected background rate in the ITP population for an annual incidence rate of hospital contact for infection which is reported to be 15.3%. (26) 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. 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 to rilzabrutinib treatment). Two (0.7%) participants experienced a TEAE of infection Grade ≥3 that was considered by the Investigator as related to rilzabrutinib. The most common infections were COVID-19 in 3 (1.1%) participants and pneumonia, sepsis, and UTI in 2 (0.7%) participants each. **Background incidence/prevalence** A systematic literature review (26) focusing on the risk of infection in adult patients with ITP reported: • In Danish population-based medical databases used to identify 407 patients with primary chronic ITP diagnosed during 1996 to 2007, an annual incidence rate of hospital contact for infection of 15.3% (95% CI: 12.0-18.9).

Potential risk	Serious infections
	• The incidence rate of severe infections reported in European studies published between 2017 and 2019 ranged from 2/100 patient-years (95% CI: 1.3-3.0) to 6.3/100 patient-years (95% CI: 5.4-7.4). **Impact on individual patient** Benefit/Risk impact on the patient level, is dependent on the type of infection and the inter-patient variables, such as age, medical history of concurrent diseases (such as diabetes mellitus type 2), smoking, use of concomitant medications or immunosuppressants (IVIG and rituximab). Serious infections maybe life-threatening (and may lead to hospitalization) and/or result in fatal outcome if not treated adequately and in a timely manner.
Risk factors and risk groups	Predictors of increased risk of serious infections may occur in case of the presence of inter-patient variables, such as age (>60 years), medical history of concurrent diseases (such as diabetes mellitus type 2 or chronic obstructive pulmonary disease), smoking, absence of antibiotic prophylaxis, underlying immunosuppression that is inherent to the primary disease process use of concomitant medications (IVIG and rituximab) or immunosuppressants (eg, high dose corticosteroids use) and poor performance and/or nutritional status. A systematic literature review showed that the risk of infections in ITP patients increases in patients who received corticosteroids in a time period up to 6 months before infection and in a dose-dependent manner. Intravenous immunoglobulins and rituximab were also significantly associated with increased risk. Several studies found that stable responders and less severe disease were associated with lower risk of infection. No definite conclusions were drawn regarding the impact of splenectomy on the risk of infections in ITP patients. (26)
Preventability	**Clinical trials:** Complications of serious infections can be prevented with early detection (diagnosis) of infection leading to early action (identification of infectious etiology/agent involved and subsequent adequate treatment). Rilzabrutinib dosing should be stopped during a serious infection. All patients should be tested for latent tuberculosis prior to starting rilzabrutinib and, if positive for tuberculosis, treated adequately for tuberculosis prior to starting rilzabrutinib treatment for their ITP. Serious infections are deemed an AESI during clinical conduct. **Postmarketing:** Preventability measures are described in Part V.1 (Routine risk minimization measures). Ongoing signal evaluation will occur on a regular basis to evaluate the potential risk and identify any change in this risk during postmarketing evaluations.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Serious infections may lead to hospitalization and/or prolonged hospitalization, and thus, to increased public health care utilization, loss of economic productivity and potentially loss of work-force due to potential risk of serious infections leading to fatal outcomes.

AESI: Adverse Event of Special Interest; BTK: Bruton's Tyrosine Kinase; CI: Confidence Interval; COVID-19: Coronavirus Disease-2019; DB: Double-Blind; Fc: Fragment Crystallizable; IMP: Investigational Medicinal Product; ITP: Immune Thrombocytopenia; IVIG: Intravenous Immunoglobulin; SAE: Serious Adverse Event; TEAE: Treatment-Emergent Adverse Event; TPO RA: Thrombopoietin Receptor Agonist; UTI: Urinary Tract Infection.

Table 23 - Potential risk: Uveitis

Potential risk	Uveitis
Potential mechanism	The mechanism of onset of (non-infectious) uveitis remains unclear. A causal association with rilzabrutinib has not been established.
Evidence source(s) and strength of evidence	Literature (experience with other BTK inhibitors), clinical data.
Characterization of the risk	**ITP placebo-controlled pool:** *(Phase 3 pivotal trial PRN1008-018 [EFC17093])* No events of uveitis were reported in the ITP placebo-controlled pool, no imbalance was determined in the data evaluated. **ITP rilzabrutinib pool:** *(Phase 3 pivotal trial PRN1008-018 [EFC17093] and Phase 2 PRN1008-010A/B [DFI17124 Part A/B])* The reported event in the ITP rilzabrutinib pool falls within the general background rate of occurrence seen with drug-induced uveitis, accounting for around 0.3-0.5% of all cases. (22) One (0.4%) (1.7% of n = 60) event of iridocyclitis (a sub-type of uveitis) was reported in Phase 2 PRN1008-010A (DFI17124 Part A). This event was confounded and deemed not related to rilzabrutinib by Investigator assessment, however related to underlying disease of ulcerative colitis (the Investigator stated due to autoimmune predisposition of the participant (namely, ulcerative colitis). This event was reported as a Grade 2 initially and after 4 days reported as a Grade 1 at the End-of-Trial study visit and reported as recovering (at time of End-of-Trial closure). **Background incidence/prevalence** The incidence of uveitis has been estimated between 17 and 52 per 100 000 of population per year, and the prevalence as 38-714 cases per 100 000 of population. Uveitis is implicated in up to 25% of cases of blindness in the developing world. The most common causes of non-infectious uveitis include: Human leukocyte antigen-B27 (HLA-B27) associated anterior uveitis (4-32%), Fuchs uveitis syndrome, sarcoidosis, Vogt-Koyanagi-Harada Disease (VKHD), sympathetic ophthalmia, birdshot chorioretinopathy, multifocal choroiditis, serpiginous choroiditis, and Behcet's disease. Uveitis may manifest in any age group. However, adults aged 20-50 years are most commonly affected, with reports ranging from 60% to 80% of the total number of uveitis cases occurring in this age group. Males and females are approximately equally affected. (27) A US study performed in an administrative claims database reported an estimated prevalence of non-infectious uveitis was 121 cases per 100 000 for adults (95% CI: 117.5-124.3). (28) **Impact on individual patient** Benefit/Risk impact on the patient level, is dependent on the severity of the uveitis (potentially serious leading to vision loss if not treated adequately and on time) and the etiology of the uveitis (infectious, autoimmune, traumatic, or idiopathic causes), use of concomitant medications or immunosuppressants (immune-checkpoint inhibitors).
Risk factors and risk groups	When adjusted for age and gender, the risk of non-infectious uveitis did not show a statistically significant increase in risk observed among ITP patients exposed to rilzabrutinib. Risk factors for non-infectious uveitis are several underlying diseases (Ulcerative colitis, Fuchs uveitis syndrome, sarcoidosis, VKHD, sympathetic ophthalmia, birdshot chorioretinopathy, multifocal choroiditis, serpiginous choroiditis, and Behcet's disease) or having certain genotypes such as: HLA-B27.
Preventability	**Clinical trials:** Risk management includes instructing participants to report new onset or worsening of eye symptoms to the site study doctor. Ophthalmologic examination should be considered for

Potential risk	Uveitis
	participants who develop eye disorders, such as, however not limited to, new onset of worsening of erythema, pain, or blurred vision possibly suggestive of uveitis, as appropriate. Participants will be screened at study inclusion for medical history of eye disorders and those will be recorded in the electronic case report form. Uveitis is deemed an AESI during clinical conduct. Ongoing signal evaluation will occur on a regular basis to evaluate the potential risk and identify any change in this risk during study conduct. During the conduct of this study the occurrence of uveitis is deemed very low. Complications of uveitis can be prevented with early detection (diagnosis) of uveitis, leading to early action (identification of the uveitis etiology involved and early adequate treatment). **Postmarketing:** Preventability measures are described in Part V.1 (Routine risk minimization measures). Ongoing signal evaluation will occur on a regular basis to evaluate the potential risk and identify any change in this risk during postmarketing evaluations.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Uveitis, although rare, may lead to hospitalization and/or prolonged hospitalization, and thus, to increased public health care spending, loss of economic productivity and potentially loss of work-force due to potential risk of uveitis leading to potential blindness, although low, if not treated adequately and in a timely manner. In general, ocular discomforts do not lead to delays in consulting a healthcare professional (HCP), therefore the public heath impact is considered as low.

AESI: Adverse Event of Special Interest; BTK: Bruton's Tyrosine Kinase; CI: Confidence Interval; HCP: Healthcare Professional; HLA-B27: Human Leukocyte Antigen-B27; ITP: Immune Thrombocytopenia; n: Number of Patient; US: United States; VKHD: Vogt-Koyanagi-Harada Disease.

Table 24 - Potential risk: Embryo-fetal toxicity

Potential risk	Embryo-fetal toxicity
Potential mechanism	The mechanism responsible for the malformations remains unclear.
Evidence source(s) and strength of evidence	Non-clinical studies.
Characterization of the risk	In an exploratory rat embryo-fetal range-finding study, increased post-implantation loss and incidence of early resorptions, and decreased fetal weight were recorded at 500 mg/kg/day. Fetal external, visceral, and skeletal malformations and variations were observed at 500 mg/kg/day. In an exploratory rabbit embryo-fetal range-finding study, a slight increase in the incidence of early resorptions, possibly associated with the observed maternal toxicity, was noted at 150 mg/kg/day. Fetal visceral changes were observed at 150 mg/kg/day (AUC exposure margin of 5.6-fold), however, any test article-related association was considered to be equivocal since the incidence of the abnormalities did not increase in a dose-dependent manner.
Risk factors and risk groups	Women of childbearing potential.
Preventability	Rilzabrutinib should not be used during pregnancy and in women of childbearing potential not using contraception.

Potential risk	Embryo-fetal toxicity
	Women of childbearing potential should use effective method of contraception while taking rilzabrutinib and for 1 month after stopping treatment. If a pregnancy occurs during treatment with rilzabrutinib contact your treating physician immediately.
Impact on the benefit-risk balance of the product	Rilzabrutinib should not be used during pregnancy and in women of childbearing potential not using contraception. The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Low.

AUC: Area Under the Plasma Concentration-Time Curve.

SVII.3.2 Presentation of the missing information

Not applicable

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	None
Important potential risks	Serious infections
	Uveitis
	Embryo-fetal toxicity
Missing information	None

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The safety profile of rilzabrutinib will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, and signal detection.

The following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are in place, including:

- Specific adverse reaction follow-up questionnaire for serious infections
- Specific adverse reaction follow-up questionnaire for uveitis

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance activities include the 2 currently ongoing LTE studies (see details below in Table 25).

Table 25 - Additional pharmacovigilance activities (category 1 to 3) summary

LUNA 3 (Cat. 3)
Study short name and title: **PRN1008-018 (EFC17093):** 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).
Rationale and study objectives: Safety objectives: To evaluate the safety and tolerability of rilzabrutinib in pediatric participants (≥10 - ≤17 years) and in adult participants (≥18 years) with refractory/relapsed ITP.
Study design: Open-Label extension.
Study populations: Participants with refractory or relapsed ITP of >3 months duration (age 18 years and above) or with >6 months duration (age ≥10 to <18 years).
Milestones: • **Adult LTE Part *(planned date)***: – Clinical Study Report (CSR): 20-Mar-2026

LUNA 2 (Cat. 3)

Study short name and title:

PRN1008-010 (DFI17124): 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.

Rationale and study objectives:

Safety objectives: To characterize the safety and tolerability of 400 mg BID dose of rilzabrutinib in patients with ITP.

Study design:

Open-Label extension.

Study populations:

Male and female patients aged 18 to 80 years old (Czech Republic and Norway only: aged 18 to 65 years old) in Part B which is an OL study of rilzabrutinib in patients with ITP who have relapsed or have an insufficient response to prior therapies.

Milestones:

- **Long-Term Extension part *(planned date)*:**
  - Clinical Study Report: 27-May-2026

Clinical interaction study with oral contraceptives (Cat. 3)

Study short name and title:

A drug-drug interaction study in healthy female participants to investigate the effect of multiple doses of rilzabrutinib on combined hormonal oral contraceptive.

Rationale and study objectives:

Assess effect of multiple doses of rilzabrutinib on plasma exposure of oral contraceptives.

Study design:

Cross-over design.

Study populations:

Healthy female age >18 years to 55 years.

Milestones:

- Final protocol: Quarter (Q)2 2026
- Final CSR: Sep-2027

BID: Twice Daily; BTK: Bruton's Tyrosine Kinase; CSR: Clinical Study Report; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; OL: Open-Label; Q: Quarter.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 26 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
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.	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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing				
Clinical interaction study with oral contraceptives A drug-drug interaction study in healthy female participants to investigate the effect of multiple doses of rilzabrutinib on combined hormonal oral contraceptive. *Planned*	Assess effect of multiple doses of rilzabrutinib on plasma exposure of oral contraceptives.	Embryo-fetal toxicity	Final protocol Final CSR	Q2 2026 Sep-2027

BID: Twice Daily; BTK: Bruton's Tyrosine Kinase; CSR: Clinical Study Report; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; Q: Quarter.

RISK MANAGEMENT PLAN - PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for rilzabrutinib.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 27 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Serious infections	**Routine risk communication:** SmPC: Labeled in sections 4.4 and 4.8. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (monitoring of patients for signs and symptoms of infection). **Other routine risk minimization measures beyond the Product Information:** 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.
Uveitis	**Routine risk communication:** SmPC and Package Leaflet (PL): Not labeled. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** 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.
Embryo-fetal toxicity	**Routine risk communication:** • SmPC: Labeled in sections 4.6 and 5.3. • PL: Labeled in section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC sections 4.4 and 4.6 (pregnancy testing before initiation of treatment). **Other routine risk minimization measures beyond the Product Information:** 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.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 28: Additional risk minimization measures

Patient card	
Objectives	To strengthen labeling recommendations for embryo-fetal toxicity risk.

Rationale for the additional risk minimization activity	To complement the label and reinforce the patient's education on the risk and the measures to mitigate it.
Target audience and planned distribution path	**Target audience**: Patients **Planned distribution path**: The patient card will be included in the packaging, together with the patient leaflet.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 29 - 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• 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).	Clinical interaction study with oral contraceptives.

LTE: Long-Term Extension; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Wayrilz (Rilzabrutinib)

This is a summary of the risk management plan (RMP) for Wayrilz. The RMP details important risks of Wayrilz, how these risks can be minimized, and how more information will be obtained about Wayrilz's risks and uncertainties (missing information).

Wayrilz's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how Wayrilz should be used.

This summary of the RMP for Wayrilz should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Wayrilz's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Wayrilz is authorized for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments. (see SmPC for the full indication). It contains rilzabrutinib as the active substance, and it is given by oral administration.

Further information about the evaluation of Wayrilz's benefits can be found in Wayrilz's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

Link to the EPAR summary landing page to be added by EMA.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Wayrilz, together with measures to minimize such risks and the proposed studies for learning more about Wayrilz's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Wayrilz, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Wayrilz are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Wayrilz. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 30 - List of important risks and missing information

Important identified risk	None
Important potential risks	Serious infections
	Uveitis
	Embryo-fetal toxicity
Missing information	None

II.B Summary of important risks

Table 31 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious infections

Serious infections	
Evidence for linking the risk to the medicine	Mechanism of action, clinical data.
Risk factors and risk groups	Predictors of increased risk of serious infections may occur in case of the presence of inter-patient variables, such as age (>60 years), medical history of concurrent diseases (such as diabetes mellitus type 2 or chronic obstructive pulmonary disease), smoking, absence of antibiotic prophylaxis, underlying immunosuppression that is inherent to the primary disease process use of concomitant medications (intravenous immunoglobulin [IVIG] and rituximab) or immunosuppressants (eg, high dose corticosteroids use) and poor performance and/or nutritional status. A systematic literature review showed that the risk of infections in ITP patients increases in patients who received corticosteroids in a time period up to

Serious infections	
	6 months before infection and in a dose-dependent manner. Intravenous immunoglobulins and rituximab were also significantly associated with increased risk. Several studies found that stable responders and less severe disease were associated with lower risk of infection. No definite conclusions were drawn regarding the impact of splenectomy on the risk of infections in ITP patients. (26)
Risk minimization measures	**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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • PRN1008-018 (EFC17093) Long-Term Extension (LTE). • PRN1008-010 (DFI17124), LTE. See [Section VI.II.C.2] of this summary for an overview of the post-authorization development plan.

ITP: Immune Thrombocytopenia; IVIG: Intravenous Immunoglobulin; LTE: Long-Term Extension; SmPC: Summary of Product Characteristics.

Table 32 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Uveitis

Uveitis	
Evidence for linking the risk to the medicine	Literature (experience with other Bruton's tyrosine kinase [BTK] inhibitors), clinical data.
Risk factors and risk groups	When adjusted for age and gender, the risk of non-infectious uveitis did not show a statistically significant increase in risk observed among ITP patients exposed to rilzabrutinib. Risk factors for non-infectious uveitis are several underlying diseases (Ulcerative colitis, Fuchs uveitis syndrome, sarcoidosis, vogt-koyanagi-harada disease (VKHD), sympathetic ophthalmia, birdshot chorioretinopathy, multifocal choroiditis, serpiginous choroiditis, and Behcet's disease) or having certain genotypes such as: human leukocyte antigen-B27 (HLA-B27).
Risk minimization measures	**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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • PRN1008-018 (EFC17093), LTE. • PRN1008-010 (DFI17124), LTE.

Uveitis	
	See [Section VI.II.C.2] of this summary for an overview of the post-authorization development plan.

BTK: Bruton's Tyrosine Kinase; HLA-B27: Human Leukocyte Antigen-B27; ITP: Immune Thrombocytopenia; LTE: Long-Term Extension; PL: Package Leaflet; SmPC: Summary of Product Characteristics; VKHD: Vogt-Koyanagi-Harada Disease.

Table 33 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Embryo-fetal toxicity

Embryo-fetal toxicity	
Evidence for linking the risk to the medicine	Non-clinical studies.
Risk factors and risk groups	Women of childbearing potential.
Risk minimization measures	**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)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Clinical interaction study with oral contraceptives See [Section VI.II.C.2] of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Wayrilz.

II.C.2 Other studies in post-authorization development plan

Table 34 - Other studies in post-authorization development plan

PRN1008-018 (EFC17093) - LUNA 3 (Cat. 3)
Purpose of the study: Safety objectives: To evaluate the safety and tolerability of rilzabrutinib in pediatric participants (≥10 - ≤17 years) and in adult participants (≥18 years) with refractory/relapsed ITP.

PRN1008-010 (DFI17124) - LUNA 2 (Cat. 3)
Purpose of the study:
Safety objectives: To characterize the safety and tolerability of 400 mg twice daily (BID) dose of rilzabrutinib in patients with ITP.
Clinical interaction study with oral contraceptives (Cat. 3)
Purpose of the study:
Safety objective: Assess effect of multiple doses of rilzabrutinib on plasma exposure of oral contraceptives.

BID: Twice Daily; ITP: Immune Thrombocytopenia.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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ANNEX 4.1 SPECIFIC ADVERSE REACTION FOLLOW-UP QUESTIONNAIRE FOR SERIOUS INFECTIONS

sanofi

Rilzabrutinib (WAYRILZ®)
Serious Infections
Follow-up Questionnaire (FUQ)

The goal of this questionnaire is to collect the very essential information on reported event(s) of **Serious Infections with Rilzabrutinib**. For any other additional adverse event(s), please complete the corresponding "other experienced adverse event(s)" section at the end of this form.
By providing this information, you will make a useful contribution to the safety of this product for the benefit of patients.
**Fields to be completed in compliance with local data privacy regulation.*

Sanofi Case ID:	**Program ID:**
Reporter Information* *(person who provides the information reported on this form)*: Name or Initials: Qualification: ☐Health Care Professional (HCP) ☐Non-HCP Email address: Phone Number:	
Patient Information*: Name or Initials or ID: Gender: ☐Male ☐Female ☐Unknown Date of Birth: Age or Age Group:	

SPECIFIC INFORMATION

CONCOMITANT MEDICATIONS/VACCINATIONS

List of any immunosuppressant drugs (e.g., glucocorticoids, monoclonal antibodies, intravenous gamma globulin) used concurrently or within the past 6-12 months as relevant based on half-life of product (specify name, indication, dose, dates of administration):

Name	Indication	Daily Dose	Route	Start Date	End date
				Click here to enter a date.	Click here to enter a date.
				Click here to enter a date.	Click here to enter a date.
				Click here to enter a date.	Click here to enter a date.
				Click here to enter a date.	Click here to enter a date.

List any vaccines against bacterial organisms and in particular:

	Yes	No	Date (DD/MMM/YYYY), including details
Meningococcus	☐	☐	
Pneumococcus	☐	☐	
Haemophilus influenzae B	☐	☐	
Influenza virus	☐	☐	
Booster vaccinations	☐	☐	
COVID-19 vaccinations	☐	☐	
Any other immunizations relevant to reported infection	☐	☐	

MEDICAL HISTORY/RISK FACTORS			
	Yes	**No**	**Specify details**
Previous/chronic infection history (HIV, hepatitis, recurrent urinary tract infections, etc.)	☐	☐	
Indwelling lines/catheters	☐	☐	
Recent surgical operations	☐	☐	
Comorbidities associated with increased risk of infections (e.g.: hematologic and/or solid organ malignancies, inherited or acquired immunodeficiencies, asplenia, cerebrospinal fluid leak, cochlear implants, elderly age, diabetes, chronic kidney/liver/heart disease, solid organ transplant recipient)	☐	☐	
Current or former smoker	☐	☐	If yes, specify duration and packs per day:
CLINICAL COURSE			
	Yes	**No**	**Specify details (if relevant)**
Was the patient's infection diagnosed prior to the first dose of rilzabrutinib?	☐	☐	State if unknown.
Was the time elapsed between the first dose of rilzabrutinib and the onset of infection known?	☐	☐	
Was the time elapsed between the last dose of rilzabrutinib and the onset of infection known?	☐	☐	
Was the causative organism identified?	☐	☐	
Did the patient present with signs and symptoms?	☐	☐	If yes, specify severity and start/end dates:
Was the site / anatomical location of infection identified?	☐	☐	
Was the source of infection identified?	☐	☐	
Was the type of infection known?	☐	☐	If yes, specify whether the infection was bacterial, viral, or fungal:
Does the patient have a history of a **similar** infection in the past?	☐	☐	If yes, specify what and when:
Was the patient treated for the infection?	☐	☐	If yes, briefly list the management/treatment (e.g., drugs, procedures, including dates) of the infection:
Did the patient require blood pressure and respiratory support?	☐	☐	If yes, specify type and dates of additional support:
Did the patient require intensive care unit (ICU) admission?	☐	☐	If yes, specify dates of care in ICU:
INVESTIGATIONS/LAB EXAMS			
LABORATORY DATA *performed:* **YES** ☐ **NO** ☐ **Date:** Click here to enter a date.			

	DATE (DD/MMM/YYYY)	RELEVANT RESULTS
Microbiologic test results (e.g. blood/urine/cerebrospinal fluid/abscess cultures, viral PCR or serologies, etc.) YES ☐ NO ☐		
White blood cell counts, differential and inflammatory markers (e.g. CRP) YES ☐ NO ☐		
Imaging findings relevant to infection YES ☐ NO ☐		
Specialist consultation/s YES ☐ NO ☐		

ACTION TAKEN			
	Yes	**No**	**Specify details (if relevant)**
Was rilzabrutinib discontinued because of the event?	☐	☐	If yes, did the event improve or resolve following rilzabrutinib interruption or discontinuation? ☐Yes ☐No Details (i.e., how many days until resolution):
Was rilzabrutinib later resumed?	☐	☐	If yes, did the event reappear after rilzabrutinib was resumed? ☐Yes ☐No Details:

Sanofi Suspect Product Batch Number:

Adverse Event Information:

Seriousness: ☐ Non-Serious ☐ Serious (select at least one criteria below)

☐Death ☐Life-threatening ☐Hospitalization or prolongation of hospitalization

☐Persistent or significant disability or incapacity ☐Medically significant (as per HCP)

☐Suspected transmission of infectious agent ☐Congenital anomaly, birth defect

Outcome:

☐ Recovered/Resolved ☐ Recovered/Resolved with Sequelae ☐ Not Recovered/Not Resolved

☐ Recovering/Resolving ☐ Fatal ☐ Unknown

Specify date of resolution or date of death, if applicable: _____

If patient recovered with sequelae, describe sequelae: _____

Event Relationship to Sanofi product: ☐Related ☐Not Related ☐Unknown

ADDITIONAL INFORMATION
Please provide any other relevant additional information **regarding the reported event** (e.g., other suspect product(s), other additional information on reported adverse event, patient's medical history, concomitant medications, etc.):
Please provide relevant information regarding **any other experienced adverse event(s)** (e.g., event onset date(s), outcome(s), if it led to hospitalization, relationship(s) with Sanofi product, etc.):
Additional requests for the reporter (if any):

ANNEX 4.2 SPECIFIC ADVERSE REACTION FOLLOW-UP QUESTIONNAIRE FOR UVEITIS

sanofi

Rilzabrutinib (WAYRILZ®)
Uveitis
Follow-up Questionnaire (FUQ)

The goal of this questionnaire is to collect the very essential information on reported event(s) of **Uveitis with Rilzabrutinib**. For any other additional adverse event(s), please complete the corresponding "other experienced adverse event(s)" section at the end of this form.
By providing this information, you will make a useful contribution to the safety of this product for the benefit of patients.
**Fields to be completed in compliance with local data privacy regulation.*

Sanofi Case ID:	**Program ID:**
Reporter Information* *(person who provides the information reported on this form)*: Name or Initials: Qualification: ☐Health Care Professional (HCP) ☐Non-HCP Email address:	Phone Number:
Patient Information*: Name or Initials or ID: Date of Birth:	Gender: ☐Male ☐Female ☐Unknown Age or Age Group:

SPECIFIC INFORMATION

CONCOMITANT MEDICATIONS/VACCINATIONS

List any systemic medications, in particular antibiotics (e.g., rifabutin, moxifloxacin, sulfonamides), antivirals (e.g., cidofovir), bisphosphonates (e.g., alendronate, pamidronate), immunosuppressants, and biologics, used concurrently or within the past 6-12 months as relevant based on half-life of product (specify name, indication, dose, dates of administration):

Name	Indication	Daily dose	Route	Start date	End date
				Click here to enter a date.	Click here to enter a date.
				Click here to enter a date.	Click here to enter a date.
				Click here to enter a date.	Click here to enter a date.

List any topical ocular agents, in particular prostaglandin analogues (e.g., latanoprost, bimatoprost, travoprost) and alpha-agonists (e.g., brimonidine), used concurrently or within the past 6-12 months as relevant based on half-life of product (specify name, indication, dose, dates of administration):

Name	Indication	Daily dose	Route	Start date	End date
				Click here to enter a date.	Click here to enter a date.
				Click here to enter a date.	Click here to enter a date.
				Click here to enter a date.	Click here to enter a date.

List any vaccine administered within the past 3 months (e.g., vaccine against Hepatitis A (HAV), Hepatitis B (HBV), Human papilloma virus (HPV), Influenza, COVID-19, Varicella Zoster Virus (VZV), Measles-mumps-rubella viruses (MMR), Yellow Fever, or any other vaccines)	
Name	**Dates (DD/MMM/YYYY), including details**

MEDICAL HISTORY/RISK FACTORS			
	Yes	**No**	**Specify details**
Previous uveitis episode or Vogt-Koyanagi-Harada (VKH) syndrome	☐	☐	
Eye disorders (e.g., conjunctivitis, episcleritis or scleritis, other eye conditions [please specify precisely])	☐	☐	
Recent ocular surgery or trauma	☐	☐	
Autoimmune diseases (e.g., Behçet's disease, HLA-B27 positivity, inflammatory bowel disease, SLE, psoriatic arteritis or other skin disorders, sarcoidosis, spondyloarthropathy, vasculitis, ulcerative colitis, other autoimmune conditions [please specify precisely])	☐	☐	
Comorbidities potentially associated with increased risk of uveitis (e.g.: infectious diseases [especially toxoplasmosis, herpes viruses (HSV, VZV), CMV, tuberculosis, syphilis, Lyme disease, HIV/AIDS], type 1 diabetes mellitus, multiple sclerosis, thyroid disorders, family history of autoimmune disease)	☐	☐	
Current or former smoker	☐	☐	If yes, specify duration and packs per day:

CLINICAL COURSE			
	Yes	**No**	**Specify details (if relevant)**
Was the patient's uveitis (incl. VKH syndrome) diagnosed prior to the first dose of rilzabrutinib?	☐	☐	*State if unknown*
Was the time elapsed between the first dose of rilzabrutinib, and the onset of uveitis (incl. VKH syndrome) known?	☐	☐	
Was the time elapsed between the last dose of rilzabrutinib, and the onset of uveitis (incl. VKH syndrome) known?	☐	☐	
Precise the eye involvement: • OD (right eye) • OS (left eye)	☐ ☐ ☐	☐ ☐ ☐	

• Bilateral			
Precise the uveitis type: • Anterior (anterior chamber) • Intermediate (vitreous) • Posterior (retina or choroid) • Panuveitis (all segments)	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	
Did the patient present with ocular signs and symptoms? (e.g., conjunctival hyperaemia, blurred vision, photophobia, eye pain, floaters, injected conjunctiva)	☐	☐	If yes, specify severity and start/end dates:
Was the patient treated for the uveitis?	☐	☐	If yes, briefly list the management/treatment (e.g., drugs, procedures, including dates) of the uveitis:
Was the patient referred to an ophthalmologist?	☐	☐	If yes, specify type and dates of additional support: Provide a copy of consultation report if available:
INVESTIGATIONS/LAB EXAMS			
EXAMINATION *performed:* **YES** ☐ **NO** ☐ **Date:** Click here to enter a date.			
	DATE (DD/MMM/YYYY)		**RELEVANT RESULTS**
Intraocular pressure (OD and OS) YES ☐ NO ☐			
Visual acuity (OD and OS) YES ☐ NO ☐			
Slit lamp examination YES ☐ NO ☐			
Fundoscopic examination YES ☐ NO ☐			
Optical Coherence Tomography (OCT) YES ☐ NO ☐			
Fluorescein angiography YES ☐ NO ☐			
LABORATORY DATA *performed:* **YES** ☐ **NO** ☐ **Date:** Click here to enter a date.			
	DATE (DD/MMM/YYYY)		**RELEVANT RESULTS**
Microbiologic test results YES ☐ NO ☐			
Inflammatory markers (ESR, CRP) YES ☐ NO ☐			
HLA-B27 testing YES ☐ NO ☐			
ACTION TAKEN			
	Yes	**No**	**Specify details (if relevant)**
Was rilzabrutinib discontinued because of the event?	☐	☐	If yes, did the event improve or resolve following rilzabrutinib interruption or discontinuation? ☐Yes ☐No Details (i.e., how many days until resolution):

Was rilzabrutinib later resumed?	☐	☐	If yes, did the event reappear after rilzabrutinib was resumed? ☐Yes ☐No Details:

Sanofi Suspect Product Batch Number:

Adverse Event Information:

Seriousness: ☐ Non-Serious ☐ Serious (select at least one criteria below)

☐Death ☐Life-threatening ☐Hospitalization or prolongation of hospitalization

☐Persistent or significant disability or incapacity ☐Medically significant (as per HCP)

☐Suspected transmission of infectious agent ☐Congenital anomaly, birth defect

Outcome:

☐ Recovered/Resolved ☐ Recovered/Resolved with Sequelae ☐ Not Recovered/Not Resolved

☐ Recovering/Resolving ☐ Fatal ☐ Unknown

Specify date of resolution or date of death, if applicable: _____

If patient recovered with sequelae, describe sequelae: _____

Event Relationship to Sanofi product: ☐Related ☐Not Related ☐Unknown

ADDITIONAL INFORMATION
Please provide any other relevant additional information **regarding the reported event** (e.g., other suspect product(s), other additional information on reported adverse event, patient's medical history, concomitant medications, etc.):
Please provide relevant information regarding **any other experienced adverse event(s)** (e.g., event onset date(s), outcome(s), if it led to hospitalization, relationship(s) with Sanofi product, etc.):
Additional requests for the reporter (if any):

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Key messages of the additional risk minimization measures

The marketing authorization holder (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 labeling 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:
  - A pregnancy test should be performed before start of treatment with rilzabrutinib.
  - 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.
  - 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.
  - 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 (HCP) about contraception while taking rilzabrutinib.
- Instruct patient to refer to patient information leaflet (PIL) for additional information about the safety of rilzabrutinib.