EU-RISK MANAGEMENT PLAN FOR CENRIFKI® (TOLEBRUTINIB)

Risk Management Plan (RMP) Version number	Version 0.7
Data Lock Point (DLP)	11-SEP-2024
Date of final sign-off	01-APR-2026

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

Rationale for submitting an updated RMP	Not applicable
Summary of significant changes in this RMP	Not applicable

RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	Not applicable	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][a], [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

TABLE OF CONTENT

LIST OF TABLES

ABBREVIATIONS

ADR:	Adverse Drug Reaction
AESI:	Adverse Event of Special Interest
AIDS:	Acquired Immunodeficiency Syndrome
ALT:	Alanine Transaminase
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
ATP:	Adenosine Triphosphate
AUC:	Area Under The Curve
AUC_{0-24h}:	Area Under the Plasma-Concentration Time Curve from Time Zero to 24 Hours
BMSD:	Big MS Data Network
BTK:	Bruton's Tyrosine Kinase
BTKi:	Bruton's Tyrosine Kinase Inhibitor
CD:	Cluster of Differentiation
CI:	Confidence Interval
C_{max}:	Maximum Plasma Concentration
$C_{max,u}$:	Unbound Maximum Plasma Concentration
CNS:	Central Nervous System
COVID-19:	Coronavirus Disease-2019
C-SSRS:	Columbia Suicide Severity Rating Scale
CTCAE:	Common Terminology Criteria for Adverse Event
CYP:	Cytochrome P450
DALA:	Drug Abuse Liability Assessment
DILI:	Drug-Induced Liver Injury
DLP:	Data Lock Point
EBV:	Epstein-Barr Virus
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EGFR:	Endothelium Growth Factor Receptor
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
EU:	European Union
F:	Female
GBD:	Global Burden of Disease
GFR:	Glomerular Filtration Rate
GI:	Gastrointestinal
GP:	Glycoprotein
GVP:	Good Pharmacovigilance Practices
HAC:	Hepatology Assessment Committee
HCP:	Healthcare Professional
hERG:	human Ether-a-go-go-Related Gene
HI:	Hepatic Impairment
HIV:	Human Immunodeficiency Virus
HRQoL:	Health-Related Quality of Life

IC_{50}:	Half Maximal Inhibitory Concentration
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFNβ-1a:	Interferon Beta-1a
IFNβ-1b:	Interferon Beta-1b
Ig:	Immunoglobulin
IMP:	Investigational Medicinal Product
INN:	International Nonproprietary Name
IR:	Incidence Ratio
LFT:	Liver Function Test
LOAEL:	Low-Observed-Adverse-Effect-Level
M:	Male
MAH:	Marketing Authorization Holder
MedDRA:	Medical Dictionary for Regulatory Activites
MRHD:	Maximum Recommended Human Dose
MRI:	Magnetic Resonance Imaging
MS:	Multiple Sclerosis
N:	Total Number of Patient
NOAEL:	No-Observed-Adverse-Effect-Level
nrSPMS:	Non-Relapsing Secondary Progressive Multiple Sclerosis
NYHA:	New York Heart Association
PASS:	Post-Authorisation Safety Study
PIL:	Patient Information Leaflet
PIRA:	Progression Independent of Relapse Activity
PK:	Pharmacokinetic
PL:	Package Leaflet
PML:	Progressive Multifocal Leukoencephalopathy
PMS:	Progressive Multiple Sclerosis
PO:	Per Oral
PPMS:	Primary Progressive Multiple Sclerosis
PSUR:	Periodic Safety Update Report
PTC:	Product Technical Complaint
Q:	Quarter
QPPV:	Qualified Person Responsible for Pharmacovigilance
QR:	Quick Response
RI:	Renal Impairment
RMP:	Risk Management Plan
RMS:	Relapsing forms of Multiple Sclerosis
RRMS:	Relapsing-Remitting Multiple Sclerosis
SAE:	Serious Adverse Event
SIR:	Standardized Incidence Ratio
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query
SMR:	Standardized Mortality Ratio
SPMS:	Secondary-Progressive Multiple Sclerosis
$t_{1/2}$:	Half-life
TB:	Tuberculosis

TDAR:	T-cell Dependent Antibody Response
TEAE:	Treatment-Emergent Adverse Event
UK:	United Kingdom
ULN:	Upper Limit of Normal
URL:	Uniform Resource Locator
US:	United States

PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance (International Nonproprietary Name [INN] or common name)	Tolebrutinib
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Not yet assigned
Marketing Authorization Holder (MAH)	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Cenrifki
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Tolebrutinib is an inhibitor of Bruton's tyrosine kinase (BTK).
	Summary of mode of action: *Tolebrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). Tolebrutinib forms a covalent bond with cysteine 481 near the ATP-binding site leading to inhibition of BTK enzymatic activity in B cells and microglia. The BTK signalling pathway is critical for B cell and myeloid cell functions, including central nervous system (CNS)-resident macrophages and microglia, implicated in the pathophysiology of multiple sclerosis (MS). Although the exact mechanism by which tolebrutinib exerts its therapeutic effect in MS is not fully understood, there is evidence to support it inhibits the activation of B cells, macrophages and microglia in the periphery and CNS.*
	Important information about its composition: Not applicable
Hyperlink to the product information	Refer to electronic common technical document (e-CTD) sequence 0000, Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	Current: *Cenrifki is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years.*
	Proposed: Not applicable
Dosage in the EEA	Current: *The recommended dose is 60 mg orally once a day with a meal.*

	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: *Cenrifki is available as an orange, drop shape, film-coated tablet debossed with "60" on one side,* containing 60 mg of tolebrutinib.
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the European Union (EU)?	Yes

ATC: Anatomical Therapeutic Chemical; ATP: Adenosine Triphosphate; BTK: Bruton's Tyrosine Kinase; CNS: Central Nervous System; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; MAH: Marketing Authorization Holder; MS: Multiple Sclerosis; RMP: Risk Management Plan.

PART II: SAFETY SPECIFICATION

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

Cenrifki is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years.

The epidemiology of multiple sclerosis is summarized in the following table.

Table 6 - Epidemiology of Multiple sclerosis

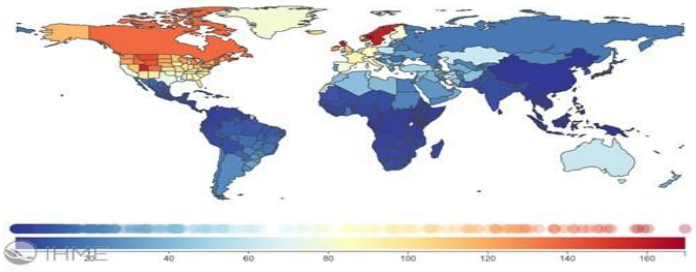
Indication	Multiple sclerosis
Incidence	Based on 2019 data from the Global Burden of Disease (GBD) project, the global age-standardized incidence rate of MS is 0.74 per 100 000 person-years. (1)The incidence of MS varies widely according to World Bank geographic region [Table 6a]. The highest age-standardized incidence rates are observed in North America (3.57 cases per 100 000 person-years), Europe and Central Asia (2.15 cases per 100 000 person-years). The lowest incidence rates are observed in East Asia and Pacific (0.21 cases per 100 000 person-years).
Prevalence	The worldwide age-standardized prevalence of MS, according to 2019 data compiled by the GBD project, is 21.25 cases per 100 000 persons. The age-standardized prevalence of MS is highest in North American (103.79 cases per 100 000 persons), Europe and Central Asia (59.04 cases per 100 000 persons). (1) The World Bank region with the lowest age-standardized prevalence of MS is East Asia and Pacific (3.75 cases per 100 000 persons) [Table 6b]. It is important to note that even within regions the prevalence of MS may vary by country.

Table 6a - Age-standardized incidence rates per 100 000 person-years of MS for the global population and by World Bank region, from GBD 2019 (accessed Apr-2024)

Region	Incidence Rate per 100 000 person-years (95% CI)
East Asia and Pacific	0.21 (0.18, 0.25)
Europe and Central Asia	2.15 (1.92, 2.38)
Latin America and Caribbean	0.59 (0.49, 0.69)
Middle East and North Africa	1.35 (1.14, 1.57)
North America	3.57 (3.29, 3.84)
South Asia	0.42 (0.35, 0.50)
Sub-Saharan Africa	0.35 (0.29, 0.41)
Global	0.74 (0.65, 0.83)

CI: Confidence Interval; GBD: Global Burden of Disease; MS: Multiple Sclerosis.

Figure a - Age-standardized prevalence per 100 000 persons of MS, from GBD 2019 (accessed Apr-2024)



Indication	Multiple sclerosis
	Table 6b - Age-standardized prevalence per 100 000 persons of MS for the global population and by World Bank region, from GBD 2019 (accessed Apr-2024)

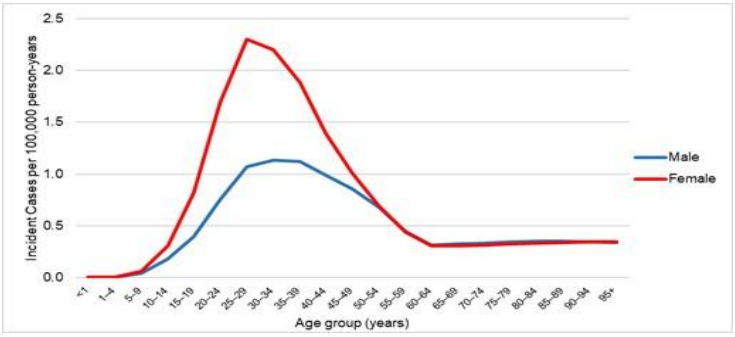
Region	Prevalence per 100 000 persons (95% CI)
East Asia and Pacific	3.75 (3.01, 4.52)
Europe and Central Asia	59.04 (52.04, 66.80)
Latin America and Caribbean	13.90 (11.20, 16.56)
Middle East and North Africa	37.23 (30.87, 43.91)
North America	103.79 (95.42, 112.13)
South Asia	8.34 (6.63, 10.12)
Sub-Saharan Africa	6.88 (5.47, 8.30)
Global	21.25 (18.52, 23.91)

CI: Confidence Interval; GBD: Global Burden of Disease; MS: Multiple Sclerosis.

Demographics of the population in the authorized or proposed indication

The average age of MS diagnosis worldwide is 32 years. (2) The general pattern of age at MS diagnosis is consistent across geographic regions, such that incidence is low in children, then increases rapidly and peaks between ages 25 and 35 years, and then declines in later adulthood [Table 6c]. (1) (3)

Figure b - Global incidence rates per 100 000 person-years of MS stratified by sex and age group, from GBD 2019 (accessed Apr-2024)



Women have a higher risk of MS than men. The overall female to male sex incidence ratio has been reported to range from 1.5:1 to 3.0:1. (4) (5) (6) The sex incidence ratio varies by age, increasing from 1:1 at the onset of puberty and returning to 1:1 in later adulthood. (1) Higher overall age-standardized incidence rates are consistently observed among women (World Bank region-specific range 0.24 to 4.94 cases per 100 000 in 2019) compared to men (World Bank region-specific range of range of 0.18 to 2.23 cases per 100 000 in 2019) across all geographic regions [Table 6c].

Table 6c - Age-standardized incidence rates per 100 000 person-years of MS for the global population and by World Bank region, stratified by sex, from GBD 2019 (accessed Apr-2024)

Region	Female	Male
East Asia and Pacific	0.24	0.18
Europe and Central Asia	2.69	1.62
Latin America and Caribbean	0.73	0.45
Middle East and North Africa	1.75	0.99
North America	4.94	2.23
South Asia	0.51	0.33
Sub-Saharan Africa	0.45	0.24
Global	0.93	0.55

GBD: Global Burden of Disease; MS: Multiple Sclerosis.

Indication	Multiple sclerosis
	Other risk factors for MS include the following: • Genetics: Over 200 genetic variants have been associated with an increased risk of MS. (7) • Vitamin D deficiency: Inadequate vitamin D exposure increases the risk of MS. (3) The association of latitude with the duration and intensity of sunlight exposure is thought to, at least partially, explain observed increased MS prevalence among regions further from the equator as described in ecological studies. (8) • Obesity: Obesity in early life (from childhood through young adulthood) increases MS risk in both males and females. (3) (9) • Epstein-Barr virus (EBV): Infection with EBV has been associated with an up to 30 times increased risk of MS. Epstein-Barr virus infection during adolescence and adulthood often manifests as infectious mononucleosis, which is also associated with an increased risk of MS. The occurrence of MS in individuals who are EBV negative is rare. (10) (11) • Smoking: Cigarette smokers have a higher risk of MS than non-smokers. The risk of MS increases with duration and intensity of smoking. (3)
Main existing treatment options	The clinical armamentarium for treating relapses and acute magnetic resonance imaging (MRI) activity has further increased over the past few years. Main treatment options (country/regional differences exist) in MS are IFNβ-1a, IFNβ-1b, glatiramer acetate, teriflunomide, dimethyl fumarate, diroximel fumarate, fingolimod, cladribine, natalizumab, alemtuzumab, ocrelizumab, mitoxantrone, ofatumumab, ozanimod, ublituximab, siponimod and ponesimod. Most products are approved for relapsing-remitting multiple sclerosis (RRMS), only few are approved in relapsing secondary-progressive multiple sclerosis (SPMS). There is no global consensus on treatment strategy and/or algorithm. In an individualized approach, treatment decisions are based on the efficacy and safety profile of each drug, on their mechanism of action, and on patient preference and convenience. Currently, there is no treatment available to delay or prevent the chronic accumulation of disability in non-relapsing secondary-progressive multiple sclerosis (nrSPMS).
Natural history of the indicated condition in the untreated population including mortality and morbidity	Approximately 85% of patients with MS worldwide are initially diagnosed with RRMS, which is characterized by alternating phases of relapses and remission. (12) (13) If left untreated, the majority of these patients will transition to SPMS, where neurological deficits accumulate, leading to a continuous progression of disability. (14) Secondary-progressive multiple sclerosis can occur with or without occasional relapses, resulting in either relapsing or non-relapsing SPMS (nrSPMS). Patients with nrSPMS do not experience relapses but continue to face an accumulation of physical and neurological disabilities, with symptoms such as cognitive impairment, balance and gait disturbances, loss of bladder function, and sexual dysfunction. In recent years, attention has shifted towards progression independent of relapse activity (PIRA), which can begin early in the course of MS. Progression independent of relapse activity accounts for approximately half of the disability worsening in RRMS; while in SPMS, the majority of disease progression is driven by PIRA, although a small proportion of relapse-associated worsening is still observed. The burdensome consequences of MS result in physical disabilities (such as impaired ambulation) and cognitive impairments (such as depression), which limit employability, daily activities, and overall health-related quality of life (HRQoL). (15) Life expectancy is shortened in the MS population, compared to the general population, by 7-14 years on average. (16) (17) (18) (19) People with MS have about a 3 times increased risk of all-cause mortality compared to individuals without MS. (20) (21) Overall survival is worse for MS patients with primary progressive disease course compared to relapsing remitting disease course. (17) (18) Compared to the non-MS population, women have an overall higher mortality (pooled Standardized Mortality Ratio [SMR] 2.57 [95% CI 2.53 to 2.61]) than men (pooled SMR 2.47 [95% CI 2.42 to 2.52]). (20) (21) Despite a

Indication	Multiple sclerosis
	worse SMR, women with MS have been reported to have a slower disability progression rate and a longer life expectancy than men with MS. (22) (23) (24) In MS, about 50–70% of deaths could be considered MS-related, with MS being either the main cause or a contributing factor. Additionally, cardiovascular and cerebrovascular diseases, cancer, and infections are also considered major causes of death. (25)
Important co-morbidities	The most common comorbidities observed in MS patients include the following: • Cardiovascular and cerebrovascular diseases (including ischemic heart disease, congestive heart failure, ischemic stroke, and peripheral vascular disease. (26) • Psychiatric disorders (including depression and anxiety). (27) • Diabetes. (26) (28) • Hypertension. (26) (28) (29) • Hypercholesterolemia/hyperlipidemia. (26) (29) • Autoimmune disorders (including chronic thyroid disorder). (29) (30) (31) • Pain (including migraine and fibromyalgia). (29) (32) • Chronic lung disease (including asthma and chronic obstructive pulmonary disease). (29) (30) (31)

CI: Confidence Interval; EBV: Epstein-Barr Virus; GBD: Global Burden of Disease; HRQoL: Health-Related Quality of Life; IFNβ-1a: Interferon Beta-1a; IFNβ-1b: Interferon Beta-1b; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; nrSPMS: Non-Relapsing Secondary-Progressive Multiple Sclerosis; PIRA: Progression Independent of Relapse Activity; RRMS: Relapsing-Remitting Multiple Sclerosis; SMR: Standardized Mortality Ratio; SPMS: Secondary-Progressive Multiple Sclerosis.

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

The summary of the preclinical safety evaluation of tolebrutinib was as follows:

For Tolebrutinib:

- In vivo safety pharmacology studies were conducted in rats and dogs. Tolebrutinib had no effects on cardiovascular or respiratory systems in dogs or in the CNS in rats at the highest dose evaluated (30 mg/kg per oral [PO]). Tolebrutinib inhibited human ether-a-go-go-related gene (hERG) potassium channel tail currents with an half maximal inhibitory concentration (IC_{50}) of 9.1 µM (4.13 µg/mL), which is 2908-times higher than the clinical unbound maximum plasma concentration ($C_{max,u}$) at 60 mg (1.42 ng/mL fed state in POH0855).
- Repeat dose toxicity studies were conducted in rats and dogs. There were no adverse effects of tolebrutinib in rats up to the highest dose administered which were 30 mg/kg/day for 14 or 28 days, and 50 mg/kg/day for 13 weeks. In a 6-month toxicity study in rats, target-related effects on immune function included T cell-dependent antibody response (TDAR) findings of decreased immunoglobulin (Ig) G and IgM responses to antigen; clinical observations of skin lesions; microscopic findings of erosion, ulcer, and focal acanthosis/hyperkeratosis; and nematode infestation in the rectum. Target-related adverse effects on platelet aggregation were manifested as hemorrhage in the eye, pancreas, nasal cavity, and mesenteric lymph nodes. Target related, species specific (rats only) effects in the pancreas included fibrosis and inflammation. While a No-Observed-Adverse-Effect-Level (NOAEL) was not observed, the adverse effects seen in the 6-month toxicity study of tolebrutinib in rats are similar to reported exaggerated pharmacology and/or toxicity of other bruton's tyrosine kinase inhibitor (BTKi). The low observed-adverse-effect-level (LOAEL) was 2 mg/kg/day. In the 2-year tolebrutinib carcinogenicity study in rats, haemorrhages, skin lesions, immune system effects, and pancreatic findings occurred at the lowest dose administered corresponding to 1.2- and 4.4-times the steady-state area under the curve (AUC) at the maximum recommended human dose (MRHD), in male and female rats. Increased mortality occurred in male rats at exposures 10-times steady-state AUC at the MRHD, notably as a result of premature euthanasia due to severe intraocular haemorrhages. Taken together, these findings indicate that prolonged tolebrutinib treatment appears to lower the exposure margin for toxicities to the clinically relevant area of concern.
- In the 28-day toxicity study in dogs, tolebrutinib-related adverse findings were observed at ≥8 mg/kg/day and consisted of decreased total protein, albumin, globulin, albumin/globulin, resulting in fluid alterations (interstitial oedema, ascites). No effects were observed following the recovery period. The 28-day dog NOAEL was 2 mg/kg/day in males and 8 mg/kg/day in females. In the 9-month tolebrutinib toxicity study in dogs, a non-adverse haemorrhagic tendency was seen in multiple organs from 15-times the

steady-state AUC at the MRHD. There were no adverse effects of tolebrutinib at the highest dose administered for 14 days (30 mg/kg/day) or 13 weeks (8 mg/kg/day).

- Tolebrutinib did not exert relevant genotoxic potential in vitro or in vivo. Tolebrutinib was negative for genotoxic potential in the Ames test and the in vivo micronucleus tests in rats. Increased structural aberrations were observed in the in vitro chromosome aberration test at concentrations which produced substantial cytotoxicity. Tolebrutinib shares similar structures with 2 impurities (RA15660132 (M443) and RA15960096 (M527)) and the M2 metabolite, which resulted in negative Ames, positive in vitro micronucleus, and negative in vivo micronucleus/comet tests. All 4 have the same alerting structural features for clastogenicity; the alpha beta unsaturated amide and aromatic amine. As the micronucleus/comet tests were negative for 3 compounds, using read-cross, the effect with tolebrutinib at highly toxic concentrations can be considered as being biologically not relevant.
- Tolebrutinib was non-carcinogenic in rats at the highest doses administered (2 and 6 mg/kg/day in males and females, respectively). Tolebrutinib was non-carcinogenic in mice at the highest dose administered (330 mg/kg/day).
- There were no effects on fertility in male and female rats at tolebrutinib up to the highest dose of 25 mg/kg/day (247x and 759x human exposure in males and females, respectively).
- In the embryo-fetal toxicity study in rats, no adverse effects were observed at 161x the human exposure at 60 mg (10 mg/kg/day). At 25 mg/kg/day (744x human exposure), increased post-implantation loss (early resorptions), lower number of live fetuses, and a minimal decrease in mean fetal body weight were observed. No external, visceral, or skeletal malformations were observed.
- In the embryo-fetal toxicity study in rabbits, no adverse effects were observed up to the highest dose of 10 mg/kg/day (315x human exposure).
- In the definitive pre- and postnatal developmental toxicity study, rats were administered tolebrutinib once daily during gestation through parturition, lactation and weaning. There were no adverse effects observed in the offspring. The tolebrutinib NOAEL for F0 maternal and F1 prenatal and postnatal development was 15 mg/kg/day (447x human exposure).
- Exploratory 14-day oral toxicity studies of SAR442168 in juvenile rats demonstrated that doses ≥200 mg/kg/day were not well tolerated (mortality / early euthanasia, adverse clinical signs, body weight loss / decreased body weight gain, decreased food consumption, and macroscopic findings in the kidney, liver, gastrointestinal (GI) tract, lymph node spleen and thymus). At 100 mg/kg/day, effects on clinical signs, body weight gain, food consumption, and macroscopic findings in the kidneys occurred. The maximum tolerated dose was 100 mg/kg/day.
- Tolebrutinib was not phototoxic in vitro in 3T3 cells.

- Although hepatotoxicity was not noted in the nonclinical repeat-dose studies in mice, rats or dog with tolebrutinib, mechanistic studies were performed in order to investigate potential for hepatotoxicity. While dose-related multifocal necrosis with inflammatory infiltration occurred in rats orally administered extremely high doses of the M2 metabolite (≥300 mg/kg/day) in an exploratory 3-day toxicity study, the AUC exposure ratios at the NOAEL of 150 mg/kg/day in rats compared to human M2 metabolite exposure were greater than 1000-fold. Whole genome transcript profiling of tolebrutinib and the M2 metabolite in human, rat, and dog liver spheroids showed a similar profile across all 3 species, with no clear evidence of a direct mechanism of hepatoxicity identified to account for the liver injury observed clinically. The in vitro cytotoxicity IC_{50} of tolebrutinib and M2 metabolite in liver spheroids was similar between human, rat, and dog with an IC_{50} ≥32 µM. This concentration is >1000-fold higher than the clinical maximum plasma concentration (C_{max}) (0.0264 µM) at 60 mg in POH0855, suggesting low potential for cytotoxicity.
- No evidence of dependence and abuse potential has been observed for tolebrutinib or its major metabolites. No similarities to known drugs of abuse according to chemical structure, mechanism of action, pharmacology, toxicology, and clinical data exist. Therefore, no nonclinical abuse liability studies (eg, self-administration, drug discrimination) were performed.
- A summary of tolebrutinib exposure multiples in relation to clinical exposure is provided below:

Table 7 - Tolebrutinib exposure multiples in relation to clinical exposure

Study type	Species	Sex	NOAEL (mg/kg/day)	$AUC_{0\text{-}24h}$ (ng.h/mL)	Exposure margin[f]
6-month repeat-dose	Rat	M	2[g]	711[a]	23x
		F		884[a]	29x
9-Month repeat-dose	Dog	M	12	11500[b]	377x
		F		9240[b]	303x
Carcinogenicity	Mouse	M	330	23260 ng/mL[c]	1938x
		F		24609 ng/mL[c]	2051x
	Rat	M	2	306[d]	10x
		F	6	2150[d]	70x
Embryo-fetal toxicity	Rat	F	10	4900[e]	161x
	Rabbit	F	10	9610[e]	315x

a Exposure reported Week 26.

Study type	Species	Sex	NOAEL (mg/kg/day)	AUC_{0-24h} (ng.h/mL)	Exposure margin[f]

b Exposure reported Day 273.
c Plasma concentrations reported Day 176 1-hour post-dose.
d Exposure reported Day 28.
e Exposure reported Gestation Day 12.
f Comparison of tolebrutinib exposure in animal plasma (AUC_{0-24h} or C_{max}) at the NOAEL/LOAEL with the human exposure at 60 mg fed state in POH0855 (30.5 ng.h/mL, 12.0 ng/mL, respectively).
g LOAEL value.
AUC_{0-24h}: Area Under the Plasma-Concentration Time Curve from Time Zero to 24 Hours; C_{max}: Maximum Plasma Concentration;
F: Female; LOAEL: Low-Observed-Adverse-Effect-Level; M: Male; NOAEL: No-Observed-Adverse-Effect-Level.

For M2 metabolite:

- The M2 metabolite is a covalent inhibitor of BTK with similar activity as the parent drug and exhibited higher human exposure than the parent drug. It was formed with adequate exposure in female rabbits but not in other nonclinical species. Thus, select toxicity studies (in vitro genotoxicity, in vivo rat and mouse) were performed with the M2 metabolite. Safety pharmacology studies other than the hERG assay were not conducted with the M2 metabolite because human clinical data were available when the M2 metabolite was discovered.
- The M2 metabolite inhibited hERG potassium channel tail currents with an IC_{50} of 29.3 µM (13.3 µg/mL), which is 3982-times higher than the clinical M2 $C_{max,u}$ at 60 mg tolebrutinib (3.34 ng/mL fed condition in POH0855).
- Repeat-dose oral administration of the M2 metabolite to rats for 26 weeks generally resulted in adverse effects similar to that seen with tolebrutinib. Primary effects included hemorrhage, pancreatic islet pigment/fibrosis in males, and an increased incidence of nematode parasites in the cecum, colon, and/or rectum. A slightly increased incidence of hair loss and/or thinning was observed. No effects occurred on immunophenotyping or TDAR. The LOAEL was 3.5 mg/kg/day.
- The M2 metabolite did not exert relevant genotoxic potential in vitro or in vivo. The M2 metabolite was negative in the Ames test and positive in the in vitro micronucleus test in human lymphocytes. A follow-up in vivo micronucleus / comet test in rats was negative. As such, M2 is considered non-genotoxic in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S2 (1R) criteria.
- The carcinogenic potential of the M2 metabolite was incorporated into the 6-month oral carcinogenicity study of tolebrutinib in mice. No carcinogenic potential was observed at 1.75 mg/kg/day.

- The M2 metabolite had no effect on fertility, reproductive performance, or early embryonic development in rats up 7 mg/kg/day, the highest dose administered (M2 exposure 26x and 23x human M2 exposure, in males and females, respectively).
- A stand-alone embryo-fetal toxicity study was not conducted with the M2 metabolite because it is formed with adequate exposure in rabbits following oral administration of tolebrutinib. As such, the embryo-fetal toxicity study of tolebrutinib in rabbits also evaluated the M2 metabolite. Dose-dependent incomplete hyoid ossification was noted at clinically relevant exposure of the M2 metabolite (<1.3-times the steady-state AUC of M2 at the MRHD of tolebrutinib). The human relevance is unknown.
- In the pre- and postnatal developmental toxicity study, rats were administered the M2 metabolite once daily during gestation through parturition, lactation, and weaning. There were no adverse effects observed in the offspring. The NOAEL for F0 maternal and F1 prenatal and postnatal development was 7 mg/kg/day, the highest dose administered (10x human M2 exposure).
- A summary of M2 metabolite exposure multiples in relation to clinical exposure is provided below:

Table 8 - M2 metabolite exposure multiples in relation to clinical exposure

Type of study	Species	Dose (mg/kg/day)	NOAEL (mg/kg/day)	M2 metabolite AUC_{0-24} at NOAEL (ng.h/mL)	Exposure ratio[a]
26-week toxicity	Rat	3.5, 7	3.5[b]	476 (M) 903 (F)	6.2x (M) 11.8x (F)
Micronucleus and comet assay	Male rat	500, 1000, 2000	2000	815 000	10,626x
26-week carcinogenicity study	Mouse	1.75	1.75	146.0 ng/mL(M)[c] 226.7 ng/mL (F)[c]	5.2x 8.0x
Fertility study	Rat	3.5, 7	7	1980 (M) 1730 (F)	25.8x (M) 22.6x (F)
Embryo-fetal toxicity	Pregnant rabbit[d]	2.5, 5, or 10	10	103	1.3x
Pre- and postnatal development toxicity	Pregnant rat	3.5, 7	7	743	9.7x

a Exposure ratio based on M2 exposure following 60 mg tolebrutinib fed state in POH0855 (76.7 ng.h/mL, 28.3 ng/mL).
b LOAEL exposure provided for the 26-week study in rats at Week 26 since a NOAEL was not identified.
c Plasma concentrations on Day 176 at 1 h post-0 dose.
d M2 metabolite estimated exposure from the embryo-fetal toxicity study of tolebrutinib in rabbits at 10 mg/kg/day.
AUC_{0-24h}: Area Under the Plasma-Concentration Time Curve from Time Zero to 24 Hours; F: Female;
LOAEL: Low-Observed-Adverse-Effect-Level; M: Male; NOAEL: No-Observed-Adverse-Effect-Level.

The key non-clinical findings are presented in the following table.

Table 9 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • **The immune system** - Rats: Decreased IgG and IgM response to antigen; clinical observations of skin lesions; microscopic skin findings of erosion, ulcer, and focal acanthosis/hyperkeratosis; and nematode infestation in the rectum. - Dogs: Decreased absolute counts and relative proportions of B cells (CD21+); minimal to slight decreased cellularity of various lymphoid organs / tissues.	The skin findings observed in the pre-clinical toxicity studies may be a result an off-target engagement of the endothelium growth factor receptor (EGFR). Skin and subcutaneous tissue disorder adverse events were observed in tolebrutinib clinical trials. No safety issues expected in humans as most events are correlated to bleeding complications.
• **Haemorrhage** - Rats: Haemorrhage in the eye, pancreas, nasal cavity, and mesenteric lymph nodes. - Dogs: Minimal to moderate congestion/haemorrhage in the mesenteric and/or retropharyngeal lymph node, stomach, colon, ileum, testis and/or kidney.	Bruton tyrosine kinase inhibitor (BTKi) is thought to inhibit collagen-mediated platelet activation and interfere with the von Willebrand mediated coagulation pathway. Hemorrhage adverse events were observed in tolebrutinib clinical trials (see Section SVII.1.2) Hemorrhages is an important potential risk for tolebrutinib (see Section SVII.1.2).
• **The Pancreas:** - Rats: Fibrosis and inflammation. - Dogs: Minimal pancreatic oedema associated with decreased serum albumin.	Pancreatic lesions in rats are likely to be a species-specific class effect of BTKi, which may exacerbate islet-centered pathology which is unlikely relevant to humans. However, no difference between tolebrutinib and comparator (teriflunomide or placebo) observed for pancreatic conditions, new onset diabetes or increased lipase. Therefore, no safety issues are expected in humans.
• **Potential for liver toxicity** - Repeat doses of tolebrutinib in rat, mouse or dog did not result in hepatotoxicity. Whole genome transcript profiling of tolebrutinib in human, rat, and dog liver spheroids showed a similar profile across all 3 species, with no clear evidence of a direct mechanism of hepatoxicity identified to account for the liver injury observed clinically. The M2 metabolite showed a similar transcriptional profile to tolebrutinib. The tolebrutinib cytotoxicity IC_{50}	No intrinsic (direct or predictable) liver toxicity was demonstrated in preclinical studies. However, liver injury was observed in tolebrutinib clinical trials and drug-induced liver injury (DILI) is an important identified risk (see Section SVII.1.2).

Key Safety Findings	Relevance to human usage
(approximately 32 µM) in liver spheroids was >1000-fold higher than the clinical Cmax (0.0264 µM at 60 mg in POH0855), suggesting low potential for cytotoxicity. Three species of liver spheroids (human, rat, dog) showed similar cytotoxic potential. M2 metabolite showed minimal to no cytotoxicity.	
• **Reproductive and Developmental Toxicity** - Dose-dependent incomplete hyoid ossification was noted at clinically relevant exposure of the M2 metabolite in the embryo-foetal development study of tolebrutinib in rabbits (<1.3-times the steady-state AUC of M2 at the MRHD of tolebrutinib). - No effects of M2 on fertility or pre- and post-natal development studies in rats at clinically relevant exposures. - No effects of tolebrutinib on reproductive, embryo-fetal and pre-/post-natal development observed in rats and rabbits at exposures sufficiently in excess to human exposure (>100x)	There is insufficient information on embryo-fetal development regarding the active metabolite M2, therefore, a risk to the unborn child cannot be excluded. Tolebrutinib is not recommended during pregnancy and in women of childbearing potential not using contraception. "Use in breastfeeding" and "Reproductive toxicity" will be monitored in future periodic safety update reports (PSURs) (see Section SIV.1).

AUC: Area Under the Curve; BTKi: Bruton Tyrosine Kinase Inhibitor; CD: Cluster of Differentiation; C_{max}: Maximum Plasma Concentration; DILI: Drug-Induced Liver Injury; EGFR: Endothelium Growth Factor Receptor; IC_{50}: Half Maximal Inhibitory Concentration; Ig: Immunoglobulin; MRHD: Maximum Recommended Human Dose; PSUR: Periodic Safety Update Report.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

This section includes summary information on the clinical trial exposure. The data are being pooled across phase 2 and phase 3 studies, as well as presented separately for nrSPMS and Relapsing forms of Multiple Sclerosis (RMS).

The data are stratified for relevant categories, including:

- Duration of exposure
- Age group and gender
- Baseline renal impairment

Duration of exposure

A total of 1886 participants (nrSPMS and RMS) were exposed to tolebrutinib 60 mg in completed/unblinded phase 2 (DRI15928, LTS16004) and phase 3 (EFC16645, EFC16033, EFC16034) studies. Of these, 1645 and 1431 participants were exposed to tolebrutinib for at least 1 year (48 weeks) and at least 2 years (96 weeks), respectively.

Table 10 - Duration of exposure to tolebrutinib 60 mg - Pool B (nrSPMS and RMS) safety population

Cumulative for nrSPMS + RMS Duration of exposure (at least)	Participants	Participant-years
≥12 weeks	1807	4292.9
≥24 weeks	1764	4279.0
≥36 weeks	1702	4244.2
≥48 weeks	1645	4199.4
≥72 weeks	1531	4072.5
≥96 weeks	1431	3915.0
≥120 weeks	1174	3375.8
≥144 weeks	698	2180.7
≥168 weeks	215	735.5
Total	1886	4301.2

RMS: includes tolebrutinib 60 mg exposed participants in DRI15928, LTS16004, EFC16033 and EFC16034
nrSPMS: includes tolebrutinib 60 mg exposed participants in EFC16645
Exposure calculated as last dose of tolebrutinib 60 mg (up to interim CSR database lock for LTS16004) - first dose of tolebrutinib 60 mg + 1 including any gaps between DRI15928 and LTS16004 and open-label treatment in EFC16645
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_dur_byind_s_t.sas
OUT=REPORT/OUTPUT/cdc_dur_byind_poolb_s_t_i.rtf (05DEC2024 6:53)
CSR: Clinical Safety Report; nrSPMS: Non Relapsing Secondary Progressive Multiple Sclerosis; RMS: Relapsing forms of Multiple Sclerosis.

A total of 828 participants were exposed to tolebrutinib 60 mg in the completed/unblinded nrSPMS study (EFC16645). Of these, 689 and 562 were exposed to tolebrutinib for at least 1 year (48 weeks) and at least 2 years (96 weeks), respectively.

Table 11 - Duration of exposure to tolebrutinib 60 mg - EFC16645 (nrSPMS) safety population

nrSPMS Duration of exposure (at least)	Participants	Participant-years
≥12 weeks	788	1734.6
≥24 weeks	769	1728.0
≥36 weeks	727	1704.1
≥48 weeks	689	1673.5
≥72 weeks	625	1602.7
≥96 weeks	562	1502.3
≥120 weeks	430	1223.4
≥144 weeks	246	760.5
≥168 weeks	74	247.2
Total	828	1738.6

nrSPMS: includes tolebrutinib 60 mg exposed participants in EFC16645
Exposure calculated as last dose of tolebrutinib 60 mg - first dose of tolebrutinib 60 mg + 1 including open-label treatment
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_dur_byind_s_t.sas
OUT=REPORT/OUTPUT/cdc_dur_byind_645_s_t_i.rtf (05DEC2024 6:53)
nrSPMS: Non Relapsing Secondary Progressive Multiple Sclerosis.

A total of 1058 participants (RMS) were exposed to tolebrutinib 60 mg in completed/unblinded RMS studies (DRI15928, LTS16004, EFC16033 and EFC16034). Of these, 956 and 869 were exposed to tolebrutinib for at least 1 year (48 weeks) and at least 2 years (96 weeks), respectively.

Table 12 - Duration of exposure to tolebrutinib 60 mg - RMS safety population

RMS Duration of exposure (at least)	Participants	Participant-years
≥12 weeks	1019	2558.3
≥24 weeks	995	2551.0
≥36 weeks	975	2540.1
≥48 weeks	956	2525.8
≥72 weeks	906	2469.8
≥96 weeks	869	2412.7
≥120 weeks	744	2152.4
≥144 weeks	452	1420.2
≥168 weeks	141	488.3
Total	1058	2562.5

RMS: includes tolebrutinib 60 mg exposed participants in DRI15928, LTS16004, EFC16033 and EFC16034
Exposure calculated as last dose of tolebrutinib 60 mg (up to interim CSR database lock for LTS16004) - first dose of tolebrutinib 60 mg + 1 including any gaps between DRI15928 and LTS16004
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_dur_byind_s_t.sas
OUT=REPORT/OUTPUT/cdc_dur_byind_rms_s_t_i.rtf (05DEC2024 6:53)
CSR: Clinical Safety Report; RMS: Relapsing forms of Multiple Sclerosis.

Exposure by age group and gender

Approximately 64% of participants were female and 57% were older than 40 years of age in the combined nrSPMS (phase 3 study EFC16645) and RMS (phase 2 studies DRI15928, LTS16004 and phase 3 studies EFC16033, EFC16034) tolebrutinib 60 mg exposed population.

Table 13 - Exposure to tolebrutinib 60 mg by age group and gender - Pool B (nrSPMS and RMS) safety population

nrSPMS + RMS				
	Participants		Participant-years	
Age group	M	F	M	F
≤40 years	301	517	702.7	1220.1
>40 years	370	698	801.9	1576.4
Total	671	1215	1504.6	2796.5

RMS: includes tolebrutinib 60 mg exposed participants in DRI15928, LTS16004, EFC16033 and EFC16034
nrSPMS: includes tolebrutinib 60 mg exposed participants in EFC16645
Exposure calculated as last dose of tolebrutinib 60 mg (up to interim CSR database lock for LTS16004) - first dose of tolebrutinib 60 mg + 1 including any gaps between DRI15928 and LTS16004 and open-label treatment in EFC16645
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_pary_by_raceage_s_t.sas
OUT=REPORT/OUTPUT/cdc_pary_by_raceage_poolb_s_t_i.rtf (05DEC2024 6:53)
CSR: Clinical Safety Report; F: Female; M: Male; nrSPMS: Non Relapsing Secondary Progressive Multiple Sclerosis; RMS: Relapsing forms of Multiple Sclerosis.

A majority of participants (60%) exposed to tolebrutinib 60 mg in the nrSPMS study (EFC16645) were female. All exposed participants were in the 18 to 60 year age range per inclusion criteria, with 83% >40 year of age.

Table 14 - Exposure to tolebrutinib 60 mg by age group and gender - EFC16645 (nrSPMS) safety population

nrSPMS				
	Participants		Participant-years	
Age group	M	F	M	F
≤40 years	63	79	149.4	169.8
>40 years	270	416	559.8	859.6
Total	333	495	709.2	1029.4

nrSPMS: includes tolebrutinib 60 mg exposed participants in EFC16645
Exposure calculated as last dose of tolebrutinib 60 mg - first dose of tolebrutinib 60 mg + 1 including open-label treatment
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_pary_by_raceage_s_t.sas
OUT=REPORT/OUTPUT/cdc_pary_by_raceage_645_s_t_i.rtf (05DEC2024 6:53
F: Female; M: Male; nrSPMS: Non Relapsing Secondary Progressive Multiple Sclerosis.

A majority of participants (68%) exposed to tolebrutinib 60 mg in RMS studies (phase 2 studies DRI15928, LTS16004 and phase 3 studies EFC16033, EFC16034) were female. All exposed participants were in the 18 to 55 year age range per inclusion criteria, with approximately two-thirds ≤40 years of age.

Table 15 - Exposure to tolebrutinib 60 mg by age group and gender - RMS safety population

RMS				
	Participants		Participant-years	
Age group	M	F	M	F
≤40 years	238	438	553.3	1050.3
>40 years	100	282	242.1	716.8
Total	338	720	795.4	1767.1

RMS: includes tolebrutinib 60 mg exposed participants in DRI15928, LTS16004, EFC16033 and EFC16034
Exposure calculated as last dose of tolebrutinib 60 mg (up to interim CSR database lock for LTS16004) - first dose of tolebrutinib 60 mg + 1 including any gaps between DRI15928 and LTS16004
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_pary_by_raceage_s_t.sas
OUT=REPORT/OUTPUT/cdc_pary_by_raceage_rms_s_t_i.rtf (05DEC2024 6:53)
CSR: Clinical Safety Report; F: Female; M: Male; RMS: Relapsing forms of Multiple Sclerosis.

Exposure by baseline renal impairment (using glomerular filtration rate [GFR])

Table 16 - Duration of exposure to tolebrutinib 60 mg by renal impairment (creatinine clearance at baseline) - Pool B (nrSPMS and RMS) safety population

nrSPMS + RMS		
Renal impairment	Participants	Participant-years
Missing	2	4.8
<30 mL/min (severe renal impairment)	0	0
≥30 to <50 mL/min (moderate renal impairment)	1	2.7
≥50 to ≤80 mL/min (mild renal impairment)	157	340.0
>80 mL/min (mild renal impairment)	1726	3953.6
Total	1886	4301.2

RMS: includes tolebrutinib 60 mg exposed participants in DRI15928, LTS16004, EFC16033 and EFC16034
nrSPMS: includes tolebrutinib 60 mg exposed participants in EFC16645
Exposure calculated as last dose of tolebrutinib 60 mg (up to interim CSR database lock for LTS16004) - first dose of tolebrutinib 60 mg + 1 including any gaps between DRI15928 and LTS16004 and open-label treatment in EFC16645
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_pary_byrenal_s_t.sas
OUT=REPORT/OUTPUT/cdc_pary_byrenal_poolb_s_t_i.rtf (05DEC2024 6:53)
CSR: Clinical Safety Report; nrSPMS: Non Relapsing Secondary Progressive Multiple Sclerosis; RMS: Relapsing forms of Multiple Sclerosis.

Table 17 - Duration of exposure to tolebrutinib 60 mg by renal impairment (creatinine clearance at baseline) - EFC16645 (nrSPMS) safety population

nrSPMS		
Renal impairment	Participants	Participant-years
Missing	2	4.8
<30 mL/min (severe renal impairment)	0	0
≥30 to <50 mL/min (moderate renal impairment)	1	2.7
≥50 to ≤80 mL/min (mild renal impairment)	105	218.4
>80 mL/min (mild renal impairment)	720	1512.7
Total	828	1738.6

nrSPMS		
Renal impairment	**Participants**	**Participant-years**

nrSPMS: includes tolebrutinib 60 mg exposed participants in EFC16645
Exposure calculated as last dose of tolebrutinib 60 mg - first dose of tolebrutinib 60 mg + 1 including open-label treatment
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_pary_byrenal_s_t.sas
OUT=REPORT/OUTPUT/cdc_pary_byrenal_645_s_t_i.rtf (05DEC2024 6:53)
nrSPMS: Non Relapsing Secondary Progressive Multiple Sclerosis.

Table 18 - Duration of exposure to tolebrutinib 60 mg by renal impairment (creatinine clearance at baseline) - RMS safety population

RMS		
Renal impairment	**Participants**	**Participant-years**
<30 mL/min (severe renal impairment)	0	0
≥30 to <50 mL/min (moderate renal impairment)	0	0
≥50 to ≤80 mL/min (mild renal impairment)	52	121.6
>80 mL/min (mild renal impairment)	1006	2440.9
Total	1058	2562.5

RMS: includes tolebrutinib 60 mg exposed participants in DRI15928, LTS16004, EFC16033 and EFC16034
Exposure calculated as last dose of tolebrutinib 60 mg (up to interim CSR database lock for LTS16004) - first dose of tolebrutinib 60 mg + 1 including any gaps between DRI15928 and LTS16004
PGM=PRODOPS/SAR442168/OVERALL/ISS_2024/REPORT/PGM/cdc_pary_byrenal_s_t.sas
OUT=REPORT/OUTPUT/cdc_pary_byrenal_rms_s_t_i.rtf (05DEC2024 6:53)
CSR: Clinical Safety Report; RMS: Relapsing forms of Multiple Sclerosis.

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

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

Table 19 - 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
The participant has a history of infection or may be at risk for infection including: • Transplantation (including solid organ, stem cell, and bone marrow transplantation) and/or antirejection therapy; • Progressive multifocal leukoencephalopathy (PML); • Human immunodeficiency virus (HIV); • Active or latent tuberculosis (TB); • Reactivation of hepatitis B and C viruses indicating acute or chronic infection.	Bruton's tyrosine kinase inhibitor are immunomodulators that may have the potential for immunosuppressive effects that could lead to infections or lead to reactivation of viral opportunistic infections/co-infections.	No	Patients with immunocompromised conditions may be at higher risk of (serious) infections, as adequately addressed in summary of product characteristics (SmPC) sections 4.3 (contraindications), 4.4 (warnings and precautions for use), and 4.5 (Interaction with other medicinal products and other forms of interaction). No additional risk minimization activities or additional pharmacovigilance activities are needed.
The presence of psychiatric disturbance or substance abuse as evidenced by: • A history of any psychiatric disease, behavioral condition, or depression requiring hospitalization; • A documented history of attempted suicide or suicidal ideation of category 4 or 5 according to the Columbia Suicide Severity Rating Scale (C-SSRS) Active alcohol use disorder or a history of alcohol or drug abuse.	Precautionary measure given that tolebrutinib crosses the blood brain barrier.	No	The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when tolebrutinib is used according to the product label. The section 4.4 of SmPC appropriately addresses the risk of suicidal ideation and behavior. This exclusion criterion does not meet the level of importance to be retained in missing information.
Conditions that may predispose the patient to excessive bleeding: • A bleeding disorder or known platelet dysfunction; • A platelet count <150 000/µL;	The mechanism for the bleeding events in this class of products is not well understood, with a potential mechanism being the inhibition of collagen-mediated platelet activation,	No	Hemorrhages is an important potential risk. The sections 4.4 and 4.5 of SmPC appropriately address this risk. Exclusion of populations that predispose patients to excessive bleeding are stated in the adverse drug reaction (ADR) section of the

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
• Major surgery within 4 weeks or has planned any elective major surgery; • A history of significant bleeding event including but not limited to cerebral or GI bleeding; • Patients taking concomitant anticoagulant or antiplatelet therapies.	spreading, and aggregation in vitro; however, prolonged bleeding was not observed in a primate model of bleeding.		SmPC. This exclusion criterion does not meet the level of importance to be retained in missing information.
Patients with history of or presence of significant cardiovascular impairment (including Stage III or IV cardiac failure according to New York Heart Association [NYHA] classification).	Not included in the clinical development program as patients with clinically significant cardiovascular disease may affect ability to conduct meaningful safety and efficacy evaluation. The exclusion criterion for patients with cardiac impairment was not related to any cardiovascular toxicity of tolebrutinib, however, cardiovascular toxicity was observed for approved BTKi.	No	Safety profile in this patient population is not expected to be different compared to that of patients without cardiovascular disease. Exposure in this population is not considered to be an area of missing information requiring further characterization since non-clinical safety data did not indicate a potential for cardiovascular toxicity.
Patients with history of or presence of severe renal impairment.	May affect ability to conduct meaningful safety and efficacy evaluation in clinical trials. The exclusion criterion was unrelated to renal toxicity.	No	In BEX16018, an excretion balance/metabolism study, tolebrutinib was weakly excreted in urine (14.0% via the urine compared to 78.0% via the feces). Metabolites were found in the urine, however, no parent compound was quantifiable. In POP16399, a study to evaluate the pharmacokinetic (PK) of tolebrutinib in severely renal impaired (without dialysis), participants versus matched participants with normal renal function, following a single oral dose of 60 mg tolebrutinib under fed conditions, total and unbound AUC increased by a maximum of 64% and 21% for tolebrutinib and M2, respectively in the renal impaired group. The use of tolebrutinib 60 mg was not

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			evaluated in patients with severe renal impairment requiring dialysis. In addition, the likelihood of patients experiencing renal impairment requiring dialysis is considered low in the MS population, given that studies report a prevalence of renal disease in MS patients ranging from 0.74% to 2.49% and renal failure occurring in 0% to 0.78%. (33) (34) (35) Therefore, given the weak renal excretion observed in the Phase 1 study and low incidence of patients with MS leading to renal failure, this exclusion criteria does not meet the level of importance to be retained as missing information. As per SmPC Section 4.2 and 5.2, there is very limited data in patients with severe renal impairment (<30 mL/min creatinine clearance) and participants requiring dialysis were not studied. There are no data in patients on dialysis. No dose adjustment is required for patients with mild or moderate renal impairment.
Patients with hepatic impairment or risk factors including: • Acute liver disease, cirrhosis, chronic liver disease (unless considered stable for >6 months); • Alanine Transaminase (ALT) >1.5 x Upper Limit of Normal (ULN) OR Aspartate Aminotransferase (AST) >1.5 x ULN OR alkaline phosphatase >2 x ULN (unless caused by non-liver-related disorder or explained by a stable chronic liver disorder) OR total bilirubin >1.5 x ULN (unless due to Gilbert syndrome or non-liver-related disorder);	Liver injury has been observed in other BTKi (class effect). Patients with pre-existing liver conditions may be susceptible to drug induced liver injury.	No	Drug-induced liver injury (DILI) is an important identified risk. Patients with moderate to severe hepatic impairment, as well as patients with baseline serum ALT or AST greater than 1.5 x ULN, alkaline phosphatase greater than 2 x ULN (unless explained by a stable chronic liver disorder) or total bilirubin greater than 1.5 x ULN (unless due to Gilbert syndrome or non-liver-related disorder), are contraindicated from tolebrutinib use (SmPC Section 4.3). Per the SmPC Section 4.2, no dosage adjustment is necessary for patients with mild hepatic impairment based on Study POP16398 in participants with

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
• Elevated transferrin saturation (>50% in males and >40% in females) and/or with elevated ferritin levels >500 µg/L; • Current alcohol intake >2 drinks per day for men and >1 drink per day for women.			mild hepatic impairment, showing no clinically significant difference in tolebrutinib and M2 exposures between participants with mild hepatic impairment and those with normal hepatic function, although caution must be exercised when initiating treatment in these patients.
Patients receiving concomitant potent and moderate inducers of cytochrome P450 (CYP) 3A or potent inhibitors of CYP2C8 hepatic enzymes.	These medications were excluded given the potential for drug interactions that would potentially confound the efficacy and safety assessments of the trial.	No	Drug interactions have been well characterized in two PK studies (Studies INT16726 and INT16385). In study INT16726: • Repeated administration of gemfibrozil (a potent CYP2C8 inhibitor) 600 mg, twice daily with a single dose of 60 mg tolebrutinib under fed conditions increased the AUC values of tolebrutinib by 8.4-fold while M2 AUC values decreased by 25-fold. • Repeated administration of rifampicin (a potent CYP inducer) 600 mg, once daily with a single 60 mg dose tolebrutinib under fed conditions, decreased the AUC values of tolebrutinib and M2 by 6.2- and 1.9-fold, respectively. In study INT16385: • Repeated administration of itraconazole 200 mg once daily with a single 60 mg dose of tolebrutinib under fed conditions increased tolebrutinib AUC and Cmax by 1.78- and 1.88-fold, respectively; and M2 AUC and Cmax by 1.64- and 1.37-fold, respectively. • Repeated administration of pantoprazole 40 mg twice daily with a single 60 mg dose of tolebrutinib under fed conditions did not increase the AUC of tolebrutinib (no

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			change) and M2 (slight decrease by 14%), but decreased the Cmax of tolebrutinib and M2 by 34% and 39%, respectively. These drug interactions are captured in SmPC Sections 4.2, 4.4 and 4.5. This exclusion criterion does not meet the level of importance to be retained in missing information. No additional risk minimization activities or additional pharmacovigilance activities are needed.
A female patient who is pregnant or breastfeeding.	Excluding pregnant or breastfeeding females is a standard precautionary measure that is often applied in clinical trials.	No	There is limited clinical data available for the use of tolebrutinib in pregnancy and breastfeeding. No additional risk minimization activities or additional pharmacovigilance activities are needed to address “Use during pregnancy or breastfeeding”. Therefore this topic does not meet the criterion to be retained as missing information in the RMP. “Use in breastfeeding” and “Reproductive toxicity” will be monitored in future PSURs.
The patient has sensitivity to tolebrutinib or excipients.	Excluding patients with hypersensitivity to the investigational medicinal product is a standard precautionary measure that is often applied in clinical trials.	No	The SmPC section 4.3 contraindicates the use of tolebrutinib in patients with hypersensitivity to tolebrutinib or any of the inactive ingredients listed in section 6.1. Considering this contraindication, use in this patient population is not considered to be relevant for missing information classification.
Pediatric patients (below 18 years)	The target population in the clinical trials were adults ≥18 years.	No	The product is not expected to be used in pediatric patients since the indication targets adults only. Therefore, it does not qualify as missing information, as per good pharmacovigilance practices (GVP) module V.

ADR: Adverse Drug Reaction; ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; AUC: Area Under the Curve; BTKi: Bruton Tyrosine Kinase Inhibitor; C_{max}: Maximum Plasma Concentration; C-SSRS: Columbia Suicide Severity Rating Scale; CYP: Cytochrome P450; DILI: Drug-Induced Liver Injury; GI: Gastrointestinal; GVP: Good Pharmacovigilance Practices; HIV: Human

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale

Immunodeficiency Virus; MS: Multiple Sclerosis; NYHA: New York Heart Association; PSUR: Periodic Safety Update Report; PK: Pharmacokinetic; PML: Progressive Multifocal Encephalopathy; RMP: Risk Management Plan; RMS: Relapsing forms of Multiple Sclerosis; SmPC: Summary of Product Characteristics; TB: Tuberculosis; ULN: Upper Limit of Normal.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or adverse reactions with a long latency that is beyond the study period.

The clinical development programme has at least a probability of 84% to detect ADRs that are uncommon (≥1/1000 to <1/100) or more frequent. Indeed, with approximately 1886 patients exposed in the Phase 2/3 clinical program, the probability to observe at least one occurrence of an adverse event in the tolebrutinib 60 mg group is 95%, if this event truly occurs in at least 0.16% of the population, meaning that adverse events with a frequency greater than 1 in 625 could be detected in the tolebrutinib 60 mg group with a 95% probability.

Cumulative effects are not anticipated due to the short half-life of tolebrutinib and extensive metabolism. Tolebrutinib is extensively metabolized to numerous metabolites (19 metabolites in plasma and 14 metabolites in excreta), which were primarily excreted in feces (MEH099). After single doses up to 300 mg and repeated doses up to 240 mg, the half-life ($t_{1/2}$) values for tolebrutinib and M2 in plasma were similar (4.4 to 6.6 hours) and did not vary according to dose after single and repeated once a day administration, with no accumulation after repeated administration.

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

Table 20 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Excluded from clinical development program. Very limited data are available concerning the use of tolebrutinib in pregnant women. During the conduct of tolebrutinib phase 2 and 3 clinical trials, a total of 48 pregnancies were reported. Of the 48 pregnancies, 36 were reported in female participants during the treatment-emergent period. Of the 36 pregnancies in female participants, 17 were reported in the tolebrutinib arm compared to 18 in teriflunomide. In the blinded study EFC16035 (ongoing study in patients with [PPMS]), there is 1 ongoing pregnancy. In the tolebrutinib arm, there were 3 live birth, 6 elective termination, 4 spontaneous abortion and 4 ongoing pregnancies. The exposure time from

Type of special population	Exposure
	probable date of conception to tolebrutinib discontinuation ranged from 4 to 74 days with an average of 40 days. In the teriflunomide arm, there were 7 live birth, 2 abortions, 5 elective termination, 1 spontaneous abortion and 3 ongoing pregnancies. Among the pregnancies with live birth in both tolebrutinib and teriflunomide arms, there were no malformations identified. Of the 48 pregnancies, 12 were reported in female partners of male participants. Seven (7) were reported in the tolebrutinib arm, 4 were reported in the teriflunomide arm, and 1 was in the blinded study (EFC16035). In the tolebrutinib arm, there were 3 live birth, 2 abortions, and 2 ongoing pregnancies. In the teriflunomide arm, there were 3 live birth and 1 ongoing pregnancy. In the blinded study, there was 1 spontaneous abortion.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities • Patients with hepatic impairment	Study participants with moderate to severe hepatic impairment were not included in MS pivotal studies. POP16398 was a Phase 1 study assessing non MS participants with mild hepatic impairment. A total of 10 study participants were enrolled: 7 study participants with mild hepatic impairment (HI) (Child-Pugh Score - A) and 3 healthy control study participants with normal liver function. The PK population of the study was completed by including 4 matched historical control participants with normal hepatic function from Study POP16399 to ensure the appropriate PK comparison with an equal number of participants in each arm.
• Patients with renal impairment	Tolebrutinib is weakly excreted in urine based on the excretion balance/metabolism study (BEX16018), therefore the PK of tolebrutinib and M2 was assessed in a reduced design phase 1 study (POP16399) with only severe renal impaired population (not on dialysis). POP16399 included a total of 24 non MS study participants: 12 study participants with severe renal impairment (RI) (defined as GFR <30 mL/min, and not requiring dialysis) and 12 healthy control study participants with normal renal function. During the Phase 3 pivotal studies [N = 1886], no participants with severe RI (requiring or not requiring dialysis) were included ;158 (8.4%) participants with mild (≥50 to ≤80 mL/min) or moderate (≥30 to <50 mL/min) renal impairment have been randomized and treated with tolebrutinib. Cumulative exposure of patients with renal impairment in the RMS and nrSPMS trials are provided in Table 16, Table 17 and Table 18.
• Patients with cardiovascular impairment	Study participants with severe cardiac impairment were not included in multiple sclerosis pivotal studies.
• Immunocompromised patients	Study participants with HIV, hepatitis B, hepatitis C, active or latent tuberculosis, transplant and/or antirejection therapy and PML were not included in multiple sclerosis pivotal studies.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not relevant.
Populations with relevant different race and/or ethnic origin	Study TDU16117 was a Phase 1, single-center, randomized, double-blind, placebo-controlled, incomplete block, 3-period crossover, single-dose escalation study to determine the safety, tolerability, and PK of orally administered tolebrutinib tablets in 19 healthy east Asian (Japanese/Chinese/Korean) male participants, using single doses of tolebrutinib at 7.5, 30, and 60 mg.

Type of special population	Exposure

GFR: Glomerular Filtration Rate; HI: Hepatic Impairment; HIV: Human Immunodeficiency Virus; MS: Multiple Sclerosis; N: Total Number of Patient; nrSPMS: Non-Relapsing Secondary-Progressive Multiple Sclerosis; PK: Pharmacokinetic; PML: Progressive Multifocal Leukoencephalopathy; PPMS: Primary Progressive Multiple Sclerosis; RI: Renal Impairment; RMS: Relapsing forms of Multiple Sclerosis.

Pregnant or breastfeeding women were not included in the clinical development program. Very limited data are available concerning the use of tolebrutinib in pregnant or breastfeeding women. However, pregnant and breastfeeding women are part of the target population. The use of tolebrutinib in pregnant or breastfeeding women will be monitored in future PSURs.

Patients with moderate to severe hepatic impairment were not included in the MS pivotal studies and are contraindicated to use tolebrutinib in SmPC. Patients with mild hepatic impairment reported no safety patterns and tolebrutinib was well tolerated in Phase 1 study POP16398 in non-MS participants with mild hepatic impairment. No dosage adjustment is necessary for patients with mild hepatic impairment although caution must be exercised when initiating treatment in these patients. Therefore, patients with hepatic impairment are not considered missing information.

There is very limited data in patients with severe renal impairment and therefore patients with severe renal impairment should be treated only if the benefit outweighs the risk as stated in SmPC section 4.2 and 5.2. Tolebrutinib has not been studied in patients requiring dialysis. In Phase 1 study POP16399, non-MS participants with severe renal impairment (without dialysis) reported no safety patterns and tolebrutinib was well tolerated. Based on clinical pharmacology studies, tolebrutinib is weakly excreted in the urine. No adjustments are needed in patients with renal impairment. Patients with history of or presence of significant renal impairment (ie, undergoing dialysis) were not included in the MS pivotal studies as their inclusion may affect the ability to conduct meaningful safety and efficacy evaluation. In addition, a low incidence of patients with MS leading to renal failure has been observed. (33) (34) (35) Therefore, patients with renal impairment are not considered missing information.

Patients with mild to moderate cardiovascular impairment were not specifically excluded from tolebrutinib clinical studies. Patients with severe cardiovascular impairment were not included in the MS pivotal studies as patients with clinically significant cardiovascular disease may affect ability to conduct meaningful safety and efficacy evaluation. The exclusion criterion for patients with cardiac impairment was not related to any cardiovascular toxicity of tolebrutinib and the safety profile in this patient population is not expected to be different compared to that of patients without disease burden. Therefore, patients with cardiovascular impairment are not considered missing information.

Patients with HIV, hepatitis B, hepatitis C, active or latent tuberculosis, transplant and/or antirejection therapy and PML were excluded from the MS pivotal studies given that immunomodulating agents are known to have a potential for immunosuppressive effects that could lead to infections or lead to reactivation of viral opportunistic infections/co-infections. Other immunocompromised patients were not specifically excluded from MS pivotal studies. Therefore, immunocompromised patients are not considered missing information.

Patients with a disease severity different from inclusion criteria in clinical trials is not considered relevant for the target population and therefore is not considered missing information.

To date, there is no information to suggest that patients of specific racial or ethnic origins are adversely affected by tolebrutinib. There were no restrictions concerning ethnic origin that were outlined in the clinical protocol and tolebrutinib pharmacokinetics are unlikely to be affected by intrinsic ethnic factors.

To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of tolebrutinib in the currently proposed indication.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

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

PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

A Drug Abuse Liability Assessment (DALA) was performed for tolebrutinib. No evidence of dependence and abuse potential has been observed for tolebrutinib or its major metabolites. No similarities to known drugs of abuse according to chemical structure, mechanism of action, pharmacology, toxicology, and clinical data exist. Therefore, no nonclinical studies (eg, self-administration, drug discrimination) or specific human abuse liability clinical trials were conducted. Given the data demonstrating lack of abuse liability at the proposed therapeutic dose of 60 mg once a day, no risks to the public health because of abuse are anticipated. The current data support the non-scheduling of the drug at the therapeutic indication dose.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

EFC16645 (HERCULES), mentioned in subsequent sections, refers to the pivotal phase 3, randomized, DB, 2-arm, placebo-controlled, parallel group, multicenter study evaluating the effect of 60 mg tolebrutinib once daily compared to placebo in participants with nrSPMS.

Pool A, mentioned in subsequent sections, refers to the pool of safety data from phase 3, pivotal, active-controlled studies in RMS, EFC16033 (GEMINI 1) and EFC16034 (GEMINI 2). This provides an integrated analysis of the two pivotal RMS phase 3 studies including the same dosing regimen and comparator (teriflunomide), and approximately the same treatment duration.

Refer to e-CTD sequence 0000, Module 2.7.4 Summary of Clinical Safety.

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

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

- Pharmacological class effect common to other members of the pharmacological class not thought to be an important identified or potential risk with tolebrutinib:
  - Cytopenia
    - Neutropenia: In EFC16645, a similar incidence of neutropenia events was observed between tolebrutinib (12 participants, 1.6%) compared to placebo (8 participants, 2.1%). For patients treated with tolebrutinib, all events were non-serious, Grade 1 or 2 intensity and participants had recovered. In Pool A, a higher incidence of neutropenia events was observed in teriflunomide (92 participants, 9.8%) compared to tolebrutinib (24 participants, 2.6%). A low, similar rate of severe (Grade 3 or higher) neutropenia events was observed between tolebrutinib (0.7%) and teriflunomide (0.7%). All Grade 3 or higher events were non-serious and had recovered. In the tolebrutinib arm, no participants had an infection associated with neutropenia in EFC16645, and 5 out of 554 participants who experienced infections had concurrent neutropenia or leukopenia in pool A.
    - Thrombocytopenia: From study EFC16645, a similar incidence of participants experiencing any grade of thrombocytopenia or platelet count decreased was observed in tolebrutinib (4 participants, 0.5%) compared to placebo (2 participants, 0.5%). For participants treated with tolebrutinib, all events were non-serious, Grade 1 or 2 intensity and participants had recovered. Among participants treated with tolebrutinib, one asymptomatic participant met the threshold for the adverse event of special interest (AESI): thrombocytopenia (platelet count $<75 \times 10^9$/L, (Common Terminology Criteria for Adverse Events [CTCAEs] grade 2 or higher). The event was not associated with hemorrhage and was considered not related to the investigational medicinal product (IMP) by the Investigator. The event resolved after study intervention interruption without corrective treatment. For Pool A, a similar

incidence of participants experiencing any grade of thrombocytopenia or platelet count decreased was observed in tolebrutinib (4 participants, 0.4%) compared to teriflunomide (3 participants, 0.3%). For patients treated with tolebrutinib, all events were non-serious, Grade 1 or 2 intensity and all participants had recovered. For AESI of thrombocytopenia (platelet count <75 x 10^9/L), no events were reported in either treatment arm.

- Anemia: In EFC16645, a higher incidence of anemia events was observed in tolebrutinib (16 participants, 2.1%) compared to placebo (2 participants, 0.5%). A majority of anemia events were mild-to-moderate and non-serious. A low incidence of severe anemia events (4 participants, 0.5%) was observed for participants treated with tolebrutinib. All severe anemia events were non-serious and participants recovered. Similarly, in Pool A, a higher incidence of anemia events was observed in tolebrutinib (37 participants, 4.0%) compared to teriflunomide (16 participants, 1.7%). A majority of anemia events were Grade 1 or 2 intensity (35/37 participants) and recovered (27/37 participants). There is no imbalance seen in severe anemia events (Grade 3 and above, incidence 0.2% in tolebrutinib compared to 0.1% in teriflunomide) in Pool A. Both participants with severe anemia in tolebrutinib arm had events that were non-serious. One event had recovered while one had not recovered at time of last contact. None of the events led to study intervention discontinuation. The majority of anemia events reported were in female participants <45 years of age (of reproductive age) and likely related to other factors including the ADR of heavy menstrual bleeding.
- It is important to note that tolebrutinib is not indicated in patients with oncological diseases (hematological malignancies), who may have a higher risk of developing neutropenia, thrombocytopenia or anemia. Although anemia was observed at a higher incidence in tolebrutinib arms, a majority of events were mild and self-limiting.
- The risk is not considered as an important risk for the RMP of tolebrutinib since routine risk minimization measures and routine pharmacovigilance activities appropriately address this topic.

- Other reasons for considering the risks not important:
  - Drug-drug interactions (CYP interactions):
    - Given the in vitro characterizations and completed clinical interactions studies, it is confirmed that drug-drug interactions with tolebrutinib does not qualify as an important risk since it will not require additional pharmacovigilance activities or risk minimization activities beside routine measures. As such it is not listed as a safety concern in the RMP. It is appropriately described in SmPC.

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

Risk considered important for inclusion in the RMP list of safety concerns:

- Important identified risks:
  - Drug-Induced Liver Injury (DILI)

  - Serious Infections

- Important potential risks:
  - Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)
  - Malignancies
  - Haemorrhages

The following topics are considered missing information in the RMP:

- None

Table 21 - Important identified risk considered for inclusion in the list of safety concerns: Drug-Induced Liver Injury (DILI)

Drug-Induced Liver Injury (DILI)	
Scientific evidence that has led to the inclusion	Clinical trial data for tolebrutinib Data from other BTK inhibitors.
Risk-benefit impact	Drug-induced liver injury (DILI) has been observed in tolebrutinib clinical trials and is considered an important identified risk. One patient developed liver failure requiring a liver transplant and had a fatal outcome due to a post operative complication. In tolebrutinib clinical trials, liver injury was time-delimited and manageable with appropriate monitoring, including weekly liver monitoring during the high-risk period. Considering that: • The overall incidence of liver injury is 4.6% (AESI of ALT >3 × ULN among tolebrutinib exposed participants) in pivotal Phase 3 studies for tolebrutinib and the incidence of serious cases is 0.5% (treatment emergent serious adverse event (SAE) among tolebrutinib exposed participants); and • Risk minimization measures, including educational materials for prescribers and patients, specifically address this risk with reminder of the need for monitoring for the first 24 months (including close monitoring for the high-risk window of the first 12 weeks after starting therapy); The benefit-risk balance is positive in conjunction with implementation of appropriate measures to characterize this risk.

AESI: Adverse Event of Special Interest; ALT: Alanine Transaminase; BTK: Bruton Tyrosine Kinase; DILI: Drug-Induced Liver Injury; SAE: Serious Adverse Event; ULN: Upper Limit of Normal.

Table 22 - Important identified risk considered for inclusion in the list of safety concerns: Serious Infections

Serious Infections	
Scientific evidence that has led to the inclusion	Non-clinical studies: TDAR findings of decreased IgG and IgM were observed in non-clinical studies with tolebrutinib ([see Part II Module SII] for more details). Clinical trial data for tolebrutinib. Data from other BTK inhibitors.
Risk-benefit impact	Serious infections have been observed in tolebrutinib clinical trials and is considered an important identified risk.

Serious Infections	
	In completed MS tolebrutinib clinical trials, no serious infections led to a fatal outcome and no imbalance was observed for opportunistic infections. Since the cut-off of this dossier, one fatal case of pneumonia (bacterial) occurred in a participant from the Long-term safety study, LTS17043, for which, based on the information provided, the causal role of tolebrutinib cannot be fully excluded. However, multiple factors may have contributed to this outcome, including a delay in patient seeking care for symptoms, and the timeliness and choice of appropriate work-up and treatment for pneumonia and sepsis during this participant's hospitalization. In addition, in EFC17262 (myasthenia gravis study), there was 1 participant with an SAE of COVID-19 pneumonia leading to death in the tolebrutinib arm assessed as not related to the study intervention by the Investigator. The overall benefit-risk profile remains favorable.

BTK: Bruton Tyrosine Kinase; COVID-19: Coronavirus Disease-2019; Ig: Immunoglobulin; MS: Multiple Sclerosis; SAE: Serious Adverse Event; TDAR: T-Cell Dependent Antibody Response.

Table 23 - Important potential risk considered for inclusion in the list of safety concerns: Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)

Scientific evidence that has led to the inclusion	Clinical trial data for tolebrutinib Data from other BTK inhibitors.
Risk-benefit impact	Atrial arrythmias were observed at a low frequency, but there was a small numerical imbalance observed for atrial fibrillation and atrial flutter. In tolebrutinib clinical trials, all reported events were mild-to-moderate in intensity and resolved with no sequelae or complications. Given the biological plausibility and potential class effect for all BTK inhibitors, atrial arrythmias (atrial fibrillation and flutter) is considered as an important potential risk. However, the overall benefit-risk profile remains favorable.

BTK: Bruton Tyrosine Kinase.

Table 24 - Important potential risk considered for inclusion in the list of safety concerns: Malignancies

Malignancies	
Scientific evidence that has led to the inclusion	Data from other BTK inhibitors.
Risk-benefit impact	There does not appear to be an increased risk of malignancy with tolebrutinib in the clinical trial experience. As no evidence of a causal association between tolebrutinib and the development of malignancies has been identified, no impact on the risk-benefit balance of the product is currently considered.

BTK: Bruton Tyrosine Kinase.

Table 25 - Important potential risk considered for inclusion in the list of safety concerns: Haemorrhages

Haemorrhages	
Scientific evidence that has led to the inclusion	Non-clinical studies: Haemorrhages noted in rats and dogs ([see Part II Module SII] for more details). Clinical trial data for tolebrutinib. Data from other BTK inhibitors.
Risk-benefit impact	There was no imbalance observed in the AESI of moderate to severe hemorrhagic events in both Study EFC16645 and pool A. Imbalances were observed for nonserious and mild hemorrhagic events. None of these events were associated with thrombocytopenia. Given the biological plausibility and class effect for all BTK inhibitors, haemorrhages is considered as an important potential risk. The overall benefit-risk profile remains favorable.

AESI: Adverse Event of Special Interest; BTK: Bruton Tyrosine Kinase.

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 for RMP inclusion have been determined for tolebrutinib:

- Important identified risks:
  - Drug-Induced Liver Injury (DILI)
  - Serious Infections
- Important potential risk:
  - Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)
  - Malignancies
  - Haemorrhages
- Missing information:
  - None

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

Table 26 - Important Identified risk: Drug-Induced Liver Injury (DILI)

Important Identified Risk	Drug-Induced Liver Injury (DILI)
Potential mechanism	The exact mechanisms are unknown however, it may be related to an underlying BTKi induced idiopathic immune response.

Important Identified Risk	Drug-Induced Liver Injury (DILI)
Evidence source(s) and strength of evidence	Clinical trial data for tolebrutinib. Data from other BTK inhibitors.
Characterization of the risk	Frequency: In non-clinical studies, no liver toxicity has been observed at any tested dose in any species. In Phase 2 DRI15928, 1 participant each in tolebrutinib 30 and 60 mg arms had a moderate and mild ALT >3 × ULN, respectively. Both cases were non-serious, tolebrutinib treatment was continued and participants resolved. In Phase 2 LTS16004, AESI of 'increased ALT >3 × ULN' was reported in 7 participants, including 1 participant with serious cholelithiasis. All participants recovered from events and a majority (6 out of 7) of participants remained on tolebrutinib treatment. Overall, in both Study EFC16645 and pool A, AESI of ALT >3 × ULN was observed in 4.6% of tolebrutinib exposed participants. In Study EFC16645, the percentage of participants with treatment-emergent AESI of increase of ALT >3 × ULN was higher in the tolebrutinib arm compared to the placebo arm (3.6 versus 1.3%, respectively), while in pool A the incidence was similar between study intervention arm (5.5% in the tolebrutinib group and 5.2% in the teriflunomide arm). Severity and nature of risk: In EFC16645, 44% (12 out of 27) of the AESI 'Increased ALT >3 x ULN' were Grade 3 or above. According to the Hepatology Assessment Committee (HAC), in 2 participants in the tolebrutinib arm and none in the placebo arm, the HAC assessed Hy's law cases as probably related. In Pool A, 49% (25 out of 51) of the AESI 'Increased ALT >3 x ULN' were Grade 3 or above. In 2 participants in the tolebrutinib arm and none in the teriflunomide arm, the HAC assessed Hy's law cases as probably or possibly related. Seriousness and outcome: In EFC16645, most of the events of AESI ALT > 3 x ULN were non-serious (24 out of 27). Most of the events resolved (except the treatment-emergent adverse event (TEAE) leading to death and 1 participant with nonserious Grade 2 alanine aminotransferase increased that did not recover). In Pool A, most of the events of AESI ALT > 3 x ULN were non-serious (45 out of 51). Most of the events resolved (48 out of 51). One participant with Grade 2 transaminase increase was recovering at time of last contact and two participants with events Grade 3 Alanine aminotransferase increased did not recover at time of last contact. None of the participants died due to AESI of increased ALT >3 x ULN. For cases determined to be possibly or probably related to IMP by the HAC,16 of 17 participants in the tolebrutinib arm experienced an onset of ALT increase within the first 90 days after treatment initiation (outlier at Day 757). Background incidence/prevalence: The general population incidence of DILI is 12-24 per 100 000 person-years. (36)(37)(38)(39) In MS patients untreated with any disease-modifying drugs, the crude rate of acute liver injury is about 68 per 100 000 person-years. (40) Multiple Sclerosis therapeutics have been associated with hepatoxicity to varying extents. (41) Impact on individual patient: May be fatal, life-threatening or result in liver transplantation.

Important Identified Risk	Drug-Induced Liver Injury (DILI)
Risk factors and risk groups	Risk Groups: Unknown. Patient or group factors for liver injury are unknown. The primary period for risk appears to be within the first 3 months of exposure to tolebrutinib. No additive or synergistic factors have been identified. While all occurrences have occurred with 60 mg daily dosing, no clear dose-related risks have been established. Concomitant use of tolebrutinib with other hepatotoxic products especially during the first 12 weeks of administration should be undertaken with caution, and alternative options for those drugs should be considered if possible. The use of herbal or dietary supplements with potential hepatotoxicity should be avoided during tolebrutinib treatment.
Preventability	The predictability of DILI is unknown. Tolebrutinib is contraindicated inpatients with baseline serum ALT greater than 1.5 times ULN or AST greater than 1.5 times ULN or alkaline phosphatase greater than 2 times ULN (unless caused by non-liver-related disorder or explained by a stable chronic liver disorder) or total bilirubin greater than 1.5 times ULN (unless due to Gilbert syndrome or non-liver-related disorder). Avoid use of herbal supplements with potential hepatoxicity during tolebrutinib treatment. The ability to minimize or mitigate serious outcomes is done through early detection of liver injury via clinical symptoms and laboratory testing and the prompt discontinuation of any potential hepatotoxic agents including tolebrutinib.
Impact on the benefit-risk balance of the product	The benefit-risk balance is positive in conjunction with implementation of appropriate measures to characterize (see [RMP Part III]) and minimize this risk (see [RMP Part V]).
Public health impact	Considering that: • The overall incidence of liver injury is 4.6% (AESI of ALT >3 × ULN among tolebrutinib exposed participants) in pivotal Phase 3 studies for tolebrutinib and the incidence of serious cases is 0.5% (treatment emergent SAE among tolebrutinib exposed participants); and • Risk minimization measures, including educational materials for prescribers and patients, specifically address this risk with reminder of the need for monitoring for the first 24 months (including close monitoring for the high-risk window of the first 12 weeks after starting therapy); The benefit-risk balance is positive in conjunction with implementation of appropriate measures to characterize this risk.

AESI: Adverse Event of Special Interest; ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; BTK: Bruton Tyrosine Kinase; BTKi: Bruton Tyrosine Kinase Inhibitor; DILI: Drug-Induced Liver Injury; HAC: Hepatology Assessment Committee; IMP: Investigational Medicinal Product; MS: Multiple Sclerosis; SAE: Serious Adverse Event; TEAE: Treatment-Emergent Adverse Event; ULN: Upper Limit of Normal.

Table 27 - Important Identified risk: Serious Infections

Important Identified Risk	Serious Infections
Potential mechanism	Tolebrutinib is an immunomodulator of B-cells and innate immune cells, which has been associated with a potential increased risk of infection.
Evidence source(s) and strength of evidence	Non-clinical studies. Clinical trial data for tolebrutinib. Data from other BTK inhibitors.

Important Identified Risk	Serious Infections
Characterization of the risk	Frequency: In non-clinical studies, decreased IgG/IgM response to antigen and absolute counts/relative proportions of B cells (CD21+) were observed in animals (see Table 9). Study EFC16645: Incidence rates of treatment-emergent infections were higher in tolebrutinib (54.4%) compared with placebo (49.3%) arm. Pool A: Incidence rates of treatment-emergent infections were similar between tolebrutinib (59.4%) and teriflunomide (58.1%) arms. Severity and nature of risk: EFC16645: Majority of infections were mild to moderate in severity and participants recovered without change to tolebrutinib treatment. Severe treatment-emergent infections that met AESI criteria (CTCAE Grade 3 or higher) occurred in 5.2% of participants in tolebrutinib arm and in 2.9% of participants in the placebo arm. There were 5 grade 4 events reported in 4 participants: COVID-19 pneumonia and urinary tract infection in one participant, pneumonia pneumococcal, pneumonia, and COVID-19 pneumonia. All 4 participants recovered from the events. There were no grade 5 infections reported. Pool A: Majority of infections were mild to moderate in severity and participants recovered without change to tolebrutinib treatment. Severe treatment-emergent infections that met AESI criteria (CTCAE Grade 3 or higher) occurred in 2.3% of participants in tolebrutinib arm and in 1.9% of participants in the teriflunomide arm. There were no grades 4 or 5 infections reported in the tolebrutinib arm. Since the cut-off of this dossier, one fatal case of pneumonia (bacterial) occurred in a participant from the Long-term safety study, LTS17043, for which, based on the information provided, the causal role of tolebrutinib cannot be fully excluded. However, multiple factors may have contributed to this outcome, including a delay in patient seeking care for symptoms, and the timeliness and choice of appropriate work-up and treatment for pneumonia and sepsis during this participant's hospitalization. Seriousness and outcome: Study EFC16645: Incidence rates of treatment-emergent serious infections that met AESI criteria (CTCAE Grade 3 or higher) were higher in tolebrutinib (4.8%) compared with placebo (2.9%). In the majority of participants (36 out of 39 participants and in the tolebrutinib arm and all participants in the placebo arm) the event of severe infection was assessed as serious, mainly because they required hospitalization. The percentage of participants with treatment-emergent AESI of severe infection leading to study intervention discontinuation was low and similar between arms (0.1% in the tolebrutinib arm and 0.8% in the placebo arm). Most of the TEAEs resolved for participants (35 out of 39) while 2 participants resolved with sequelae and 2 participants had not recovered at time of last contact. None of the serious infections led to a fatal outcome. Pool A: Incidence rates of treatment-emergent serious infections that met AESI criteria (CTCAE Grade 3 or higher) were similar between tolebrutinib (1.9%) and teriflunomide (1.6%) arm. The number of participants with AESI leading to study intervention discontinuation was low (1 participant in the tolebrutinib arm and none in the teriflunomide arm). Most of the TEAEs resolved for participants (14 out of 17) while 3 participants resolved with sequelae. None of the serious infections led to a fatal outcome.

Important Identified Risk	Serious Infections
	Background incidence/prevalence: Multiple sclerosis patients untreated with any disease-modifying drugs are hospitalized for infections at a rate of 18.1-58.3 per 1000 person-years. (40)(42)(43)(44) The risk of hospitalized infection is 2-3 x increased in MS patients compared to the general population. (42)(43)(44)(45)(46) Impact on individual patient: May be life-threatening or result in hospitalization.
Risk factors and risk groups	No risk factors have been identified for serious infections occurring in patients being treated with tolebrutinib.
Preventability	Predictability is unknown. Tolebrutinib is contraindicated in patients with severe immunodeficiency (eg, acquired immunodeficiency syndrome [AIDS]), bone marrow disease, or severe, uncontrolled active infections (See SmPC Sections 4.3, 4.4 and 4.8). The use of live attenuated or live vaccines may carry a risk of infections and must therefore be avoided. Patients with active acute or chronic infections must not start treatment until the infection is resolved. Patients should be treated for signs and symptoms of infection, evaluated promptly, and treated appropriately.
Impact on the benefit-risk balance of the product	Serious infections may have an impact on the risk-benefit due to potentially severe or life-threatening outcomes. However, a large number of events observed in clinical trials involved COVID-19 infection due to the pandemic. The benefit-risk balance remains positive.
Public health impact	Considering that • The overall incidence of serious infections was higher in EFC16645 (4.8% in tolebrutinib arm versus 1.9% in placebo) and comparable in Pool A (1.9% in tolebrutinib arm versus 1.6% in teriflunomide). • This risk can be managed as part of routine standard of care. The public health impact is considered limited.

AESI: Adverse Event of Special Interest; AIDS: Acquired Immunodeficiency Syndrome; BTK: Bruton Tyrosine Kinase; CD: Cluster of Differentiation; COVID-19: Coronavirus Disease-2019; CTCAE: Common Terminology Criteria for Adverse Events; IG: Immunoglobulin; MS: Multiple Sclerosis; SmPC: Summary of Product Characteristics; TEAE: Treatment-Emergent Adverse Event.

Table 28 - Important Potential risk: Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)

Important Potential Risk	Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)
Potential mechanism	The pathological mechanism of atrial arrhythmia is not fully understood but has been potentially related to off target binding for other approved BTK inhibitors. (47)
Evidence source(s) and strength of evidence	Clinical trial data for tolebrutinib. Data from other BTK inhibitors.
Characterization of the risk	Frequency: Study EFC16645: Under AESI atrial arrhythmia, Atrial fibrillation was reported in 3 participants (0.4%) receiving tolebrutinib. Pool A: Under AESI atrial arrhythmia, Atrial flutter was reported in 1 participant (0.1%) on tolebrutinib.

Important Potential Risk	Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)
	Severity and nature of risk: EFC16645: Under AESI atrial arrhythmia, one atrial fibrillation event was Grade 2, while two atrial fibrillation events were Grade 3. Pool A: One atrial flutter event was Grade 2. Seriousness and outcome: Study EFC16645: Investigational medicinal product was temporarily interrupted in 1 participant, however, the event was assessed as not related to IMP by the investigator. All 3 participants recovered with no sequelae or complications reported. Pool A: The participant with atrial flutter recovered with no sequelae or complications reported. Background incidence/prevalence: Atrial fibrillation is prevalent in 0.4-1.0% of the United States (US) general population. (26)(48) Multiple sclerosis patients have approximately 2x greater prevalence of comorbid cardiac arrhythmias. (49)(50)(51) Impact on individual patient: May result in hospitalization.
Risk factors and risk groups	No risk factors have been identified for atrial arrythmias (atrial fibrillation and atrial flutter) occurring in patients being treated with tolebrutinib.
Preventability	Predictability is unknown.
Impact on the benefit-risk balance of the product	Atrial arrythmias (atrial fibrillation and atrial flutter) may have an impact on the risk-benefit due to potentially severe clinical consequences including shock, cardiac arrest and thromboembolic events. In tolebrutinib MS pivotal studies, atrial fibrillation and atrial flutter events were observed at a low frequency and were manageable. The benefit-risk balance is considered positive.
Public health impact	Overall, there was no significant difference in the risk of atrial fibrillation/atrial flutter among tolebrutinib participants in the Study EFC16645 and Pool A compared to a reference group of MS participants identified in Sweden (Standardized Incidence Ratio [SIR] = 1.59, 95% CI: 0.41-3.52); and also compared to Swedish population controls (SIR = 1.18, 95% CI: 0.31-2.62). (52) Most events were mild to moderate, manageable and did not result in sequelae or complications. Thus, no impact on public health is anticipated.

AESI: Adverse Event of Special Interest; BTK: Bruton Tyrosine Kinase; CI: Confidence Interval; IMP: Investigational Medicinal Product; MS: Multiple Sclerosis; SIR: Standardized Incidence Ratio; US: United States.

Table 29 - Important Potential risk: Malignancies

Important Potential Risk	Malignancies
Potential mechanism	There is no clear mechanism linking BTK inhibitors with subsequent development of malignancies.
Evidence source(s) and strength of evidence	Data from other BTK inhibitors and immunomodulators.
Characterization of the risk	Frequency: The incidence of malignancies reported in completed Phase 3 RMS and nrSPMS clinical trials was 1.2% (21/1685, experiencing 22 events, incidence ratio [IR]: 5.3

Important Potential Risk	Malignancies

per 1000 person-years) in the tolebrutinib group, compared to 0.9% (8/939, IR: 3.7 per 1000 person-years) in teriflunomide and 0.5% (2/375, IR: 2.7 per 1000 person-years) in the placebo group. In the pooled RMS studies, 9/933 (1.0%) participants experienced malignancy cases in the tolebrutinib group (IR: 4.1 per 1000 person-years). In study EFC16645 (nrSPMS), malignancies occurred in 12/752 (1.6%) tolebrutinib-treated patients (IR: 6.9 per 1000 person-years).

Malignancies were distributed across various anatomical locations with the most common being breast cancer (8/22, 36.4%), and 2 participants experiencing each of the following: bladder, hematological, renal and skin cancers. The remaining malignancies were reported as single occurrences.

As shown in [Table 29a] below, the analysis on observed versus expected cases of malignancies in study participants treated with tolebrutinib, the observed number of cases seen in tolebrutinib-treated participants is comparable to the expected rate in an MS population.

Table 29a - Observed number of malignancies among tolebrutinib-treated participants in the pooled Completed Phase 3 Studies versus expected number of malignancies

Reference population	Incidence Rate Tolebrutinib Population	Incidence Rate Reference Population	Observed Number of Participants with a Malignancy	Expected Number of Participants with a Malignancy	SIR (95% CI)
Fois, 2010, UK (53)	0.005332	0.00757	21	29.81	0.70 (0.44, 1.04)
Sun, 2013, Taiwan (54)	0.005332	0.00529	21	20.83	1.01 (0.62, 1.49)
Nørgaard, 2019, Denmark (55)	0.005332	0.00576	21	22.68	0.93 (0.57, 1.36)
Castelo-Branco, 2020, Sweden (56)	0.005332	0.00585	21	23.04	0.91 (0.56, 1.34)
Grytten, 2021, Norway (57)	0.005332	0.00507	21	19.97	1.05 (0.65, 1.55)
Kuiper, 2022, The Netherlands (58)	0.005332	0.00473	21	18.63	1.13 (0.70, 1.66)
Mariottini, 2022, Italy (59)	0.005332	0.00400	21	15.75	1.33 (0.82, 1.96)
Greenfield, 2023, Canada (60)	0.005332	0.00576	21	22.68	0.93 (0.57, 1.36)
Pierret, 2024, France (61)	0.005332	0.00799	21	31.47	0.67 (0.41, 0.98)

CI: Confidence Interval; SIR: Standardized Incidence Ratio; UK: United Kingdom.

Severity and nature of risk:

Among malignancies in tolebrutinib-treated participants across all studies, 1/22 (4.5%) event was Grade 1, 6/22 (27.3%) were Grade 2, 14/22 (63.6%) were Grade 3, and one case of chronic myeloid leukemia (Grade 4, 4.5%) was reported in EFC16645. No Grade 5 malignancies were reported.

Seriousness and outcome:

Important Potential Risk	Malignancies
	Among malignancies in tolebrutinib-treated participants across all studies,18/22 (81.8%) were reported as serious adverse events, while 4/22 (18.2%) were non-serious. Six of 22 (27.3%) events had recovered, 1/22 (4.5%) was recovering, and 15/22 (68.2%) had not recovered at the time of the last follow-up. There were no fatal cases reported. Background incidence/prevalence: Refer to [Table 29a] above. Impact on individual patient: The impact of malignancy on individual patients varies considerably depending on the type, stage, and location of the malignancy, as well as patient-specific factors such as age, comorbidities, and overall health status. Malignancies may significantly impact treatment decisions for the underlying condition, potentially requiring temporary or permanent discontinuation of immunomodulatory therapies.
Risk factors and risk groups	Based on the available clinical trial data with tolebrutinib, no specific risk factors for malignancies have been identified. In general, cancer risk factors include increasing age, tobacco use, high body mass index, low fruit and vegetable intake, lack of physical activity, alcohol consumption, certain viral and bacterial infections (such as human papillomavirus, hepatitis B and C, and *H. pylori*), exposure to ultraviolet and ionizing radiation, and various environmental and occupational exposures to carcinogens. (62)
Preventability	Healthcare providers should ensure that patients remain current with age-appropriate cancer screening programs, as recommended by local health authorities.
Impact on the benefit-risk balance of the product	Malignancies may have an impact on the risk-benefit balance due to their potentially serious outcomes. However, in tolebrutinib completed Phase 3 studies, malignancies were reported with an incidence rate of 5.332 per 1000 person-years which is comparable to the rate reported in epidemiological studies of MS populations (ranging from 4.0 to 7.99 per 1000 person-years). The benefit-risk balance remains positive.
Public health impact	Considering that: • The incidence of malignancies in tolebrutinib-treated patients is comparable to rates reported in epidemiological studies of MS populations. • Malignancies were distributed across various anatomical locations with the most common being breast cancer. Breast malignancies are generally detectable through routine screening programs. • Standard cancer screening practices according to national guidelines are considered sufficient for risk management. The public health impact is considered limited.

BTK: Bruton Tyrosine Kinase; CI: Confidence Interval; IR: Incidence Ratio; MS: Multiple Sclerosis; nrSPMS: Non-Relapsing Secondary-Progressive Multiple Sclerosis; RMS: Relapsing Forms of Multiple Sclerosis; SIR: Standardized Incidence Ratio; UK: United Kingdom.

Table 30 - Important Potential risk: Haemorrhages

Important Potential Risk	Haemorrhages
Potential mechanism	BTK inhibitors can cause bleeding by inhibiting platelet receptors and signaling pathways that are important for platelet activation and adhesion. This effect is mediated by off-target inhibition of BTK, other Tec family kinases, and glycoprotein (GP)Ib. Ibrutinib in particular is hypothesized to induce platelet

Important Potential Risk	Haemorrhages
	receptor shedding of GPIb-IX-V and integrin αIIb β3 involved in the regulation of thrombus formation. (63)
Evidence source(s) and strength of evidence	Non-clinical studies. Clinical trial data for tolebrutinib. Class effect with data from other BTK inhibitors.
Characterization of the risk	**Frequency:** Study EFC16645: Incidence rates of treatment-emergent haemorrhage events under standardized medical dictionary for regulatory activities [MedDRA] query (SMQ) Haemorrhage terms (excl laboratory terms) were higher in tolebrutinib (12.8%) compared with placebo (5.3%) arm. Pool A: Incidence rates of treatment-emergent haemorrhage events under SMQ Haemorrhage terms (excl laboratory terms) were higher in tolebrutinib (16.8%) compared with teriflunomide (8.2%) arm. For both EFC16645 and Pool A, imbalances were observed for nonserious and mild haemorrhagic events while similar rates were observed for moderate to severe haemorrhagic events. **Severity and nature of risk:** Study EFC16645: A majority of bleeding events were mild in severity and participants recovered without change to tolebrutinib treatment. Moderate to severe treatment emergent hemorrhagic events that met AESI criteria (CTCAE grade 2 or above) occurred in 0.8% of participants in the tolebrutinib arm compared to 1.3% of participants in the placebo arm. There were no grade 4 or grade 5 hemorrhagic events reported in the tolebrutinib arm. Pool A: A majority of bleeding events were mild in severity and participants recovered without change to tolebrutinib treatment. Moderate to severe treatment emergent hemorrhagic events that met AESI criteria (CTCAE grade 2 or above) occurred in 2.1% of participants in the tolebrutinib arm compared to 1.7% of participants in the teriflunomide arm. There were no grade 4 or grade 5 hemorrhagic events reported in the tolebrutinib arm. **Seriousness and outcome:** Study EFC16645: Of the 6 (0.8%) participants who experienced AESIs of moderate to severe treatment emergent hemorrhagic events in the tolebrutinib arm, 2 participants had SAEs for which they were hospitalized. Both participants recovered. None of the moderate to severe hemorrhage events led to a fatal outcome. Pool A: Of the 20 (2.1%) participants who experienced AESIs of moderate to severe treatment emergent hemorrhagic events in the tolebrutinib arm, 3 participants had SAEs for which they were hospitalized. All participants recovered. None of the moderate to severe hemorrhagic events led to a fatal outcome in the tolebrutinib arm. **Background incidence/prevalence:** There is limited information available on background rates of hemorrhage in the MS population. Note, patients with MS had an approximately threefold higher risk of hemorrhagic stroke than the general population. (49)(64) **Impact on individual patient:** May be life-threatening or result in hospitalization.
Risk factors and risk groups	Patients with bleeding disorders, known platelet dysfunction, platelet counts below 150000/mcL or when using tolebrutinib concomitantly with anticoagulants, antiplatelet agents, or other medicinal products that may increase bleeding risk.

Important Potential Risk	Haemorrhages
Preventability	Monitor patients more frequently for signs and symptoms of bleeding when concurrent administration of anticoagulant, antiplatelet or other medications that may increase bleeding risk is unavoidable. Before any planned surgery, evaluate whether to stop tolebrutinib for 3 to 7 days before and after the procedure, considering the nature of the surgery and the risk of bleeding. If bleeding occurs, depending on bleeding severity, interrupt or discontinue tolebrutinib and provide appropriate symptomatic treatment.
Impact on the benefit-risk balance of the product	Haemorrhages may have an impact on the risk-benefit due to potentially severe or life threatening outcomes including life-threatening bleeding or shock. In tolebrutinib MS pivotal studies, moderate to severe haemorrhage were observed at a low frequency and were manageable. The benefit risk balance is considered positive.
Public health impact	Considering that: • The overall incidence of moderate to severe hemorrhagic events was similar in EFC16645 and in Pool A. An imbalance was observed in EFC16645 and Pool Afor mild hemorrhagic events. • This risk can be managed as part of routine standard of care. The public health impact is considered limited.

AESI: Adverse Event of Special Interest; BTK: Bruton Tyrosine Kinase; CTCAE: Common Terminology Criteria for Adverse Events; GP: Glycoprotein; MedDRA: Medical Dictionary for Regulatory Activities; MS: Multiple Sclerosis; SAE: Serious Adverse Event; SMQ: Standardized MedDRA Query.

SVII.3.2. Presentation of the missing information

Not applicable

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 31 - Summary of the safety concerns

Important identified risks	Drug-induced liver injury (DILI)
	Serious Infections
Important potential risks	Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)
	Malignancies
	Haemorrhages
Missing information	None

DILI: Drug-Induced Liver Injury.

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

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The safety profile of tolebrutinib 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, product technical complaints (PTCs) relating to adverse events, and signal detection.

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

- Specific adverse reaction follow-up questionnaire for atrial arrhythmias.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance activities include:

- The ongoing LTS17043 clinical trial that will help to better assess and characterize the safety profile of tolebrutinib, including the important risks of drug-induced liver injury (DILI), serious infections, atrial arrhythmias, malignancies, and haemorrhages. Safety data will be pooled across parent studies in the Clinical Study Report to enhance signal detection sensitivity, while PSURs will present data by individual parent study and intervention received. Exposure-adjusted incidence rates for AESIs and SAEs will be presented descriptively and contextualized using external comparator data (eg, observed vs expected analyses) from published epidemiological studies, large electronic healthcare databases, and historical control data from similar MS populations. Further methodological details are provided in [Part VII Annex 3 Part A].
- One post-authorization safety study (PASS) (see details below and synopsis in [Part VII Annex 3]) to measure the effectiveness of the additional risk minimization measures:
  - PASS Adherence to Liver Function Monitoring

Table 32 - Additional pharmacovigilance activities (category 1 to 3) summary

LTS17043 - An Interventional, Phase 3 Extension Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants with Relapsing Multiple Sclerosis, Primary Progressive Multiple Sclerosis, or Nonrelapsing Secondary Progressive Multiple Sclerosis (category 3)
Study short name and title
LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.
Rationale and study objectives
To determine the long-term safety and tolerability of tolebrutinib in participants with RMS and progressive multiple sclerosis (PMS).

Study design
This is a Phase 3 extension, global, multicenter, open Label study to assess the long-term safety and tolerability of tolebrutinib in adult participants (aged ≥18 years) with RMS, PPMS, or nrSPMS who were previously enrolled in the Phase 2b LTS16004 study or 1 of the 4 Phase 3 tolebrutinib pivotal studies (GEMINI 1 [EFC16033], GEMINI 2 [EFC16034], HERCULES [EFC16645], or PERSEUS [EFC16035]).
Study populations
Participants with RMS, PPMS, or nrSPMS who completed the Phase 2b LTS16004 study or 1 of the 4 Phase 3 pivotal tolebrutinib studies (EFC16033, EFC16034, EFC16645, EFC16035) on IMP. OR
Participants in the Phase 2b LTS16004 study or in 1 of the 4 Phase 3 tolebrutinib pivotal study who temporarily discontinued IMP due to a national emergency and completed the study visits.
Milestones
Interim data reported in PSUR
Final report: 2031[a]

ToleAdhere - A Post-Authorisation Safety Study (PASS) To Assess Adherence To Liver Function Monitoring Among Multiple Sclerosis Patients Taking Tolebrutinib (category 3)

Study short name and title
ToleAdhere - Adherence to Liver Function Monitoring.
Rationale and study objectives
To describe adherence to liver function monitoring, and the incidence and severity of DILI, among MS patients who are users of tolebrutinib.
Study design
Descriptive cohort study.
Study populations
Patients identified across real-world data sources that are part of the Big MS Data Network (BMSD), such as Denmark, and potentially other EU countries.
Milestones
Final report of study results: Q1 2033

a Subject to change since milestones for enrolment are dependent on ongoing parent study timelines.

BMSD: Big MS Data Network; DILI: Drug-Induced Liver Injury; EU: European Union; IMP: Investigational Medicinal Product; MS: Multiple Sclerosis; nrSPMS: Non-Relapsing Secondary Progressive Multiple Sclerosis; PASS: Post-Authorisation Safety Study; PMS: Progressive Multiple Sclerosis; PPMS: Primary Progressive Multiple Sclerosis; PSUR: Periodic Safety Update Report; Q: Quarter; RMS: Relapsing forms of Multiple Sclerosis.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 33 - 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				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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				
LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis. Status: Ongoing.	To determine the long-term safety and tolerability of tolebrutinib in participants with RMS and PMS.	• Drug-Induced Liver Injury (DILI) • Serious Infections • Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter) • Malignancies • Haemorrhages	Final report	Interim data in PSUR 2031[a]
ToleAdhere - Adherence to Liver Function Monitoring. Status: Planned.	To describe adherence to liver function monitoring, and the incidence and severity of DILI, among MS patients who are users of tolebrutinib.	Patients' adherence to risk minimization activities for safety concerns pertaining to the risk of DILI.	Final report	Q1 2033

a Subject to change since milestones for enrolment are dependent on ongoing parent study timelines

DILI: Drug-Induced Liver Injury; MS: Multiple Sclerosis; PMS: Progressive Multiple Sclerosis; PSUR: Periodic Safety Update Report; Q: Quarter; RMS: Relapsing forms of Multiple Sclerosis.

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 tolebrutinib.

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

V.1 ROUTINE RISK MINIMIZATION MEASURES

Routine risk minimization measures are in place for the safety risks of this medicinal product as conveyed in the labeling information.

Table 34 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Drug-Induced Liver Injury (DILI)	**Routine risk communication:** • SmPC sections 4.3, 4.4 and 4.8. • Package Leaflet (PL) sections 2 and 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring of liver enzymes and symptoms suggestive of hepatic dysfunction, in SmPC section 4.4 and patient information leaflet (PIL) section 2. **Other routine risk minimization measures beyond the Product Information:** Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS.
Serious Infections	**Routine risk communication:** • SmPC sections 4.3, 4.4, 4.5 and 4.8. • PL sections 2 and 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation to monitor and treat signs and symptoms of infections, in SmPC section 4.4 and PIL section 4. **Other routine risk minimization measures beyond the Product Information:** Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS.
Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)	**Routine risk communication:** • SmPC section 4.4. • PL section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation to monitor signs and symptoms for atrial fibrillation/flutter, and manage as appropriate, in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information:** Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS.
Malignancies	**Routine risk communication:** • SmPC section 4.4. • PL section 2.

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None. **Other routine risk minimization measures beyond the Product Information:** Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS.
Haemorrhages	**Routine risk communication:** • SmPC sections 4.4 and 4.5. • PL section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation to monitor signs and symptoms of bleeding, and manage, as appropriate in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information:** Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS.

DILI: Drug-Induced Liver Injury; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

The table below presents a detailed overview of the educational materials in place to minimize the risk of liver injury.

Table 35 - Additional risk minimization measures

Prescriber Guide	
Objectives	• To educate prescribers on: - The nature of the DILI risk; - The importance on need for adherence to the recommended liver function tests (LFTs) monitoring schedule; - Need to take appropriate actions, as needed, as per liver function test algorithm. • To facilitate a conversation with the patient about DILI. • To remind the prescriber to provide the Patient's Guide to the patient and inform patients that a patient card is included in the pack and that patients should carry this card with them at all times during treatment.
Rationale for the additional risk minimization activity	Considering the nature of DILI and the requirements for LFT monitoring, the rationale is to complement the label and reinforce prescriber's education on some specific information pertaining to the risk of DILI.
Target audience and planned distribution path	**Target audience:** Prescribers eg, neurologists and healthcare professionals (HCPs) experienced in the treatment of MS patients.

	Distribution paths: To be adapted country by country depending on each local situation and public health system: hard copies by mail and/or face to face, electronic format (eg, email, web link, quick response [QR] Code/Uniform Resource Locator [URL]). **Periodicity of the distribution:** One distribution prior to or at launch. Redistribution (eg, once a year, ad-hoc) can occur according to local regulatory requirements or national health systems.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance. PASS ToleAdhere - Adherence to Liver Function Monitoring.
Patient Guide	
Objectives	To educate on: • The nature of the DILI risk; • The importance on need for adherence to the recommended LFT monitoring schedule; • Need to pay attention to certain signs that could indicate potential liver problems, and if these occur, to promptly contact their prescriber.
Rationale for the additional risk minimization activity	Considering the nature of DILI and the requirements for LFT monitoring, the rationale is to complement the label and reinforce patient's education on some specific information pertaining to the risk of DILI.
Target audience and planned distribution path	**Target audience:** Patients. **Distribution paths**: Distribution via prescribing/treating physicians. To be adapted country by country depending on each local situation and public health system: hard copies by mail and/or face to face, electronic format (eg, email, web link, QR Code/URL). **Periodicity of the distribution:** One distribution prior to or at launch. Redistribution (eg, once a year, ad-hoc) can occur according to local regulatory requirements or national health systems.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance. PASS ToleAdhere - Adherence to Liver Function Monitoring.
Patient Card	
Objectives	To educate on: • The seriousness of the DILI risk; • The importance of adherence to the recommended LFT monitoring schedule; • The signs and symptoms that could indicate potential liver problems, and if these occur, to promptly contact their prescriber.
Rationale for the additional risk minimization activity	Reminder to emphasize the serious DILI risk and importance of adherence to LFT monitoring schedule.

Target audience and planned distribution path	**Target audience:** Patients. **Distribution paths**: Included into the pack. **Periodicity of the distribution:** Not applicable since into the pack.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance. PASS ToleAdhere - Adherence to Liver Function Monitoring.

DILI: Drug-Induced Liver Injury; HCP: Healthcare Professional; LFT: Liver Function Test; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; QR: Quick Response, URL: Uniform Resource Locator.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 36 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Drug-Induced Liver Injury (DILI)	**Routine risk minimization measures:** • SmPC sections 4.3, 4.4 and 4.8. • Package Leaflet (PL) sections 2 and 4. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** Educational materials: • Prescriber Guide. • Patient Guide. • Patient Card.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis. • PASS ToleAdhere - Adherence to Liver Function Monitoring.
Serious Infections	**Routine risk minimization measures:** • SmPC sections 4.3, 4.4, 4.5 and 4.8. • PL sections 2 and 4. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)	**Routine risk minimization measures:** • SmPC section 4.4. • PL section 2. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire for atrial arrhythmias. **Additional pharmacovigilance activities:** LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.
Malignancies	**Routine risk minimization measures:** • SmPC section 4.4. • PL section 2. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.
Haemorrhages	**Routine risk minimization measures:** • SmPC sections 4.4 and 4.5. • PL section 2. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.

DILI: Drug-Induced Liver Injury; MS: Multiple Sclerosis; PASS: Post Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Cenrifki (Tolebrutinib)

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

Cenrifki's SmPC and its PL give essential information to HCPs and patients on how Cenrifki should be used.

This summary of the RMP for Cenrifki 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 Cenrifki's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Cenrifki is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (see SmPC for the full indication). It contains tolebrutinib as the active substance and it is given by oral route.

Further information about the evaluation of Cenrifki's benefits can be found in Cenrifki'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

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

Important risks of Cenrifki, together with measures to minimize such risks and the proposed studies for learning more about Cenrifki's risks, are outlined in the next sections.

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 Cenrifki, these measures are supplemented with additional risk minimization measures (aRMMs) mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment 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 Cenrifki 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 Cenrifki. 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 37 - List of important risks and missing information

Important identified risks	Drug-induced liver injury (DILI)
	Serious Infections
Important potential risks	Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)
	Malignancies
	Haemorrhages
Missing information	None

DILI: Drug-Induced Liver Injury.

II.B Summary of important risks

Table 38 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Drug-Induced Liver Injury (DILI)

Drug-Induced Liver Injury (DILI)	
Evidence for linking the risk to the medicine	Clinical trial data for tolebrutinib. Data from other BTK inhibitors.
Risk factors and risk groups	Risk Groups: Unknown. Patient or group factors for liver toxicity are unknown. The primary period for risk appears to be within the first 3 months of exposure to tolebrutinib. No additive or synergistic factors have been identified. While all occurrences have occurred with 60 mg daily dosing, no clear dose-related risks have been established. Concomitant use of tolebrutinib with other hepatotoxic products especially during the first 12 weeks of administration should be undertaken with caution, and alternative options for those drugs should be considered if possible. The use of

Drug-Induced Liver Injury (DILI)	
	herbal or dietary supplements with potential hepatotoxicity should be avoided during tolebrutinib treatment.
Risk minimization measures	**Routine risk minimization measures:** • SmPC sections 4.3, 4.4 and 4.8. • PL sections 2 and 4. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** Educational materials: • Prescriber Guide. • Patient Guide. • Patient Card.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis. • PASS ToleAdhere - Adherence to Liver Function Monitoring.

BTK: Bruton Tyrosine Kinase; MS: Multiple Sclerosis; PASS: Post Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 39 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious Infections

Serious Infections	
Evidence for linking the risk to the medicine	Non-clinical studies. Clinical trial data for tolebrutinib. Data from other BTK inhibitors.
Risk factors and risk groups	No risk factors have been identified for serious infections occurring in patients being treated with tolebrutinib.
Risk minimization measures	**Routine risk minimization measures:** • SmPC sections 4.3, 4.4, 4.5 and 4.8. • PL sections 2 and 4. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.

BTK: Bruton Tyrosine Kinase; MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 40 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)

Atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter)	
Evidence for linking the risk to the medicine	Clinical trial data for tolebrutinib. Data from other BTK inhibitors.
Risk factors and risk groups	No risk factors have been identified for atrial arrythmias (atrial fibrillation and atrial flutter) occurring in patients being treated with tolebrutinib.
Risk minimization measures	**Routine risk minimization measures:** • SmPC section 4.4. • PL section 2. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.

BTK: Bruton Tyrosine Kinase; MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 41 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Malignancies

Malignancies	
Evidence for linking the risk to the medicine	Data from other BTK inhibitors and immunomodulators.
Risk factors and risk groups	Based on the available clinical trial data with tolebrutinib, no specific risk factors for malignancies have been identified. In general, cancer risk factors include increasing age, tobacco use, high body mass index, low fruit and vegetable intake, lack of physical activity, alcohol consumption, certain viral and bacterial infections (such as human papillomavirus, hepatitis B and C, and *H. pylori*), exposure to ultraviolet and ionizing radiation, and various environmental and occupational exposures to carcinogens. (62)
Risk minimization measures	**Routine risk minimization measures:** • SmPC section 4.4. • PL section 2. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.

BTK: Bruton Tyrosine Kinase; MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 42 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Haemorrhages

Haemorrhages	
Evidence for linking the risk to the medicine	Non-clinical studies. Clinical trial data for tolebrutinib. Class effect with data from other BTK inhibitors.
Risk factors and risk groups	Patients with bleeding disorders, known platelet dysfunction, platelet counts below 150000/mcL or when using tolebrutinib concomitantly with anticoagulants, antiplatelet agents, or other medicinal products that may increase bleeding risk.
Risk minimization measures	**Routine risk minimization measures:** • SmPC sections 4.4 and 4.5. • PL section 2. • Legal Status: Restricted medical prescription: The treatment should be initiated and supervised by a physician experienced in the management of MS. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis.

BTK: Bruton Tyrosine Kinase; MS: Multiple Sclerosis; 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 Cenrifki.

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

Table 43 - Other studies in post-authorization development plan

LTS17043 - A Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Multiple Sclerosis (category 3)
Purpose of the study: To determine the long-term safety and tolerability of tolebrutinib in participants with RMS and PMS.
ToleAdhere - Adherence to Liver Function Monitoring (category 3)
Purpose of the study: To describe adherence to liver function monitoring, and the incidence and severity of DILI, among MS patients who are users of tolebrutinib.

DILI: Drug-Induced Liver Injury; MS: Multiple Sclerosis; PMS: Progressive Multiple Sclerosis; RMS: Relapsing forms of Multiple Sclerosis.

REFERENCES

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results [Internet]. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2020 [cited 2024 Apr 29]. Available from https://vizhub.healthdata.org/gbd-results/

2. The Multiple Sclerosis International Federation, Atlas of MS 3rd Edition Part I: Mapping multiple sclerosis around the world – key epidemiology findings[Internet]. England and Wales: The Multiple Sclerosis International Federation; September 2020 [cited 2024 Aug 26]. Available from: https://www.msif.org/wp-content/uploads/2020/12/Atlas-3rd-Edition-Epidemiology-report-EN-updated-30-9-20.pdf

3. Ascherio A, Munger KL. Epidemiology of multiple sclerosis: From risk factors to prevention - An update. Semin Neurol. 2016 Apr;36(2):103-14.

4. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 2010 May;9(5):520-32.

5. Ramagopalan SV, Byrnes JK, Orton SM, Dyment DA, Guimond C, Yee IM, et al. Sex ratio of multiple sclerosis and clinical phenotype. Eur J Neurol. 2010 Apr;17(4):634-7.

6. Trojano M, Lucchese G, Graziano G, Taylor BV, Simpson S Jr, Lepore V, et al. Geographical variations in sex ratio trends over time in multiple sclerosis. PLoS One. 2012;7(10):e48078.

7. Goris A, Vandebergh M, McCauley JL, Saarela J, Cotsapas C. Genetics of multiple sclerosis: lessons from polygenicity. Lancet Neurol. 2022 Sep;21(9):830-42.

8. Simpson S Jr, Wang W, Otahal P, Blizzard L, van der Mei IAF, Taylor BV. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. J Neurol Neurosurg Psychiatry. 2019 Nov;90(11):1193-200.

9. Schreiner TG, Genes TM. Obesity and Multiple Sclerosis-A Multifaceted Association. J Clin Med. 2021 Jun 18;10(12):2689.

10. Ascherio A, Munger KL. Epstein-barr virus infection and multiple sclerosis: a review. J Neuroimmune Pharmacol. 2010 Sep;5(3):271-7.

11. Bjornevik K, Münz C, Cohen JI, Ascherio A. Epstein-Barr virus as a leading cause of multiple sclerosis: mechanisms and implications. Nat Rev Neurol. 2023 Mar;19(3):160-71.

12. Koutsouraki E, Costa V, Baloyannis S. Epidemiology of multiple sclerosis in Europe: A Review. Int Rev Psychiatry. 2010;22(1):2-13.

13. Perrone V, Veronesi C, Giacomini E, Citraro R, Dell'Orco S, Lena F, et al. The Epidemiology, Treatment Patterns and Economic Burden of Different Phenotypes of Multiple Sclerosis in Italy: Relapsing-Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis. Clin Epidemiol. 2022 Nov 6;14:1327-37.

14. Ziemssen T, Bhan V, Chataway J, Chitnis T, Campbell Cree BA, Havrdova EK, et al. Secondary Progressive Multiple Sclerosis: A Review of Clinical Characteristics, Definition, Prognostic Tools, and Disease-Modifying Therapies. Neurol Neuroimmunol Neuroinflamm. 2022 Nov 22;10(1):e200064.

15. Berrigan LI, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S, et al. Health-related quality of life in multiple sclerosis: Direct and indirect effects of comorbidity. Neurology. 2016 Apr 12;86(15):1417-24.

16. Koch-Henriksen N, Laursen B, Stenager E, Magyari M. Excess mortality among patients with multiple sclerosis in Denmark has dropped significantly over the past six decades: a population based study. J Neurol Neurosurg Psychiatry. 2017 Aug;88(8):626-31.

17. Harding K, Anderson V, Williams O, Willis M, Butterworth S, Tallantyre E, et al. A contemporary study of mortality in the multiple sclerosis population of south east Wales. Mult Scler Relat Disord. 2018 Oct;25:186-91.

18. Lunde HMB, Assmus J, Myhr KM, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psychiatry. 2017 Aug;88(8):621-5.

19. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. JAMA. 2021 Feb 23;325(8):765-79.

20. Smyrke N, Dunn N, Murley C, Mason D. Standardized mortality ratios in multiple sclerosis: Systematic review with meta-analysis. Acta Neurol Scand. 2022 Mar;145(3):360-70.

21. Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. J Neurol Neurosurg Psychiatry. 2016 Mar;87(3):324-31.

22. Koch M, Kingwell E, Rieckmann P, Tremlett H; UBC MS Clinic Neurologists. The natural history of secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2010 Sep;81(9):1039-43.

23. Voskuhl RR. The effect of sex on multiple sclerosis risk and disease progression. Mult Scler. 2020 Apr;26(5):554-60.

24. Ribbons KA, McElduff P, Boz C, Trojano M, Izquierdo G, Duquette P, et al. Male Sex Is Independently Associated with Faster Disability Accumulation in Relapse-Onset MS but Not in Primary Progressive MS. PLoS One. 2015 Jun 5;10(6):e0122686.

25. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of multiple sclerosis. Rev Neurol. 2016:172(1):3-13.

26. Marrie RA, Reider N, Cohen J, Stuve O, Trojano M, Cutter G, et al. A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. Mult Scler. 2015 Mar;21(3):318-31.

27. Peres DS, Rodrigues P, Viero FT, Frare JM, Kudsi SQ, Meira GM, et al. Prevalence of depression and anxiety in the different clinical forms of multiple sclerosis and associations with disability: A systematic review and meta-analysis. Brain Behav Immun Health. 2022 Jul 6;24:100484.

28. Marrie RA, Patten SB, Tremlett H, Wolfson C, Warren S, Svenson LW, et al. Sex differences in comorbidity at diagnosis of multiple sclerosis: A population-based study. Neurology. 2016 Apr 5;86(14):1279-86.

29. Dai D, Sharma A, Phillips AL, Lobo C. Patterns of Comorbidity and Multimorbidity Among Patients With Multiple Sclerosis in a Large US Commercially Insured and Medicare Advantage Population. J Health Econ Outcomes Res. 2022 Nov 21;9(2):125-33.

30. Edwards NC, Munsell M, Menzin J, Phillips AL. Comorbidity in US patients with multiple sclerosis. Patient Relat Outcome Meas. 2018 Feb 13;9:97-102.

31. Marrie RA, Cohen J, Stuve O, Trojano M, Sørensen PS, Reingold S, et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult Scler. 2015 Mar;21(3):263-81.

32. Salter A, Lancia S, Kowalec K, Fitzgerald KC, Marrie RA. Investigating the Prevalence of Comorbidity in Multiple Sclerosis Clinical Trial Populations. Neurology. 2024 Mar 12;102(5):e209135.

33. Alugba G, Urhi A, Olateju IV, Onyemarin H, Uzzi C, Oshiba-Fowode T, et al. Renal diseases associated with multiple sclerosis: A narrative review. Medicine (Baltimore). 2022 Dec 2;101(48):e31959.

34. Marrie RA, Reider N, Stuve O, Trojano M, Sorrenson PS, Cutter GR, et al. The incidence and prevalence of comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders in multiple sclerosis: A systematic review. Mult Scler. 2015;21(3):332-41.

35. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. Renal Failure in Patients with Neurogenic Lower Urinary Tract Dysfunction. Neuroepidemiology. (2001) 20 (2): 138-43.

36. Shen T, Liu Y, Shang J, Xie Q, Li J, Yan M, et al. Incidence and Etiology of Drug-Induced Liver Injury in Mainland China. Gastroenterology. 2019 Jun;156(8):2230-41.

37. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013 Jun;144(7):1419-25.

38. Sgro C, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology. 2002 Aug;36(2):451-5.

39. Suk KT, Kim DJ, Kim CH, Park SH, Yoon JH, Kim YS, et al. A prospective nationwide study of drug-induced liver injury in Korea. Am J Gastroenterol. 2012 Sep;107(9):1380-7.

40. Ng HS, Zhu F, Zhao Y, Yao S, Lu X, Ekuma O, et al. Adverse Events Associated With Disease-Modifying Drugs for Multiple Sclerosis: A Multiregional Population-Based Study. Neurology. 2024 Feb 13;102(3):e208006.

41. Meunier L, Larrey D. Hepatotoxicity of Drugs Used in Multiple Sclerosis, Diagnostic Challenge, and the Role of HLA Genotype Susceptibility. Int J Mol Sci. 2023 Jan 3;24(1):852.

42. Persson R, Lee S, Ulcickas Yood M, Wagner Usn Mc CM, Minton N, Niemcryk S, et al. Infections in patients diagnosed with multiple sclerosis: A multi-database study. Mult Scler Relat Disord. 2020 Jun;41:101982.

43. Nelson RE, Xie Y, DuVall SL, Butler J, Kamauu AW, Knippenberg K, et al. Multiple Sclerosis and Risk of Infection-Related Hospitalization and Death in US Veterans. Int J MS Care. 2015 Sep-Oct;17(5):221-30.

44. Knapp R, Hardtstock F, Wilke T, Maywald U, Chognot C, Craveiro L, et al. Comparing the risk of serious infections in patients with and without MS: A German claims data analysis. Mult Scler Relat Disord. 2023 Apr;72:104583.

45. Langer-Gould AM, Smith JB, Gonzales EG, Piehl F, Li BH. Multiple Sclerosis, Disease-Modifying Therapies, and Infections. Neurol Neuroimmunol Neuroinflamm. 2023 Oct 9;10(6):e200164.

46. Castelo-Branco A, Chiesa F, Conte S, Bengtsson C, Lee S, Minton N, et al. Infections in patients with multiple sclerosis: A national cohort study in Sweden. Mult Scler Relat Disord. 2020 Oct;45:102420.

47. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024 Jan 2;149(1):e1-e156.

48. Lakshminarayan K, Anderson DC, Herzog CA, Qureshi AI. Clinical epidemiology of atrial fibrillation and related cerebrovascular events in the United States. Neurologist. 2008 May;14(3):143-50.

49. Capkun G, Dahlke F, Lahoz R, Nordstrom B, Tilson HH, Cutter G, et al. Mortality and comorbidities in patients with multiple sclerosis compared with a population without multiple sclerosis: An observational study using the US Department of Defense administrative claims database. Mult Scler Relat Disord. 2015 Nov;4(6):546-54.

50. Kang JH, Chen YH, Lin HC. Comorbidities amongst patients with multiple sclerosis: a population-based controlled study. Eur J Neurol. 2010 Sep;17(9):1215-19.

51. Chou IJ, Kuo CF, Tanasescu R, Tench CR, Tiley CG, Constantinescu CS, et al. Comorbidity in multiple sclerosis: its temporal relationships with disease onset and dose effect on mortality. Eur J Neurol. 2020 Jan;27(1):105-12.

52. Jadidi E, Mohammadi M, Moradi T. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. Mult Scler. 2013 Sep;19(10):1336-40.

53. Fois AF, Wotton CJ, Yeates D, Turner MR, Goldacre MJ. Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson's disease: record linkage studies. J Neurol Neurosurg Psychiatry. 2010;81(2):215-21.

54. Sun LM, Lin CL, Chung CJ, Liang JA, Sung FC, Kao CH. Increased breast cancer risk for patients with multiple sclerosis: a nationwide population-based cohort study. Eur J Neurol. 2014;21(2):238-44.

55. Nørgaard M, Veres K, Didden EM, Wormser D, Magyari M. Multiple sclerosis and cancer incidence: A Danish nationwide cohort study. Mult Scler Relat Disord. 2019;28:81-5.

56. Castelo-Branco A, Chiesa F, Bengtsson CE, Lee S, Minton NN, Niemcryk S, et al. Non-infectious comorbidity in patients with multiple sclerosis: A national cohort study in Sweden. Mult Scler J Exp Transl Clin. 2020;6(3):2055217320947761.

57. Grytten N, Myhr KM, Celius EG, Benjaminsen E, Kampman MT, Midgard R, et al. Incidence of cancer in multiple sclerosis before and after the treatment era- a registry- based cohort study. Mult Scler Relat Disord. 2021;55:103209.

58. Kuiper JG, Overbeek JA, Foch C, Boutmy E, Sabidó M. Incidence of malignancies in patients with multiple sclerosis versus a healthy matched cohort: A population-based cohort study in the Netherlands using the PHARMO Database Network. J Clin Neurosci. 2022;103:49-55.

59. Mariottini A, Forci B, Gualdani E, Romoli M, Repice AM, Barilaro A, et al. Incidence of malignant neoplasms and mortality in people affected by multiple sclerosis in the epoch of disease-modifying treatments: A population-based study on Tuscan residents. Mult Scler Relat Disord. 2022;60:103679.

60. Greenfield J, Metz LM, Khakban A, Llorian ER, Michaux KD, Traboulsee A, et al. Cancer risk, disease-modifying therapy, and age in multiple sclerosis: A retrospective population-based cohort study. Mult Scler Relat Disord. 2023;80:105091.

61. Pierret C, Mulliez A, Le Bihan-Benjamin C, Moisset X, Bousquet PJ, Leray E. Cancer Risk Among Patients With Multiple Sclerosis: A 10-Year Nationwide Retrospective Cohort Study. Neurology. 2024;103(9):e209885.

62. American Cancer Society. Known and Probable Human Carcinogens [Internet]. USA: American Cancer Society; 2024 Aug 01 [cited 2025 Oct 27]. Available from: https://www.cancer.org/cancer/risk-prevention/understanding-cancer-risk/known-and-probable-human-carcinogens.html

63. Dobie G, Kuriri FA, Omar MMA, Alanazi F, Gazwani AM, Tang CPS, et al. Ibrutinib, but not zanubrutinib, induces platelet receptor shedding of GPIb-IX-V complex and integrin αIIbβ3 in mice and humans. Blood Adv. 2019 Dec 23;3(24):4298-311.

64. Cho EB, Yeo Y, Jung JH, Jeong SM, Han KD, Shin DW, et al. Risk of stroke in multiple sclerosis and neuromyelitis optic spectrum disorder: a Nationwide cohort study in South Korea. J Neurol Neurosurg Psychiatry. 2022 Aug 26:jnnp-2022-329628.

PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

ANNEX 4.1 SPECIFIC ADVERSE REACTION FOLLOW-UP QUESTIONNAIRE FOR ATRIAL ARRHYTHMIAS

sanofi

Tolebrutinib (CENRIFKI®)
Atrial Arrhythmia
Follow-up Questionnaire (FUQ)

The goal of this questionnaire is to collect the very essential information on reported event(s) of **Atrial Arrhythmia with Tolebrutinib**. 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.

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			
PREVIOUS RELEVANT HISTORY AND CONCURRENT DISORDERS			
	YES	**NO**	***Specify details – ONSET Date (DD/MMM/YYYY)***
Atrial arrhythmias	☐	☐	
Atrial fibrillation	☐	☐	
Atrial flutter	☐	☐	
Myocarditis/Pericarditis	☐	☐	
Coronary artery disease	☐	☐	
Valvular disease	☐	☐	
Cardiac murmur	☐	☐	
Pulmonary edema	☐	☐	
Viral infections/viral illness	☐	☐	
Sick sinus syndrome	☐	☐	
Hypertension	☐	☐	
Diabetes mellitus	☐	☐	
Myocardial infarction	☐	☐	
Stroke	☐	☐	
Transient ischemic attack	☐	☐	
Thromboembolism	☐	☐	
Vascular disease	☐	☐	
Cardiomyopathy	☐	☐	
Chronic obstructive pulmonary disease	☐	☐	
Heart failure	☐	☐	
Congestive heart failure	☐	☐	
Obesity	☐	☐	
Chronic kidney disease	☐	☐	
Sleep apnea	☐	☐	
Hyperlipidemia	☐	☐	
Electrolyte imbalance of K^+, Ca^{2+}	☐	☐	

Alcohol consumption	☐	☐	*Include duration and extent (number of drinks per week)*
Current or former smoker	☐	☐	*Include duration and extent (number of packs per day)*
Illicit/recreational drug use	☐	☐	
Hyperthyroidism	☐	☐	
Implantation of pacemaker	☐	☐	
Other (specify):	☐	☐	

DOCUMENTATION OF THE ADVERSE EVENT		
Main diagnosis:		**Start Date (DD/MM/YYYY):**
Are the following signs and symptoms associated?	***Tick box if applicable***	***Specify Onset Date (DD/MMM/YYYY) if applicable***
Dizziness or confusion	☐	
Difficulty breathing or shortness of breath	☐	
Chest pain or tightness	☐	
Syncope or loss of consciousness	☐	
Fatigue	☐	
Edema (legs, ankles or feet)	☐	
Orthopnea	☐	
Palpitations	☐	
Presyncope	☐	

LABORATORY RESULTS

LABORATORY DATA *performed:* ***YES*** ☐ **NO** ☐ **Date:** Click here to enter a date.

Test	**Result**	**Reference Range**	**Date of test (DD/MMM/YYYY)**
Comprehensive metabolic panel (CMP) (i.e., sodium level, potassium level, blood urea nitrogen, creatinine)			
Thyroid function tests (TFTs)			

ADDITIONAL TEST DATA (to be performed at local level)

	Not tested	**Negative result**	**Positive result**	**Date of test (DD/MMM/YYYY)**	**Titration**
C-Reactive Protein (CRP)	☐	☐	☐		

OTHER INVESTIGATIONS

	DATE (DD/MMM/YYYY)	**RELEVANT RESULTS**
Chest x-ray: YES ☐ NO ☐ *(if YES is ticked, a report needs to be attached)*		
Echocardiogram: YES ☐ NO ☐ *(if YES is ticked, a report needs to be attached)*		
Electrocardiogram: YES ☐ NO ☐ *(if YES is ticked, a report needs to be attached)*		
Coronary angiogram: *(if YES is ticked, a report needs to be attached)* YES ☐ NO ☐		
Telemetry or Holter results:		

YES ☐ NO ☐ *(if YES is ticked, a report needs to be attached)*		
Nuclear Scan: YES ☐ NO ☐ *(if YES is ticked, a report needs to be attached)*		
Cardiac specialist consultation YES ☐ NO ☐		

OTHER INVESTIGATIONS (i.e., Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, etc.)		
Date (DD/MMM/YYYY)	**NATURE**	**RESULTS**
Click here to enter a date.		
Click here to enter a date.		

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

Prior to the launch of Cenrifki in each Member State, the marketing authorization holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at minimizing the risk of drug-induced liver injury (DILI).

The MAH shall ensure that in each Member State where Cenrifki is marketed, all healthcare professionals and patients who are expected to prescribe, dispense, or use Cenrifki have access to/are provided with the following educational package:

- Healthcare professionals (HCPs) educational materials
- Patients' educational materials

1. HCP educational materials:

- Summary of Product Characteristics (SmPC).
- Prescriber Guide.

1.1. Prescriber Guide:

The **Prescriber Guide** includes the following key elements:

- List of contraindications
- Relevant information about the risk of DILI, its monitoring and management:
  - Background:
    - Clinically significant DILI has been reported in tolebrutinib Phase 3 clinical trials, including one patient who developed liver failure resulting in transplant and subsequently died due to a post-transplant complication.
    - Incidence of increased serum alanine transaminase (ALT) cases in clinical trials, consistently with SmPC information.
    - All cases of ALT elevations >20x the upper limit of normal (ULN) or ALT elevations >3x ULN with concurrent bilirubin increases >2x ULN occurred within 12 weeks of initiating tolebrutinib treatment.
    - Justification for the weekly monitoring during the first 12 weeks
  - Treatment initiation:
    - Obtain serum transaminase and total bilirubin levels before initiation then weekly in the first 12 weeks, monthly in months 4 to 12, then every 6 months between months 12 and 24, of tolebrutinib therapy:
      - Consider additional monitoring when tolebrutinib is given with other potentially hepatotoxic medicinal products.
  - During treatment:

  - Follow recommended actions (including therapy modifications) for the management of elevated transaminases and symptoms suggestive of hepatic dysfunction.
  - Avoid the use of herbal or dietary supplements with potential hepatotoxicity.

- Important information to communicate to patient:
  - Provide the Patient Guide to the patient and inform the patients that a Patient Card is included in the pack and that the patient should carry this card with them at all times during treatment.
  - Educate patient on the importance on doing the serum transaminase and total bilirubin tests before initiation then weekly in the first 12 weeks, monthly in months 4 to 12, then every 6 months between months 12 and 24, of tolebrutinib therapy.
  - Educate patient on signs and symptoms of DILI.
  - Educate patient on the importance to alert the prescriber in case of elevated liver enzymes.
  - Educate patient on the importance to alert the prescriber in case of signs of DILI.
  - Educate patient to immediately inform the prescriber in case of missed liver function test.
  - Educate patient to avoid the use of herbal or dietary supplements with potential hepatotoxicity during treatment.

2. Patient educational materials

- Package leaflet
- Patient Guide
- Patient Card

2.1. Patient Guide:

The Patient Guide includes the following key elements:

- A recommendation to read the Product information leaflet and Patient Guide prior to initiating treatment.
- A description of the risk of DILI.
- A description of the signs and symptoms of DILI.
- A description of the best course of action if signs and symptoms of DILI present themselves.
- Importance and need to do serum transaminase and total bilirubin tests before initiation then weekly in the first 12 weeks, monthly in months 4 to 12 then every 6 months between months 12 and 24, of tolebrutinib therapy.
- Immediately inform the prescriber in case of missed liver function test.

2.2. Patient Card:

The Patient Card (included in each pack, together with the package leaflet) is aligned with the product labelling and includes the following key elements:

- Remind the patient that tolebrutinib can cause serious liver problems and requires strict adherence to regular liver-function monitoring.
- Symptoms can include tiredness, nausea, vomiting, pain in the abdomen, fever, rash or itching of your skin, loss of appetite or interest in food, dark urine, or yellowing of skin or eyes.
- Seek medical attention or advice immediately if symptoms of liver problems occur.
- Include contact details of the prescribing physician.