23 April 2026
EMADOC-1829012207-21436
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cenrifki

International non-proprietary name: tolebrutinib

Procedure No. EMEA/H/C/006386/0000

Note

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

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List of abbreviations

9-HPT	9-Hole Peg Test
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AI	Acceptable intake
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARR	Annualised relapse rate
AST	Aspartate Aminotransferase
AUC	Area under the time-curve
BBB	Blood brain barrier
BCS	Biopharmaceutics Classification System
BMD	Benchmark dose
BTK(i)	Bruton's tyrosine kinase (inhibitor)
CDI	Confirmed disability improvement
(c)CDP	(composite) Confirmed disability progression
CDW	Confirmed disability worsening
Chi3L1	Chitinase 3-like 1 protein
C_{max}	Peak plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus Disease-2019
CQA	Critical Quality Attribute
CSF	Cerebrospinal fluid
CSR	Clinical study report
C-SSRS	Columbia-suicide severity rating scale
Ctrough	Trough observed plasma concentration
CVLT-II	California Verbal Learning Test-II
CYP	Cytochrome P450
DALA	Drug abuse liability assessment
DB	Double-blind
DBP	Diastolic blood pressure
DCS	Developability classification system
DILI	Drug-induced liver injury
DMT	Disease modifying therapy
DSC	Differential scanning calorimetry
DVS	Dynamic Vapour Sorption
EAE	Experimental autoimmune encephalitis
EAIR	Exposure-adjusted incidence rate
EAT	Enhanced Ames Test
EC	European Commission
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
EDSS	Expanded disability status scale
EFD	Embryo-foetal development
EOS	End of study
FEED	Fertility and early embryonic developmental
FMEA	Failure mode effect analysis
GGT	Gamma-glutamyl transferase

gMG	Generalised myasthenia gravis
GMP	Good Manufacturing Practice
HAC	Hepatology assessment committee
HCD	Historical control data
HLT	High-level term
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRMS	High resolution mass spectrometry
HS-GC	Head space gas chromatography
ICE	Intercurrent events
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IC-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
IC_{50}	Half maximal inhibitory concentration
IDMC	Independent data monitoring committee
Ig	Immunoglobulin
IMP	Investigational medicinal product
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
(m)ITT	(modified) intent-to-treat
KM	Kaplan-Meier
LC(-MS)	Liquid chromatography (mass spectrometry)
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LDPE	Low Density Polyethylene
LFTs	Liver function tests
LOAELs	Lowest observed adverse effect levels
LS	Least square
LTS	Long term safety
MAA	Marketing authorisation application
MAD	Multiple ascending dose
MATE	Multidrug and toxin extrusion protein
MF	Mutant frequencies
MCP-Mod	2-step Multiple Comparison Procedure with Modelling
MO	Major Objection
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MTD	Maximum tolerated dose
NCI CTCAE	National cancer institute common terminology criteria for adverse events
Nfl	Neurofilament
NMR	Nuclear Magnetic Resonance
NO(A)EL	No observed (adverse) effect level
nrSPMS	Non-relapsing secondary progressive MS
NSAID	Nonsteroidal anti-inflammatory drug
OATP	Organic-anion-transporting polypeptide
OAT	Organic anion transporter
OCT	Organic cation transporter
OL	Open-label

PBPK	Physiologically Based Pharmacokinetic
PCSA	Potentially clinically significant abnormality
Ph. Eur.	European Pharmacopoeia
PIRA	Progression independent of relapse activity
PIRMA	Progression independent of relapse and MRI activity
PML	Progressive multifocal leukoencephalopathy
PMS	Progressive multiple sclerosis
PopPK	Population PK
PPMS	Primary progressive multiple sclerosis
PPND	Pre- and postnatal development
PRL	Paramagnetic rim lesions
PROs	Patient-reported outcomes
PT	Preferred term
PY	Participant years
QbD	Quality by design
QD	Once daily
QTPP	Quality target product profile
RAW	Relapse associated worsening
RD	Risk difference
RH	Relative Humidity
RMS	Relapsing multiple sclerosis
RR	Relative risk
RRMS	Relapsing-remiting multiple sclerosis
RRR	Relative risk reduction
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SDMT	Symbol digit modalities test
SE	Standard error
SIRs	Standardised incidence ratios
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA queries
SOC	System organ class
SPMS	Secondary progressive multiple sclerosis
SUSAR	Suspected unexpected serious adverse reaction
SWI	Susceptibility-weighted imaging
T25-FW	Timed 25-foot walk
TBILI	Total bilirubin
TDAR	T cell-dependent antibody response
TEAE	Treatment-emergent adverse event
TGA	Thermo-Gravimetric Analysis
t_{max}	Time to reach the maximum concentration
ULN	Upper limit of normal
UV	Ultraviolet
Vd	Apparent volume of distribution
Vss	Steady-state volume of distribution
WBC	White blood cell
XR(P)D	X-Ray (Powder) Diffraction

1. Regulatory information and recommendations on the procedure

1.1. Legal basis, and dossier content

The legal basis for this application refers to:

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

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

1.2. Scientific advice

Table 1 Scientific advice and protocol assistance

Date	Reference number/ Coordinator(s)	Brief summary of the advice
14 November 2019	EMEA/H/SA/4302/1/2019/II	The Scientific advice pertained to the following clinical aspects: The proposed clinical pharmacology programme to support registration in the treatment of relapsing and progressive forms of multiple sclerosis (MS), including the influence of renal and hepatic impairment on the pharmacokinetics (PK), the plan to assess the potential effect of other drugs on the PK, and the physiologically based pharmacokinetic (PBPK) models to assess the potential effect of SAR442168 on the PK of other drugs; the approach to conduct one population PK analysis by collecting data from one Phase 3 study in relapsing multiple sclerosis (over the two 2 phase 3 RMS studies) and from the Phase 3 in primary progressive multiple sclerosis (PPMS) to characterise the PK and sources of inter-subject variability in patients with relapsing and progressive forms of MS; the design of the two identical Phase 3 trials in adults with relapsing MS (RMS), including the population and treatment duration; the proposed phase 3 trial in progressive forms of MS including the plan to conduct an interim analysis to support registration for the treatment of primary progressive forms of MS; the proposed trial in non-relapsing secondary progressive MS (SPMS) including the plan to conduct an interim analysis to support registration for the treatment of non-relapsing SPMS (nr-SPMS); the planned long-term safety (LTS) study to enrol patients from all Phase 3 trials (RMS, PPMS and nr-SPMS); whether cognitive performance as measured by Symbol Digit Modalities Test (SDMT) is a relevant marker of treatment benefit in MS (RMS, PPMS and nr-SPMS); adequacy of the proposed monitoring measures for the Phase 3 trials to generate the safety information and the proposed size of the (combined RMS, PPMS and nr-SPMS) safety database.
28 May 2020	EMEA/H/SA/4302/2/2020/III	The Scientific advice pertained to the following non-clinical and clinical aspects: • The proposed overall non-clinical development plan to support the Phase 3 clinical development programme and registration; drug-drug interaction studies. • Dose selection for phase 3 studies; regarding RMS phase 3 trials: study duration and analysis of annualised relapse rate (ARR) based on a fixed; treatment duration as a sensitivity analysis; regarding nr-SPMS: acceptability of SAR442168 as monotherapy; measurements of cognitive performance of as markers of treatment benefit in MS; regarding PPMS study: use of external control data; updated safety monitoring plan for all four phase 3 trials; testing of a mobility device (actigraphy) during the progressive MS trials; potential label covering both RMS, PPMS and nr-SPMS.
10 December 2020	EMEA/H/SA/4302/3/2020/I	The Scientific advice pertained to the following quality aspects: Selection of starting materials

1.3. Eligibility to the centralised procedure

The applicant Sanofi Winthrop Industrie submitted on 29 January 2025 an application for Marketing Authorisation to the European Medicines Agency (EMA) for CENRIFKI (Tolebrutinib), through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 June 2023.

The applicant applied for the following indication: CENRIFKI is a brain penetrant Bruton's tyrosine kinase inhibitor (BTKi) indicated for the treatment of non-relapsing secondary progressive multiple sclerosis (nrSPMS) in adults.

1.4. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/PE/0000181294 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000181294 was not yet completed as some measures were deferred.

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

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

1.6. Applicant's request for consideration

1.6.1. New active substance status

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

1.6.1.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that tolebrutinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

1.7. Patient experience data

Table 2 Patient experience data relevant to the application

Patient experience data submitted with this application				Section where discussed (if applicable)
☐	Patient experience data submitted by the applicant:			
	☐	Clinical outcome assessments (COAs) such as		
		☐	Patient-reported outcomes (PRO)	
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
X	Other patient experience data not submitted by the applicant but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		
	X	CHMP early dialogue with patient organisations		5.3.8, 5.3.9
	☐	Third party interventions from patients and patient groups		
	☐	Other (such as medical literature, summaries/analysis from patient engagement activities - please specify)		

1.8. Steps taken for the assessment of the product

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

Rapporteur:	Janet Koenig
Co-Rapporteur:	Thalia Marie Estrup Blicher

The application was received by the EMA on	29 January 2025
The procedure started on	20 February 2025
The CHMP Rapporteur's first Assessment Report was received on	12 May 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	14 May 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	26 May 2025

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 June 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	23 September 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 October 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	16 October 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 January 2026
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	29 January 2026
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 February 2026
The CHMP Rapporteur circulated the CHMP Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 March 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to CENRIFKI on	23 April 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	23 April 2026

1.9. CHMP outcome

1.9.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.9.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.9.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of CENRIFKI is favourable in the following indication(s):

Cenrifki is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (see section 5.1).

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.9.3.1. Divergent position(s)

Divergent position to the majority recommendation on Benefit/risk – Full CHMP opinion is appended to this report.

1.9.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.9.5. Other conditions and requirements of the marketing authorisation

1.9.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.9.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.9.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.9.6.2. Additional risk minimisation measures

Prior to the launch of Cenrifki in each Member State, the Marketing Authorisation 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 minimising 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 > 20 x the upper limit of normal (ULN) or ALT elevations > 3 x ULN with concurrent bilirubin increases > 2 x 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 patient 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 package 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.

1.9.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

2. Introduction

2.1. Therapeutic Context

MS is a chronic immune-mediated inflammatory disorder, resulting in demyelination and neurodegeneration within the central nervous system (CNS). MS is the leading cause of neurologic disability in young adults globally (Thompson, 2018). Disability accumulation is the result of both neuroinflammatory and neurodegenerative processes. MS typically progresses along a continuum of increasingly evident neurodegeneration. Most people with MS (approximately 85%) have relapsing-remitting multiple sclerosis (RRMS) at diagnosis (Olek, 2021). Approximately 50% diagnosed with RRMS transition to SPMS within 20 years following disease onset (Brieva, 2025). In a related but distinct phenotype observed in approximately 10% of people with MS, there is a progressive course from the outset without relapse activity classified as PPMS.

The global prevalence of MS has increased to an estimated 2.9 million people in 2023. In the US, MS has also become more prevalent (i.e., 288/100000 persons in 2020; 163/100 000 persons reported 2008 to 2010) and increasingly diverse. In 2020, the estimated prevalence of MS in Europe was 142.81 per 100000 persons while in Canada it was 290 per 100000 persons.

The clinical course of MS has historically been divided into 3 phenotypes (RRMS, SPMS, and PPMS). RRMS is manifested by episodes of new or worsening neurologic symptoms followed by symptom-free periods of recovery, eventually leading to cumulative deficits secondary to axonal injury that may increase acutely with each new relapse. Over time in most people with MS, relapses will ultimately reduce in frequency or stop completely. However, neurologic deficits continue to accrue, and an underlying disability progression becomes apparent, which for people with MS can have a major impact on quality of life by causing considerable disruption to daily living and life roles including work, physical independence, mobility, social interaction, and participation in leisure activities.

When followed for longer periods (over 25 to 35 years), based on cohort and natural history studies respectively, approximately 60 to 90% of people with RRMS will transition to SPMS, a clinically more severe and disabling phase of the disease characterised by both CNS-compartmentalised inflammation and increased neurodegeneration. There is no distinct transition between relapsing remitting MS and SPMS. Clinically, SPMS is defined as steadily progressing neurologic dysfunction without unequivocal recovery, which is predominantly independent of relapses (Olek, 2021). A total of 85 to 95% of patients with SPMS are free of clinical relapses, based on real world studies (Frahm, 2021; Mathey, 2021).

The patients with RRMS tend to be younger in age and less disabled. Since the onset of SPMS tends to be delayed, these patients are typically older, more disabled, and more likely to have comorbidities. There is no single definitive biomarker or diagnostic test for SPMS; the clinical diagnosis of SPMS is challenging and usually made retrospectively, based on the patient's history or worsening after an initial relapsing disease course (Cree, 2021).

Though less frequent, clinical relapses and new radiographic acute inflammatory lesions can also occur in SPMS and PPMS patients. Thus, the modifying term "activity" has been proposed to identify patients with relapses and/or MRI focal and acute inflammatory activity. While this modifier reflects a relevant treatment aspect of the disease, it does not incorporate other underlying pathological processes driving disability progression that are common to all MS phenotypes.

Based on present evidence, MS is regarded as a continuum rather than discrete subtypes. Indeed, numerous studies have analysed the pathologies associated with the different MS phenotypes and have concluded that patients with MS share qualitatively similar (but quantitatively different) features

independent of the phenotype and clinical course, including inflammation and neurodegeneration, both of which are already present at disease onset. These pathological processes include acute inflammation, chronic (non-resolving) inflammation, demyelination, oxidative stress, axonal damage, neuronal loss, and remyelination. The interplay between these shared pathological processes along the spectrum of the disease is thought to contribute to the MS phenotype.

Not only do the different phenotypes of MS share similar and overlapping pathophysiological mechanisms (Dobson, 2019), but a key common feature is also disability, which occurs across the entire spectrum of MS, beginning in RRMS (Sharrad, 2023). Disability accrual in MS can be broadly categorised as either progression independent of relapse activity (PIRA) or relapse associated worsening (RAW). Moreover, the term PIRMA (progression independent of relapse and MRI activity) has recently been introduced to indicate disability accrual in the absence of both clinical relapses and new MRI acute inflammatory lesions in the brain and/or spinal cord (Ciccarelli, 2024). Prevention or slowing of disability accrual is an unmet medical need for all individuals with MS.

Disability accrual was previously thought to be the defining feature of progressive forms of MS. However, recent studies (Calabrese, 2024; Portaccio, 2024) have uncovered an underlying accrual of disability also in RMS populations, where 80% to 90% of overall disability accumulation occurred independent of relapses (i.e., PIRA) (Kappos, 2020). The central importance of PIRA in RMS has recently been confirmed in additional studies (Sharrad, 2023; Lublin, 2022 and Tur, 2023) with the combined data from these studies indicating that PIRA starts early in the disease process, occurs in all MS phenotypes, and becomes the principal driver of disability accumulation in both the relapsing and progressive phases of the disease.

Of note, there are several definitions of PIRA that have been applied in the literature, encompassing the baseline EDSS, confirmation period, confirmation magnitude, absence of relapses between baseline and accrual score or absence of relapses during the confirmation period (Mueller, 2023) that affect incidence and persistence of PIRA. Inflammation is the key driver of MS pathology and can be categorised into acute and chronic. Acute inflammation involves the breakdown of the BBB, allowing autoreactive lymphocytes to migrate into the CNS. Once there, it is believed that B lymphocytes (and other antigen-presenting cells) present autoantigens to their cognate T lymphocytes, inducing their re-activation with subsequent secretion of proinflammatory cytokines, thus promoting focal white matter demyelination characterised by perivenular inflammation. Macrophages and microglia sense the tissue damage and respond by additional release of cytokines, propagating axonal loss (Bar-Or, 2021). Acute focal inflammation can be observed as Gd-enhancing T1-hyperintense lesions (Gd+ lesions) on MRI, and the perivenular topography can be detected using susceptibility-based MRI. Focal inflammation can resolve, leaving behind an astroglial scar, the residual of which is detected as T2-hyperintensity on MRI. A subset of these lesions will develop into persistent T1-hypointensities, the MRI correlate of irreversible axonal loss (Fischer, 2015). The principal reason for the irreversible physical and cognitive disability seen in MS is thought to be neuroaxonal loss (Cree, 2021). However, only 20% to 40% of SPMS patients have identifiable T1-hypointense lesions on MRI, highlighting the limitations of traditional MRI measures in capturing disability. The clinic-radiological paradox has been defined as this mismatch between focal lesions on MR scans from patients with MS and clinical disability (Truyen, 1996; Fouad, 2021).

Chronic inflammation manifests as diffuse glial activation at the rim of chronic active lesions that can reach considerable distances into normal-appearing white matter with predominant lymphocytic inflammation in the meninges and perivascular space resulting in neuroaxonal damage; chronic inflammation is compartmentalised behind the BBB, is thought to be a key pathological driver of disability progression independent of relapse activity even in early MS, and is not easily detected by conventional MRI measures (Magliozzi, 2007). Failure of remyelination is another important pathobiological contributor to neuroaxonal damage which is believed to be the main determinant of disability (Goldschmidt, 2009). Recent developments in MRI methods have made advances in

visualising these previously undetectable pathologic processes, such as chronic active lesions appearing as paramagnetic rim lesions (PRLs) on susceptibility weighted sequences (Absinta, 2019; Dal-Bianco, 2021). PRLs are specific for MS; their diagnostic specificity and role in earlier detection of MS is highlighted by the inclusion in the 2024 proposed revisions to the McDonald diagnostic criteria (Thompson, 2018). PRLs arise from Gd+ lesions, show a direct relationship with disability severity, and appear resistant to treatments with mechanisms targeting acute focal inflammation (Absinta, 2019; Maggi, 2023). MS patients with more than 4 PRLs have demonstrated accelerated disability accrual, and specifically accelerated PIRA (Absinta, 2019; Maggi, 2023), thus PRLs may be informative of the pathological basis for PIRA.

Disability is measured in clinical trials using 3- and 6-month CDP using Expanded Disability Status Scale (EDSS) or a composite endpoint using EDSS, 9-hole peg test (9-HPT) and timed 25-Foot Walk test (T25-FW). Despite the success in reduction of relapse rates and the RAW component of disability, disability accumulation in general and PIRA in particular, remains a significant unmet need in the MS population.

Existing evidence shows that the biological factors that underly focal inflammation and relapse are distinct from those driving disability accrual (Kuhlmann, 2023). Central to the pathophysiology of disability progression in MS is CNS compartmentalised inflammation in the form of activated macrophages and microglia (Healy, 2022; Guerrero, 2020). These CNS-restricted immune cells are thought to drive the progression of disability in MS (Faissner, 2019).

Present disease-modifying treatments (DMTs) have been approved for different types of MS in the EU and comprise small molecules, peptides, recombinant proteins and monoclonal antibodies. The approved treatment options for MS are primarily focused on relapsing phenotypes. There remains a significant unmet need for effective treatments in progressive forms of MS, e.g., to slow disability progression across the spectrum of MS. To date, only the s.c. injection of interferon beta-1b (*"Betaferon"*, EMEA/H/C/81) and the oral administration of siponimod (*"Mayzent"*, EMEA/H/C/4712) are specifically licensed for SPMS; however, their approval is limited to SPMS with active disease as evidenced by relapses or imaging features of inflammatory activity. Further, there are several medicinal products for the treatment of relapsing forms of MS with active disease which can be used for the treatment of SPMS with relapses. At present, there are no approved DMT in non-active SPMS or SPMS, encompassing both, active and non-active SPMS.

2.2. Aspects of development

The tolebrutinib clinical development programme for (non-relapsing) SPMS includes eleven Phase 1 clinical pharmacology studies in healthy participants and hepatically or renally impaired participants, as well as PK and pharmacodynamics (PD) data in patients with (nr)SPMS and RMS. Evaluation of tolebrutinib for (nr)SPMS is based on five clinical trials contributing to efficacy and safety, i.e. a double-blind, placebo-controlled pivotal phase 3 study EFC16645 (also referred to as Study HERCULES) in (nr)SPMS, two supportive double-blind, active-controlled phase 3 studies EFC16033 and EFC16034 (also referred to as studies GEMINI 1 and GEMINI 2) in RMS, a double-blind, placebo-controlled, cross-over, dose-finding Phase 2b study DRI15928 in RMS and its ongoing follow-up Phase 2b long-term extension study LTS16004 (see table section 5.1.2).

There are two Phase 3 studies, i.e., a double-blind, placebo-controlled study EFC16035 (PERSEUS) in patients with PPMS and a long-term study LTS17043 including patients previously enrolled in one of the aforementioned MS tolebrutinib studies (i.e., GEMINI 1 and 2, HERCULES, LTS16004 and EFC16035) that were still ongoing at the time of the submission of the marketing authorisation

application (MAA). Efficacy data were not available. During the procedure, the applicant provided on 14th December 2025 topline efficacy and safety results of study EFC16035 (PERSEUS).

2.2.1. Scientific advice/Protocol assistance

The applicant received national scientific advice regarding the non-clinical and clinical development of tolebrutinib by AEMPS on 11th December 2018. Subsequently, centralised scientific advice was granted three times by the CHMP (see section 1.3). In addition, non-clinical and clinical matters of the MAA were discussed with the Rapporteurs in the pre-submission meeting on 15th November 2024.

The European Paediatric Committee (PDCO) agreed on the PIP of tolebrutinib on 14th August 2020 thereby granting a waiver for paediatric patients below 10 years of age and a deferral for treatment of MS patients from 10 to less than 18 years of age (P/0310/2020). The PDCO later accepted to defer the initiation and completion of paediatric investigations in the PIP due to the delayed finalisation of the clinical programme in adults on 31st January 2024 (P0019/2024) and agreed to further modify the timelines on 6th December 2024 PIP decision (EMA/PE/0000181294).

2.3. Description of the product

Tolebrutinib (also termed SAR442168 and PRN2246 in the dossier) is a CNS-penetrant small molecule with nanomolar potency, that binds irreversibly to and inactivates BTK. BTK is a non-receptor tyrosine kinase of the Tec family with important roles in the growth and differentiation of haematopoietic cells (Rozkiewicz D *et al*., 2023). BTK connects to the signalling from various receptors including the B cell receptor, FC gamma receptor, Fc epsilon receptor and toll-like receptors. Accordingly, BTK signalling is critical in B cells and myeloid cells including CNS-resident macrophages and microglia. Each of these cell types are implicated in the pathophysiology of MS. The exact mechanism of action of tolebrutinib in MS therapy has not been completely unravelled. However, the covalent binding of the acryloyl moiety of tolebrutinib to cysteine 481 near the ATP-binding site of BTK is thought to inhibit the inflammatory BTK activity in B cells, macrophages and microglia in the periphery and CNS. The same cysteine 481 is also bound by other BTK inhibitors, which are currently licensed in the EU for various types of B cell malignancies (ibrutinib, *"Imbruvica"*, EMEA/H/C/3791; zanubrutinib, *"Brukinsa"*, EMEA/H/C/4978); acalabrutinib, *"Calquence"*; EMEA/H/C/5299; pirtobrutinib, *"Jaypirca"*, EMEA/H/C/5863).

The initially requested indication was: *"CENRIFKI is a brain penetrant Bruton's tyrosine kinase inhibitor (BTKi) indicated for the treatment of non-relapsing secondary progressive multiple sclerosis (nrSPMS) in adults".*

The revised indication for tolebrutinib is: "*CENRIFKI is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (see section 5.1)"*.

Tolebrutinib has been formulated as immediate-release film-coated tablets of 60 mg each for once daily oral administration. To mitigate the risk of drug-induced liver injury (DILI), hepatic aminotransferases, alkaline phosphatase and bilirubin should be monitored prior to treatment initiation, weekly within the first 3 months of therapy and then monthly up to the 12th months of treatment. Subsequently, liver monitoring should be continued as warranted. In case of DILI, the therapy should be interrupted to identify the possible cause. Treatment with tolebrutinib may be resumed if an alternative cause was identified and hepatic aminotransferases have decreased to <1.5x upper limit of normal (ULN). If aminotransferases rise again to >3x ULN and/or a relationship with tolebrutinib cannot be excluded, the clinical therapy with tolebrutinib should be permanently discontinued.

2.4. Inspection issues

2.4.1. GMP inspection(s)

No inspection required.

2.4.2. GLP inspection(s)

No inspection required.

2.4.3. GCP inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

The finished product is presented as a film-coating tablet containing 60 mg of tolebrutinib as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone type A, magnesium stearate;

Film-coating: Hypromellose, titanium dioxide, yellow iron oxide (E172), red iron oxide (E172) and macrogol - polyethylene glycol (400).

The product is available in polyamide/aluminium/poly(vinyl chloride) - aluminium blisters.

3.2. Active substance

3.2.1. General information

The chemical name of tolebrutinib is 4-amino-3-(4-phenoxyphenyl)-1-[(3*R*)-1-(prop-2-enoyl)piperidin3-yl]-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one corresponding to the molecular formula $C_{26}H_{25}N_5O_3$. It has a relative molecular mass of 455.52 and the following structure:

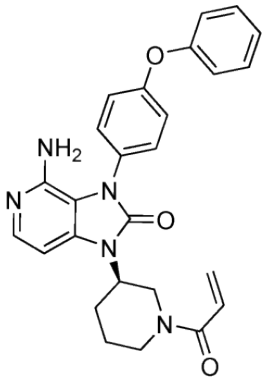


Figure 1 ***active substance structure***

The chemical structure of tolebrutinib was elucidated by a combination of elemental analysis, IR, UV, NMR, and HRMS methods. The solid-state properties of the active substance were measured by XRPD, DSC, TGA, microscopy & DVS.

The active substance is a white to beige non-hygroscopic powder. It is poorly soluble in aqueous media and exhibits pH dependent solubility; aqueous solubility is greater at lower pH values.

Tolebrutinib exhibits stereoisomerism due to the presence of one chiral centre, the active substance is present in the (*R*) configuration. The stereocenter originates in one of the starting materials and is suitably controlled in the relevant starting material specification.

Polymorphism has been observed for tolebrutinib and the most thermodynamically stable form was selected for development of the active substance. The stability studies also demonstrated that this form was stable throughout storage of the active substance. Polymorphic form is controlled in the specification of the active substance.

3.2.2. Manufacture, characterisation, and process controls

The active substance is manufactured at one manufacturing site. Satisfactory information concerning GMP standards was provided.

Tolebrutinib is synthesised in six main steps using well defined starting materials with acceptable specifications.

The description of the tolebrutinib manufacturing process is acceptable, and the operating parameters and in-process controls are suitably presented and justified. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance is in accordance with the EU guideline on the chemistry of active substances. The information provided with respect to impurities was initially not acceptable and a number of Major Objections (MOs) were raised. The information provided with respect to the nitrosmamines risk assessment of the active substance was not acceptable, and an updated assessment was requested which among other aspects took into consideration any risk posed by the amine moieties in the active substance. To resolve this MO the applicant provided an updated risk assessment and addressed the potential risk from vulnerable amine moieties a control for a nitrosamine impurity is included in the specification of the finished product. An MO was raised as one of the starting materials is a potential mutagenic impurity. The applicant was requested to provide analytical data substantiating the theoretical purge of this compound and this request was maintained during the procedure. To resolve this MO the applicant provided analytical data to substantiate the purge of the compound and justify the absence of control of this in the active substance specification. An impurity is composed of polymeric forms of the active substance, and an MO was raised as the information on the characterisation and control of polymeric impurities was initially not considered sufficient. To resolve this MO the applicant provided further information on the characterisation of the impurities and justification for the selected method of analysis based on insolubility of the polymeric forms. The active substance synthetic process was revised to designate critical steps to control polymerisation and the limit for polymeric impurities in the active substance was tightened, this limit is also toxicologically justified.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. This updated process is the same as the proposed commercial process and that used during the pivotal clinical studies.

The active substance is packaged in a container closure which complies with Commission Regulation (EU) 10/2011, as amended.

3.2.3. Specification

The active substance specification includes test and acceptance criteria for the following parameters; appearance, colour, identification, assay, related impurities, residual solvents, polymorphism, residue on ignition, water content and microbiological quality.

The active substance specification parameters and limits are in line with relevant guidelines and are acceptable. Related impurities which are present above the ICH Q3A qualification threshold have been appropriately toxicologically qualified.

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

Batch analysis data for 26 batches of the active substance manufactured throughout the clinical development programme were provided. This includes analysis of 3 commercial scale batches and also includes clinical batches which were manufactured at commercial scale.

3.2.4. Stability

Stability data from three commercial scale batches of the active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) were provided. Photostability testing following ICH guideline Q1B was performed on one batch. Results under stressed conditions in solution phase (acidic, basic, oxidative, and $FeCl_3$) were provided. In the solid phase the active substance was exposed to increased light and increased temperature with and without high humidity.

The parameters tested are similar to those described in the proposed specification with additional parameters included. Additional testing was performed for a specified enantiomeric impurity via chiral HPLC. The results of this testing support that a control for this is not required in the active substance specification as the amount present remains low and below relevant ICH thresholds. Additional testing was also performed for particle size (laser light diffraction) and potential polymorphism was measured by both DSC & XRPD during stability studies. The results of the stability studies support that particle size is not impacted by storage during stability and that DSC is suitable for routine control of polymorphism.

Under long term and accelerated conditions, no relevant changes were observed for any of the parameters tested. The photostability testing shows that the active substance is not sensitive to light. Under stress testing conditions, degradation of the active substance was noted with consequent increases in impurities. In the solution phase, high degradation was observed under oxidative conditions, moderate degradation was seen under acidic and basic conditions, while degradation catalysed by $FeCl_3$ was low. In the solid phase, degradation remained low under all conditions. The studies demonstrate the stability indicating nature of the analytical methods.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container without temperature restrictions.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

The finished product is available as an immediate release tablet containing 60 mg of tolebrutinib. The tablets are film coated, drop-shaped (approximatively 12.7 in length x 7.9 mm in width), orange tablets debossed with "60" on one side.

The aim of development was to create an acceptable immediate release oral solid dosage form, and the quality target product profile (QTPP) outlined in Table 3 was defined during development. This was used to inform the critical quality attributes (CQAs) of the formulation to be evaluated during development which included; assay, uniformity of dosage, dissolution, appearance, identification, water content, degradation products, disintegration, microbiological quality and polymorphism.

Table 3 Quality Target Product Profile

QTPP element	Target
Therapeutic indications	Multiple sclerosis
Drug delivery requirement	Oral immediate release
Dosage form	Film-coated tablet
Dosage strength(s)	60 mg
Dose regimen	Once a day
Dosage form attributes	Drop shape, 12.7x7.9 mm, no scoring, orange film-coated
Primary packaging	Blister[a] or bottle depending on country. Child proof.

a Childproof tamper evidence blister through the use of dose pack as secondary packaging retained for proposed commercial presentation.

The physicochemical properties of active substance which could impact the performance of the finished product are appropriately controlled. The active substance is poorly soluble and relevant controls for the polymorphic form are included in the active substance specification. It has been demonstrated that the polymorphic form of the active substance does not change during manufacture and storage of the finished product

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the non-compendial colouring agents contained in the in-house film coating mixture. The in-house specifications for this coating is acceptable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The applicant has sufficiently described the evolution of the formulation design from initial concept up to the final formulation, including presentation of formulations used in clinical studies. In early clinical development, an oral solution was developed and following this, a 2.5 mg tablet formulation was investigated. The tolebrutinib content of the tablets was increased to 60 mg per tablet together with several minor modifications to the formulation. The final formulation was used during clinical studies and is the same as that intended for authorisation.

The dissolution method development was initially not considered adequate. An MO was raised as the operating parameters and proposed dissolution limit were not sufficiently justified. In addition to this, the discriminatory power of the method had not been sufficiently substantiated. To resolve this the applicant provided further information justifying the selection of the dissolution method and tightening the proposed dissolution specification. It was demonstrated that the method was suitably discriminatory by evaluating the impact of altered process parameters on the dissolution profiles. The proposed dissolution method was therefore considered acceptable in view of the revised limit to be applied for finished product dissolution.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. The manufacturing development was evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. Risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps. Overall, the established in-process controls are considered acceptable and relevant critical process parameters have been adequately identified.

The primary packaging is polyamide/aluminium/poly(vinyl chloride) - aluminium blisters. The materials comply with relevant Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.3.2. Manufacture of the product and process controls

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The manufacturing process consists of seven main steps: weighing, wet granulation, drying & screening, blending, compression, film coating & packaging. The manufacturing process is considered a standard process.

The information with respect to the manufacturing process of the finished product is acceptable, satisfactory information is provided concerning critical steps and in-process controls. The proposed bulk-holding time has been sufficiently justified and is acceptable.

The manufacturing process is considered standard, and the applicant has provided a prospective manufacturing process validation protocol for the finished product. The proposed validation protocol which is to be conducted on three consecutive commercial scale batches is acceptable.

3.3.3. Product specification

The finished product release & shelf life specifications include appropriate tests for this kind of dosage form; appearance), identification, assay, degradation products, a nitrosamine impurity, uniformity of dosage units by content uniformity, dissolution, water content, and microbiological quality.

The specifications and acceptance criteria are acceptable and in accordance with relevant guidelines. The limits for degradation products are acceptable and in accordance with ICH Q3B requirements.

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

The originally provided nitrosamine risk assessment for the finished product was not acceptable. A nitrosamine impurity was detected and the proposed control strategy for this was not acceptable as the applicant's proposed acceptable intake was not considered toxicologically appropriate. An acceptable intake of 400 ng/day based on the carcinogenic potency categorisation approach was considered appropriate, and while this acceptable intake was not exceeded, a limit for this impurity had to be included in the specification of the finished product. The levels present on stability batches were above 10% of the agreed acceptable intake at the 36 month time-point and as an additional mitigation measure the use of a low nitrite content excipient was implemented for future batches. An updated nitrosamines risk assessment was requested along with appropriate control of the impurity in the finished product specifications. To resolve the MO, the applicant suitably controlled the nitrosamine in the specifications of the finished product, and updated their risk assessment to account for all potential and suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

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

Batch analysis results were provided for 22 batches including 3 consecutive commercial scale primary stability batches. The results of the commercial scale batches confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.3.4. Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 36 months under long-term conditions (30 °C/75% RH) and for up to 6 months under accelerated (40 °C/75% RH) conditions were provided. Higher humidity was used than is recommended in ICH Q1 guidance – 75% RH instead of 65% RH. This is acceptable as it presents an increased challenge to stability. The batches of the medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the shelf-life specifications. Additional testing was also performed for enantiomeric purity (chiral HPLC), polymorphism (XRPD), tablet mass, tablet disintegration time and tablet breaking force. Under long term conditions the product remained within specifications; an increase in the nitrosamine impurity was observed at the later time-points tested in the stability batches but the levels remained below the specified limit and relevant acceptable intake. The method used for testing the nitrosamine impurity was not available for the testing of the batches stored under accelerated conditions and for this reason an instruction to store at or below 30 °C is warranted.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not photosensitive.

Stress testing studies have been adequately conducted and revealed suitable stability of the drug product. The results of stress testing experiments are sufficiently discussed, and mass balances have been calculated. Failure to reach mass balance under certain conditions is also discussed and appropriately justified. Based on these studies, the stability indicating character of the analytical methods has been demonstrated.

Based on available stability data, the proposed shelf-life of 36 months not stored above 30 °C as stated in the SmPC is acceptable.

3.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure Quality MOs were raised on the provision of information concerning potential impurities. This included a MO related to the nitrosamine impurities assessment, a MO related to the demonstration of the purge of a potentially mutagenic impurity in the active substance and an MO regarding the control of polymeric forms of the active substance. To resolve these objections the applicant provided information to substantiate that known and potential impurities were appropriately considered and controlled. The nitrosamines risk assessment was revised and a control for a relevant nitrosamine impurity was implemented in the specification of the finished product. It has been demonstrated that the acceptable intake for this impurity is not exceeded during manufacture or storage of the finished product. A MO was also raised concerning the method proposed for dissolution testing of the finished product. To resolve this the applicant demonstrated that the method was appropriate and suitably discriminatory; the limit for dissolution of the finished product was also tightened as requested.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

3.6. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

The non-clinical development of tolebrutinib is comprehensive and generally exceeds the recommendations of prevailing ICH or European guidelines. All pivotal safety pharmacology and toxicology studies were conducted in compliance with GLP.

4.2. Analytical methods

Tolebrutinib and its metabolites were quantified in plasma by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), which was properly validated in compliance with GLP and ICH M10 principles for toxicokinetic determination in non-clinical safety studies. The method was also validated for determination of two impurities in rat plasma. The tissue distribution, brain penetrance, mass-balance and placental transfer of ^{14}C-labelled tolebrutinib was followed by quantitative whole-body autoradiography with liquid scintillation counting and LC-MS/MS. ^{3}H-labelled tolebrutinib, ^{3}H-labelled M2 and other metabolites were additionally used for evaluation of *in vitro* metabolic profiles.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Tolebrutinib potently and comparably inhibited non-receptor tyrosine kinases of the Tec family in biochemical assays, i.e. BTK (half maximal inhibitory concentration (IC_{50}) of 0.7 ± 0.6 nM), BMX, TEC and TXK (IC_{50} of 1.0 - 1.7 nM), whereas the remaining Tec family member ITK required clearly higher inhibitory concentrations (IC_{50} of 365 ± 161 nM). Tolebrutinib also demonstrated high inhibitory potency for the non-receptor Src tyrosine kinase BLK (IC_{50} of 0.6 ± 0.2) and the EGF receptor tyrosine kinase family members ErbB4 (IC_{50} of 1.0 ± 0.1 nM) and EGFR (IC_{50} of 4.1 ± 0.6 nM).

The fast time-dependent BTK inhibition of tolebrutinib endured for up to 24 h. No unbound tolebrutinib was detectable after incubation with excess BTK followed by trypsinisation, which supports the proposed irreversible covalent binding of tolebrutinib to BTK. The BTK inhibition of tolebrutinib resulted in potent interference with the activation of the B cell receptor, in Fcγ and Fcε receptors *in vitro*. Still, tolebrutinib did not affect the function or viability of those cells, which do not express BTK.

The tolebrutinib metabolite M2 unveiled similar IC_{50} and kinetic parameters for BTK blockade like its parent compound, but the efficiency of the BTK inhibition by M2 was 62 % of that of tolebrutinib, based on the biochemical covalent efficiency constant kinact/KI. Accordingly, M2 was about 2-fold less potent than tolebrutinib in the inhibition of B cell activation. Other tolebrutinib metabolites showed less effective BTK inhibition or were not followed, because their polar structures were regarded to hinder their cellular permeation as a prerequisite for effective BTK inhibition.

The BTK inhibition of tolebrutinib resulted in anti-inflammatory *in vivo* effects in the rat model of passive Arthus hypersensitivity reaction and in an experimental autoimmune encephalitis (EAE) mouse model of human MS. Prophylactic oral doses of 0.5, 2 and 5 mg/kg/day tolebrutinib for three days prior to the induction of the Arthus reaction in rats, dose-dependently prevented acute dermal inflammations by up 83.9 to 99.8 % compared to prednisolone-treated controls. The dose-related

inhibition of dermal inflammations by tolebrutinib correlated with dose-dependent BTK occupancy in splenocytes between 72 to 97 %. The prevention of the Arthus reaction by tolebrutinib in rats was therefore attributed to the inhibition of the BTK-mediated FcγR inflammatory signalling.

In the EAE model in mice, prophylactic oral administration of 1 or 5 mg/kg/day tolebrutinib before the onset of symptoms for 28 days dose-dependently reduced the EAE severity as a measure of motor impairments. The amelioration of EAE symptoms at the peak of the disease on day 14 correlated with BTK occupancies of 68 % and 63 % in monocytes from brain and spinal cord preparations and 82 % in peripheral splenocytes at 1 h after dosing of 5 mg/kg tolebrutinib. When tolebrutinib had disappeared from the systemic circulation at 24 h post dose, the BTK occupancy was lower but persisted at 47 % and 25 % in monocytes from brain and spinal cord tissues and 32 % in splenocytes.

A similarly sustained and more pronounced BTK occupancy of each 97 % was confirmed in splenocytes of healthy rats and mice at 1 h after three once daily oral doses of 2 mg/kg and 5 mg/kg tolebrutinib, respectively. Although tolebrutinib was undetectable in plasma by 14 h, BTK occupancies of 80 % in rats and 72 % in mice were determined at 24 h after the third dose. Thus, tolebrutinib confers enduring BTK inhibition *in vivo*.

4.3.1.2. Secondary pharmacodynamics

Secondary PD screening only revealed minor antagonistic activity of tolebrutinib to the dopamine transporter (61.9 %) and agonistic activity at the μ-opioid receptor (54.6 %) *in vitro* at a concentration of 10 μM, which was 370-fold higher than the clinical C_{max} at the maximum recommended human dose (MRHD). No other relevant interactions were identified for tolebrutinib or its M2 and M8 metabolites.

4.3.1.3. Safety pharmacology

Tolebrutinib and its active metabolite M2 concentration-dependently inhibited hERG potassium channel currents with IC_{50} values of each 9.1 μM and 29.3 μM. In a combined cardiovascular and respiratory safety pharmacology study of tolebrutinib in telemetered Beagle dogs, shortened QTcV interval and mild-moderate increases in blood pressure occurred early after 30 mg/kg tolebrutinib suggesting a direct effect on cardiac conduction. However, tolebrutinib did not alter gross behavioural, physiological or neurological functions and body temperature in a modified Irwin test in rats.

4.3.1.4. Pharmacodynamic drug interactions

No PD drug interaction studies have been conducted with tolebrutinib.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

The PK of tolebrutinib was investigated in rats and dogs. Additional studies with the active human M2 metabolite were performed in rats and in mice.

Single oral doses of tolebrutinib were rapidly absorbed between 0.25 – 1 h in female rats and 1 – 2 h in male dogs. Similarly, the orally administered metabolite M2 was quickly absorbed with time to reach the maximum concentration (t_{max}) of 0.5 h in rats and 0.6 h in mice. Peak plasma concentration, C_{max}, was 4-fold higher in rats compared to dogs after oral administration of 20 mg/kg indicating low

absorption in dogs as a consequence of faster metabolism or increased clearance. The oral half-lives of tolebrutinib and M2 were short to moderate in mice, rats and dogs (1.1 to 2.8 h), respectively. The absolute oral bioavailability of tolebrutinib and M2 was generally low in rodents at 2 to 10 mg/kg doses and reached 80 to 100 % following a 10-fold dose increase suggesting saturation of first pass metabolism and clearance. In dogs, the oral bioavailability of tolebrutinib varied at 55.2 % and 82.5 % following 100 mg and 20 mg tolebrutinib solutions administered as oral capsule. In general, bioavailability-dose-relationships for tolebrutinib were opposing between species with decreased bioavailability at a lower dose in rats compared to increased bioavailability at a reduced dose in dogs. The apparent volume of distribution (Vd) for M2 in rats was similar to steady-state volume of distribution (Vss) determined for tolebrutinib. However, M2 was cleared much faster than tolebrutinib (Clearance, 1530 vs 36 mL/min/kg) despite a comparable half-life, indicating that M2 significantly distributed into tissue compared to tolebrutinib. Moreover, while M2 demonstrated similar absorption to that of tolebrutinib, bioavailability and systemic exposure were substantially higher especially at high doses of M2 (100 mg/kg; bioavailability above 95% and area under the time-curve (AUC) above 62000 ng.h/mL in both rodent species).

4.3.2.2. Distribution

Tolebrutinib almost equally distributed between blood and plasma. Tolebrutinib and M2 demonstrated extensive to moderate plasma protein binding. The mean unbound plasma fractions of tolebrutinib were 6.46 % in mice, 4.0 – 4.50 % in rats, 5.64 % in rabbits, 10.8 % in dogs and 11.8 % in humans, whereas those of M2 were 14.9 % in mice, 27.2 % in rats, 15.0 % in dogs, 14.9 % in monkeys and 11.8 % in humans.

Radioactively labelled tolebrutinib widely distributed into tissues of pigmented rats within 2 h after a single oral dose of 30 mg/kg/day. Highest concentrations were determined in the bile duct, gastrointestinal tract, liver, kidney and urinary bladder contents consistent with the sites of absorption and excretion of tolebrutinib. High levels were further detected in the uveal tract/retina > urinary bladder wall > preputial gland > liver > kidney cortex > Harderian gland > adrenal cortex > Meibomian glands. In the liver, the radioactivity remained quantifiable for up to 168 h. At the last time point at 672 h post dose, radioactivity could solely be quantified in blood, skin and uveal tract/retina, suggesting an association with melanin-containing tissues.

In contrast, the radioactivity in brain and spinal cord could only be traced for up to 2 h after administration with low maximum tissue/plasma radioactivity ratios of 0.121 and 0.167, respectively. Still, another investigation with single oral administration of 2 and 5 mg/kg unlabelled tolebrutinib in rats revealed slightly higher C_{max} and AUC-based cerebrospinal fluid/unbound tolebrutinib plasma ratios of 0.32 and 0.29, respectively, indicating modest CNS exposure, as supported by *in vitro* studies showing sufficient BTK potency at this level.

Tolebrutinib-related radioactivity was found to cross the placenta and could be confirmed in foetuses and amniotic sac as well as uterus and placenta of pregnant rabbits. Foetal levels were approximately 14.4 % to 23.3 % of maternal plasma concentrations.

4.3.2.3. Metabolism

Tolebrutinib revealed low metabolic stability with higher metabolism in human compared to animal liver microsomes, hepatocytes or liver S9 fractions *in vitro*. Accordingly, single oral doses of ^{14}C-labelled tolebrutinib were generally more extensively metabolised in humans compared to animals. The extractable plasma radioactivity amounted to just 40.2 % in humans, while it was 85.2 - 89 % in mice, 74.1 – 77.9 % in rats and 65.2 – 67.2 % in dogs. Thus, tolebrutinib is highly metabolised in humans

but only moderate to low metabolised in the animal species, and metabolite profiles differ markedly between animals and humans.

Overall, 21 phase I and four phase II metabolites were identified in human plasma, urine and faeces. The main metabolism of tolebrutinib is the oxidative opening of the piperidine ring, which generates the major carboxylic acid metabolite M8 accounting for 18 % of the human plasma radioactivity in steady state. M8 retains an intact acrylamide moiety but lacks any BTK inhibition (IC_{50} >5000 nM). M8 is formed at similar (rats, rabbits and dogs) or higher levels (mice) in animals compared to humans.

Oxygenation or hydroxylation of the piperidine ring and/or "core" moiety of tolebrutinib results in the formation of the prominent M2 metabolite, which is formed at 4.38 % of total drug-related radioactivity in human plasma but at 5-fold higher levels than tolebrutinib. M2 demonstrated similar covalent BTK inhibition like tolebrutinib *in vitro* (see above) but was only detected at slightly higher exposure levels in female rabbits and is not generated in other animal species.

In addition, modifications of the acrylamide moiety via cleavage, epoxidation and subsequent hydrolysis as well as reductions represent 12.1 % of the dose in humans and 24.9 %, 20.4 %, and 6.77 % of the administered doses in rat, dog and male mouse, respectively. For example, the vicinal diol racemate of the two oxidised diastereoisomers M5/M5a is generated by these modifications. M5/M5a shows less than 50-fold potent BTK inhibition than tolebrutinib and is formed at more than 10-fold higher levels in rats and dogs compared to humans.

All other human metabolites accounted for less than 4 % of the total drug-related radioactivity in the human mass-balance evaluation.

Phase II metabolism of tolebrutinib comprising direct cysteine conjugation of the acrylamide moiety, sulfation (after double oxygenations) and glucuronidation are of negligible importance in humans (1.55 % of the excreted radioactive dose) compared to animals (more than 12 % of the administered dose in all species).

4.3.2.4. Excretion

The excretion of ^{14}C-labelled tolebrutinib was investigated following single oral doses in mice, albino and pigmented rats as well as in dogs. In addition, the biliary excretion of ^{14}C-labelled tolebrutinib was evaluated in bile-duct cannulated rats.

Tolebrutinib was almost completely excreted within the 72 h to 168 h post dose interval in all species. The predominant route of tolebrutinib elimination was via faeces. Most of the administered radioactivity was readily excreted within 48 h in rats and 72 h in dogs lacking any overt differences between sexes. Until 168 h after oral administration, up to 90.4 % of the radioactivity was recovered in faeces of albino and pigmented rats and up to 95.9 % in dogs. Given the shorter 72 h post dose interval in mice, only 79.7 % of the administered radioactive dose were recovered. In line with these observations, 70.7% of the administered radioactivity was excreted via bile over 48 h and 19.5 % in faeces of bile duct-cannulated Wistar rats.

4.3.2.5. Pharmacokinetic drug interactions

Tolebrutinib and its metabolites M2, M5/M5a, M8, M10 and M18 were evaluated for direct and time-dependent inhibition of cytochrome P450 (CYP)1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2J2 and CYP3A4/5. Tolebrutinib and M10 showed potential for inhibition of CYP3A4/5.

The possible induction of CYP1A2, CYP2B6, and CYP3A4 mRNA expression by tolebrutinib and its metabolites M2 or M8 was also investigated in human hepatocytes *in vitro*. The M8 metabolite did not

induce any of these CYP isoforms. Both tolebrutinib and M2 did not induce CYP1A2 but were found to induce CYP2B6 and CYP3A4.

Tolebrutinib and its metabolites were tested as substrates and inhibitors of the common human drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), Organic-anion-transporting polypeptides (OATP)1B1, OATP1B3, Organic Anion Transporter (OAT)1, OAT3, Organic cation transporter (OCT)1, OCT2, Multidrug and toxin extrusion protein (MATE)1, MATE2-K, bile-salt export pump (BSEP) and Multidrug resistance-associated protein 2 (MRP2). A relevant risk was only identified for inhibition of P-gp, BCRP, OATP1B1/1B3, and OCT1/2 by tolebrutinib and by M10 for inhibition of MATE1.

4.4. Toxicology

4.4.1. Repeat-dose toxicity

Repeat-dose toxicity studies with oral administration of tolebrutinib were conducted for up to 26 weeks in rats and 39 weeks in dogs. Rats and dogs were selected because of their pharmacological responsiveness, their common use in toxicology studies and/or the robust historical database. The purity and specified impurity profiles of the tolebrutinib drug substance batches in toxicity studies were representative of the clinical batches. All pivotal toxicity studies included specific immunophenotyping. In addition, the chronic toxicity study in rats was complemented with evaluations of the T cell-dependent antibody response (TDAR) and electrocardiogram (ECG) recordings were integrated into the key toxicity studies in dogs.

Immunophenotyping of B cell, T cell and NK cell subsets in pivotal investigations did not unveil any abnormalities in rats and in toxicity studies for up to 13 weeks in dogs. However, B cell levels were decreased by ~50 % after ≥1 mg/kg/day and ≥3 mg/kg/day tolebrutinib in female and male dogs of the chronic toxicity, which was related to its pharmacological activity.

The TDAR was dose-dependently reduced at ≥2 mg/kg/day tolebrutinib in the chronic toxicity study in rats as evident by lower anti-KLH IgM (up to -42 % in females and up to -78 % in males) and IgG (-31 % to -58 %) compared to vehicle-treated controls. Although these rats were still able to mount an immune response, rectal parasite infestations by nematodes were found at tolebrutinib dose ≥2 mg/kg/day in rats.

Minimal to moderate islet fibrosis and chronic inflammation with islet/peri-islet haemorrhage and haemosiderin deposits in the endocrine pancreas as well as chronic inflammation of acini in the exocrine pancreas with slight haemorrhage was observed following long-term administration of ≥2 mg/kg/day tolebrutinib in the 26 weeks toxicity study in rats. Clinical chemistry parameters of pancreatic function were unchanged in tolebrutinib treated rats. In addition, no dedicated pancreatic toxicity of tolebrutinib was noticed in dogs, except interstitial pancreas oedema, which might have been related to fluid imbalances (see below).

Moderate skin erosion/ulceration with acanthosis/hyperkeratosis, mixed cell inflammation, scabs and/or thinning hair coat was observed at ≥2 mg/kg/day tolebrutinib in the 26 weeks toxicity study in rats. The severity of the dermal lesions necessitated the premature sacrifice of one female and one male rats of the 20 mg/kg/day high dose group. Dogs were obviously less sensitive presenting only with a rough haircoat in 12 mg/kg/day high dose animals during the last treatment weeks of the chronic toxicity study.

Prolonged administration of ≥2 mg/kg/day tolebrutinib over 26 weeks in rats and ≥1 mg/kg/day over 39 weeks in dogs increased the risk for bleeding events in multiple organs. Haemorrhages were most

obvious in the ocular vitreous body and retina of rats, which contained haemosiderin-laden macrophages, but were also found in mesenteric lymph nodes. Ocular haemorrhages in rats were accompanied by protruding eyes at ≥6 mg/kg/day tolebrutinib suggesting increased ocular pressure. In dogs, haemorrhages were more widely detected in mesenteric and retropharyngeal lymph nodes, stomach, colon, ileum, kidneys, testis and ovaries. At higher doses ≥3 mg/kg/day in the chronic toxicity study in dogs, haemosiderin was identified in hepatic Kupffer cells. Nevertheless, thrombocytes, red blood cell and coagulation parameters were not affected in both species.

Minimal interstitial oedema of the pancreas was noticed after doses of ≥8 mg/kg/day tolebrutinib over 4 and 39 weeks in dogs, which was more pronounced and developed in concert with a dilatated lymphatic serosa layer of the gallbladder and ascites in the abdominal cavity after higher doses of 30 mg/kg/day tolebrutinib in the 28 days toxicity study in this species. In view of the concomitantly reduced albumin, globulin, albumin/globulin ratio and total protein levels without changes in electrolyte parameters, these oedematous changes were interpreted as fluid compartment alterations, which were reversible in the 28 days toxicity study in dogs.

The increases of white blood cells, neutrophils and monocytes in female rats administered the 20 mg/kg/day tolebrutinib high dose for 26 weeks and the comparable elevations in dogs of both sexes at doses ≥8 mg/kg/day tolebrutinib for up to 28 days are indicative of the ongoing inflammatory conditions/infections described above.

4.4.2. Genotoxicity

Tolebrutinib was not mutagenic in an Ames test in bacteria. The slight increases in chromosomal aberrations detected in human peripheral blood lymphocytes with and without metabolic activation occurred at cytotoxic concentrations and do not reflect a genotoxic effect of tolebrutinib. Accordingly, no clastogenic findings were observed in a micronucleus test *in vivo* at >4600-fold higher tolebrutinib exposures compared to humans receiving the MRHD.

Similarly, the metabolite M2 was not mutagenic in the Ames test, but weakly induced micronuclei in human peripheral blood lymphocytes *in vitro* with and without metabolic activation. In a subsequent rat micronucleus study combined with a Comet assay in liver and duodenum *in vivo*, M2 did not induce bone marrow micronuclei and did not increase Comet tail intensities in liver or duodenum up to the maximum dose, which translates into a >10000-fold safety margin regarding the human exposure at the MRHD.

4.4.3. Carcinogenicity

The carcinogenic potential of tolebrutinib was assessed in 6 months in Tg RasH2 mouse and 104 weeks rat carcinogenicity studies. Both tolebrutinib at doses up to 330 mg/kg/day and M2, which was tested in a parallel group at 1.75 mg/kg/day, did not induce treatment-related neoplastic or proliferative findings in Tg RasH2 mice. However, *zona fascicularis* hypertrophy was noted in the adrenal cortex reaching statistical significance at doses of 110 and 330 mg/kg.

At the highest doses of tolebrutinib and M2, the plasma concentration of tolebrutinib translates into a >1000-fold safety margin with respect to humans at the MRHD, whereas for M2 at least a >5-fold exposure margin was obtained.

In the rat carcinogenicity study, non-neoplastic findings in the carcinogenicity study were generally consistent with known effects of BTK inhibitors. There were no treatment-related neoplastic or proliferative findings up to the highest doses of 2 and 6 mg/kg/day tolebrutinib resulting in 10-fold and 70-fold AUC-based safety margins regarding the clinical exposure at the MRHD, respectively. Toxicity

findings from the carcinogenicity study were consistent with findings from the 6-month repeat-dose toxicity study of tolebrutinib but were noted at the lowest doses tested (0.25 mg/kg in males an 0.6 mg/kg in females), hence providing a clinically relevant exposure margin of <1.17-fold in males. Findings included immunosuppression (lymphocyte depletion) with increased infection risk (i.e. gastrointestinal nematodes and skin infection) and multiple haemorrhages including intraocular bleedings. Additionally, rat specific pancreatic lesions known from other BTK inhibitors were noted at all doses but no correlation to pancreatic tumours were observed. The severity of intraocular bleedings and skin lesions lead to premature euthanasia in 8 cases (≥0.6 mg/kg males and females) and 12 cases (≥0.25 mg/kg in males and ≥0.6 mg/kg females), respectively.

4.4.4. Developmental and reproductive toxicity

The developmental and reproductive toxicity of tolebrutinib was comprehensively investigated. In the fertility and early embryonic developmental (FEED) study, reductions of mean bodyweight gain (up to -20 %) in the gestation phase after oral administration of the 25 mg/kg/day tolebrutinib high dose suggested maternal toxicity. Nevertheless, the reductions were considered non-adverse, because body weight changes were only of low magnitude, transient and not imposed by altered food consumption. In addition, post-implantation losses were non-dose-dependently increased across all groups with the highest incidence at the 25 mg/kg/day high dose level. However, the mean numbers of live conceptuses were comparable between all groups. Hence, 25 mg/kg/day tolebrutinib did not impact on parental toxicity, male and female fertility and reproductive performance, which was established as no observed adverse effect level (NOAEL).

Embryo-foetal development studies in rats and rabbits were preceded by initial exploratory studies in non-pregnant animals followed by preliminary enabling studies in pregnant animals to facilitate the dose selection. In the pivotal embryo-foetal development (EFD) study in rats, oral doses up to 25 mg/kg/day tolebrutinib did not affect maternal toxicity, pregnancy rate, numbers of *corpora lutea* and implantation sites. The decreased mean gravid uterine weight increased post-implantation loss (early resorptions), decreased number of live foetuses, and minimal decrease in foetal body weight occurred without external, visceral or skeletal malformations. The maternal no observed effect level (NOEL) was 25 mg/kg/day, while the developmental NOEL was 10 mg/kg/day in rats.

Similarly, no effect on maternal toxicity, pregnancy rate, numbers of *corpora lutea*, implantation sites, or gravid uterine weight was observed up to 10 mg/kg/day tolebrutinib in the definitive EFD study in rabbits. Intrauterine parameters (including post-implantation loss, numbers of live and dead foetuses, resorptions), foetal body weight and sex distribution were also not affected. Moreover, no external, visceral or skeletal malformations were evident. Nevertheless, a dose-dependent incomplete ossification of the hyoid bone was seen at doses ≥5 mg/kg. The maternal and developmental NOAEL was considered by the applicant to be 10 mg/kg/day.

The effects of tolebrutinib on pre- and postnatal development (PPND) were evaluated in an exploratory dose-finding approach followed by a pivotal GLP compliant study in rats. In the definitive PPND investigation, no adverse findings were noted for the F0 generation, and the number of stillborn pups was comparable across all groups including controls. The NOAEL for F0 maternal and F1 prenatal and postnatal development was 15 mg/kg/day.

4.4.5. Toxicokinetics and exposure margins

Rats and dogs were in general dose-proportionally exposed to tolebrutinib in toxicity studies. Exposure increased more than dose-proportionally during prolonged administrations in dogs. Female rats were slightly higher exposed than male rats (<2.2-fold), but no sex difference was apparent in dogs.

Extensive safety margins were derived based on the AUC determined at the respective NOAELs or lowest observed adverse effect levels (LOAELs) in repeat-dose toxicity studies in rats and dogs compared to the mean AUC following the MRHD in fed state in humans. The lowest about 30-fold safety margin deduced from the chronic toxicity study in rats remains convenient in terms of clinical safety, because the pancreas and dermal toxicities observed at the LOAEL of 2 mg/kg/day tolebrutinib are established effects of the class of BTK inhibitors, which did not occur in the clinical program of tolebrutinib.

Extensive C_{max}- and AUC-based safety margins were derived in repeat-dose toxicity, genotoxicity and development and reproductive toxicology studies of tolebrutinib and its M2 metabolite.

4.4.6. Local tolerance

Given its oral administration, the local tolerability of tolebrutinib has not been investigated in accordance with the pertinent European guideline (EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1*).

4.4.7. Other toxicity studies

Metabolites

The active metabolite M2 (4.38 % of the total drug-related radioactivity in human plasma, but 5-fold higher levels than tolebrutinib in humans) could only be confirmed at nearly equivalent AUC in female rabbits. For this reason, the oral administration of M2 was separately qualified including GLP compliant chronic toxicity in rats as well as fertility and pre- and postnatal development in rats.

The oral toxicity of the active metabolite M2 was initially explored in a maximum tolerated dose (MTD) study over 3 days in rats. As no mortality was observed, the MTD was not reached. Nonetheless, M2 doses ≥150 mg/kg/day decreased liver weight and hepatic glycogen content, which aggravated to dose-dependent multifocal liver necrosis with sinusoidal cellularity and macrophage aggregates at ≥300 mg/kg/day. M2 further induced oedema and inflammations in the stomach at 150 mg/kg/day that deteriorated to dose-related mucosa atrophy with slight necrotic foci and glandular stomach ulcer at ≥500 mg/kg/day and extended to the non-glandular stomach at 1000 mg/kg/day. In addition, M2 dose-dependently induced mucosa atrophy in the duodenum, caecum, jejunum, ileum, colon and/or rectum at doses ≥300 mg/kg/day, which were accompanied by duodenal ulcer and inflammations. Caecum ulcer was further noticed at 150 mg/kg/day.

In the subsequent GLP compliant 26 weeks repeat-dose toxicity study with a recovery period of 6 weeks in rats, considerably lower oral doses of M2 were tested. One rat administered the 3.5 mg/kg/day low dose, and three animals of the 7 mg/kg/day high dose group had to be prematurely sacrificed at different time points of the study with signs of unilateral ocular protrusions due to intraocular haemorrhage and increased ocular pressure resulting in retinal ganglion layer degeneration. Another rat of the 7 mg/kg/day high dose group and two control rats were early euthanised due to low activity, piloerection, red nasal discharge and pale body colour resulting from gastric blood content.

Upon study termination, surviving rats administered ≥3.5 mg/kg/day M2 revealed increased hair loss and parasite infestation in the intestinal tract correlating with diminished anti-KLH IgM levels in high dose males. Moreover, non-reversible pancreatic islet pigment/fibrosis was noticed in survivors administered ≥3.5 mg/kg/day M2. Thus, a NOAEL was not established.

Mechanistic *in vitro* investigations in human, rat and dog liver spheroids unveiled no relevant cytotoxic potential of tolebrutinib and M2. Transcriptional analyses of these liver spheroid preparations unveiled

similar effects of tolebrutinib and M2, also between species.

Reproductive and developmental toxicities of M2 were evaluated in specific fertility and PPND studies, while EFD effects were assessed in the tolebrutinib rabbit EFD study. In the FEED study with oral administration of M2 in rats, no adverse effects on male and female fertility were identified. The reduced fecundity and fertility indices outside the range of historical controls were restricted to the 3.5 mg/kg/day low dose for both sexes and were therefore not related to M2 treatment. The NOAEL was 7 mg/kg/day.

In the PPND study in rats, the oral dose of 7 mg/kg/day M2 reduced the mean pre-weaning female pup weight, which was not considered adverse given the transient nature and low magnitude. Like in the FEED study, reduced fecundity and fertility indices were observed for both sexes in the F1 generation from F0 females treated with the 3.5 mg/kg/day low dose in the PPND study. Nevertheless, the indices remained above 70 % of controls and were normal in the high dose group. Findings of slight delay in pinna unfolding, balanopreputial cleavage and latency in some neurobehavioral tests (especially in male F1) were noted at dose of both 3.5 and 7 mg/kg but considered unrelated to tolebrutinib. The applicant considered 7 mg/kg as NOAEL for both F0 maternal and F1 pre- and postnatal developmental effects.

Impurities

Potential mutagenic impurities from upstream starting material of tolebrutinib, including reagents, intermediates, solvents, known/observed and predicted impurities of tolebrutinib synthesis were assessed in accordance with ICH M7(R2) requirements. As follow up of validated *in silico* predictions, several impurities were tested negative in GLP-conform Ames tests. All mutagenic impurities are controlled below the threshold of toxicological concern of 1.5 µg/day.

Some non-mutagenic impurities were toxicologically qualified based on additional negative genotoxicity data and repeat-dose toxicity studies with spiked batches of tolebrutinib.

One new N-nitrosamine impurity was identified, for which an acceptable intake (AI) of 400 ng/day was determined by the Carcinogenic Potency Categorisation Approach. The impurity was subsequently tested negative in an enhanced Ames Test (EAT), which had limitations in terms of high amount of DMSO solvent und structurally divergent positive controls. To further clarify the mutagenic risk, a GLP-conform transgenic rodent mutation assay using male Fischer F344 Big Blue® transgenic rats was performed. N-nitrosamine impurity was positive for the induction of mutant frequencies (MF) at the *cII* gene in the liver at 75 mg/kg/day. There was a statistically significant increase in MF at 37.5 mg/kg/day, but this increase was claimed to be biologically irrelevant by the study director. No increases in MF were noted in duodenum. Consequently, the NOAEL in this assay was suggested at 37.5 mg/kg/day.

Phototoxicity

Tolebrutinib was found to distribute into the uveal tract and pigmented skin in rats. In addition, the molar extinction coefficient was >1000 L mol^{-1} cm^{-1} at 290 nm. In line with ICH S10 guidance, a follow up *in vitro* 3T3 neutral red uptake assay was performed which yielded negative results. In conclusion, tolebrutinib can be considered as not phototoxic.

4.4.8. Ecotoxicity/environmental risk assessment

Table 4 Summary of main study results: Phase I

Substance (INN/Invented Name):	Tolebrutinib
CAS-number (if available):	1971920-73-6

PBT/vPvB screening			
Study type	***Test protocol***	***Result***	***Conclusion***
Bioaccumulation potential- log Kow	OECD107	2.36 at pH 5 2.97 at pH 7 3.06 at pH 9	Potential PBT: N

PBT/vPvB assessment			
Property	***Parameter***	***Result***	***Conclusion***
Bioaccumulation	log Kow	3.06 at pH 9	Potentially not B
	BCFssL	2.6 L/kgww	Not B
Persistence	Ready biodegradability	N	Potentially P
	DT50, sediment at 12°C	791 d	vP
Toxicity	NOEC aquatic fish	1.11 mg/L	not T
PBT/vPvB statement:	Tolebrutinib is considered to be not PBT, nor vPvB		

Phase I			
Parameter	***Value***	***Unit***	***Conclusion***
PECsw, default	0.0136	µg/L	≥0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Table 5 Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	***Test protocol***	***Result***	***Remarks***
Water solubility	OECD 105	86.02 mg/L at 5 9.86 mg/L at 7 10.59 mg/L at 9	shake flask 20°C
Dissociation in Water	OECD 112	no pKa value was determined	
Adsorption-Desorption Soil 1 = loamy sand	OECD 106	$K_{FOC, soil\ 1}$ = 3500.79 L/kg$_{oc}$	
Soil 2 = loam		$K_{FOC, soil\ 2}$ = 2347.57 L/kg$_{oc}$	
Soil 3 = clay		$K_{FOC, soil\ 3}$ = 8025.84 L/kg$_{oc}$	
Sludge 1 = Rural		$K_{FOC, sludge\ 1}$ = 768.13 L/kg$_{oc}$	
Sludge 2 = Urban		$K_{FOC, sludge\ 2}$ = 876.47 L/kg$_{oc}$	
Ready Biodegradability Test	OECD 301	0 % (28 d) not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = silt loam (Calwich Abbey)	OECD 308	$DT_{50, water\ 1}$ = 8.1 d $DT_{50, sediment\ 1}$ = 72.4 d $DT_{50, whole\ system\ 1}$ = 35.2 d CO_2 = 0.6 % NER_{total} = 63.5 % $NER_{type\ I}$ = 5.4 %	20 °C CO_2 and NER values at test end
Sediment 2 = sand (middle pond)		$DT_{50, water\ 2}$ = 12.8 d $DT_{50, sediment\ 2}$ = 370 d	20 °C CO_2 and NER values at

		$DT_{50,\ whole\ system\ 2}$ = 85.9 d CO_2 = 0.5 % NER_{total} = 45.4 % $NER_{type\ I}$ = 4.6 %			test end
Transformation products		>10% = N			
Phase II Aquatic effect studies					
Study type	***Test protocol***	***Endpoint***	***Value***	***Unit***	***Remarks***
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOEC / EC_{10}	1280	µg/L	Growth rate
Daphnia sp., Acute Immobilisation Test/ *Daphnia magna*	OECD 202	EC_{50}	>13000	µg/L	Immobilisation
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	EC10	802	µg/L	Reproduction per surviving adult
Fish, ELS / *Danio rerio*	OECD 210	NOEC	1110	µg/L	Mortality
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	10^4	µg/L	Total respiration, value is ≥water solubility
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD 218	NOEC	40.8	mg/kgdw	Emergence rate, 2.24% o.c.
Phase II Secondary poisoning					
Bioaccumulation Test/ *Danio rerio*	OECD 305	BCFssL,1 = BCFssL,2 =	n.d. 2.6	L/kg_{ww} L/kg_{ww}	%lipids: 5% Data at test conc. 1 <LOD for all samples; no depuration phase → no kinetic BCFkgl determinable
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	0.136 µg/L	1000 µg/L	0.00014		No risk
Surface water	0.0136 µg/L	80.2 µg/L	0.00017		No risk
Groundwater	0.0034 µg/L	8.02 µg/L	0.0004		No risk
Sediment	0.011 mg/kg dw	0.408 mg/kg dw	0.027		No risk

Considering the above data, tolebrutinib is not expected to pose a risk to the environment.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Primary pharmacodynamics

Tolebrutinib demonstrated potent inhibition of BTK, other non-receptor tyrosine kinases of the Tec family (BMX, TEC and TXK), the Src tyrosine kinase BLK as well as the EGF receptor tyrosine kinase family members ErbB4 and EGFR in a comparable range (IC_{50} of 0.7 ± 0.6 nM vs. 0.6 – 4.1 nM). Despite the pronounced inhibitory affinity of tolebrutinib for these tyrosine kinases in biochemical assays, only the presumptive inhibitions of EGFR and LCK were subsequently followed and required clearly higher concentrations of tolebrutinib in cell culture experiments. In contrast, the possible inhibitions of BMX, TEC, TXK, BLK, and ErbB4 were not further clarified *in vitro*. Of note, the individual or concomitant potency of BTK and TEC inhibition were earlier postulated to impact on the clinical bleeding risk by impairing platelet aggregation (Chen *et al*., 2018; Lipsky and Lamanna, 2020). However, later investigations suggested the involvement of targets other than TEC (von

Hundelshausen and Siess, 2021; Duan *et al*., 2021). The clinical relevance of the biochemically identified inhibition of BLK and ErbB4 by tolebrutinib were also not elucidated. Nevertheless, the toxicities observed after multiple administrations of tolebrutinib in animals are largely consistent with those known from the presently licensed BTK inhibitors ibrutinib, zanubrutinib, acalabrutinib and pirtobrutinib. These BTK inhibitors share an overlapping inhibitory receptor profile with tolebrutinib, particularly with those tyrosine kinase receptors, which harbour a comparably positioned cysteine like BTK in their active domain (BMX, TEC, TXK, BLK, EGFR, erbB4; reviewed by Estupiñan HY *et al.* 2021; see also EPARs of *"Imbruvica"*, EMEA/H/C/3791; *"Brukinsa"*, EMEA/H/C/4978; *"Calquence"*; EMEA/H/C/5299; *"Jaypirca"*, EMEA/H/C/5863). It can therefore be concluded that tolebrutinib primarily inhibits BTK which has been considered for section 5.1 of the SmPC.

The BTK inhibition of tolebrutinib was generally fast, enduring and in line with an irreversible covalent binding. Mutation scanning analysis stressed the importance of cysteine 481 in the catalytic site of BTK as the target for the inhibitory effect of currently licensed BTK inhibitors (Hamasy *et al*., 2017; Estupiñán *et al*., 2021). The molecular structure of tolebrutinib contains the same acryloyl moiety, which is responsible for covalent binding of ibrutinib and zanubrutinib to Cys481 of BTK, so the same interaction may be assumed (Estupiñan HY *et al.*, 2021). However, other BTK inhibitors interact with BTK differently (Estupiñan HY *et al.*, 2021; Lin DY and Andreotti AH, 2023), so defining the exact interaction would require further experimental confirmation.

By inhibiting BTK, tolebrutinib potently interfered with activation of the B cell receptor and Fc receptors *in vitro*. The dose-dependent and anti-inflammatory effects resulting from the BTK inhibition by tolebrutinib were shown in the rat model of passive Arthus hypersensitivity reaction and the EAE mouse model of human MS *in vivo*. PK/PD correlations in the EAE disease model and in healthy rats and mice further suggest the endurance of the BTK occupancy at 24 h post dose, when tolebrutinib had disappeared from the systemic circulation. However, therapeutic activity defined as requiring >90 % BTK occupancy sustained over 24 h was not achieved *in vivo* in the disease model (EAE mice), neither in the peripheral nor central compartment. Considering that nonclinical evidence generated in healthy animals does not reliably predict BTK occupancy and durability in diseased animals, the claim for overall efficacy (especially CNS efficacy) will need to rest on clinical trial results.

The applicant relates the BTK inhibition of tolebrutinib primarily to effects on B cells, macrophages and microglia in line with the importance of these cellular populations for MS pathology in human patients and pertinent animal models (Krämer J *et al.*, 2023; Elkjaer ML *et al.*, 2023; Li C *et al.*, 2025). Nonetheless, BTK protein levels were found to be comparable in T and B cells and the BTK inhibition with another compound not only altered predominantly the gene expression in microglia but also changed that in T cells in the EAE mouse model of human MS (Xia S *et al*., 2020; Gruber RC *et al*., 2024). Similar to BTK, tolebrutinib inhibited TXK, which together with the Tec family member ITK exerts a well-established role in T cell development (Atherly LO *et al.*, 2006). In the chronic toxicity studies, tolebrutinib reduced the TDAR at ≥2 mg/kg/day in rats and B cell counts at ≥1 mg/kg/day in dogs (see below). Concomitantly, tolebrutinib doses of 3 mg/kg/day slightly reduced total T cells and CD4+ T helper cells in male dogs, while the 12 mg/kg/day tolebrutinib top dose increased CD8+ cytotoxic T cells and CD4+/CD8+ T cells in females. These T cell alterations in dogs were interpreted as unrelated to tolebrutinib, because they were not markedly different from pre-dose levels. Although an impact of tolebrutinib on T cell populations can still not be excluded, this apparently explains the higher susceptibility of animals and human patients for infections. Still, the possible T cell contribution to the pharmacological activity of tolebrutinib seems to be of subordinate relevance compared to B cells, macrophages and microglia.

Overall, the primary PD investigations support the claimed anti-inflammatory activity of tolebrutinib, although the presented data do not allow to specifically disentangle the impact of tolebrutinib on specific immune subsets. Hence, the efficacy of the proposed oral dose of 60 mg/day tolebrutinib

needs to be demonstrated in human SPMS patients.

Secondary pharmacodynamics

The minor secondary PD interactions of tolebrutinib with the dopamine transporter and the μ-opioid receptor are clinically irrelevant, because they required >370-fold higher tolebrutinib concentrations than the mean C_{max} in patients receiving the MRHD of 60 mg.

Safety pharmacology

Safety pharmacological effects of tolebrutinib on vital functions were adequately tested in core battery studies in line with ICH S7A and ICH S7B requirements (CPMP/ICH/539/00, CPMP/ICH/423/02).

The IC_{50} for hERG channel inhibition by tolebrutinib of 9.1 μM (4.13 μg/ml) is more than 2900-fold higher than the unbound clinical $C_{max,u}$ of tolebrutinib in RMS patients at the MRHD (1.42 ng/ml). The IC_{50} of the M2 metabolite for inhibition of hERG currents of 29.3 μM (13.3 μg/ml) is even more than 3900-fold above the unbound clinical $C_{max,u}$ of M2 in RMS patients at the MRHD of tolebrutinib (3.34 ng/ml). It is noted that the M2 metabolite was not further evaluated in safety pharmacology *in vivo* studies.

In a combined cardiovascular and respiratory safety pharmacology study of tolebrutinib in telemetered dogs, no QTc prolongations were observed. Rather, tolebrutinib caused QTc interval shortening (at 30 mg/kg), along with a mild to moderate, dose-dependent increase in blood pressure (at ≥2 mg/kg). These effects appeared related to tolebrutinib and while shortened QTc interval is an important risk marker for atrial fibrillation, effects occurred far above clinically relevant exposures. In SPMS patients enrolled in phase 3 clinical trials, four cases of atrial fibrillation/atrial flutter occurred, which is a known class effect of BTK inhibitors (ibrutinib, acalabrutinib, pirtobrutinib).

Tolebrutinib did not affect neurological functions in a modified Irwin test in rats. Although the tolebrutinib exposure was not determined, it may be the extrapolated from the 28 days repeat-dose toxicity study in rats. At the NOAEL of 30 mg/kg/day, the peak plasma levels derived from the toxicity study correspond to a substantial >200-fold safety margin with respect to the clinical exposure of RMS patients receiving the MRHD.

Pharmacokinetics

Analytical determinations of tolebrutinib and its metabolites M2 and M5/M5a in plasma used LC-MS/MS methodology, which was properly validated in compliance with GLP and the principles of the ICH M10 guideline (EMA/CHMP/ICH/172948/2019).

Pharmacokinetic investigations revealed the rapid oral absorption of tolebrutinib and its M2 metabolite across species (0.25 – 2 h), which might be impacted by dose, species differences and formulation particulars. The oral bioavailability was low in rats and moderate in dogs. The plasma half-life of tolebrutinib ranged between 2.6 h and 10.9 h in rats and between 1.5 h and 2.2 h in dogs. Generally, interspecies differences in PK profiles were notable.

Tolebrutinib showed extensive binding to plasma proteins of mice, rats and rabbits and moderately bound to plasma proteins of dogs and humans, respectively. The M2 metabolite revealed similar protein binding like tolebrutinib in the range of 0.3 to 10 μM across species.

Tolebrutinib widely distributed into tissues and was detectable in the CNS of rats within 2 h. Although the maximum tissue/plasma ratios were low for brain and spinal cord, the top concentrations in CSF of each 2.78 ng/ml and 9.69 ng/ml after the 2 mg/kg and 5 mg/kg oral doses in rats coincide with the IC_{50} values determined for BTK inhibition of tolebrutinib in human whole blood, Ramos B lymphoma cells and microglia (IC_{50} of 0.2 – 4.6 ng/ml). Tolebrutinib-related radioactivity was also found to cross the placenta and was detected in foetuses, amniotic sac, uterus and placenta of pregnant rabbits. The

possible milk transfer of tolebrutinib was not determined but appropriate safety measures have been adopted into the SmPC based on clinical PK-modelling which suggests a risk of distribution into breastmilk of both M2 and tolebrutinib.

Tolebrutinib unveiled clearly lower metabolic stability in plasma of humans compared to all animal species and the metabolite profiles also differ markedly between animals and humans *in vivo*. The main human metabolite is M8 (18 % of the human AUC), which does not inhibit BTK, possibly due to the opened piperidine ring that renders its conformation less rigid. M8 showed no secondary PD interactions and is formed at similar (rats and dogs) or higher levels (mice) in animals compared to humans. It is also generated by rat S9 fraction and was, hence, concomitantly tested with tolebrutinib for genotoxicity *in vitro* and *in vivo*. It is therefore agreed that no further toxicological characterisation of M8 was performed.

The active metabolite M2 is generated by oxygenation/hydroxylation (4.38 % of the human AUC), demonstrated similar covalent BTK inhibition like tolebrutinib *in vitro* (IC_{50} of 7.25 – 9.78 nM vs. 4.13 – 4.87 nM) and lacks any secondary PD activity. Like tolebrutinib, M2 demonstrated rapid dose-related oral absorption in rodents. Contrary to other animal species, M2 only reached slightly higher exposure in female rabbits (rabbit/human plasma ratio of 1.35). For this reason, the toxicological properties M2 were further characterised including hERG interaction, chronic toxicity in rats, a standard genotoxicity battery, carcinogenicity in mice, fertility and pre-/postnatal development of rats (see below).

Another metabolite is the racemate of the oxidised M5/M5a diastereomers, which demonstrated less than 50-fold potent BTK inhibition than tolebrutinib and was initially considered a main metabolite until this was later disproven in the human mass-balance study (1.3 % of the human AUC). Accordingly, the exposure of M5/M5a was only determined in repeat-dose toxicity studies and no further investigations are warranted. No other human metabolites exceeding 10 % of the total tolebrutinib-related AUC were identified in the human mass-balance study *in vivo*, which necessitated further toxicological characterisation in line with ICH M3(R2) requirements (EMA/CPMP/ICH/286/1995).

Phase II conjugations are of higher importance in the conversion of tolebrutinib in animals than in humans and it should be noted that the different metabolic profiles across animal species and humans are also reflected in the divergent toxicities compared to adverse events in human patients.

The excretion of tolebrutinib in animals generally coincides with the human mass-balance evaluation in healthy male volunteers, which recovered 78 % of the single 60 mg dose of ^{14}C-labelled tolebrutinib in faeces and 14 % in urine. 85 % of the administered radioactivity was excreted within 72 h post dose in humans. Of note, the licensed BTK inhibitors ibrutinib, zanubrutinib and acalabrutinib are also predominantly excreted by the faecal route in animals and humans (see EPARs of *"Imbruvica"*, *"Brukinsa"* and *"Calquence"*), while this was demonstrated for pirtobrutinib only in animals (EPAR of *"Jaypirca"*).

The potential of tolebrutinib for drug interactions was investigated in accordance with ICH M12 guidance, which allowed to exclude a clinically relevant risk for inhibition and induction of CYP isozymes.

The investigations of tolebrutinib and its metabolites as substrates and inhibitors of common human drug transporters also followed ICH M12 recommendations taking earlier EMA and FDA guidelines into consideration. Using the static approach prediction with unbound maximum drug concentrations according to the ICH M12 and previous EMA and FDA guidances, the applicant identified a relevant risk for inhibition of P-gp, BCRP, OATP1B1/1B3, and OCT1/2 by tolebrutinib and by M10 for inhibition of MATE1. However, PBPK modelling is claimed to indicate a highly unlikely risk for interaction of tolebrutinib or its metabolites with any of these drug transporters. This aspect is therefore clinically pursued (see clinical assessment).

Repeat-dose toxicity

Repeat-dose toxicity studies with oral administration of tolebrutinib were conducted for up to 26 weeks in rats and 39 weeks in dogs according to ICH M3(R2) recommendations (EMA/CPMP/ICH/286/1995). Apart from initial 14-day exploratory dose-range finding studies, all pivotal studies complied with GLP. The selected doses in the tolebrutinib repeat-dose toxicity studies generally exceeded the 50-fold margin of exposure with respect to humans recommended by ICH M3(R2), except the 26-week chronic toxicity study in rats where pancreas and dermal toxicities were dose-limiting. Of note, the lack of specific recovery periods in the 26-week and 39-week toxicity studies in rats and dogs can be accepted in accordance with ICH M3(R2) requirements, because all detected toxicities are known from licensed BTK inhibitors, were predominantly induced at clinically irrelevant high tolebrutinib exposure levels, mainly found to be reversible in short-term investigations and/or can be readily monitored in humans. Overall, adverse effects of tolebrutinib in repeat-dose toxicity studies in rats and dogs appeared to develop dose- and time-dependently, which is important regarding the intended chronic clinical treatment. For example, the observed toxicities in the 2-year carcinogenicity study in rats (immune suppression, skin lesions and haemorrhagic-tendency) supported that prolonged tolebrutinib treatment appeared to lower the exposure levels for toxicities to the clinically relevant area of concern (appr. 1-fold), which has been adequately considered for section 5.3 of the SmPC taking the intended chronic clinical treatment regimen in SMPS into account. As delineated below, the toxicities observed in the toxicological investigations only partially overlap with clinical events, which could reflect the marked differences in the pharmacokinetic/metabolite profiles between animals and humans. As a consequence, the deviating target organs of toxicity (e.g. liver in humans but not in animals) limits the predictive value of the models. Nevertheless, findings were generally congruent with established scientific knowledge from licensed BTK inhibitors.

Immunophenotyping in repeat-dose toxicity studies of tolebrutinib did not unveil any abnormalities of B cell, T cell and NK cell subsets in rats and in dogs treated for up to 13-week. However, tolebrutinib doses ≥1 mg/kg/day decreased B cell levels in the chronic toxicity in dogs, which was related to its pharmacological activity. Similarly, tolebrutinib dose-dependently reduced the TDAR at ≥2 mg/kg/day in the chronic toxicity study in rats, which was accompanied by a higher susceptibility of the animals for parasite infestations and coincides with clinical events. A higher risk for infections is also known for the licensed BTK inhibitors ibrutinib, zanubrutinib, acalabrutinib and pirtobrutinib (see EPARs of *"Imbruvica"*, *"Brukinsa"*, *"Calquence"*, *"Jaypirca"*). In accordance with the weight-of-evidence review recommended by the ICH S8 guideline (CHMP/167235/2004), further investigations of immunotoxicity are therefore not required and the appropriateness of the warning in section 4.4 of the proposed SmPC was addressed from a clinical perspective.

Following long-term administration of ≥2 mg/kg/day tolebrutinib in the 26 weeks toxicity study in rats, islet fibrosis and chronic inflammation of the pancreas with islet/peri-islet haemorrhage and haemosiderin deposits was observed without any changes in clinical chemistry parameters. Pancreatic toxicity in dogs was restricted to interstitial pancreas oedema, which might have been related to fluid imbalances. Nevertheless, pancreas toxicity is a class effect of BTK inhibitors and has been comparably observed in repeat-dose toxicity studies of ibrutinib, zanubrutinib, acalabrutinib, pirtobrutinib and fenebrutinib in rats but not in other species including humans (see EPARs of *"Imbruvica"*, EMEA/H/C/3791; *"Brukinsa"*, EMEA/H/C/4978; *"Calquence"*; EMEA/H/C/5299; *"Jaypirca"*, EMEA/H/C/5863; Erickson *et al*., 2017). With respect to the well-known species-specificity of the pancreas toxicity of BTK inhibitors in rats, no further clinical measures are warranted.

Tolebrutinib doses ≥2 mg/kg/day also induced moderate skin erosion/ulceration with acanthosis/ hyperkeratosis, mixed cell inflammation, scabs and/or thinning hair coat in the chronic toxicity study in rats. The severity of the dermal lesions necessitated the premature sacrifice of two rats of the 20 mg/kg/day high dose group. Dogs were obviously less sensitive presenting only with a rough

haircoat at doses of 12 mg/kg/day during the last treatment weeks of the 39-week toxicity study. Adverse skin findings including the very common rash were noted with other BTK inhibitors in humans (see SmPCs of *"Imbruvica"*, *"Brukinsa"*, *"Calquence"* and *"Jaypirca"*) and have been linked to the off-target inhibition of EGFR, although other off-targets might be additionally involved. Dermal findings developed in tolebrutinib-treated rats with an about 30-fold safety margin regarding the clinical AUC at the MRHD and were not significantly imbalanced in the clinical program of tolebrutinib. Therefore, the clinical risk seems to be minor.

Prolonged administration of ≥2 mg/kg/day tolebrutinib over 26 weeks in rats and ≥1 mg/kg/day over 39 weeks in dogs increased the risk for bleeding events in multiple organs. Haemorrhages were most obvious in the ocular vitreous body and retina of rats, which contained haemosiderin-laden macrophages, but were also found in mesenteric lymph nodes. Ocular haemorrhages in rats were accompanied by protruding eyes at ≥6 mg/kg/day tolebrutinib suggesting increased ocular pressure. At the 20 mg/kg/day high dose level, ocular haemorrhages in combination with dermal lesions necessitated the premature sacrifice of four rats. In dogs administered 1 mg/kg/day tolebrutinib, haemorrhages were more widely detected in mesenteric and retropharyngeal lymph nodes, stomach, colon, ileum, kidneys, testis and ovaries. At higher doses ≥3 mg/kg/day, haemosiderin was identified in hepatic Kupffer cells. Nevertheless, thrombocytes, red blood cell and coagulation parameters were not affected in neither rats nor dogs. The increased bleeding tendency in multiple organs of dogs in the 9-month toxicity study at tolebrutinib doses of 1 mg/kg/day or above corresponded to an exposure margin of 15-fold the clinically relevant exposure.

An increased tendency to bruise and heavy menstrual bleeding were common during clinical treatment with tolebrutinib. Bleeding events were also very commonly reported for the licensed BTK inhibitors ibrutinib, zanubrutinib, acalabrutinib and pirtobrutinib (see EPARs of *"Imbruvica"*, *"Brukinsa"*, *"Calquence"*, *"Jaypirca"*). The underlying mechanisms of the bleeding risk are not understood and have been formerly related to the individual or concomitant inhibition of BTK and TEC, because both tyrosine kinases are involved in platelet aggregation (Chen *et al*., 2018; Lipsky and Lamanna, 2020). In fact, tolebrutinib showed comparable IC_{50} values for BTK and TEC (0.7 vs. 1.0 nM). However, more recent evaluations suggest the involvement of additional off-targets (von Hundelshausen and Siess, 2021; Duan *et al*., 2021). The observed intraocular haemorrhage is a very specific haemorrhagic event in rats, where it was noted as the primary cause of pre-mature euthanasia across studies. In addition to the occurrence in the 6-month chronic toxicity study of tolebrutinib in rats from doses ≥2 mg/kg, intraocular haemorrhages were also seen following 2-years treatment in the rat carcinogenicity study at doses ≥0.6 mg/kg tolebrutinib and for M2-treated rats in the 6-month toxicity study at the lowest dose of 3.5 mg/kg. Both studies revealed clinically relevant exposure margins of just 2.9- and <6-fold, respectively. Moreover, the eye was identified as one prominent tissue of tolebrutinib distribution relative to other tissues and persistence in the dedicated QWBA distribution study in rats.

Interstitial pancreas oedema was noticed in dogs after doses of ≥8 mg/kg/day tolebrutinib over 4 and 39 weeks, which was more pronounced and extended to a dilatated lymphatic serosa layer of the gallbladder and ascites in the abdominal cavity after elevated doses of 30 mg/kg/day tolebrutinib in the 28-day toxicity study in this species. In view of the concomitantly reduced plasma proteins (albumin, globulin, albumin/globulin ratio and total protein) without changes in electrolyte parameters, these oedematous changes were interpreted as fluid compartment alterations, which were reversible in the 28-day toxicity study in dogs. Oedema had been also identified in the 13-week toxicity study with ibrutinib in rats and as a clinical adverse event with ibrutinib and pirtobrutinib (see EPARs of *"Imbruvica"* and *"Jaypirca"*). In contrast, the clinical risk appears less pronounced for other BTK inhibitors like zanubrutinib (Tam *et al*., 2020) and no significant imbalances were found in peripheral oedema events in the clinical program of tolebrutinib. Since the NOAEL for oedema formation in the chronic toxicity study in dogs of 3 mg/kg/day translates into a >70-fold safety margin regarding the

clinical AUC at the MRHD, the clinical oedema risk of tolebrutinib is regarded negligible.

Non-formed liquid faeces were apparent following prolonged dosing ≥1 mg/kg/day tolebrutinib in the 39-week toxicity study in dogs and diarrhoea was frequent in the clinical program of tolebrutinib. Diarrhoea has been commonly reported for other licensed BTK inhibitors and might be related to EGFR off-target inhibition (see SmPCs of *"Imbruvica"*, *"Brukinsa"*, *"Calquence"*, *"Jaypirca"*; Lipsky and Lamanna, 2020). See clinical evaluation for further relevance of this finding.

These tolebrutinib-related toxicity findings in rats and dogs have been sufficiently presented in the SmPC section 5.3, considering also the lowered exposure margin to the clinically relevant area of concern upon prolonged tolebrutinib treatment.

Genotoxicity and carcinogenicity

Tolebrutinib and its active metabolite M2 did not show any clinically relevant genotoxic potential in standard battery *in vitro* and *in vivo* genotoxicity studies in line with the ICH S2(R1) guideline.

No carcinogenic potential of tolebrutinib or M2 were revealed in the 2-year carcinogenicity study in rats. Toxicities in the carcinogenicity study were consistent with those in the 6-month repeat-dose study of tolebrutinib but emerged at the lowest dose tested which correlated with a clinically relevant exposure margin of <1.2-fold in males and 4.4-fold in females the tolebrutinib AUC at the MRHD. Findings included immunosuppression (lymphocyte depletion) with increased infection risk (i.e. gastrointestinal nematodes and skin infection) and multiple haemorrhages including intraocular bleedings. Additionally, rat specific pancreatic lesions known from other BTK inhibitors were noted at all doses but no correlation to pancreatic tumours were observed. The severity of intraocular bleedings and skin lesions led to premature euthanasia at low doses in 8 and 12 cases, respectively. These observations indicate a clear time-dependency of the tolebrutinib toxicity, which is important for the intended chronic treatment regimen in SPMS patients and is therefore reflected in the SmPC.

Developmental and reproductive toxicity

A considerable program of developmental and reproductive toxicity studies was provided. The transient maternal toxicity in the tolebrutinib FEED study was not adverse. Despite the non-dose-dependently increased post-implantation losses, the mean numbers of live conceptuses were comparable between all groups. Unfortunately, no historical control data of post-implantation losses were provided. Increased post-implantation losses were also found at the same 25 mg/kg/day dose in the pivotal rat embryo-foetal development study but were not observed at the NOAEL of 10 mg/kg/day in the EFD study, which corresponds to a substantial 160x safety margin regarding the human AUC at the MRHD. The proposed NOAEL of 25 mg/kg/day tolebrutinib for parental toxicity, male and female fertility and reproductive performance is therefore accepted.

In the EFD studies of tolebrutinib, no foetal malformations, maternal toxicity or impact on pregnancy rate, numbers of *corpora lutea* and implantation sites were observed at oral doses up to 25 mg/kg/day tolebrutinib in rats and 10 mg/kg/day in rabbits. However, decreased mean gravid uterine weight, increased post-implantation loss (early resorptions), decreased number of live foetuses, and minimal decrease in foetal body weight were evident in rats.

In rabbits, a dose-dependent effect on incomplete ossification of the hyoid bone was seen in the absence of maternal toxicity at doses of ≥5 mg/kg, and its incidence exceeded that of historical controls at doses of 5 and 10 mg/kg/day (16.9 % and 22.1 %, respectively). The safety margin of tolebrutinib was sufficiently high at the NOAEL of 10 mg/kg/day, but the exposure of the M2 metabolite was less than 1.3-times the steady-state AUC of M2 at the MRHD of tolebrutinib. Hence, a relationship to tolebrutinib-treatment/M2 exposure including a specific impact on foetal ossification cannot be excluded (see below).

In the PPND study, tolebrutinib doses up to 15 mg/kg/day did not adversely affect the F0 generation and the numbers of stillborn pups. Albeit the numbers of dead/missing pups were increased within the pre-weaning period in the 15 mg/kg/day high dose group, this increased number does not appear to be tolebrutinib-related, because pups from only 4 out of 24 litters were affected and the pups were sacrificed either due to maternal moribund condition, or general clinical signs of the pups (skin: abnormal colour, pale temperature, cool to touch, missing milk band). Hence, no remarkable tolebrutinib-related adverse effects or clinical sings on PPND were observed and the proposed NOAEL of 15 mg/kg/day is agreed.

Plasma exposure was not measured in PPND studies. Nevertheless, the AUC at the NOAEL of 15 mg/kg/day was estimated using the exposure at 25 mg/kg/day in the EFD study in rats and, assuming dose proportionality, translates into a 447-fold safety margin regarding human levels at the MRHD. Similarly, the exposure at the NOAEL of 25 mg/kg/day for male fertility was derived from the AUC determined at 30 mg/kg/day in the 28 days repeat-dose toxicity study in rats and yields a 247-fold safety margin with respect to humans receiving the MRHD.

Dependence

Tolebrutinib and its metabolites did not show relevant interactions with targets involved in dependence *in vitro* and did not induce behavioural impairments or withdrawal phenomena *in vivo* with adequate exposure margins. Moreover, tolebrutinib does not exert a novel mode of action but belongs to the well-known class of BTK inhibitors with several licensed members in the EU. In accordance with the tiered approach of the pertinent EU guideline (EMEA/CHMP/SWP/94227/2004), specific evaluations of the dependence potential are therefore not required.

Metabolites

The systemic toxicity of the active metabolite M2 has been separately qualified in rats. In the initial MTD study, oral M2 doses ≥150 mg/kg/day induced hepatotoxicity, oedema and inflammations in the stomach and mucosa atrophy in the gastrointestinal tract. At the lowest dose of 150 mg/kg/day, the M2 exposure translated into substantial C_{max}- and AUC_{0-24}-based safety margins of >730-fold and >1800-fold with respect to the mean human levels at the MRHD in RMS patients.

In the pivotal 26-week repeat-dose toxicity study, two rats orally dosed with ≥3.5 mg/kg/day M2 required early termination due to unilateral ocular protrusions caused by intraocular haemorrhage with increased ocular pressure resulting in retinal ganglion layer degeneration. These findings are likely related to M2 as they resemble the ocular haemorrhages and elevated ocular pressure detected in some rats after oral doses ≥2 mg/kg/day tolebrutinib for up to 26 weeks, which also imposed the premature sacrifice of individual animals administered ≥6 mg/kg/day. The relationship to M2 is further corroborated by the red vitreous floaters in the right eye of one surviving female of the 3.5 mg/kg/day low dose group at the end of the dosing. The fatality of another rat of the 7 mg/kg/day high dose group, which had shown low activity, piloerection, red nasal discharge and pale body colour resulting from gastric blood content, could have been also related to M2, considering the increased bleeding risk associated with BTK inhibitors including tolebrutinib. Nonetheless, two control rats suffering from comparable symptoms had to be prematurely sacrificed as well, so a possible technical problem during gavage administration cannot be disregarded.

The increased hair loss, parasite infestation and decreased Anti-KLH-IgM levels, non-reversible pancreatic islet pigment/fibrosis in surviving rats treated with ≥3.5 mg/kg/day M2 coincide with similar findings after ≥2 mg/kg/day tolebrutinib in the chronic toxicity study in rats. At the LOAEL of 3.5 mg/kg/day in male and female rats, 9.6-fold and 25-fold exposure margins based on C_{max} as well as 6.2-fold and 11.8-fold exposure margins based on AUC_{0-24} can be deduced compared to humans at the MRHD, respectively. However, this margin can be reasonably anticipated to further lower upon

continuous long-term administration given the small margins for tolebrutinib exposure in the 2-year carcinogenicity study in rats. Therefore, a contribution of M2 to the clinical risks for bleedings and infections during tolebrutinib therapy cannot be neglected. However, the high exposure margins derived from the MTD study indicate that M2 does not account for the hepatoxicity findings at clinical exposure levels in human patients.

Further mechanistic *in vitro* investigations in human, rat and dog liver spheroids unveiled no cytotoxic potential of M2, whereas the cytotoxicity of tolebrutinib was limited to >1200-fold higher concentrations than the mean clinical peak plasma levels of M2 at the MRHD of tolebrutinib in human patients. Whole genome transcript profiles of these liver spheroids demonstrated similarities between tolebrutinib and M2 and also among species but did not identify a clear causal mechanism of the human hepatoxicity of tolebrutinib. Thus, the different metabolic profiles of tolebrutinib between humans and animals presumably account for the divergent adverse events across species and concomitantly preclude further meaningful non-clinical characterisation of the clinical hepatotoxic risk.

Reproductive and developmental toxicities of the M2 metabolite were evaluated in dedicated PPND studies in rats. EFD effects were assessed in the rabbit study with the highest tolebrutinib dose of 10 mg/kg providing an exposure margin of 1.3-fold the MRHD for M2. Oral administration of M2 did not affect fertility in the FEED study in rats. The exposures of male and female rats at the NOAEL of 7 mg/kg/day translate into adequate 26x and 23x safety margins with respect to the human AUC of M2 at the MRHD of tolebrutinib.

In the rabbit EFD study, dose-dependent incomplete ossification of the hyoid bone was seen at doses of ≥5mg/kg, which could reflect a developmental delay. Historical control data (HCD) of the test facility revealed the highest incidence of 15.8 % for incomplete ossification of the foetal hyoid bone. Since, incomplete ossification of the hyoid bone was dose-dependent, occurred in the absence of maternal toxicity and exceeded the HCD at doses of 5 and 10 mg/kg/day (16.9 % and 22.1 %, respectively), it may be compound-related with M2 being of predominant concern due to the clinically relevant exposure for this finding (<1.3-fold). It should be also noted that M2 irreversibly binds to BTK and that both tolebrutinib and M2 distribute to placental tissue, amniotic sac and foetus. Therefore, the possibility of a specific effect of M2 on foetal ossification at clinically relevant exposures cannot be excluded, which is adequately reflected in section 5.3 of the SmPC.

In the PPND study of the M2 metabolite in rats, findings in the F1 animals of later pinna unfolding, balanopreputial cleavage and latency in some neurobehavioral tests (especially in male F1) at a M2 dose of 3.5 mg/kg/day were further discussed and no biologically meaningful conclusions on the effect of tolebrutinib on these parameters could be made. Additionally, a potential effect of M2 on fecundity and fertility indices in the PPND study was suggested given the proportions of 72 % and 74 % for males and females at the M2 dose of 3.5 mg/kg/day. Especially, the fecundity values were markedly outside of the range of HCD (minimum values: males 88 % and females 83 %) and the internal study control group (fecundity index 100 % for both sexes). However, the fertility index remained within the HCD range. Since no dose-dependent effects were seen at the higher dose of 7 mg/kg/day, it was accepted that no clear relationship with the effect of tolebrutinib on fertility could be made.

Another major human metabolite M8 was sufficiently characterized in mice and characterized with reservations in female dogs. However, as M8 does not covalently or irreversibly bind to BTK, M8 is considered less concerning compared to M2.

Impurities

Potential mutagenic impurities have been evaluated according to the ICH M7(R2) guideline, and all mutagenic impurities are adequately controlled below the TTC of 1.5 µg/day. Non-mutagenic impurities were toxicologically qualified for mutagenicity and systemic toxicity.

For the new N-nitrosamine impurity an AI of 400 ng/day was determined by CPCA, which is agreed. N-nitrosamine impurity was subsequently tested negative in an EAT. However, the EAT had some limitations. The amount of DMSO solvent used in the pre-incubation mixture was >7 % and, hence, an inhibition of CYP enzymes relevant for activation of the N-nitrosamine impurity cannot be excluded. Although the two positive controls N-nitroso diethylamine (NDEA) and methyl(nitroso)(2-phenylethyl) amine (MNPA) showed a good response in three of five bacterial strains at the same DMSO concentration, it has to be noted that this N-nitroso-piperidine derivative structurally deviates from NDEA or MNPA. Therefore, other CYPs may be involved in the activation of the N-nitrosamine impurity and might have been inhibited by the high DMSO concentration applied in this assay. *In vitro* metabolism studies and Quantum mechanical modelling indicated that a diazonium ion could possibly be formed from the N-nitrosamine impurity metabolism, which, however, is predicted to be of low DNA reactivity. Given the uncertainties of the EAT (i.e. high DMSO concentrations, none of the positive controls structurally related to the N-nitrosamine impurity) and the potential to form a diazonium ion, a mutagenic potential cannot be completely ruled out.

Further clarification of the mutagenic risk in male Fischer F344 Big Blue® transgenic rats revealed that the N-nitrosamine impurity induced MF at the *cII* gene in the liver at 75 mg/kg/day. The statistically significant increase in hepatic MF at 37.5 mg/kg/day was interpreted as biologically irrelevant by the study director. No increases in MF were noted in duodenum. Therefore, the NOAEL was set at 37.5 mg/kg/day However, it has to be noted that there was already a statistically significant 1.4-fold increase in MF at 37.5 mg/kg/day with a clear dose trend ($p<0.001$). Taking this into consideration, the NOAEL for MF in the liver should be defined at 12.5 mg/kg/day. Nevertheless, there is currently no international agreement to derive AIs solely based on *in vivo* mutagenicity data. Therefore, the limit of 400 ng/day for the N-nitrosamine impurity derived by CPCA should be maintained.

Environmental risk

A full environmental risk assessment of tolebrutinib including all study reports for Phase I and Phase II was provided. Considering these data, tolebrutinib is not expected to pose a risk to the environment. A bioaccumulation potential is not indicated based on the log Kow <4.5. A definitive PBT/vPvB assessment is not required.

4.5.2. Conclusions

All non-clinical concerns were adequately resolved with appropriate specifications in the SmPC. The different metabolic rates and profiles of tolebrutinib between humans and animal species likely account for the divergent toxicities compared to adverse events in human patients.

Key findings identified for both tolebrutinib and the M2 metabolite in GLP compliant toxicity studies were attributable to exaggerated pharmacology namely, generalised bleeding, immune system effects, and skin lesions. Dedicated investigations of M2 provided the most reliable estimation of animal-to-human exposure margins. Overall, M2 appeared to be more toxic in animals upon prolonged oral administration and is expected to be the primary driver of toxicity in humans due to the fast metabolism of tolebrutinib and the substantially higher human exposure of M2.

Moreover, dose-dependent incomplete hyoid ossification was observed in the embryo-foetal development study of tolebrutinib in rabbits at clinically relevant M2 exposures (safety margin to human exposure at the MRHD is 315-fold for tolebrutinib, but only up to 1.3-times for the active M2 metabolite). With respect to the irreversible covalent binding of M2 metabolite to BTK, the lack of maternal toxicity and the distribution of both tolebrutinib and M2 to placental tissue, amniotic sac and foetus, a specific effect on foetal ossification cannot be excluded.

Both the higher toxicity upon prolonged administration and the foetal risk associated with the M2 metabolite should be considered for the planned chronic or life-long clinical treatment scenario.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

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

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

Studies EFC16645 and EFC16034 have been inspected by European Competent Authorities (AGES (2023), FAMHP (2023), National Center for Public Health and Pharmacy (2023)) as well as by the FDA (2025) at selected sites and the sponsor. Based on the outcomes of these inspections, the studies are considered to have been conducted adequately and there is no need for a triggered inspection.

5.1.2. Tabular overview of clinical trials

Table 6 Tabular overview of main clinical studies

Study code/ Phase/ Status at cutoff date/ Location of CSR	**Study design/Duration**	**Treatment**	**Participants randomised/treated**
DRI15928 Completed Final CSR	Phase 2b multicenter, international, randomised, double-blind, placebo-controlled, crossover, dose-ranging study to investigate the MRI efficacy and the safety of 12-week administration of once daily tolebrutinib in participants with RMS In Cohort 1, participants received 1 of the 4 tolebrutinib doses for the first 12 weeks, then crossed over to placebo for 4 weeks. In Cohort 2, participants received placebo for the first 4 weeks, then crossed over to 1 of the 4 tolebrutinib doses for 12 weeks.	Daily dose level: 5, 15, 30, or 60 mg oral tolebrutinib OR daily placebo.	130 randomised and treated with tolebrutinib and with placebo.
LTS16004*a* Interim CSR	Phase 2 long-term extension study to evaluate safety and efficacy of tolebrutinib treatment in participants with RMS who had been treated in study DRI15928	Participants were treated with the double-blind tolebrutinib dose as randomised in study DRI15928. Once the	125 enrolled. 125 treated.
Part A: Completed	Double-blind treatment was continued with the respective daily tolebrutinib dose administered in study DRI15928 until the Phase 3 dose had been selected.	Phase 3 tolebrutinib dose had been selected, Part A completers were switched to open-label treatment with the selected oral dose of 60 mg once daily with a meal in Part B.	124 treated.
Part B: Ongoing	Participants from Part A formed a single dose group receiving open-label treatment with the selected Phase 3 daily dose of tolebrutinib. Eligible participants who successfully completed the trial could be offered enrollment in a Phase 3 LTS study (LTS17043) for an additional 3 years.	All participants in Part B received the Phase 3 dose of 60 mg oral tolebrutinib once daily with a meal.	

Study code/ Phase/ Status at cutoff date/ Location of CSR	Study design/Duration	Treatment	Participants randomised/treated
EFC16645 (HERCULES) Completed, Final CSR	Phase 3, randomised, double-blind, efficacy and safety study comparing oral tolebrutinib to placebo in participants with nrSPMS An event-driven (6-month CDP) trial with a variable treatment duration (approximately median duration of 807 days in the tolebrutinib group and 770 days in the placebo group). Participants with disease progression (i.e., a 6-month CDP event) were eligible to receive OL tolebrutinib treatment or offered the possibility to switch to some other marketed treatment if available. Eligible participants who successfully completed treatment (double-blind or open-label) were invited to enroll in a separate LTS study (LTS17043) for an additional 3 years per participant, or until tolebrutinib is approved in their respective country. For participants who did not enter the LTS study and for participants who prematurely discontinued study intervention, a final follow-up visit to collect safety data was performed in the 4 weeks after their EOS visit.	60 mg oral tolebrutinib once daily with a meal OR Placebo once daily with a meal	1131 randomised and 1127 treated. 754 randomised to 60 mg tolebrutinib; 752 treated 377 randomised to placebo; 375 treated.
EFC16033 (GEMINI 1) Completed Final CSR	Phase 3, randomised, double-blind efficacy and safety study comparing 60 mg oral tolebrutinib to 14 mg oral teriflunomide in participants with RMS Event-driven (6-month CDW) trial with a variable treatment duration (median duration of 944 days in the tolebrutinib group and 940 days in the teriflunomide group). Eligible participants completing the double-blind treatment period were invited to enroll in a separate LTS study (LTS17043) for an additional 3 years per participant. For participants that completed double-blind treatment and did not enter the LTS17043 study and for participants who prematurely discontinued the study intervention, a final follow-up visit to collect safety data was performed in the 4 weeks after their last dose of study intervention.	60 mg oral, once daily tolebrutinib + placebo (to match the oral, once daily teriflunomide table) - taken with a meal. OR 14 mg oral, once daily teriflunomide tablet + placebo (to match the oral, once daily tolebrutinib tablet) - taken with a meal.	974 randomised and treated. 486 randomised to tolebrutinib; 486 treated. 488 randomised to teriflunomide; 488 treated.
EFC16034*b* (GEMINI 2) Completed Final CSR	Phase 3, randomised, double-blind efficacy and safety study comparing 60 mg oral tolebrutinib to 14 mg oral teriflunomide in participants with RMS Event-driven (6-month CDW) trial with a variable treatment duration (median duration of 897 days in the tolebrutinib group and 911 days in the teriflunomide group). Eligible participants completing the double-blind treatment period were invited to enroll in a separate LTS study (LTS17043) for an additional 3 years per participant. For participants that completed double-blind treatment and did not enter the LTS17043 study, a final follow-up visit to collect safety data was performed in the 4 weeks after their EOS visit.	60 mg oral tolebrutinib once daily + teriflunomide placebo tablet once- daily taken with a meal. OR Tolebrutinib placebo once daily + 14 mg teriflunomide tablet once daily taken with a meal.	899 randomised and 898 treated. 447 randomised to tolebrutinib; 447 treated. 452 randomised to teriflunomide; 451 treated.

a Interim analysis completed at the cutoff date of 27 September 2023.

b Study EFC16034 (GEMINI 2) was of identical design to Study EFC16033 with the exception that there were no routine PK or lymphocyte phenotype evaluations in Study EFC16034

There were two additional ongoing phase 3 studies, i.e., a double-blind, placebo-controlled study EFC16035 (PERSEUS) in patients with PPMS and a long-term study LTS17043 including those patients previously enrolled in one of the aforementioned MS tolebrutinib studies (i.e., GEMINI 1 and 2, HERCULES, LTS16004 and EFC16035). However, at the time of the initial MAA, efficacy data were not available.

5.2. Clinical pharmacology

5.2.1. Methods

Based on preclinical data, tolebrutinib and its M5/M5a metabolite (also known as PRN2677) were assayed in human plasma using a combined assay method in early clinical studies (PRN2246-001, PRN2246-002, DRI15928, BEX16018). Results of the final metabolite identification in humans with [^{14}C]-tolebrutinib (Study BEX16018) showed that M5/M5a metabolite is not a major metabolite in humans (i.e., representing less than 10% of total radioactivity with no relevant pharmacological activity). Therefore, M5/M5a was not assayed in further clinical studies. Two other metabolites, M8 and M2, were measured in Study BEX16018 with a fit-for-purpose assay method that is not described in this summary. M8 was an abundant metabolite contributing to >10% of total radioactivity but was found to be inactive with regard to BTK inhibition and was not assayed in subsequent studies. M2, while less abundant with <10% of total radioactivity, was determined to contribute substantially to the pharmacological activity of tolebrutinib. Therefore, M2 was assayed in subsequent Phase 1 and Phase 3 studies with validated methods to evaluate its PK, its sources of PK variability, and its relationship with safety and efficacy.

The initial LC-MS/MS assay methods were validated at Alturas Analytics, Inc. to support the assay of tolebrutinib and M5/M5a metabolite in plasma, urine, and CSF for the first 2 clinical studies PRN2246-001 and PRN2246-002. In later Phase 1 and 2b studies, tolebrutinib was assayed by Charles River Laboratory using a validated LC-MS/MS method with an LLOQ of 0.01 ng/mL in plasma and in CSF. Two distinct LC-MS/MS assay methods were developed and validated for M2 metabolite in human plasma (LLOQ of 0.005 ng/mL and 0.050 ng/mL, respectively) to support Phase 1 studies. The LC-MS/MS method with highest LLOQ was validated to support clinical studies with higher M2 exposure in order to minimize the dilution of clinical samples. For Phase 3 studies, a combined LC-MS/MS assay method for tolebrutinib and M2 metabolite in plasma was validated at LabCorp. Cross validation was completed successfully between the combined assay (tolebrutinib + M2 metabolite) and each of the validated assay methods for tolebrutinib and M2 at Charles River Laboratory. The validated plasma assay methods were specific, accurate, and reproducible with successful incurred sample reanalysis. All methods were developed and validated following the applicable regulatory guidelines in force at the time of their implementation. All samples were analyzed within established duration of stability. Overall bioanalytical methods appear valid and robust.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The MAA of tolebrutinib is supported by a comprehensive clinical pharmacology program, consisting of ten healthy volunteer studies, two studies in participants with organic impairment (hepatic and renal). Supportive PK data are available for patients with nrSPMS as well as RMS. Nine population PK study reports are also available, including population PK (popPK) modelling, PBPK simulations, simulations of drug-drug-interactions and exposure-response analyses.

5.2.2.2. Evaluation and qualification of models

PopPK analyses were performed using NONMEM (Version 7.5.1) and the First Order Conditional Estimation with Interaction method; the First Order method was used at some steps of the model development. In the covariate inclusion strategy, Machine Learning tools were applied using an in-

house R/Shiny interface. PK/PD analysis and E-R analyses were performed using SAS version 9.4 and/or R software (version 4.2.0).

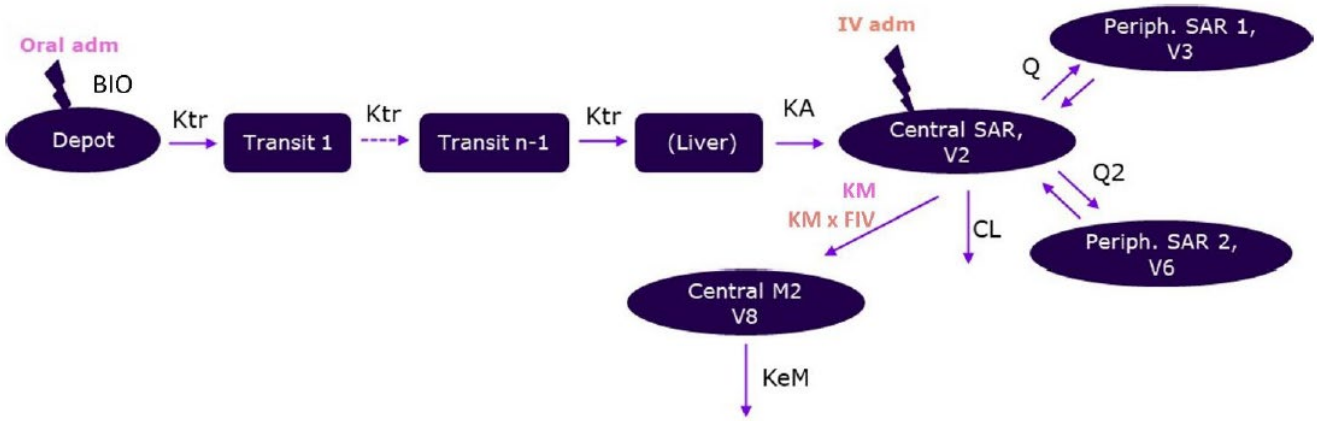
PBPK modelling was performed using Simcyp software (version 22).

5.2.2.2.1. Population Pharmacokinetics

A popPK model for tolebrutinib and its metabolite M2 was developed based on data from eight clinical studies. Study EFC16645 (HERCULES) was a Phase 3 study in participants with nrSPMS. At a 2:1 ratio the participants received 60 mg oral tolebrutinib daily or a matching placebo daily. All patients were assumed fed. Data was sparsely sampled with two PK samples collected on months 6 and 12, 0.5-1.5 h and 2.5-5 h post-dose, and one sample collected on month 9, 0.5-1.5 h post-dose and one sample EOT. The sparse patient PK data was pooled with rich sampled data from seven phase 1 clinical studies (TDU16831, TDR16862, INT16385, INT16726, POP16398, POP16399, and PKM17308) in healthy participants. The phase 1 studies were mostly single dose, except for TDR16862, with doses ranging from 60 mg to 300 mg oral tolebrutinib.

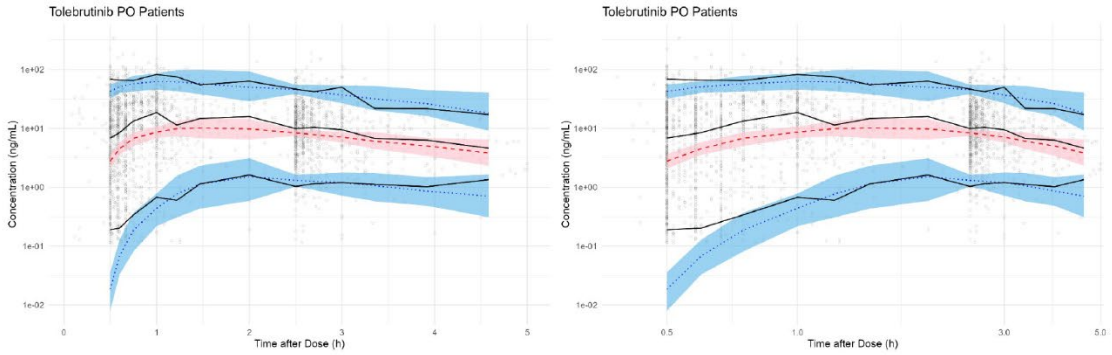
Figure 2 shows a graphical representation of the model structure.

Figure 2 Selected pharmacostatistical model



Final prediction-corrected visual predictive check for tolebrutinib and M2 stratified by healthy participants (oral/IV administration) versus patients form HERCULES (EFC16645) study are shown in Figure 3.

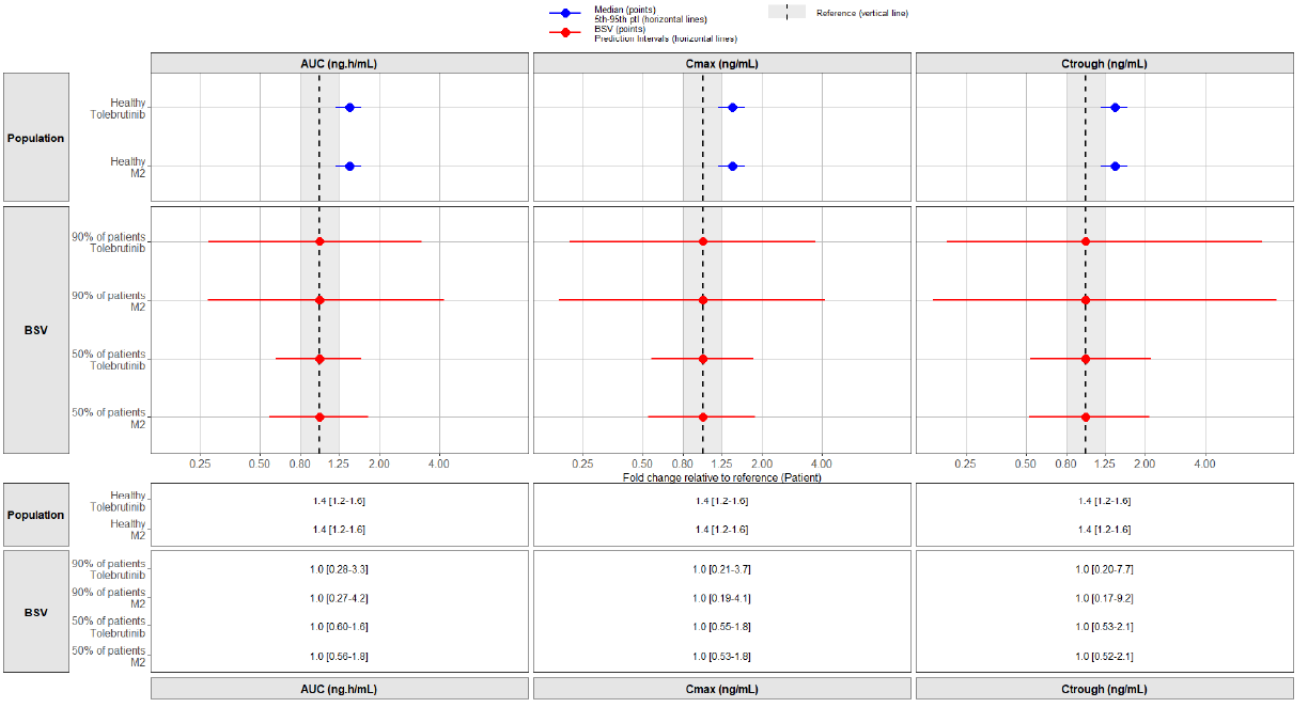
Figure 3 Prediction- corrected visual predictive check results for tolebrutinib (left) and M2 (right) in patients in semi-logarithmic scale (left) and in logarithmic scale (right)



Legend: gray dots: observations; thick solid lines: median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin. Red dashed and blue3 dotted lines: median and bounds (5th and 95th percentiles) of simulated concentrations at each time bin.

Covariate effect of SUBTYPE (patient vs healthy participants) on exposure parameters AUC, C_{max} and trough observed plasma concentration (C_{trough}) included in the final population PK model was assessed by forest plots based on 500 simulations (Figure 4).

Figure 4 Forest plots of 500 simulations based on uncertainty of fixed-effect estimates



The final popPK model for tolebrutinib and M2 was also used to estimate exposure metrics for the target population in sparsely sampled Study EFC16645. EBEs were generated from the final model and used to derive individual steady state exposures (AUC_{0-24}, C_{max}, t_{max} and $C_{through}$) for tolebrutinib and M2 by means of simulations. As the model included an interoccasion variability term with 5 occasions, all simulations were performed with 5 occasions and the individual mean computed for each nrSPMS patient in Study EFC16645.

5.2.2.2.2. Physiology based pharmacokinetic model

To build the tolebrutinib and M2 PBPK models, physico-chemical, *in vitro* ADME data and interaction parameters were used as input data. Parameters estimated/refined from clinical data for tolebrutinib were precipitation rate constant, Vss, ISEFs corresponding to enzymatic intrinsic clearances for CYP3A4 and CYP2C8, and fugut.

The mass balance and metabolic profiling Study BEX16018 (SD [14C]-60 mg tolebrutinib in fasted HP) was used to determine Fa (0.94) from tolebrutinib %-dose in feces after 72 hours (85% recovered) and inform the precipitation parameter PRC in the absorption model. Excretion data of M2 in urine was used to estimate renal clearance,M2. The fm(CYP2C8→M2) was averaged to 13%.

Parameters estimated/refined for M2 from clinical data were Vss, renal clearance and enzymatic intrinsic clearances CLintH for CYP3A4, CYP2D6 and other enzymes.

All simulations were performed using 10 trials of 10 virtual subjects with median ages, female/male ratios, formulation, food conditions, dosing regimens and durations corresponding to the ones of the relevant clinical studies.

Observed tolebrutinib and M2 PK parameters after 60, 120, 240 and 300 mg SD administration in HP under fed conditions (high fat) from Study TDU16831 (part 1a and d) were compared (Table 7 and Table 8).

Table 7 Geometric mean [CV%] of observed versus predicted tolebrutinib PK parameters after single-dose administration (60, 120, 240, 300 mg) in HP under fed (high fat) conditions (TDU16831)

Geometric Mean [CV%]	tolebrutinib 60 mg			tolebrutinib 120 mg			tolebrutinib 240 mg			tolebrutinib 300 mg		
	Obs (n=12)	Pred	Pred /Obs	Obs (n=12)	Pred	Pred /Obs	Obs (n=8)	Pred	Pred /Obs	Obs (n=8)	Pred	Pred /Obs
C_{max}	17 [83]	16.2 [79]	0.95	27.8 [66]	32.6 [80]	1.17	77.1 [72]	63.7 [81]	0.83	83.5 [52]	82.2 [79]	0.98
AUClast	43.9 [69]	44.9 [78]	1.02	89.2 [67]	91.3 [78]	1.02	193 [54]	178 [78]	0.92	292 [30]	231 [76]	0.79
AUC	51.4 [62]	45.3 [78]	0.88	89.4 [67]	91.5 [78]	1.02	194 [54]	185 [79]	0.95	293 [30]	242 [77]	0.83

Table 8 Geometric mean [CV%] of observed versus predicted M2 PK parameters after single dose administration (60, 120, 240, 300 mg) in HP under fed (high fat) conditions (TDU16831)

Geometric Mean [CV%]	M2 60 mg			M2 120 mg			M2 240 mg			M2 300 mg		
	Obs (n=13)	Pred	Pred /Obs	Obs (n=12)	Pred	Pred /Obs	Obs (n=8)	Pred	Pred /Obs	Obs (n=8)	Pred	Pred /Obs
C_{max}	37.6 [64]	42.0 [28]	1.12	79.8 [28]	84.3 [28]	1.06	195 [37]	163 [28]	0.84	213 [40]	196 [30]	0.92
AUClast	128 [53]	145 [32]	1.13	352 [30]	295 [32]	0.84	674 [34]	564 [32]	0.84	1020 [27]	662 [34]	0.65
AUC	149 [45]	145 [32]	0.97	352 [30]	295 [32]	0.84	676 [34]	593 [40]	0.88	1020 [27]	703 [51]	0.69

The Simcyp special population for mild HI (Sim-Cirrhosis CP-A, based on Child-Pugh score for mild disease) was used for model verification by comparing predicted exposure ratios (mild HI versus control) for tolebrutinib and M2, to the ones observed in POP16398 (Table 9 and Table 10).

Table 9 Geometric mean [CV%] of observed and predicted tolebrutinib exposure parameters and ratios (GMR for mild HI versus HP) after single-dose administration (60 mg) in HP and mild HI participants under fed conditions (POP16398 study)

	Exposure in HP		Exposure in mild HI		Mild HI to HP GMR			Unbound Mild HI to HP GMR		
	Obs n=7	Pred	Obs n=7	Pred	Obs n=7	Pred	Pred /Obs	Obs n=7	Pred	Pred /Obs
C_{max}	9.34 [72]	16.8 [72]	8.02 [66]	33.9 [56]	0.86 (0.48-1.53)	2.02	2.35	0.80 (0.44-1.44)	2.58	3.22
AUC	26.8 [60]	52.2 [72]	25.0 [47]	109 [49]	0.93 (0.52-1.69)	2.09	2.25	0.87 (0.50-1.53)	2.67	3.07
fu_p	0.17 [9]	0.118 [8]	0.16 [10]	0.151 [29]						

Table 10 Geometric mean [CV%] of observed and predicted M2 exposure parameters and ratios (GMR for mild HI versus HP) after single-dose administration (60 mg) in HP and mild HI participants under fed conditions (POP16398 study)

	Exposure in HP		Exposure in mild HI		Mild HI to HP GMR			Unbound Mild HI to HP GMR		
	Obs n=7	Pred	Obs n=7	Pred	Obs n=7	Pred	Pred /Obs	Obs n=7	Pred	Pred /Obs
C_{max}	23.1 [60]	40.8 [27]	25.0 [46]	49.4 [36]	1.08 (0.65-1.80)	1.21	1.12	1.06 (0.66-1.72)	1.55	1.46
AUC	69.2 [61]	163 [32]	87.2 [46]	194 [49]	1.26 (0.60-2.66)	1.19	0.94	1.24 (0.61-2.51)	1.52	1.23
fu_p	0.28 [5]	0.118 [8]	0.27 [7]	0.151 [29]						

Tolebrutinib and M2 exposures was simulated in milk of breastfeeding women under fed conditions after administration of a single 60 mg tolebrutinib dose. The perfusion-limited model in Simcyp includes metabolites and predicts the Milk-to-Plasma ratio to calculate the milk drug concentrations from the plasma concentration and estimate infant daily dose and relative infant daily dose to maternal daily dose. Table 15 show the results following a static milk intake of 0.15 L/kg/day based on Cavg or 0.20 L/kg/day based on C_{max} (worst-case).

Table 11 Predicted geometric mean (CV%) of maternal exposure in milk and corresponding infant daily dose (IDD) and relative infant daily dose to maternal daily dose (RIDD) for tolebrutinib and M2 after 60

mg SD administration of tolebrutinib in breastfeeding women (18-45 years) under fed conditions (static option with 0.15 and 0.20 L/kg/day)

	Maternal Exposure in Milk				IDD (µg/kg/day)		RIDD (%)	
Daily doses (L/kg/day)	**M/P ratio (AUC)**	**AUC_{0-24} (µg.h/L)**	**C_{max} (µg/L)**	**$C_{average}$ (µg/L)**	**$IDDC_{max}$**	**IDD $C_{average}$**	**RIDD C_{max}**	**RIDD $C_{average}$**
Tolebrutinib 0.15 L/kg/day	4.25 (34)	187 (82)	63.0 (85)	31.5 (85)	9.46 (85)	4.73 (85)	1.04 (80)	0.52 (80)
0.20 L/kg/day					12.6 (85)	6.30 (85)	1.39 (0.80)	0.69 (0.80)
M2 0.15 L/kg/day	0.17 (11)	19.9 (33)	5.88 (30)	2.94 (30)	0.88 (30)	0.44 (30)	0.097 (31)	0.048 (31)
0.20 L/kg/day					1.18 (30)	0.59 (30)	0.13 (31)	0.065 (31)
Tolebrutinib/M2	25.0	9.4	10.7	10.7	10.8	10.8	10.7	10.8

Predicted exposures are reported as mean (geometric mean) (CV%)
M/P ratios are calculated as AUC in milk/ AUC in plasma

The Milk-to-Plasma ratio for tolebrutinib (4.24) was about 25 times higher than for M2 (0.17), probably due to its higher lipophilicity.

5.2.2.3. Absorption

Tolebrutinib was rapidly absorbed following oral administration as immediate-release film-coated tablet with median t_{max} around 1 hour under fasted condition and 2 hours under fed conditions. The absolute oral bioavailability of tolebrutinib was low (geometric mean of 5.3%) under fasted condition. In the food-effect study PKM17308 the absolute oral bioavailability of tolebrutinib increased (1.98-fold) under fed conditions with no change of tolebrutinib $t_{1/2}$ after oral administration. The increase in bioavailability is assumed to be due to an increased blood flow at gut/liver level after intake of food, leading to less first-pass extraction under fed conditions. The recommendation in all Phase 3 studies was for the study participants to always take tolebrutinib 60 mg tablet with a meal to maximize exposures and minimize the PK variability of tolebrutinib and its active metabolite M2. Since similar food effect (1.77-fold increase in tolebrutinib AUC) was also demonstrated with the to-be-marketed tolebrutinib tablet (1C3), the proposed label recommendation is to always take tolebrutinib tablet with a meal.

In vitro, tolebrutinib exhibited a high permeability with only mild involvement of efflux transporters PGP and BCRP. Permeability decreased from apical to basolateral in the presence of BSA and by decreasing pH from 6.5 to 5. Opening of tight junction did not increase permeability. The metabolite M2 exhibited low permeability with some paracellular transport and no relevant pH effect. M2 is a substrate of the efflux transporters Pgp and to a low extent BCRP. Pantoprazole, which increases the pH in the stomach, decreased C_{max} by 34-39% for tolebrutinib and M2 but AUC increased only slightly for tolebrutinib and decreased slightly for M2, when a 60 mg tablet was administered in the fasted state. Similar results were obtained in the fed state. Hence, it can be assumed that H2-blockers are not decreasing bioavailability to any clinically relevant extent and therefore co-administration of proton pump inhibitors can be allowed, despite the highly pH dependent solubility of tolebrutinib.

5.2.2.4. Distribution

Tolebrutinib and M2 *in vitro* protein binding in human plasma, primarily to HSA, ranged from 87.5% to 88.9%, and from 84.9% to 91.4%, respectively. Thus, the tolebrutinib and M2 *in vitro* unbound fraction ranged from 11.1% to 12.5% and from 8.6% to 38%, respectively. *Ex vivo* unbound free fraction ranged from 16% and 17% for tolebrutinib and 27% to 29% for M2. No differences were observed between healthy participants and participants with mild hepatic or severe renal impairment.

Volume of distribution in the terminal phase (V_z) after IV administration of [^{14}C]-tolebrutinib was estimated to be 255 L (CV% 42) or 3.64 L/kg in 70 kg human (PKM17308) when fasted. This is above both the volume of plasma (3 L) and total body water of 42 L in humans, indicating a high distribution of the compound to tissues. Volume of distribution was estimated to be even higher in the fed state (305 L, CV% 34).

Following single dose oral administration of 60 and 120 mg, tolebrutinib and M2 maximum observed concentrations in CSF increased with dose with no major deviation from dose proportionality. At the 60 mg intended therapeutic dose, tolebrutinib and M2 CSF concentrations exceeded their respective BTK K_I values in enzymatic assay (0.68 and 0.17 ng/mL, respectively) for a time much longer than 500% of the $t_{1/2}$ of BTK inactivation (17 and 11 minutes, respectively, based on k_{inact}). This indicates relevant covalent BTK inhibition in CNS. Tolebrutinib concentration also exceeded the IC_{50} (0.3 ng/mL) for BTK occupancy in microglial cells.

5.2.2.5. Metabolism

Based on an *in vitro* experiment in human hepatocytes, tolebrutinib is mainly metabolized by CYP3A4 (f_m = 38%) and CYP2C8 (f_m = 34%), and to a lesser extent by CYP2D6 (f_m = 9%), and CYP2J2 (f_m = 19%). *In vitro*, M2 is formed from tolebrutinib exclusively by CYP2C8 and is mainly metabolized by CYP3A4/5 (66% to 79%) and to a lesser extent by CYP2D6 and CYP2J2.

In a human mass balance study tolebrutinib accounted for 0.75% of total radioactivity exposure in plasma. A total of 19 metabolites were characterized with 7 metabolites with exposures (expressed as a percentage of total radioactivity) greater than or equal to that of the parent. Of those only M2 is pharmacologically active on BTK and contributes to the pharmacological activity *in vivo*. M2 is an irreversible BTK inhibitor, with a potential of covalent binding that is approximately 62% of that of tolebrutinib. The estimation of the contribution of M2 to the pharmacological effect was based on total concentrations as fraction not bound to plasma proteins was similar. From exposure determination in BEX16018 of tolebrutinib and M2 at 0.25 h, 4 h and for AUC, contribution of M2 was estimated to be 75%, 53% and 79%, respectively taking the relative potency into account. Hence, the majority of the pharmacological activity should be ascribed to M2.

The major metabolite is M8 (a product of oxidative piperidine ring opening and oxidation to the carboxylic acid with preserved acryloyl moiety. The exposure to M8 in the fasted state in the BEX16018 study is 23 times the exposure to tolebrutinib and 5 times higher than the exposure to M2. M8 is without pharmacological activity, however, has retained the acryloyl moiety and is therefore still capable of covalent binding although is then not specific for BTK. Hence, M8 is capable of unspecific covalent binding to proteins and can be assumed to be present in the liver in higher amounts than in plasma. Moreover, the amount for M8 could be even higher in plasma as M8 is unstable during storage and freeze/thaw cycles. The PK of M8 was determined in 6 fasted healthy volunteers in the BEX16018 study. As M8 is not pharmacologically active, it was decided not to include it in the Bioanalysis in other clinical studies. However, M8 was ultimately considered sufficiently characterized in the non-clinical program with no further investigation in humans required.

5.2.2.6. Elimination

After single and repeated once daily ascending dose oral administration under fed conditions, tolebrutinib and M2 $t_{1/2z}$ were similar ranging from 3.0 to 7.8 hours regardless of meal composition. Following an IV infusion of 100 µg [^{14}C]-tolebrutinib dose, the mean tolebrutinib $t_{1/2z}$ was similar between fasted and fed conditions (1.95 ± 1.07 hours versus 1.77 ± 0.701 hours) and approximately 3-fold shorter than those observed after oral administration. The shorter $t_{1/2z}$ of tolebrutinib when given by the IV route suggests that the rate of elimination for tolebrutinib given by oral route is limited by the rate of GI absorption. Following a single oral dose of 60 mg [^{14}C]-tolebrutinib, the $t_{1/2z}$ of plasma radioactivity (AMS) was approximately 150 hours. This long $t_{1/2z}$ is consistent with a covalent binding of tolebrutinib and its metabolites to plasma proteins.

Excretion was mainly through faeces (78%) with the remainder in urine (14%). Tolebrutinib related-radioactivity was excreted via urine as 10 different metabolites within the first 48 hours. The major part was by phase 1 reaction (M18, M19, M13, M10, M8, M22, M5/M5a, and M2 and less by phase 2 metabolites (M20 and M6). M8 was the metabolite with the highest amount excreted via urine (5.98% of the total radioactive dose). The other metabolites each comprised below 1.5% of total radioactivity. No unchanged parent drug was detected in urine.

In faeces the major part of the radioactivity was excreted as 14 different metabolites within 72 hours. Only 3.83% of the dose was excreted as parent compound. Hence, clearance is mainly through metabolism.

5.2.2.7. Dose proportionality and time dependency

According to the applicant from 60 mg to 300 mg single doses and from 120 mg to 240 mg repeated doses of tolebrutinib administered under fed conditions, tolebrutinib and M2 C_{max} and AUC increased with no major deviation from dose proportionality. After repeated once daily doses of tolebrutinib from 7.5 mg to 90 mg under fasted conditions, no accumulation occurred. Similarly, no accumulation was observed for tolebrutinib and M2 after repeated doses of tolebrutinib from 120 to 240 mg under fed conditions. This is consistent with the short half-life and a once daily dosing regimen. However, the exposure to tolebrutinib increases more than proportional to dose, especially in the lower dose range (PRN2246-001) and the applicant's claim was not supported with presentation of summaries of PK data or plots of e.g. dose normalised AUC versus dose. The assessment of dose proportionality is therefore considered unclear.

5.2.2.8. Pharmacokinetics in the target population

Population PK analyses showed that, at 60 mg tolebrutinib once daily under fed conditions, the exposures of tolebrutinib and M2 in participants with nrSPMS in EFC16645 study were similar to those in participants with RMS in EFC16033 study, but lower than the exposures observed in healthy participants in Phase 1 studies and in participants with RMS in Phase 2b study DRI15928. There was no requirement for a standardized meal in Phase 3 studies and some participants may have had lighter and lower fat content meals than a standardized meal required in Phase 1 studies, which might explain why the drug exposures observed in Phase 3 studies were lower than those observed in Phase 1 studies.

The PK variabilities in participants with nrSPMS and RMS in EFC16645 and EFC16033 studies were very high (CV%: 60% to 65% for tolebrutinib and 56% to 58% for M2), but consistent with the variabilities observed in healthy participants in Phase 1 studies.

5.2.2.9. Special populations

In the popPK analyses with data from participants with nrSPMS (EFC16645 study) or RMS (EFC16033), age, sex, and body weight were not identified as significant covariates affecting the PK of tolebrutinib and M2 metabolite. Therefore, no dose adjustments are recommended based on age, sex, and body weight. Clinical pharmacology studies to assess the influence of race/ethnicity (TDU16117 in Chinese, Japanese, and Korean participants) and organ function impairment (POP16398 in participants with hepatic impairment and POP16399 in participants with renal impairment) have been conducted.

Renal function and ethnicity were not found to be significant covariates impacting tolebrutinib and M2 PK in nrSPMS and RMS populations. Changes in exposure in patients with mild hepatic impairment were not significant. PBPK modelling predicted an overexposure higher than the observed exposure at 240 mg tolebrutinib dose (the highest dose in Study TDR16862) in moderate and severe hepatic impaired populations.

5.2.2.10. Pharmacokinetic interaction studies

5.2.2.10.1. PK drug-drug interactions

Based on an initial *in vitro* study showing the involvement of CYP2C8 and CYP3A in the metabolism of tolebrutinib, 3 Phase 1 clinical studies were conducted in healthy participants:

• Study INT16385 with a potent CYP3A inhibitor (itraconazole) and a proton pump inhibitor (pantoprazole) co-administered with tolebrutinib in separate periods.

• Study INT16726 with a potent CYP2C8 inhibitor (gemfibrozil) and a potent CYP inducer (rifampicin) co-administered with tolebrutinib in separate periods.

• Study PKM17308 with grapefruit juice as a CYP3A4 inhibitor co-administered with tolebrutinib.

The clinical drug-drug-interactions studies above were supplemented with PBPK analysis to assess the magnitude of the effect of weak and moderate inhibitors/inducers of CYP2C8 or CYP3A on tolebrutinib PK.

Recommendations regarding coadministration of CYP3A4 and CYP2C8 inhibitors and CYP3A inducers with tolebrutinib are:

- Coadministration of any CYP3A inhibitor is allowed, because the potent CYP3A4 inhibitor itraconazole produced a mild increase in the exposure of tolebrutinib and its active metabolite M2 after coadministration with tolebrutinib 60 mg (the Phase 3 dose) under fed conditions which remained below their exposures at tolebrutinib 240 mg once daily.
- Potent and moderate CYP2C8 inhibitors should be avoided as they may increase tolebrutinib exposure with a risk of exceeding the exposure at 240 mg once daily. Weak CYP2C8 inhibitors are allowed.
- Potent and moderate CYP3A inducers (being also CYP2C8 inducers) should be avoided, as they may decrease the combined exposures of active moieties tolebrutinib and M2.

Based on the results of drug-drug-interactions study (INT16385) with pantoprazole showing no effect on tolebrutinib AUC with only a mild decrease in C_{max} (34% to 39%), coadministration of proton pump inhibitors, H2-receptor blockers, and antacids is allowed.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Tolebrutinib is an orally administered, CNS-penetrant, small molecule drug that acts as an irreversible inhibitor of BTK. BTK is an enzyme expressed in B lymphocytes and in myeloid cells, including CNS-resident microglia. BTK-mediated pathways are considered critical for the inflammatory activation of B lymphocytes, macrophages, and microglia, both in the periphery and the CNS. BTK is an essential proximal component of several signalling pathways downstream of the BCR that control B cell maturation, survival, and activation, as well as production of cytokines and antigen-dependent stimulation of T cells. Importantly, CNS-compartmentalized B cells and microglia are considered central to the immunopathogenesis of progressive MS. The exact mechanism of action of tolebrutinib in MS therapy has not been completely unravelled. However, the covalent binding of the acryloyl moiety of tolebrutinib to cysteine 481 near the ATP-binding site of BTK is thought to inhibit the inflammatory BTK activity in B cells, macrophages and microglia in the periphery and CNS.

5.2.3.2. Primary and secondary pharmacology

The PD effects of tolebrutinib were assessed by measurement of BTK occupancy in PBMCs isolated from blood samples of healthy participants following administration of tolebrutinib or placebo in Studies PRN2246-001 and TDU16117. A dose-dependent increase in BTK occupancy in PBMCs with a maximal BTK occupancy of ⩾90% was observed at 4 hours after a single dose of tolebrutinib 60 mg or higher in the SAD study and at Day 7 after repeated daily doses of tolebrutinib from 15 to 90 mg in the MAD study. Target occupancy is a measure of covalent binding to BTK and has been applied as a PD parameter in clinical studies of BTK inhibitors. However, the relationship between occupancy, pathway inhibition and clinical outcomes remain undefined. Tolebrutinib shows unwanted side-effects that are comparable to other approved BTK inhibitors. These side-effects are discussed in the safety part of the assessment report.

The NfL level in plasma, as a potential biomarker of neuronal damage, and Chi3L1 level in serum, as a potential biomarker for the progression of MS, was assessed in Phase 3 studies in patients with nrSPMS and patients with RMS. NfL is used as a marker of neuronal degeneration and it can serve as a biomarker of disease activity in MS. Chi3L1 might potentially serve as a marker of ongoing glial activation, reflecting the dynamic response of the CNS cells to the inflammatory processes in MS. Although preliminary findings have been promising, further research is needed to validate the utility of Chi3L1 measurements in the diagnosis and prediction of the progression of MS. No PK/PD relationship was identified for NfL or Chi3L1 in EFC16645 and EFC16033 studies. In the Phase 3 study in patients with nrSPMS (EFC16645) and RMS (EFC16033 and EFC16034), there were no overall consistency in NfL levels or Chi3L1 levels with tolebrutinib treatment.

The effect of tolebrutinib and the active metabolite M2 on the QTc interval was evaluated using concentration–QTc effect modelling of data obtained during a Phase 1 study with ECG recording. Overall, tolebrutinib did not show any tendency of QT prolongation. On the contrary, there was a tendency in shortening of QTc. There was not seen any influence on other ECG parameters up to a single tolebrutinib dose of 300 mg under fasted or fed conditions. The observed tendency for QTc shortening is considered to not be clinically relevant.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

No discussion was provided by the applicant.

5.2.3.4. Genetic differences in PD response

No discussion was provided by the applicant.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

No clear relationship between plasma concentration and biomarkers of neurodegeneration, lymphocyte cells or immunoglobulin levels could be established. For endpoints related to drug activity and efficacy a significant correlation was only found between drug exposures and the improvement on disability, based on time to onset of 6- and 3-month confirmed disability progression (CDP) for nrSPMS. No significant correlation was found between exposure and safety endpoints.

5.2.5. Dose selection and therapeutic window

In Phase 2b DRI15928 study in participants with MS at 5 to 60 mg once daily, increasing tolebrutinib exposure was associated with a reduction in the numbers of new Gd+ and new or enlarging T2 lesions. Based on this relationship, together with the observation that food enhances tolebrutinib exposure, the dose regimen selected for Phase 3 studies was 60 mg once daily taken with a meal.

In Phase 3 studies, tolebrutinib 60 mg once daily with a meal met the primary efficacy endpoint for 6-month CDP in nrSPMS (EFC16645) compared with placebo.

A significant correlation was identified between drug exposures and the improvement on disability, based on the 6- and 3-month CDP for nrSPMS. Higher exposures of tolebrutinib, its active metabolite M2, or their combined exposure were associated with greater delays in disability progression. These findings reinforce the need to administer tolebrutinib 60 mg dose once daily with a meal to maximize the exposures and therapeutic effect in delaying disability progression.

A clear therapeutic window was not established.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The clinical pharmacology of tolebrutinib was characterized with a comprehensive program of dedicated studies. The program consisted of ten healthy volunteer studies, including investigation of single- and multiple ascending doses, a human mass-balance study, comparison of bioavailability as well as food-effect on different formulations, and two studies in subjects with organ impairment.

Nine popPK study reports are also available, including popPK modelling, PBPK simulations, simulations of drug-drug-interactions and exposure-response analyses. For popPK supportive data were available from patients with nrSPMS as well as RMS.

Bioanalytical methods

PK bioanalytical methods appear valid and robust and the Simoa assay fit for purpose.

Modelling

The current popPK model of tolebrutinib and M2 is based on a previous model for RMS patients. The model had a 3-compartment structure for tolebrutinib and a 1-compartment for M2. The only covariate retained in the model was patients versus healthy participants on bioavailability. The model parameters were verified by both bootstrap and SIR. The prediction-corrected visual predictive check showed clear underprediction of the

immediate concentrations after IV and the absorption phase after oral administration. Thus, drug absorption is not adequately captured with the current model. The oral and IV data are modelled with separate compartments contributing to very long run-times.

When inspecting the PK profiles of earlier studies, administration of drug in tablet form with food seem to impact the concentration-time profiles in healthy participants. Even in studies with controlled food intake, great variation was observed between subjects, often with slower absorption and later t_{max} compared to fasted. In fasted subjects, PK profiles were more consistent with rapid absorption and t_{max} within 1 hour in most subjects. Food is likely interrupting dissolution of compound in the intestines and probably the main source to the observed variability not accounted for in the current model. In the Ph III patient study Hercules, two samples per subject per PK sampling occasion were collected at 0.5-1.5 h and 2.5-5 h post-dose. Food status was assumed fed. From the list of studies, food effect was investigated in at least 5 different healthy participant studies with rich sampling. Differences in exposure between patients and healthy volunteers and between patients may be due to differences in bioavailability due to differences in food intake. The effect of food on the exposure and the less standardisation in the patients hampers the prediction of the PK based on sparse sampling data. An alternative model was presented based on the dataset for the originally submitted popPK model POH1142, while omitting IV data. Interindividual variability was included for absorption parameters and clearance (not V) for tolebrutinib and on all parameters for M2. Eta shrinkage was large (>43%) for all parameters except V for M2. The exposure metrics (AUC and C_{max}) derived with the alternative model and the original model were comparable. The applicant mentions, the predictive performance is suboptimal. This is agreed. None of the models can describe the absorption phase.

After several re-modelling attempts, the applicant failed to present an acceptable popPK model for tolebrutinib and M2. The SmPC is now informed by results of non-compartmental analysis, which is acceptable.

Two exposure-response analyses of efficacy and safety of tolebrutinib and M2 in nrSPMS patients from Phase 3 study EFC16645 (HERCULES) were conducted (POH1143 and CTS0154) using AUC of tolebrutinib, M2 and tolebrutinib+M2 as exposure metrics. In POH1143, exploratory plots revealed no clear relationship between exposure parameters and the total number of new and/or enlarging T2-hyperintense lesions, the SDMT and the California Verbal Learning Test-II (CVLT-II). A slight tendency could be observed for percent change between end of study (EOS) and month 6 of brain volume loss, but with no evidence of a specific relationship. In CTS0154, the exposure-response relationship for the efficacy of tolebrutinib and M2 was assessed by univariate and multivariate Cox models. The efficacy endpoints evaluated in the exposure-efficacy analysis were time to onset of 6- and 3-month CDP for nrSPMS in EFC16645. Exposure main effect was significant in all base models. Based on Akaike information criterion, all the multivariate models had a marginally better fit than the base models. This analysis should be considered descriptive rather than predictive, as no external or internal cross-validation was carried out given the small size of the subgroups. Safety endpoints were time to hepatotoxicity event by Alanine Transaminase (ALT) Test/ Aspartate Aminotransferase (AST), severe infection, serious adverse event (SAE), and Adverse Event Hemorrhagic. Kaplan-Meier analysis and derivation of Hazard Ratio when exposed to tolebrutinib versus comparator arms were used to perform exploratory analyses of PK exposure parameters and time to hepatotoxic events. The exposure-response relationship did not show a trend between hepatotoxicity and exposure of tolebrutinib and/or M2, even at higher exposure levels. The findings suggest no major difference of SAE and severe infection frequencies with increased exposure to tolebrutinib. Observed differences were not statistically different.

A PBPK model for tolebrutinib and its active metabolite M2 was created in Simcyp v.22 using *in vitro* ADME data obtained from healthy participants in the dose range of 60 to 300 mg SD tolebrutinib and 120 to 240 mg QD tolebrutinib at fed state. Concentration-time profiles and pred/obs ratios indicated the model could fit the data well for tolebrutinib and M2 following a single dose and after QD dosing across different dose levels. When the PBPK model was applied for simulation of the effect of hepatic impairment on exposure several

fold-overprediction occurred compared to observed, falsely indicating impact on exposure. The PBPK model is not considered qualified for prediction of induction due to the complexity of tolebrutinib metabolism. Clinical drug-drug interactions (DDI) data with gemfibrozil (as a strong CYP2C8 inhibitor) have already indicated a significant impact on tolebrutinib exposure (i.e., increase in AUC by 8.4-and C_{max} by 5.4-fold) which implies that significant DDI impact could also be expected with moderate CYP2C8 inhibitors. Therefore, a similar recommendation for moderate inhibitors (i.e., "should be avoided") is provided in the SmPC regardless of any modelling. The PBPK model for tolebrutinib and M2 was used to investigate distribution into breast milk and indicated that both tolebrutinib and M2 distribute into breast milk. Impact on offspring was never investigated in the non-clinical setting. In summary, the PBPK platform is not considered qualified for the intended uses (renal impairment, hepatic impairment, breast feeding, DDI induction), and recommendations based on modelling is not required for moderate inhibitors, thus all PBPK statements have been removed from the SmPC.

Pharmacokinetics

Tolebrutinib is rapidly absorbed with median t_{max} around 1 hour under fasted condition and 2 hours under fed conditions. The absolute oral bioavailability under fasted conditions is low (geometric mean of 5.3%) but was found to almost double when taken with food. The food effect on tolebrutinib was investigated in a number of dedicated studies and compared across four different formulations. Although there are differences within the extent of the effect the overall trend is similar with all formulations. AUC of tolebrutinib increases while the metabolic ratio (M2/tolebrutinib) decreases.

Absolute bioavailability was determined in study PKM17308 at three different scenarios with concomitant administration of an intravenous infusion of a ^{14}C-labeled tolebrutinib and an oral dose of 60 mg tolebrutinib. The three scenarios were fasted alone, fed alone and fed with grapefruit juice. Grapefruit juice was introduced in the study to estimate fraction of intestinal metabolism of the first pass metabolism as grapefruit juice is anticipated to block CYP3A4 at the intestinal lining and not impact CYP3A4 in the liver. Substantial variability was observed in this study and 3 subjects were discarded as outliers. However, the combined evidence from metabolism, bioavailability, mass balance and drug interaction studies show that the main part of the first pass metabolism is taking place in the liver by CYP2C8 with a small contribution of CYP3A4/5 (approximately 80%). The remainder is estimated to take place in the gut by CYP3A4/5 (approximately 20%).

While early Phase 2 dose-finding did not include specific instructions for food intake the Phase 3 studies specifically instructed patients to always take tolebrutinib with a meal. On visits patients received both the meal and IMP at the clinical site. At home patients recorded timing of intake of food and medication in a diary. Overall compliance was reported to be high.

It is unclear what effect tolebrutinib would have if taken without food. During the dose-finding phase no lower boundary for efficacy was established. As patients cannot be expected to always follow their instructions the therapeutic window and effective exposure range were discussed. A potential underexposure and lack of efficacy, especially when the drug is taken without food, cannot be excluded. However, it is encouraging that a very high compliance with food intake recommendations was reported from the Phase 3 studies.

As the popPK model is not robust enough for covariate analysis, the wording on elderly, race, gender and body weight in the SmPC had to be based on data obtained with non-compartmental analysis. The wording on PK variability with regard to race, gender and body weight was adjusted to be based on descriptive statistics on PK data obtained by non-compartmental analysis.

According to the PBPK model exposure under dual inhibition of CYP3A and CYP2C8 would still be within safety margins established in the multiple ascending dose study. Treatment decisions will ultimately have to be based on clinical observations of efficacy and/or safety.

Tolebrutinib shows a complex metabolism primarily by CYP3A4 and CYP2C8. An active metabolite (M2) has been identified with a potential of covalent binding to BTK that is approximately 62% of that of tolebrutinib. M2 is formed exclusively by CYP2C8 and shows average exposure levels that are several multitudes of tolebrutinib. Drug-drug-interaction studies revealed significant changes to AUC and C_{max} for tolebrutinib and M2 when given with an at least moderate CYP2C8 inhibitor or moderate CYP3A inducer. Strong CYP3A4 inhibitors however produced only a minor increase.

Recombinant human CYP3A5 showed no depletion of tolebrutinib, indicating that it is not metabolised by this enzyme. *In vitro* study results indicate an involvement of CYP3A5 in the metabolism of M2 (21% depletion of M2 metabolite). On human hepatocytes CYP3A and CYP2D6 represent almost the totality (98%) of M2 metabolite clearance with minor involvement of CYP2J2.By incubating tolebrutinib with hepatocytes from 3 separate donors (MIH0967) with and without CYP selective inhibitors, the contribution of individual CYP to the metabolism of tolebrutinib could be estimated. This was done at 0.03, 0.1, 1 and 10 µM. As the plasma concentration is below 0.1 µM, the estimation was performed using the lowest concentrations. Moreover, saturation was observed at 1 and 10 µM for CYP2J2.

The indigenous role of CYP2J2 is metabolising arachidonic acid to e.g. biologically active eicosatrienoic acid epoxides. CYP2J2 is mainly expressed in the heart.

In a preliminary study, rhCYP2J2 fully catalysed the metabolism of [3H]-tolebrutinib as evidenced by the complete disappearance of unchanged drug. A new study was presented further evaluating the fate of tolebrutinib, M2 and M8 after incubation with CYP2J2 (Study MIV0758). In here, a state-of-the-art metabolite identification study was presented using radiolabelled compounds, radio-chromatography and FTMS for metabolite identification. Moreover, the amount of radiolabelled compound bound to CYP2J2-related protein during the incubation was quantified. 14C-tolebrutinib and 3H-M2 were extensively metabolized by CYP2J2 isoform (biotransformation>99%) and both showed similar metabolic profiles: the major metabolites result from cleavage of phenyl moiety or hydroxylation(s). The presence of GSH adducts show the reactivity of metabolites formed. 14C-M8 was highly metabolized by CYP2J2 isoform (biotransformation >70%) and two metabolites were identified: mono hydroxylation and cleavage of phenyl moiety. The covalent binding to rhCYP2J2 isoform was also evaluated and considered as significant for 14C-tolebrutinib (25.5% of total radioactivity) and 3H-M2 (26% of total radioactivity) incubations. The covalent binding was induced by metabolism and occurred only in the presence of NADPH.

No significant covalent binding was observed with 14C-M8 under the experimental conditions.

M8, which comprise of the majority of the tolebrutinib related radioactivity in circulation, is therefore not of concern for heart tissue in relation to CYP2J2. Whereas for tolebrutinib and M2, which together are responsible for the pharmacological effects, there is a potential for CYP2J2 mediating off-target covalent binding in heart tissue, since more than 25% of the material added in the incubations was found in the protein pellets as non-extractable radioactivity. However, it is reassuring that CYP2J2 is highly capable of metabolising tolebrutinib and M2 to non-reactive glutathione conjugates and that tolebrutinib had no effects on the cardiovascular system in dogs, although, it is not known if the dog version of CYP2J2 has the same selectivity for substrates as the human CYP2J2.

Inhibition of CYP2J2 may be associated, at least indirectly, with cardiac dysrhythmias, aberrant cardiac remodelling, heart failure and myocyte injury as shown in CYP2J2 silenced cardiac myocytes *in vitro* (Leow et al, 2024). However, a direct effect has not been documented yet.

The potential for adverse cardiac effects of tolebrutinib has been characterised in non-clinical studies, however M2 was not tested as it is not formed in dogs and no standalone *in vivo* safety pharmacology studies were performed for M2. Anticipating that the mechanism by which tolebrutinib binds covalently to CYP2J2 is similar to M2, the potential negative effects of M2 on cardiac tissues could, in this case, be anticipated to be similar as well. Then the safety margins established in dogs in the 9-months repeat-dose

toxicity study is important information indicating that covalent binding to CYP2J2 of tolebrutinib and M2 is of less a concern.

It is noted that atrial fibrillation/atrial flutter may be linked to the underlying condition and observed cases in clinical studies can be confounded by concomitant medication. Hence observed cases, except one, were not *per se* regarded related to treatment with tolebrutinib.

All in all, the concern for long term effects on heart tissue or heart-related adverse effects in nrSPMS patients remains and the applicant has agreed to update section 4.4 of the SmPC with a warning regarding atrial fibrillation/atrial flutter as this was observed in clinical studies.

There were several positive *in vitro* perpetrator DDI signals of tolebrutinib and/or its metabolites towards CYP3A, P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, and MATE1. All these positive *in vitro* signals were investigated by the applicant by PBPK modelling only and finally all DDI risks were excluded. The applicant has added warnings for potential interactions to the SmPC and will investigate potential transporter interactions in a dedicated study.

Genotyping for CYP2C8 and CYP2D6 was performed in the majority of Phase 1 studies.

The applicant has provided a new review of data on CYP2C8 genetic polymorphism. In the dataset analysed two poor metabolisers and 25 intermediate metabolisers were identified as well as 61 normal metabolisers. It is however not completely clear what population was the basis for this analysis. There were four subjects where metaboliser status could not be determined.

For the poor metabolisers the values for AUC for tolebrutinib and M2 are within the range of normal metabolisers. Overall values for intermediate metabolisers are similar to normal metabolisers. The provided data, together with examples from the scientific literature, might indicate that CYP2C8 metaboliser status has less effect on PK than enzyme inhibition, which is likely due to residual activity even in poor metabolisers. Plasma levels of tolebrutinib and M2 do not correlate with signs of liver injury nor does CYP2C8 metaboliser status correlate with liver enzyme increases. However, when poor CYP2C8 metaboliser status is known, caution should be exercised and appropriate warnings were implemented in the SmPC.

A similar analysis was performed for CYP2D6, which only has a minor role in the clearance of tolebrutinib. While trends of higher exposure for the poor metaboliser group of CYP2D6, no clinically relevant effect of polymorphism of CYP2D6 was noted on AUC or C_{max}.

The exposure to tolebrutinib increases more than proportional to dose, especially in lower dose range (PRN2246-001), but close to dose proportional for doses between 60 and 300 mg.

Available PK data (NCA) from healthy volunteers (fed or fasted) and patients (fed) for tolebrutinib and M2 show very limited or no accumulation. Although no data is available for the 60 mg dose fed, the data set is considered sufficient to support the claim of no accumulation of tolebrutinib and M2.

The inter-occasion variability (interindividual variability) in C_{max}, AUC and t_{max} was evaluated on data obtained from Study EFC16645. The % difference between the first (reference point), second and third occasion was included in the analysis. For tolebrutinib, these differences were very small for AUC (maximum <0.2%) but large for C_{max} (mean difference 9%, maximum difference 118%) and C_{trough} (mean difference 6%, maximum difference 126%). For t_{max}, these differences were high (mean difference 39%, maximum difference 927%). For M2, the differences between occasion 1 and occasion 2 or 3 were in the same order of magnitude, but slightly lower, than the one of tolebrutinib. Hence, overall, the interindividual variability in AUC was low, i.e. the bioavailability appears to vary very little within the same individual, even though the variability on C^{max} and tmax was high.

The inter-individual variability is moderate to high for both C_{max} and AUC in healthy volunteers and in patients. This is ascribed primarily to the low bioavailability, 5-10% depending on feeding state. The high

proportion of first pass metabolism (90-95%) happening both at intestinal and hepatic level will inherently result in very high variability. As the PopPK model is not considered acceptable, other possible causes for variability will not be discussed here. See instead section on special populations, where the assessment of individual causes of variability is based on studies with NCA analyses.

PK data from nrSPMS patients were presented as a pool of exposure data obtained in months 6, 9 and 12 in table 41 in Clin Pharm Sum. The PK data was estimated using the PopPK model due to sparse sampling. Compared with data from human volunteers in study TDU16831 Part 1d, it appears that the exposure is lower in patients than in human volunteers. More specifically, it was clarified, that the geometric mean value of AUC was 27% lower in participants from Study EFC16645 (24.0 ng.h/mL) compared to healthy volunteers (32.9 ng.h/mL) with the population PK model. This difference is most likely due to the high PK variability of tolebrutinib (CV% on AUC: 60.2% to 63.2%) and due to the difference of sample size in each population (178 healthy volunteers and 669 participants). When geometric mean AUCs was determined by NCA in Phase 1 clinical studies at 60 mg under fed conditions, the AUC in participants from Study EFC16645 was 10% to 52% lower. The difference could also be due to less control of feeding state in patients.

Safety margins were sufficient for tolebrutinib, however the pharmacologically active metabolite M2 was not formed in animals in amounts providing safety margins to the high exposure in humans. Therefore, a stand-alone toxicology program was conducted for M2. Exposure ratios were based on M2 exposure following 60 mg tolebrutinib in fed state observed in study POH0855 (76.7 ng.h/mL, 28.3 ng/mL). It should be noted that LOAEL exposure was provided for the 26-week study in rats at Week 26 since a NOAEL was not identified. Effects observed included premature euthanasia due to hemorrhage in the eye or stomach. These findings appear not to be relevant to humans as no similar safety issues were identified.

Pharmacodynamics

While tolebrutinib has a well-defined primary target in BTK the actual efficacy is assumed to be the result of anti-inflammatory effects, that are less specific. No robust biomarker was identified that correlates well with efficacy and/or safety data. The complex pathways involved allow for several points of PD interaction. The potential for PD interactions as well influences of genetic differences on the PD response was adequately discussed.

The relationship between plasma exposure and the number of new Gd+ and new and/or enlarging T2 lesions was investigated in a Phase 2b study in RMS patients. Gd+ lesions are associated with active demyelination and enlarging T2 lesions is a common measure used to monitor and predict treatment response in MS. The numbers of new Gd+ and new or enlarging T2 lesions decreased with increasing tolebrutinib exposure after 12-weeks in RMS patients. Whether this can be extrapolated to nrSPMS patients is discussed in the clinical efficacy section.

For the primary efficacy endpoint time to onset of 6-month CDP, a significant correlation was found between drug exposures and the improvement on disability. No significant correlation was found between exposure and the safety endpoints hepatotoxicity, SAE, severe infections and haemorrhagic events.

5.2.6.2. Conclusions

The clinical pharmacology of tolebrutinib has been thoroughly investigated and an overall robust data package has been provided.

The applicant failed to present an acceptable popPK model describing tolebrutinib PK.

The PK of tolebrutinib is complex with overall low bioavailability which is significantly affected by co-administration with food, high variability and an extensive metabolism for which the major part of the metabolites has retained the acryloyl moiety. Three major CYPs are involved in the clearance of

tolebrutinib, namely CYP2C8, CYP3A4 and CYP2J2. Inhibition of CYP2C8 results in unacceptable increase in exposure to tolebrutinib and significant decreases of M2, while induction of CYP3A4 and CYP2C8 leads to unacceptable decrease in exposure to tolebrutinib and M2. CYP2J2 is involved in the clearance of tolebrutinib and is the only CYP identified to be responsible for clearance of M8. CYP2J2 is mainly expressed in cardiac tissues, hence a concern for delayed adverse effects on the heart. Although data are limited prior knowledge of CYP2C8 metaboliser status was not required in the clinical studies and, in absence of a related safety signal, should therefore also not be required for routine decision making. However, in case CYP2C8 poor metaboliser status of an individual patient is already known caution should be exercised. *In vitro* signals for drug-drug-interactions are not sufficiently addressed by modelling and require either dedicated clinical studies or a fully qualified model.

For PD, the mechanism by which tolebrutinib exerts its therapeutic effect in MS is not fully characterised. However, the BTK pathway is considered critical for the inflammatory activation of B lymphocytes, macrophages, and microglia, both in the periphery and the CNS. The biomarkers used are considered relevant, although the clinical relevance of BTK occupancy is unknown and importantly, no PK/PD relationship was identified for NfL or Chi3L1. Mean decreases from baseline in median B cell (CD19+) counts and a mild decrease from baseline in mean IgM levels was observed in the tolebrutinib group in patients with nrSPMS in study EFC16645.

5.3. Clinical efficacy

5.3.1. Dose response study

The doses to be used were established based on pre-clinical data and on the results of the phase I studies (see also Clinical Pharmacology (PK/PD) as well as the non-clinical sections).

One double-blind, phase 2b, cross-over, dose-finding study has been performed.

A Phase 2b dose-finding study for SAR442168, a Bruton's tyrosine kinase inhibitor, in participants with relapsing multiple sclerosis (Study DRI15928)

Study DRI15928 was conducted from 29 March 2019 to 02 January 2020.

It was a multi-center, randomised, double-blind, placebo-controlled, cross-over study evaluating 4 doses of tolebrutinib (5, 15, 30 and 60 mg daily) in subjects with RMS. The study was conducted at 40 study centres in 10 countries across Europe and North America.

A 2-step randomisation process was used to assign eligible participants (1:1) to 1 of 2 cohorts, then further randomly assign participants within each cohort (1:1:1:1) to 1 of 4 tolebrutinib dose groups (5, 15, 30, and 60 mg tablets administered once daily with or without food): Cohort 1: Participants received 1 of the 4 tolebrutinib doses for the first 12 weeks, then crossed over to placebo for 4 weeks. Cohort 2: Participants received placebo for the first 4 weeks, then crossed over to 1 of the 4 tolebrutinib doses for 12 weeks. Having finished the double-blind treatment period (i.e., Week 16), participants were given the option to enroll in a separate long-term extension study to assess the safety and efficacy of tolebrutinib (study LTS16004).

Subjects with RMS (either RRMS or relapsing SPMS) according to the 2017 revision of the McDonald criteria, who were 18 to 55 years old and had an EDSS score ≤ 5.5 were included into the study. Disease activity criteria for subjects included at least 1 documented relapse within the previous year OR ≥2 documented relapses within the previous 2 years OR ≥1 active Gd+ brain lesion on a MRI in the past 6 months and prior to screening. Treatment-naive patients, and, after an appropriate wash-out period (no wash-out was required for interferon beta or glatiramer acetate), patients previously

treated with MS drugs other than BTK inhibitors were allowed to participate. Concomitant DMTs were prohibited. Patients were excluded from the study in case of a relapse in the 30 days prior to randomisation.

Patients were randomised to receive 5 mg, 15 mg, 30 mg or 60 mg tolebrutinib once daily for 12 weeks or placebo for 4 weeks. Tolebrutinib was given orally, once daily, as film-coated tablets of 2.5 or 15 mg dose strengths. The matching placebo tablets were also given orally once daily. To maintain the blinding, each participant was given a total of 4 tablets, either of tolebrutinib or tolebrutinib and placebo, to achieve 5, 15, 30, and 60 mg daily doses. The investigational medicinal products (IMPs) could be taken with or without food and at any time of the day. However, it was recommended to be as consistent as possible with respect to timing and fed state throughout the study.

The primary objective was to determine the dose-response relationship for tolebrutinib to reduce the number of new active brain lesions. Secondary objectives encompassed the evaluation of efficacy of tolebrutinib on disease activity as assessed by imaging measures; to evaluate the safety and tolerability of tolebrutinib.

The primary endpoint was the number of new Gd+ lesions not present at the previous MRI at the end of 12 weeks of tolebrutinib treatment (Week 12 for Cohort 1 and Week 16 for Cohort 2) as detected by brain MRI. Secondary endpoints were the number of new or enlarging T2 lesions at the end of 12 weeks of tolebrutinib treatment (compared with the previous visit MRI findings); total number of Gd+ lesions at the end of 12 weeks of tolebrutinib treatment; adverse events (AEs), SAEs, potentially clinically significant abnormalities in laboratory tests, ECG, or vital signs during the study period. PK/PD: correlations with PK/PD, efficacy and safety endpoints; PK of tolebrutinib; BTK occupancy changes over study period; lymphocyte phenotype subset changes over the 12 weeks of tolebrutinib treatment; immunoglobulin level changes over study period. Brain MRI scans were performed at Week 0 (baseline), and Weeks 8, 12, 16, 20, and 24.

The primary efficacy population was the modified intent-to-treat (mITT) population, which consisted of all randomly assigned participants exposed to the study intervention, analysed according to the treatment assigned by randomisation. The primary efficacy endpoint (dose-response relationship for tolebrutinib to reduce the number of new Gd+ lesions) was analysed using a 2-step Multiple Comparison Procedure with Modelling (MCP-Mod) techniques. The primary analysis was based on pooled data of Cohorts 1 and 2 for each of the tolebrutinib doses (i.e., data at Week 12 for Cohort 1 and at Week 16 for Cohort 2 for the number of new Gd+ lesions at the end of 12 weeks of tolebrutinib treatment).

A total of 130 patients were randomised. All the participants randomly assigned in each treatment group were treated, completed the treatment period, and completed the study period, with the exception of 1 participant in the placebo/tolebrutinib 60 mg group who did not complete the treatment period due to withdrawal of consent (study procedure). The median age at baseline was 36.0 years. The majority of participants were female (91 [70%]) and 119 out of 130 (91.5%) participants were white. All 130 participants were diagnosed with RMS (128 [98.5%] with RRMS and 2 [1.5%] with relapsing SPMS) with a mean EDSS score of 2.5, a median time since first diagnosis of 3.5 years, and a median time since first symptoms of MS of 4.9 years. A total of 101 (77.7%) participants had 1 relapse, 20 (15.4%) participants had 2 relapses, and 6 (4.6%) participants had ≥3 relapses within a year prior to screening. Of the 78 participants having an MRI in the 6 months prior to screening, 41 reported ≥1 active Gd+ brain lesion. The mean (SD) number of Gd+ lesions at baseline was sufficiently balanced with 2.20 (5.86), 2.28 (5.93), 0.71 (1.83), 1.91 (4.91), 2.09 (4.89) and 1.76 (4.65) under placebo, SAR 5, SAR 15, SAR 30 and SAR 60, respectively.

According to the Clinical Study Report (CSR), there was a significant number of missing records detailing meal status relative to administering study drug at clinical visits with PK sampling. The fed status was properly documented in 35% (135/389) of the total visits with collection of meal status. Among the total "well-documented" visits, 85% of participants took the IMP under fed conditions and 15% were documented as "fasted", and 60% (78/130) of participants had at least 1 documented visit (of these 78 participants, the intake of the IMP with or without food was adequately balanced across the different dosage arms) detailing the meal status with fed conditions recorded for 77% (60/78) participants, meaning that most of the PK assessments were made based on fed conditions. Accordingly, PK parameters were determined for 130 participants by considering the well-documented food intake status at each clinical visit and imputing fed conditions when meal information was missing.

Efficacy results:

Primary efficacy endpoint: A dose-response relationship between tolebrutinib and a reduction in the number of new Gd+ brain lesions after 12 weeks of treatment has been observed. Based on the data, an exponential dose-response curve was considered the best-fitting dose-response for the relationship between tolebrutinib and the number of new Gd+ lesions.

The observed means (SD) of new Gd+ lesion counts at the end of 12 weeks of treatment were 1.39 (3.20), 0.77 (1.48), 0.76 (3.31) and 0.13 (0.43) in the tolebrutinib 5 mg, 15 mg, 30 mg and 60 mg group, respectively. A nominal significant reduction in the mean number of new Gd+ lesions was demonstrated with tolebrutinib 60 mg (p-value = 0.0178), compared to placebo (0.13 (0.43) and 1.03 (2.50) lesions, respectively), corresponding to an adjusted relative reduction at 12 weeks of 85.02% (95% CI: 28.02% to 96.88%) versus placebo, but not in the lower dose groups.

Secondary efficacy endpoints: New or enlarging T2 lesions: The observed means (SD) of new or enlarging T2 lesions at the end of 12 weeks of treatment were 1.90 (3.97), 1.32 (1.83), 1.30 (4.90) and 0.23 (0.62) in the SAR442168 5 mg, 15 mg, 30 mg and 60 mg group, respectively. A nominal significant reduction in the mean number of new and enlarging T2 lesions was demonstrated with tolebrutinib 60 mg (p-value = 0.0001), compared to placebo (0.23 (0.62) and 2.12 (5.16) lesions, respectively), corresponding to a relative reduction at 12 weeks of 89.34% (95% CI: 68.39% to 96.41%; versus placebo, but not in the lower dose groups. At the end of 12 weeks of SAR442168 treatment, a linear dose-response relationship was observed and selected as the best-fitting dose-response per the MCP-Mod approach. Gd+ lesions: the observed means (SD) of total Gd+ lesions at the end of 12 weeks of treatment were 1.77 (4.10), 0.87 (1.59), 1.18 (4.87) and 0.29 (0.86) in the SAR442168 5 mg, 15 mg, 30 mg and 60 mg group, respectively. There was no significant dose-response relationship at the end of 12 weeks of treatment with tolebrutinib.

5.3.2. Main study

5.3.2.1. Study EFC16645

5.3.2.1.1. Study title

A Phase 3, randomised, double-blind, efficacy and safety study comparing SAR442168 to placebo in participants with non-relapsing secondary progressive multiple sclerosis (HERCULES).

5.3.2.1.2. Study design

This was a Phase 3, randomised, double-blind (DB), placebo-controlled, two-arm, parallel-group, event-driven [(based on 6-month CDP] study with a variable treatment duration to evaluate the efficacy and safety of tolebrutinib in participants with SPMS and an absence of clinical relapses for at least 24 months. The study comprised 3 phases: 1) screening period: starting 1 month before randomisation; 2) treatment period: assuming a recruitment period of approximately 24 months and 48 months study duration, the study was projected to have an estimated mean treatment duration of 33 to 36 months; 3) safety follow-up period**:** 4 weeks after the last dose of study treatment (for participants completing IMP treatment [DB or open-label (OL), if initiated after 6-month CDP] if not entering the Phase 3 LTS study and for participants who prematurely discontinued study intervention).

As pre-specified, a study end date was announced when approximately 288 events of 6-month CDP (primary endpoint) were projected to have occurred, after which all participants still on study had a final EOS efficacy assessment visit within - 2 to + 4 weeks of the announced date.

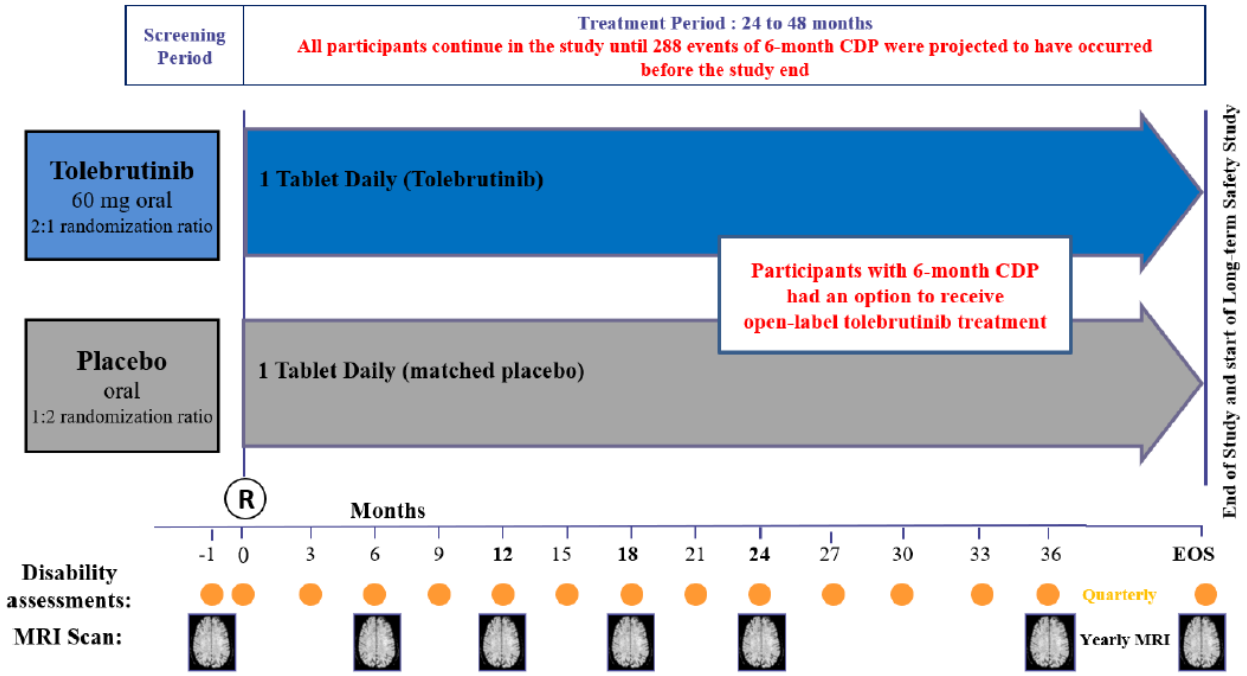
A participant was considered to have completed the study if he/she completed all periods of the study including the EOS visit, whether remaining on IMP or not.

Participants with 6-month CDP were eligible to receive OL treatment (tolebrutinib) or offered the possibility to switch to some other marketed treatment if available.

Subjects who completed the study and were taking the IMP treatment until the end of the trial (double-blind or open-label) were eligible to enroll in the open-label extension study LTS17043 where open-label tolebrutinib was provided.

Eligible participants were randomly assigned 2:1 to tolebrutinib (60 mg once daily) or matching placebo (once daily). Randomisation was stratified by age at screening (>40 versus ≤40 years) and geographic region (US versus non-US).

Figure 5 Study EFC16645 design



5.3.2.1.3. Treatment

Tolebrutinib (60 mg) or placebo once daily was administered as film-coated tablets under fed conditions. When possible, the meal with which tolebrutinib was taken (e.g., breakfast, lunch, or dinner) should be consistent throughout the study.

Dose modification was not foreseen in this study. Treatment might need to be interrupted or permanently discontinued if deemed necessary due to an AE.

Therapies for MS noted in the exclusion criterion were not permitted after randomisation while the participant was on study treatment. Short-term use (3 to 5 days) of glucocorticoids (e.g., for MS relapse treatment or an acute illness) and local corticosteroids (e.g., topical, nasal, ocular, otic, intra-articular) were allowed. In the case of MS relapse, treatments were allowed as per local routine practice (e.g., high dose IV methylprednisolone for 3 to 5 days). The date and time of relapse treatment administration as well as the name and dosage regimen of the medication had to be recorded.

Medications for treatment of MS symptoms (e.g., walking impairment, fatigue, spasticity, incontinence, pain) should be maintained at a stable dose prior to screening and for the duration of the treatment period, if clinically feasible.

If a participant achieved the primary endpoint (6-month CDP), they could, in conjunction with the Treating Investigator, choose to receive one of the following:

1. To switch to open-label tolebrutinib treatment; OR

2. To switch to a non-study treatment approved for nrSPMS in their respective country. In this case, the participant discontinued permanently the IMP and was encouraged to remain in the study for planned clinical visits until the common study end.

In case the participant and investigator opted for the provision of open-label medicine, they remained blinded to the original treatment assignment.

All individual blinded data were reviewed and all queries resolved, if possible, before the switch to the open-label treatment to ensure data integrity for primary assessment. Prior to initiation of open-label treatment, the Investigator confirmed that there has been no adjudicated relapse within 90 days prior to the onset or confirmation of 6-month CDP. Based on individual symptoms and assessed risk of further progression, the Investigator and participant could choose for the participant to remain on the initial double-blind treatment after achieving 6-month CDP.

The initial treatment assignment was kept blinded from participants, any Investigator site staff, and the Sponsor until the study end.

5.3.2.1.4. Randomisation

At Visit 2 (day 1) participants were centrally assigned to randomised study intervention via interactive response technology. The randomisation was stratified by age at screening (>40, ≤40 years) and geographic region (US versus non-US). The Treating Investigator, Examining Investigator/rater, clinical site staff, and Sponsor's clinical trial team members had no access to the randomisation (treatment) codes. The interactive response technology was programmed with blind-breaking instructions.

5.3.2.1.5. Blinding

In order to maintain the study blind and ensure participant safety, each site had 2 types of Investigators: A Treating Investigator and an Examining Investigator/rater (blinded). In view of the extended duration of this study, each site identified primary and back-up Treating and Examining Investigators/raters. A Treating Investigator could not change roles to Examining Investigator/rater during the study.

The Treating Investigator was the physician responsible for participant's medical management and should be a neurologist experienced in the care of MS patients. The Treating Investigator had no access to efficacy data including EDSS scores other than the score at screening but received alerts on 6-month CDP. The Treating Investigator had access to the participant's other collected data and followed the participant, collected safety events, and made treatment decisions based on the participant's clinical response and laboratory findings.

The Examining Investigator/rater was responsible for assessment of the EDSS including the screening EDSS score assessment and other clinical efficacy tests and had access only to data needed for these assessments. The Examining Investigator/rater could delegate assessment of T25-FW, 9-HPT, SDMT and CVLT-II to qualified study staff. The Examining Investigator/rater had no access to scores and prior EDSS assessments. Whenever possible, the same individual was to perform the examinations for the full study duration. The Examining Investigator/rater was not aware of which visit a participant was completing.

All efforts were made to keep the Examining Investigator/rater blinded to a participant's treatment assignment, treatment dates, and consequently to AE data, non-neurological symptoms, laboratory data, concomitant and prior medications, and any other information not related to the EDSS and other efficacy assessments. Examining Investigators were not aware of any AEs necessitating increased monitoring. Participants were instructed not to discuss any symptoms related to the IMP with the Examining Investigator/rater; the Examining Investigator/rater reminded the participant of this at the start of the examination and did not ask any questions that were not related to the neurological examination. Participants were asked not to communicate any co-medication used or symptoms unless requested by the Examining Investigator/rater for efficacy evaluation. Participants were not informed

about their EDSS scores at any time during the study. They were informed of 6-month CDP by the Treating Investigator in order to make decisions regarding the possibility of possible open-label treatment.

An Independent Data Monitoring Committee (IDMC), composed of external experts in the disease, biostatistics, or clinical research, was responsible for overseeing the safety of participants throughout the study. The IDMC reviewed and evaluated the unblinded safety data and made appropriate recommendations to the Sponsor regarding the conduct of the clinical trial. In addition, the IDMC reviewed results of a planned interim futility analysis based on approximately half of the targeted number of 6-month CDP events and provided a recommendation according to a pre-specified futility criterion. No unblinded results or data were shared with the Sponsor. To maintain continuous blinding and study integrity, the analyses were conducted by an independent statistician who directly transferred data to DMC members.

The Relapse Adjudication Committee evaluated all suspected relapses reported during the study using blinded data. Relapses, as adjudicated by the committee, had to meet protocol-defined criteria. This committee was composed of independent neurologists with expertise in MS clinical research and trained on the study procedures.

An Independent Hepatology Assessment Committee (HAC) (established on 28 July 2022 after Amendment Protocol 06) conducted a blinded review of all cases of ALT >3 × ULN with total bilirubin (TBILI) >2 × ULN or ALT >8 × ULN. Subsequently, HAC members were unblinded to treatment assignment in certain cases of interest and provided guidance on case evaluation and risk mitigation. The recommendations made by this committee were provided to the IDMC.

5.3.2.1.6. Patient population

The study was conducted at 267 centers that screened at least 1 participant in 31 countries/regions worldwide (Argentina, 5 sites; Australia, 6 sites; Austria, 3 sites; Belarus, 2 sites; Belgium, 4 sites; Bulgaria, 7 sites; Canada, 10 sites; China, 12 sites; Czech Republic, 6 sites; Denmark, 2 sites; Finland, 3 sites; France, 13 sites; Germany, 7 sites; Greece, 7 sites; Hungary, 6 sites; India, 6 sites; Israel, 4 sites; Italy, 12 sites; Japan, 6 sites, Lithuania, 3 sites; Netherlands, 2 sites, Norway, 3 sites, Poland, 10 sites, Portugal, 3 sites, Romania, 8 sites, Russia, 25 sites, Spain, 14 sites; Turkey, 10 sites; Ukraine, 16 sites; United Kingdom, 9 sites; and US, 43 sites). A total of 246 centers randomised at least 1 participant.

Main inclusion criteria:

- Previous diagnosis of RRMS in accordance with the 2017 revised McDonald criteria and a current diagnosis of SPMS in accordance with the clinical course criteria revised in 2013 and endorsed by an Adjudication Committee
- Male and female patients aged 18 to 60 years, inclusive
- Documented evidence of disability progression observed during the 12 months before screening. Eligibility was analysed by an Adjudication Committee (see below)
- Absence of clinical relapses for at least 24 months
- EDSS score at screening from 3.0 to 6.5 points, inclusive

Main exclusion criteria:

- history of certain infections or at risk for infection e.g., history of T-lymphocyte or T-lymphocyte-receptor vaccination, transplantation and/or antirejection therapy; participant has

received any live (attenuated) vaccine within 2 months before the first treatment visit; participant has a lymphocyte count less than the lower limit of normal at the Screening Visit; history of diagnosis of progressive multifocal leukoencephalopathy (PML) or evidence of findings suggestive of PML on the screening MRI; history of infection with human immunodeficiency virus ; history of active or latent tuberculosis ; risk of developing or having reactivation of hepatitis: results at screening for serological markers for hepatitis B and C indicating acute or chronic infection.

- psychiatric disturbance or substance abuse, e.g., history of any psychiatric disease, behavioral condition, or depression requiring hospitalisation within 2 years prior to the Screening Visit; a documented history of attempted suicide or suicidal ideation of category 4 or 5 according to the Columbia Suicide Severity Rating Scale baseline/screening version over the 6 months prior to the Screening Visit, OR if in the Investigator's judgment, the participant is at risk for a suicide attempt.
- any screening laboratory values outside normal limits or abnormal ECGs as per the Investigator’s judgment, or had conditions that could predispose the participant to excessive bleeding (e.g., bleeding disorder or known platelet dysfunction at any time prior to the Screening Visit; a platelet count <150 000/µL at the Screening Visit) or that could adversely affect participation in the study or make the primary efficacy endpoint non-evaluable (e.g., history or presence of significant other concomitant illness according to the Investigator’s judgment such as, but not limited to cardiovascular, renal, neurological, endocrine, gastrointestinal, metabolic, pulmonary, or lymphatic disease that would adversely affect participation in this study.
- Acute liver disease, cirrhosis, chronic liver disease (unless considered stable for >6 months).
- Confirmed screening ALT >1.5 × ULN OR AST >1.5 × ULN OR alkaline phosphatase (ALP) >2 × ULN (unless caused by non-liver-related disorder or explained by a stable chronic liver disorder) OR total bilirubin >1.5 × ULN (unless due to Gilbert syndrome or non-liver-related disorder).
- At screening, elevated transferrin saturation (>50% in males and >40% in females) and/or with elevated ferritin levels >500 µg/L.

Exclusions related to medications:

Subjects could be MS-treatment naïve or could have had received prior disease modifying treatment except for any lymphoid irradiation, bone marrow transplantation, mitoxantrone (with evidence of cardiotoxicity following treatment, or cumulative lifetime dose >120 mg/m2), other strongly immunosuppressive treatments with very long-lasting effects.

Before randomisation, an eligibility adjudication committee of MS experts evaluated anonymised data of participants to endorse the diagnosis of nrSPMS and confirm disability progression during the last 12 months and an absence of clinical relapses for at least 24 months. Any increase in EDSS score was sufficient to confirm disability progression. If an EDSS score was unavailable or disability progression was not confirmed by EDSS assessment, disability progression was to be further explained by a functional systems assessment. In addition, objective neurologic findings were also to be used to support disability progression (a validated checklist for trial eligibility was provided to the site).

5.3.2.1.7. Objectives and estimands

5.3.2.1.7.1. Primary objective

The primary objective of study EFC16645 was to determine the efficacy of tolebrutinib compared to placebo in delaying disability progression in nrSPMS.

Estimand for the primary objective

Table 12 Estimands for primary objective

Population	Patients with non-relapsing secondary progressive multiple sclerosis
Treatment condition	Assignment to tolebrutinib, regardless of discontinuation, compared to assignment to placebo, regardless of discontinuation.
Endpoint (variable)	Time from randomisation to onset of 6-month CDP
Population-level summary	hazard ratio for tolebrutinib compared to placebo, adjusted age at screening (>40, ≤40 years), geographical region (US, non-US), baseline EDSS score and baseline Gd+ lesions (present, absent).
Intercurrent events (ICE) and strategy to handle them	
Treatment discontinuation	Treatment policy

The clinical question of interest is on the effect of tolebrutinib compared to placebo in the time from start of treatment to onset of 6-month CDP irrespective of whether treatment was followed or not.

Statistical methods for estimation and sensitivity analysis on primary estimand

Analysis sets

The intent-to-treat (ITT) Analysis Set served as the basis for the formal analysis of efficacy.

- **Intent-to-treat (ITT) population:** primary analysis population for efficacy, defined as all randomised participants according to the intervention group allocated by the randomisation schedule, irrespective of the study intervention received.
- **Safety population:** All participants randomly assigned and exposed to study intervention, regardless of the amount of exposure, analysed according to the treatment actually received. Randomised participants for whom it was unclear whether they took the study medication were included in the safety population as randomised. The PD analyses were performed on the safety population.
- **PK population**: All participants in the safety population with at least one non-missing PK sample after first dose of the study intervention. Participants were analysed according to the treatment actually received.

Analysis methods

Analysis of the ***primary efficacy endpoint***

Censoring rules in the primary ITT analysis were:

- For participants who completed the study without an initial onset of 6-month CDP, the participant was censored at the date of the last EDSS assessment.
- For participants who had an initial onset of 6-month CDP but completed the study at the study end date without a 3-month confirmation, the participant was censored at the date of last EDSS assessment.
- For participants who prematurely discontinued the study before confirmation of an onset of 6-month CDP, regardless of having an initial onset, the participant was censored at the date of the last EDSS assessment.

For participants who met 3-month CDP criteria and continued to meet the criteria for EDSS disability progression through the final study assessment but did not reach 6-month confirmation due to end of study, the 6-month CDP event status was imputed via a multiple imputation method.

For participants who met 3-month CDP but completed the study at the study end date without 6-month confirmation, the 6-month CDP event status of the participant was determined by a multiple imputation approach only if all additional EDSS assessments after 3-month confirmation to participant's end-of-study also met the criteria for disability progression.

Only EDSS assessments measured more than 90 days after the onset of an adjudicated relapse, if present, were used to determine onset of 6-month CDP. For the purpose of CDP confirmation, only EDSS scores measured more than 90 days after an adjudicated relapse, if present, were used.

If a participant died due to MS, it was considered a confirmed disability progression regardless of the baseline EDSS or the change in EDSS.

The time to onset of 6-month CDP was analysed by a Cox proportional hazards model with terms for intervention group, age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline Gd+ lesions (0, ≥1). The HR, its 95% CI and the p-value for comparing tolebrutinib to placebo were estimated from this model. A log-rank test stratified by age at screening (>40, ≤40 years) and geographic region (US, non-US) was also used to compare tolebrutinib to placebo. To include all participants in the analysis, the baseline Gd+ lesion presence or absence was imputed for a few participants with a missing baseline count.

The following sensitivity analyses, without any imputation, were performed to evaluate the impact of missing data on the results of the main analytical approach to the primary analysis:

- Participants with a potential onset of disability progression but without 6-month confirmation due to missing data, regardless of reason, were considered to have confirmed progression with the time to onset being the time to the initial EDSS increase. Of note, a potential onset is invalidated if there is any non-confirmatory EDSS in the confirmation period that does not meet the minimum change required for progression.
- Participants with missing or incomplete 6-month CDP were treated as censored at the last EDSS assessment date.

For the above analyses, the same Cox proportional hazards model as described for the primary endpoint were performed without imputation.

An additional *post hoc* sensitivity analysis for 6-month CDP was performed where all participants with at least one adjudicated relapse during the study were excluded from the analysis set. The same statistical analysis methods as for the primary analysis were utilised but without imputation.

Analyses of ***secondary endpoints***

Time to onset of 3-month CDP, 3-month sustained increase in T25-FW and 9-HPT, and 6-month CDI were analysed using similar methods as for the primary endpoint, but without imputation.

Continuous efficacy endpoints (percent change in brain volume, change in cognitive function, and change in MSQoL-54 at EOS) were analysed using a mixed model repeated measures approach in the ITT population. The model included change/percent change values for the respective endpoint at each scheduled visit as response variables, and treatment, age at screening (>40, ≤40 years), geographic region (US, non-US), visit, treatment by-visit interaction, baseline value for the endpoint being assessed and baseline value-by-visit interaction as covariates. For brain volume, the Month 6 value serves as the reference value rather than baseline.

Categorical efficacy endpoints with count data (new and/or enlarging T2 hyperintense over the study period after baseline) were analysed using a negative binomial regression model in the ITT population. The model included the total count of lesions across all scheduled MRI scans during the study period as the response variable, with treatment group, age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline T2 lesion count as covariates. Log-transformed time from screening MRI to the last available scheduled MRI scan was the offset variable.

To control the Type 1 error rate for the study, a hierarchical testing procedure was applied at a 2-sided 5% significance level. If statistical significance was achieved for the primary endpoint, a selected set of secondary endpoints were tested using a pre-specified hierarchical testing order.

Given that participants who reach the primary endpoint of 6M-CDP were eligible to switch to OL tolebrutinib, including data after the switch could impact the analysis of secondary endpoints: number of new/enlarging T2 lesions per year, time to onset of sustained 20% increase in the 9-HPT (T25-FW) for at least 3 months, and percent change in brain volume at EOS compared to Month 6. Sensitivity analyses excluding data after initiation of OL therapy were performed for these endpoints.

No other sensitivity, supplementary, or subgroup analyses were performed for the secondary endpoints.

Analyses of the primary endpoint were conducted for the following subgroups: geographic region (US, non-US; Eastern Europe, Western Europe, North America, Rest of World), age at screening (>40, ≤40 years), sex (Male or Female), race (White, Black or African American, Asian, Other), baseline Gd+ lesions (present, absent), baseline EDSS score (≤4.5, >4.5; ≤5.5, >5.5), prior DMT use (0, 1, ≥2), duration since RMS symptom onset (≤5, >5 to ≤10, >10 years) and adjudicated relapse during the study (yes, no).

The treatment effect (tolebrutinib compared to placebo) for the primary endpoint was provided, as well as the corresponding 95% CI, for each subgroup separately, using the same methods as described above. Forest plots of hazard ratios and the corresponding 95% CIs were provided.

Treatment by subgroup interaction and its p-value were derived from a Cox proportional hazards model with terms for treatment group, age at screening (>40, ≤40), region (US, non-US), baseline EDSS score, baseline Gd+ lesions (present, absent), subgroup (if different than the aforementioned covariates) and treatment by subgroup interaction as covariates. If quantitative treatment by subgroup interaction was detected with nominal p-value <0.1 for any subgroup factor, a further investigation was performed to evaluate possible qualitative interaction.

Approximately 1700 participants were planned to be screened to achieve up to 1290 randomly assigned to study intervention (2:1 randomisation ratio of tolebrutinib to placebo). The study was planned as an event-driven trial based on 6-month CDP. The study was planned to continue until approximately 288 events are projected to have occurred to provide 80% power to detect a 30% risk

reduction in 6-month CDP with tolebrutinib compared to placebo (2-sided α = 0.05). The following assumptions were used for the calculations: 2-year placebo event rate of 23.6%; annual discontinuation rate of 10%; constant hazard rates using a log-rank test; estimated enrollment period of 24 months with the last randomised participant followed for 24 months.

A subgroup analysis based on the adjudicated relapses during the study was conducted. However, a subgroup definition based on a post-baseline event cannot be interpreted causally, since assignment to the subgroup may be partially due to the randomised treatment. Effects between treatments given within subgroups may not be fully attributed to the treatment since treatment groups within the subgroup may not be comparable. Hence, this subgroup analysis is considered to be purely exploratory with unclear interpretation.

A non-binding interim futility analysis was to be performed when approximately 50% of the primary endpoint events are observed. The futility criterion was determined by calculating the predictive power, which is a weighted average of the conditional power (11). Futility of the study may be declared only when the predictive power for the primary endpoint is below 10%, which is equivalent to the condition that the hazard ratio between tolebrutinib and placebo derived from the primary analysis is greater than or equal to 0.92. The futility interim analysis was conducted by an independent statistics group and reviewed by the IDMC. Neither the Sponsor's team nor the Investigator's staff had access to the treatment information at the individual participant level or group level before the study was formally unblinded after study completion or after the IDMC recommendation and Sponsor agreement for stopping the trial. The details of the interim analysis were included in the DMC statistical analysis plan (SAP).

All changes in the planned analyses for the study were implemented by SAP Version 3.0.

A *post hoc* analysis was performed to examine the primary endpoint (6-month CDP) in the subgroup of participants without Gd+ lesions at baseline. This supportive analysis utilised the same approach as for the primary analysis of the primary endpoint in order to utilise full information from the incomplete data. That is, for participants who met 3-month CDP and continued to meet the EDSS criteria for disability progression through the final study assessment but did not reach 6-month confirmation due to the end of study, the 6-month CDP event status was imputed via a multiple imputation method.

Additional *post hoc* analyses on the primary endpoint without imputation were performed to assess the relationship between MRI biomarkers and tolebrutinib treatment response. PRLs represent areas of chronic inflammation, demyelination, and axonal transection in white matter, correlate with relapse-independent disability accumulation, and appear to be resistant to treatment by currently approved therapies (Absinta et al., 2019; Maggi et al., 2023). As the ability of PRLs to predict disability treatment response is of interest, a *post hoc* sub-group analysis of the effect of tolebrutinib on time to onset of 6-month CDP was conducted in the subset of participants with PRL assessment according to the number present at baseline: 0, 1-3, and ≥4, respectively.

5.3.2.1.7.2. Secondary objectives

Secondary objectives were to evaluate the efficacy of tolebrutinib compared to placebo on clinical endpoints, MRI lesions, cognitive performance, physical function and quality of life.

Estimands for the secondary objectives

Estimands were generally not defined for secondary or tertiary endpoints. However, for the 3-month CDP, the same estimand strategy as defined for the primary time to 6-month CDP was used. In contrast to the analysis for 6-month CDP (event status was multiply imputed in case 3-month CDP was

confirmed, but 6-month confirmation was not possible due to), no imputation was implemented for 3-month CDP event status with only a potential onset.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

To control the Type 1 error rate for the study, a hierarchical testing procedure was applied at a 2-sided 5% significance level, i.e., each hypothesis was formally tested only if the preceding one was significant at the 5% level. If statistical significance was achieved for the primary endpoint, a selective set of secondary endpoints was tested following the hierarchical testing procedure shown below:

• Time to onset of 3-month CDP as assessed by the EDSS score

• Number of new and/or enlarging T2 hyperintense lesions per year

• Time to onset of sustained 20% increase in the 9-HPT for at least 3 months

• Time to onset of sustained 20% increase in the T25-FW for at least 3 months

• Time to onset of CDI confirmed over at least 6 months

• Percent change in brain volume as detected by MRI scans at the EOS compared to Month 6

Tertiary objectives

To evaluate efficacy of tolebrutinib on disease progression and activity in nrSPMS, assessed by other clinical and imaging measures and by self-reported assessment.

5.3.2.1.8. Results

5.3.2.1.8.1. Participant flow and numbers analysed

The date first participant enrolled was 24 September 2020 and the date last participant completed was 29 August 2024. A total of 1438 persons were screened for the study. Of these, 307 (21.3%) failed screening, primarily related to history of infection or at risk for infection 43 (3.0%).

The remaining screened participants (n= 1131) were enrolled and randomised as follows: 754 to tolebrutinib and 377 to placebo. 4/1131 participants were randomised but not exposed to study intervention: 2/754 participants in the tolebrutinib group (1 due to withdrawal by the participant and 1 due to not eligible but randomised by error) and 2/377 participants in the placebo group (both due to eligibility not confirmed but randomised by error).

Overall, 869 participants completed the study: 580 participants in the tolebrutinib group and 289 participants in the placebo group (including those subjects, who started the DB study intervention period on tolebrutinib or placebo but switched over to OL tolebrutinib).

626 participants completed the DB study intervention period: 434 participants in the tolebrutinib group and 192 in the placebo group. 196 participants switched over to OL tolebrutinib: 120 participants in the tolebrutinib group and 76 in the placebo group (hereafter referred to as "tolebrutinib/tolebrutinib group" and "placebo/tolebrutinib group"). Of note, 5 participants from the DB tolebrutinib group did not have disease progression but erroneously switched to OL treatment.

There were 318 participants (42.2%) in the tolebrutinib arm and 183 (48.5%) in the placebo arm who discontinued DB treatment. The most frequently reported reason for permanent DB study intervention discontinuation was "progressive disease" (116 in the tolebrutinib group and 76 in the placebo group).

Participants with progressive disease (6-month CDP) were given the option to switch to OL tolebrutinib or to switch to another DMT. 4 patients per group switched to alternative DMT after 6-month disease progression.

There were 122 (16.2%) and 67 (17.8%) subjects who did not complete the DP phase in the tolebrutinib and placebo arms, respectively due to reason "withdrawal by participant" with the occurrence of "adverse events", "study procedure" and "other" designated as potential (sub)reasons. While "adverse events" and "study procedure" only included a minority of these subjects, most of the subjects were included under the (sub)reason "other". In addition, there was another category of "other reasons" for which there are also a non-negligible number of patients in particular for the tolebrutinib arm. Overall, there were ten participants in the tolebrutinib group and 12 in the placebo group who switched over to another DMT after study intervention discontinuation due to the reasons "withdrawal by participant, other" or "other" reason.

The percentage of participants who permanently discontinued OL study intervention was similar between the tolebrutinib/tolebrutinib and placebo/tolebrutinib groups (3.3% and 2.4%, respectively). The most frequently reported reason for permanent OL study intervention discontinuation was "withdrawal by subject" (17 in the tolebrutinib/tolebrutinib group and 6 in the placebo/tolebrutinib group).

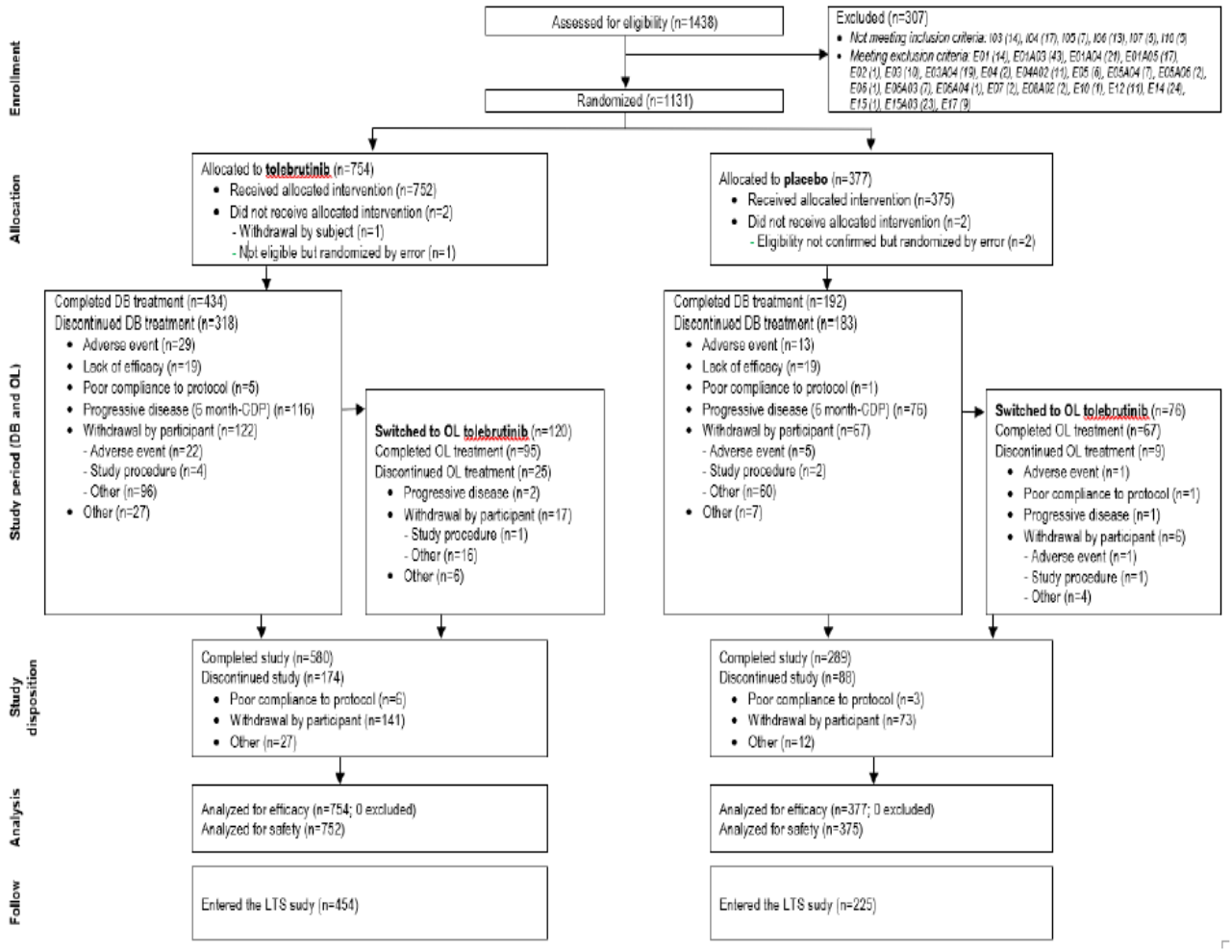
A total of 3 participants (2 in the tolebrutinib group and 1 in the placebo group) died during the study (refer to clinical safety).

Table 13 Patient disposition (randomised population)

n (%)	Placebo (N=377)	tolebrutinib 60 mg (N=754)	All (N=1131)
Randomized and not treated	2 (0.5)	2 (0.3)	4 (0.4)
Randomized and treated	375 (99.5)	752 (99.7)	1127 (99.6)
DB Treatment completed	192 (50.9)	434 (57.6)	626 (55.3)
DB Treatment permanently discontinued	183 (48.5)	318 (42.2)	501 (44.3)
Main reason for premature DB treatment discontinuation			
Adverse event	13 (3.4)	29 (3.8)	42 (3.7)
Lack of efficacy	19 (5.0)	19 (2.5)	38 (3.4)
Poor compliance to protocol	1 (0.3)	5 (0.7)	6 (0.5)
Progressive disease	76 (20.2)	116 (15.4)	192 (17.0)
Withdrawal by subject	67 (17.8)	122 (16.2)	189 (16.7)
Other	7 (1.9)	27 (3.6)	34 (3.0)
Reason for DB treatment withdrawal by subject[a]			
Adverse event	5 (1.3)	22 (2.9)	27 (2.4)
Study procedures	2 (0.5)	4 (0.5)	6 (0.5)
Other	60 (15.9)	96 (12.7)	156 (13.8)
Switched to OL tolebrutinib	76 (20.2)	120 (15.9)	196 (17.3)
OL treatment completed	67 (17.8)	95 (12.6)	162 (14.3)
OL treatment permanently discontinued	9 (2.4)	25 (3.3)	34 (3.0)
Main reason for premature OL treatment discontinuation			
Adverse event	1 (0.3)	0	1 (<0.1)
Lack of efficacy	0	0	0
Poor compliance to protocol	1 (0.3)	0	1 (<0.1)
Progressive disease	1 (0.3)	2 (0.3)	3 (0.3)
Withdrawal by subject	6 (1.6)	17 (2.3)	23 (2.0)
Other	0	6 (0.8)	6 (0.5)
Reason for OL treatment withdrawal by subject[a]			
Adverse event	1 (0.3)	0	1 (<0.1)
Study procedures	1 (0.3)	1 (0.1)	2 (0.2)
Other	4 (1.1)	16 (2.1)	20 (1.8)
Study disposition			
Completed study	289 (76.7)	580 (76.9)	869 (76.8)
Discontinued from study	88 (23.3)	174 (23.1)	262 (23.2)
Main reason for study discontinuation			
Poor compliance to protocol	3 (0.8)	6 (0.8)	9 (0.8)
Site terminated by sponsor	0	0	0
Study terminated by sponsor	0	0	0
Withdrawal by subject	73 (19.4)	141 (18.7)	214 (18.9)
Other	12 (3.2)	27 (3.6)	39 (3.4)
Status at last contact	377 (100)	754 (100)	1131 (100)
Alive	376 (99.7)	752 (99.7)	1128 (99.7)
Dead	1 (0.3)	2 (0.3)	3 (0.3)
Entered LTS study	225 (59.7)	454 (60.2)	679 (60.0)

Note: percentages are calculated using the number of participants randomised as denominator
DB: Double-blind, OL: open-label, LTS: long-term safety
a This is a further breakdown of the reasons for withdrawal by subject reported above, as collected in the standard CRF

Figure 6 Participant flow



Analyses sets:

The ITT analyses set was used for analyses of efficacy. The safety analysis Set was used for safety and PD analyses.

1127 subjects were treated in the study, i.e., 752 subjects with tolebrutinib and 375 subjects with placebo.

Table 14 Analysis populations

n (%)	Placebo (N=377)	tolebrutinib 60 mg (N=754)	All (N=1131)
Randomized population	377 (100)	754 (100)	1131 (100)
Intent-to-treat (ITT) population	377 (100)	754 (100)	1131 (100)
Safety population	375 (100)	752 (100)	1127 (99.6)
Pharmacokinetics (PK) population	119 (31.7)	696 (92.6)	815 (72.1)

Percentages are calculated using the number of participants randomised as denominator.
For safety and PK populations, participants are tabulated according to the study intervention actually received.

5.3.2.1.8.2. Deviations from study plan

The original protocol was dated 28 February 2020, and there were 12 protocol amendments and 1 administrative amendment to the protocol.

Changes to the original protocol included 10 global and 2 local amendments (1 for Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Spain, and United Kingdom, and 1 for France, i.e., to incorporate country-specific guidelines).

Additionally, an administrative protocol amendment (dated 07 March 2024) was also submitted to the FDA regarding inconsistency in information presented in the tables included in Appendix "Example of drugs with a potential to change tolebrutinib metabolism or absorption".

Liver injury cases were identified with tolebrutinib exposure in Phase 3 studies (reference is made to safety, section 5.4.4, AESI – increase of ALT>3 x ULN).). Consequently, updates of increased monitoring of liver enzymes were incorporated in the protocol amendment 06 (dated 23 May 2022) and further modified through protocol amendments 07 (dated 13 September 2022), 08 (dated 14 December 2022), 09 (dated 12 July 2023), 10 (dated 28 September 2023), 11 (dated 20 November 2023), and 12 (dated 20 December 2023), accompanied by the implementation of a Independent HAC.

On 27 June 2022, the FDA placed clinical MS studies conducted with tolebrutinib on partial clinical hold, stopped enrollment of new participants at US sites and suspended dosing of the study intervention for those participants at US sites who had been on study for ≤60 days. Participants at US sites who had completed >60 days in the study could continue the study intervention. The FDA partial clinical hold was modified on 27 October 2023. Following implementation of amended protocol 11 (dated 20 November 2023), the partial clinical hold was excepted as follows:

• Participants who met 6-month CDP could initiate OL tolebrutinib treatment

• Participants who interrupted the study intervention due to the partial hold (within first 60 days) but remained in trial, could reinitiate the study intervention

A pause in enrolment was also requested by France HA on 05 July 2022, by Hungary HA on 25 July 2022, by Argentina HA and Israel HA on 04 August 2022, and by Japan HA on 21 December 2022. The enrolment hold was lifted by France HA on 04 November 2022, by Hungary HA on 03 November 2022, by Argentina HA on 18 November 2022, by Israel HA on 15 January 2024, and by Japan HA on 22 January 2024. The last participant of Study EFC16645 was randomised on 12 January 2023.

Following the DMC recommendation on 08 August 2022, the Sponsor decided to pause enrolment globally. Following the HAC and DMC meeting on 30 August 2022, the IDMC recommended continuing the study on 06 September 2022 as the potential benefit-risk ratio remained acceptable and global enrolment was resumed.

Protocol deviations

Protocol deviations were categorised as automatic if directly identifiable from the clinical database data, and manual if not directly derived from the data. Manual deviations were primarily based on monitoring activities. The classification of each deviation was determined by the team before the database lock.

Using a comprehensive and cautious approach, deviations were categorised based on their severity and likelihood of occurrence as outlined below:

• Minor protocol deviations were conditions, practices, and processes that were not expected to harm or violate the rights, safety, or well-being of participants, or the quality or integrity of the data.

• Major protocol deviations were conditions, practices, and processes that could potentially adversely affect the rights, safety, or well-being of participants, or the quality or integrity of the data.

• Critical protocol deviations were conditions, practices, and processes that adversely affected the rights, safety, or well-being of participants, or the quality or integrity of the data.

Notably, exceptional deviations pertain to protocol deviations occurring during emergency situations, like the COVID-19 pandemic or the Ukraine/Russia conflict.

Site-level protocol deviations referred to manual deviations at a specific clinical site, while study-level protocol deviations impacted the entire study, with either all or none of the participants being affected in each case.

Participant-level protocol deviations:

There were no critical protocol deviations. The numbers (%) of participants with at least 1 major protocol deviation were similar between intervention groups (251 [33.3%] in the tolebrutinib group and 130 [34.5%] in the placebo group).

The most frequently reported category of major protocol deviations was "assessments/procedures" (159 [21.1%] participants in the tolebrutinib group and 80 [21.2%] in the placebo group). The second most frequently reported category of major protocol deviations was "concomitant medications/ therapy (45 [6.0%] participants in the tolebrutinib group and 21 [5.6%] in the placebo group). In the category of "randomisation procedure, major protocol deviations were reported in 3 (0.4%) participants in the tolebrutinib versus 4 (1.1%) participants in the placebo group. Overall, 8 (1.1%) participants in the tolebrutinib group and 2 (0.5%) participants in the placebo group had at least 1 major protocol deviation related to the COVID-19 pandemic or other emergency situations.

Most of the major protocol deviations were balanced across study intervention groups, with no apparent distribution pattern, and therefore, according to the applicant, were unlikely to have any impact on the overall outcome of the study.

There were 1 study-level major protocol deviation (included the delayed implementation of a solution to collect efficacy data for the 9-HPT, T25-FW, SDMT, and CVLT-II assessments in the database) and 95 site-level major deviations. According to the applicant, none were considered critical.

Of the 95 site-level major deviations, the most commonly reported was study assessment/procedure performed by unqualified/unblinded personnel (57 deviations, majority of which were due to examining Investigator's training completion; a total of 40 sites impacted), followed by: 10 deviations related to site organisation, resourcing and capability issues (9 sites impacted); 6 deviations related to staffing changes not documented (6 sites impacted); 6 deviations related to source data issues (6 sites impacted); 6 deviations related to delegation of duty issues (6 sites impacted); 3 deviations related to not timely evaluation of MRI scans completed by radiology facility; 3 deviations related to missing regulatory document (3 sites impacted); 2 deviations related to delay of communication with the Investigator or IRB/IEC (1 site impacted); 1 deviation related to non-compliance or deviation related to local process (1 site impacted); 1 deviation related to IRT issue (not related to the randomisation procedure; 1 site impacted).

According to the applicant, all deviations were followed up in a timely manner and with proper evaluation resulting in no impact on data integrity.

5.3.2.1.8.3. Baseline data

Demographic data for the randomised population are reported in Table 15. Mean age was 48.9 (8.0) years with a range of 20 to 60 years. Most participants were female (61.5%), white (92.9%) and not Hispanic or Latino (94.2%). 418 (37.0%) subjects were enrolled in Western Europe, 407 (36.0%) in Eastern Europe, 162 (14.3%) in North America and 144 (12.7%) in the Rest of the world. Demographic characteristics were generally balanced between the tolebrutinib and the placebo group.

Table 15 Baseline demographic characteristics (Randomised Population)

Characteristic	Placebo (N=377)	tolebrutinib 60 mg (N=754)	All (N=1131)
Age (years)			
N	377	754	1131
Mean (SD)	48.9 (8.0)	48.9 (8.0)	48.9 (8.0)
Median (min, max)	50.0 (27, 60)	51.0 (20, 60)	51.0 (20, 60)
Q1, Q3	43.0, 56.0	43.0, 56.0	43.0, 56.0
Age Category, n (%)			
<=40 years	63 (16.7)	130 (17.2)	193 (17.1)
>40 years	314 (83.3)	624 (82.8)	938 (82.9)
Sex, n (%)			
Male	135 (35.8)	300 (39.8)	435 (38.5)
Female	242 (64.2)	454 (60.2)	696 (61.5)
Race, n (%)			
White	348 (92.3)	703 (93.2)	1051 (92.9)
Black or African American	4 (1.1)	6 (0.8)	10 (0.9)
Asian	19 (5.0)	36 (4.8)	55 (4.9)
American Indian or Alaska Native	0	1 (0.1)	1 (<0.1)
Native Hawaiian or other Pacific Islander	0	0	0
Multiple	0	1 (0.1)	1 (<0.1)
Unknown	2 (0.5)	5 (0.7)	7 (0.6)
Not reported	4 (1.1)	2 (0.3)	6 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	18 (4.8)	44 (5.8)	62 (5.5)
Not Hispanic or Latino	359 (95.2)	706 (93.6)	1065 (94.2)
Unknown	0	2 (0.3)	2 (0.2)
Not reported	0	2 (0.3)	2 (0.2)
Region, n (%)			
United States	37 (9.8)	74 (9.8)	111 (9.8)
Non United States	340 (90.2)	680 (90.2)	1020 (90.2)
North America	46 (12.2)	116 (15.4)	162 (14.3)
Western Europe	150 (39.8)	268 (35.5)	418 (37.0)
Eastern Europe	134 (35.5)	273 (36.2)	407 (36.0)
Rest of the world	47 (12.5)	97 (12.9)	144 (12.7)
Weight (kg)			
Mean (SD)	70.77 (16.19)	72.47 (17.08)	71.90 (16.80)
Median (min, max)	69.50 (38.5, 125.0)	70.35 (37.0, 143.4)	70.00 (37.0, 143.4)
Body mass index (BMI) (kg/m2)			
N	377	753	1130

Characteristic	Placebo (N=377)	tolebrutinib 60 mg (N=754)	All (N=1131)
Mean (SD)	24.77 (5.32)	25.08 (5.41)	24.97 (5.38)
Median (min, max)	24.02 (13.8, 48.7)	24.31 (14.8, 57.4)	24.22 (13.8, 57.4)

Note: N = Number of participants assessed. Percentages are calculated using number of participants assessed as denominator.

Baseline disease characteristics are presented in Table 16.

Table 16 Baseline clinical characteristics (Randomised Population)

Characteristic	Placebo (N=377)	tolebrutinib 60 mg (N=754)	All (N=1131)
Time since symptom of RRMS onset (years)			
N	377	754	1131
Mean (SD)	17.55 (8.43)	17.13 (8.33)	17.27 (8.37)
Median (min, max)	16.29 (1.0, 41.6)	16.10 (1.1, 43.9)	16.15 (1.0, 43.9)
Time since diagnosis of SPMS (years), n (%)			
<1	45 (11.9)	113 (15.0)	158 (14.0)
>=1 to <5	127 (33.7)	242 (32.1)	369 (32.6)
>=5 to <10	84 (22.3)	155 (20.6)	239 (21.1)
>=10	121 (32.1)	244 (32.4)	365 (32.3)
Mean (SD)	8.388 (7.783)	7.905 (7.321)	8.066 (7.478)
Median (min, max)	5.547 (0.00 ; 35.74)	5.417 (0.00 ; 41.33)	5.487 (0.00 ; 41.33)
Time since most recent relapse (years)			
N	377	752	1129
Mean (SD)	7.63 (5.47)	7.43 (5.31)	7.50 (5.37)
Median (min, max)	6.15 2.0 ; 36.0	5.68 2.0 ; 32.8	5.76 2.0 ; 36.0
Previous disease modifying therapy, n (%)			
0	89 (23.6)	205 (27.2)	294 (26.0)
1	102 (27.1)	200 (26.5)	302 (26.7)
>=2	186 (49.3)	349 (46.3)	535 (47.3)
Baseline EDSS score[a]			
Mean (SD)	5.59 (0.94)	5.49 (0.99)	5.53 (0.98)
Median (min, max)	6.00 2.5, 6.8	6.00 2.8 ; 6.5	6.00 2.5 ; 6.8
Baseline EDSS score, n (%)			
<=4.5	71 (18.8)	183 (24.3)	254 (22.5)
>4.5	306 (81.2)	571 (75.7)	877 (77.5)
<=5.5	145 (38.5)	309 (41.0)	454 (40.1)
>5.5	232 (61.5)	445 (59.0)	677 (59.9)
Gd-T1 lesions at baseline, n (%) (observed data)			
N	373	742	1115
Presence	49 (13.1)	93 (12.5)	142 (12.7)
Absence	324 (86.9)	649 (87.5)	973 (87.3)

Characteristic	Placebo (N=377)	tolebrutinib 60 mg (N=754)	All (N=1131)
Mean (SD)	0.6 (3.5)	0.4 (2.0)	0.5 (2.6)
Median (min, max)	0.0 (0 ; 54)	0.0 (0 ; 35)	0.0 (0 ; 54)
Gd-T1 lesions at baseline, n (%) (imputed data)			
N	377	754	1130
Presence	49 (13.0)	93 (12.3)	142 (12.6)
Absence	328 (87.0)	661 (87.7)	989 (87.4)

[a] Average of screening and randomisation EDSS.

No clinically important differences were observed in the use of concomitant medications during the DB study intervention period between intervention groups.

Table 17 Treatment compliance in DB treatment period (Safety population)

	Placebo (N=375)	tolebrutinib 60 mg (N=752)
Compliance (%)		
Number	375	752
Mean (SD)	97.56 (7.69)	97.84 (6.56)
Median	99.64	99.62
Q1 ; Q3	98.44 ; 100.00	98.29 ; 100.00
Min ; Max	21.6 ; 100.0	13.7 ; 100.0
Participants with >=80% compliance	365 (97.3)	741 (98.5)
Participants with <80% compliance	10 (2.7)	11 (1.5)

IMP: investigational medicinal product; DB: double-blind
Note % of compliance for a participant is defined as the number of days that the participant took the IMP as specified in the protocol divided by the total number of days that the participant was planned to take IMP during the treatment period.

5.3.2.1.8.4. Outcomes and estimation

Primary efficacy endpoint: time to onset of 6-month confirmed disability progression

Primary analysis:

The primary objective was to determine the efficacy of tolebrutinib compared to placebo in delaying disability progression in nrSPMS. A 6-month CDP required that the EDSS score at progression, the 6-month confirmatory EDSS score and any EDSS scores obtained in between met the disability progression criteria. Only EDSS assessments measured more than 90 days after the onset of an adjudicated relapse, if present, were used to determine onset of 6-month CDP. For the purpose of CDP confirmation, only EDSS scores measured more than 90 days after an adjudicated relapse, if present, were used.

Regarding the considered estimand strategy, treatment discontinuation was defined as the only incurrent event but death was considered to be an event, implicitly considering the composite estimand strategy for death. All other potential intercurrent events (as change to OL treatment or change in background medication) were not considered by the applicant were hence implicitly be handled by a treatment policy strategy, which appears acceptable.

Participants who completed the study without an initial onset of 6-month CDP, or who had an initial onset of 6-month CDP but completed the study at the common study end date without a 3-month confirmation, or who prematurely discontinued the study before confirmation of an onset of 6-month CDP, regardless of having an initial onset, were censored at the date of the last EDSS assessment.

Specific non-confirmed events were imputed via a multiple imputation method (reference is made to the statistical methods above).

Tolebrutinib showed a 31% risk reduction compared to placebo for the time to 6-month CDP based on EDSS that was statistically significant (hazard ratio 0.693 (95% CI: 0.546 to 0.880), p=0.0026).

The absolute risk reduction of 6-month CDP at month 12 was 5.1% and at month 24 8.3% compared to placebo, corresponding to a number needed to treat of 12 to prevent one CDP event. At month 48, the absolute reduction in risk of 6-month CDP was 10.3% compared to placebo, corresponding to a number needed to treat of 10 to prevent one CDP event.

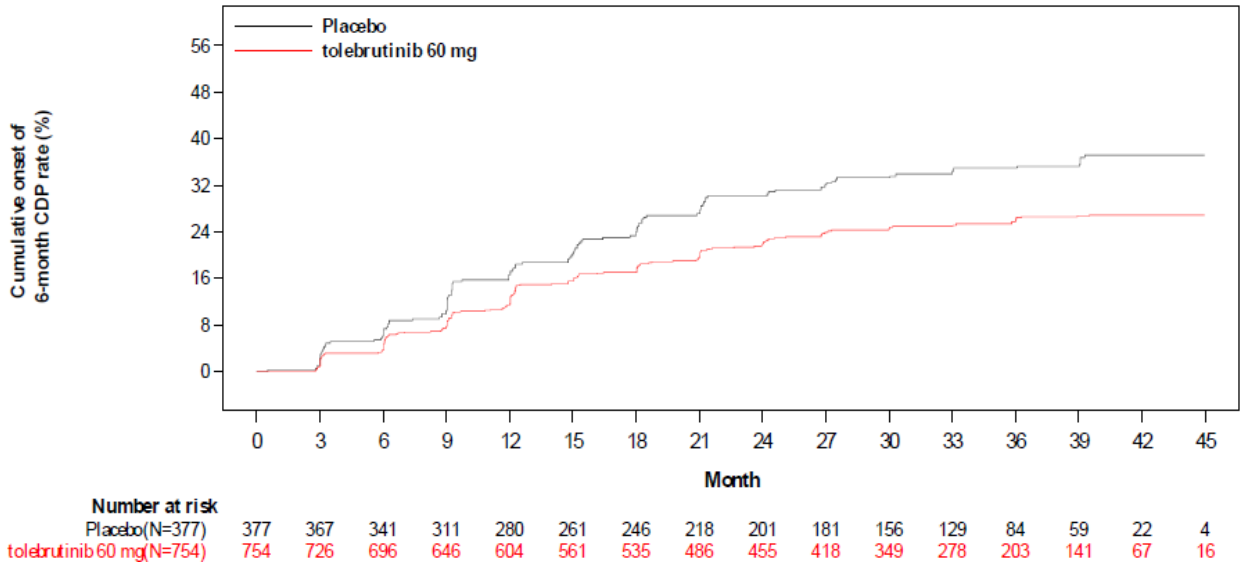
Table 18 Analysis of time to onset of 6-month CDP (ITT population)

	Placebo (N=377)	tolebrutinib 60 mg (N=754)
Number of participants with 6-month CDP, n (%)	116 (30.7)	171 (22.6)
Number of participants who were censored, n (%)	261 (69.3)	583 (77.4)
Time to onset of 6-month CDP (months)		
Number	116	171
Mean (SD)	13.13 (8.32)	13.29 (8.18)
Median	11.97	12.04
Q1 ; Q3	6.25 ; 18.15	6.16 ; 18.32
Min ; Max	0.5 ; 39.1	2.8 ; 37.4
Kaplan-Meier estimates of proportion of participants with >= 1 event (95% CI)[a] at		
Month 12	0.166 (0.130, 0.207)	0.115 (0.093, 0.140)
Month 18	0.240 (0.196, 0.286)	0.170 (0.144, 0.199)
Month 24	0.302 (0.253, 0.351)	0.219 (0.188, 0.251)
Month 30	0.334 (0.282, 0.386)	0.245 (0.213, 0.279)
Month 36	0.350 (0.297, 0.403)	0.261 (0.226, 0.297)
Month 42	0.372 (0.310, 0.434)	0.269 (0.232, 0.307)
Month 48	0.372 (0.310, 0.434)	0.269 (0.232, 0.307)
Absolute difference (95% CI) in Kaplan-Meier estimates at		
Month 12		-0.051 (-0.099, -0.003)
Month 24		-0.083 (-0.142, -0.023)
Month 36		-0.089 (-0.153, -0.024)
Month 48		-0.103 (-0.176, -0.030)
Hazard Ratio (95% CI)[b]		0.693 (0.546, 0.880)
Cox model p-value		0.0026
Stratified Log-Rank test p-value[c]		0.0020

Note: Participants who complete the study without an initial onset of disability progression or have an initial onset of disability progression but complete the study at the common study end date without 3-month confirmation or prematurely discontinue the study before 6-month confirmation of an onset of disability progression will be censored at their last EDSS assessment date. Missing events will be imputed via multiple imputation method described in SAP Section 3.2.3.
a Derived from Kaplan-Meier estimates.; b Derived using Cox proportional-hazards model with robust variance estimation. Covariates are treatment group, age at screening (>40, <=40 years), geographic region (US, non-US), baseline EDSS score and baseline Gd-enhancing T1 lesions (presence, absence); c Derived from log-rank test with stratification of age at screening (>40, <=40 years) and geographic region (US, non-US).

Kaplan-Meier estimates of cumulative incidence rate of 6-month CDP onset were calculated based on imputed data (see Figure 7).

Figure 7 Kaplan-Meier plot of cumulative incidence rate of onset of 6-month CDP (ITT population)



CDP confirmed disability progression

Secondary efficacy endpoints (multiplicity-controlled)

The selected set of secondary endpoints were tested following the hierarchical testing procedure.

Table 19 Summary of the multiplicity adjustment for both primary and secondary efficacy endpoints (ITT population)

Category	Endpoint		Comparison between Placebo and tolebrutinib 60 mg
Primary Endpoint	6-month CDP	Hazard Ratio (95% CI)	0.693 (0.546, 0.880)
		Cox model p-value	**0.0026**
		Adjusted significance level	0.05
Secondary Endpoints	3-month CDP	Hazard Ratio (95% CI)	0.757 (0.607, 0.944)
		Cox model p-value	**0.0134**
		Adjusted significance level	0.05
	New and/or enlarging T2-hyperintense lesions	Relative risk (95% CI)	0.622 (0.432, 0.897)
		p-value[a]	**0.0110**
		Adjusted significance level	0.05
	Sustained 20% increase in 9-HPT for at least 3 months	Hazard Ratio (95% CI)	0.972 (0.735, 1.286)
		Cox model p-value	0.8428
		Adjusted significance level	0.05
	Sustained 20% increase in T25-FW for at least 3 months	Hazard Ratio (95% CI)	0.767 (0.640, 0.919)
		Cox model p-value	0.0040
		Adjusted significance level	NA
	6-month CDI	Hazard Ratio (95% CI)	1.882 (1.102, 3.214)
		Cox model p-value	0.0206
		Adjusted significance level	NA
	Brain Volume	LS Mean difference (95% CI)	0.082 (-0.034, 0.197)
		p-value for the difference between groups	0.1646
		Adjusted significance level	NA

a Chi-square test for relative risk
All values in bold font are statistically significant according to the hierarchical testing procedure

Time to onset of 3-month confirmed disability progression

27.6% and 34.2% in the tolebrutinib and the placebo group experienced a 3-month CDP. Tolebrutinib significantly reduced the risk of 3-month CDP by 24% compared with placebo (HR of 0.757 (95% CI: 0.607 to 0.944, p=0.0134).

Total number of new and/or enlarging T2-hyperintense lesions

The adjusted mean number of new and/or enlarging T2-hyperintense lesions per year was 1.835 and 2.948 for tolebrutinib and placebo, respectively, corresponding to a 38% relative reduction in favour of tolebrutinib (RR [95% CI]: 0.622 [0.432 to 0.897]; p=0.0110). The percentage of participants who did not develop any new and/or enlarging T2-hyperintense lesions during the study period was greater in the tolebrutinib group as compared with the placebo group (58.2% versus 49.1%).

Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with the primary analysis of this endpoint [relative risk (95% CI) 0.627 (0.439, 0.896) p= 0.0103].

Time to onset of sustained 20% increase in the 9-Hole Peg Test for at least 3 months

The percentage of participants with sustained 20% increase (worsening) in the 9-HPT confirmed over at least 3 months was similar in the tolebrutinib group (19.0%) as compared to the placebo group (19.6%) (HR 0.972 (95% CI: 0.735 to 1.286, p=0.8428).

Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with those of the primary analysis of this endpoint.

Given that the null hypothesis was not rejected, the hierarchical testing stopped at this endpoint. As a result, only nominal p-values are provided for the subsequent multiplicity-controlled efficacy endpoints.

Time to onset of sustained 20% increase in the T25-FW for at least 3 months

The percentage of participants with sustained 20% increase (worsening) in the T25-FW confirmed over at least 3 months was 41.1% in the tolebrutinib group as compared to 49.6% in the placebo group. Tolebrutinib reduced the risk of sustained 20% increase in the T25-FW confirmed over at least 3 months by 23% compared with the placebo (HR 0.767, 95% CI: 0.640 to 0.919, nominal p=0.0040).

Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with the primary analysis of this endpoint [HR of 0.760 (95% CI: 0.632 to 0.915, nominal p=0.0037].

Time to onset of 6-month confirmed disability improvement

The percentage of participants achieving 6-month CDI was higher in the tolebrutinib group (8.6%) compared against the placebo group (4.5%) (HR [95% CI]: 1.882 [1.102 to 3.214]; nominal p=0.0206).

Percent change in brain volume at the end of study compared to Month 6

The LS mean (SE) percent change in brain volume at the EOS compared to Month 6 was -0.694% (0.0336%) in the tolebrutinib group and -0.776% (0.0479%) in the placebo group (LS mean difference [95% CI]: 0.082 [0.034 to 0.197]; nominal p=0.1646).

Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with the primary analysis of this endpoint.

Other prespecified secondary endpoints

The study included a number of prespecified secondary endpoints which were not included in the statistical testing hierarchy (i.e. none of them were multiplicity-controlled). Therefore, results do not

formally contribute to the confirmatory strategy. However, the following endpoints are taken into account when discussing the contextualisation of the results:

Annualised adjudicated relapse rate

The adjusted annualised adjudicated relapse rate was 0.033 in the tolebrutinib group and 0.032 the placebo group (relative risk of 1.036 (95% CI: 0.628 to 1.708).

Total number of new Gd+ lesions

The adjusted mean number of new Gd+ lesions per scan was 0.154 in the tolebrutinib group as compared 0.229 in the placebo group (RR [95% CI]: 0.671 [0.390 to 1.153]) p = 0.1485.

Change from baseline in number of phase rim lesions in susceptibility-weighted imaging (SWI) MRI through the EOS

The number of phase rim lesions, as assessed by SWI MRI, was summarised and plotted: At baseline the mean (SD) number of rim lesions was 2.6 (4.5) and 3.1 (5.3) in the tolebrutinib and the placebo group, respectively. At EOS the mean (SD) number of rim lesions was 3.1 (5.4) and 3.2 (5.7) in the tolebrutinib and the placebo group, with a mean change from baseline of 0.2 (0.9) and 0.4 (1.8), respectively.

Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20 Summary of efficacy for trial EFC16645 (i.e. HERCULES)

Title: A Phase 3, randomised, double-blind, efficacy and safety study comparing SAR442168 to placebo in participants with nonrelapsing secondary progressive multiple sclerosis (HERCULES)		
Study identifier	Study number: EFC16645 EudraCT/EU trial number: 2020-000647-30 IND: 140884 NCT: NCT04411641 WHO: U1111-1246-7768	
Design	Study EFC16645 was a Phase 3, randomised, double-blind, 2-arm, placebo-controlled (2:1), parallel group, multicenter, event-driven (6-month CDP) trial with a variable treatment duration expected to range from approximately 24 to 48 months.	
	Duration of main phase:	approximately 24 to 48 months
Hypothesis	Superiority	
Treatments groups	Tolebrutinib 60 mg group	Treatment: 1 tablet of tolebrutinib 60 mg Route of administration: oral use Number randomised: 754 participants
	Placebo group	Treatment: 1 tablet of matching placebo Route of administration: oral use Number randomised: 377 participants

Endpoints and definitions	Primary endpoint	6-month confirmed disability progression (CDP)	Time to onset of 6-month CDP defined as follows: • Increase of ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.0, OR • Increase of ≥0.5 point when the baseline EDSS score is >5.0
	Key Secondary	3-month confirmed disability progression (CDP)	Time to onset of 3-month CDP defined as follows: • Increase of ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.0, OR • Increase of ≥0.5 point when the baseline EDSS score is >5.0
	Secondary	New and/or enlarging T2-hyperintense lesions	Total number of new and/or enlarging T2-hyperintense lesions as detected by MRI, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline up to and including the EOS visit
	Secondary	9-Hole Peg Test (9-HPT)	Time to onset of sustained 20% increase in the 9-HPT for at least 3 months
	Secondary	Timed 25 Foot Walk (T25-FW)	Time to onset of sustained 20% increase in the T25_FW for at least 3 months
	Secondary	6-month Confirmed Disability Improvement (CDI)	Time to onset of CDI defined as a ≥1.0 point decrease on the EDSS score from baseline confirmed over at least 6 months
	Secondary	Brain Volume	Percent change in brain volume loss as detected by MRI scans at the EOS compared to Month 6
Database lock	27 September 2024		
Results and Analysis			
Analysis description	**Primary Analysis: 6-month CDP**		
Analysis population and time point description	Intent to treat population, defined as all randomised participants according to the intervention group allocated by the randomisation, irrespective of the study intervention received. Data up to end of study (EOS)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Tolebrutinib 60 mg
	Number of subjects	377	754
	Hazard Ratio (95% CI)		0.693 (0.546, 0.880)
	Relative Risk Reduction		31%
	Cox model p-value		0.0026
Analysis description	**Secondary Endpoint Analysis: 3-month CDP**		

Analysis population and time point description	Intent to treat population, defined as all randomised participants according to the intervention group allocated by the randomisation, irrespective of the study intervention received. Data up to end of study (EOS)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Tolebrutinib 60 mg
	Number of subjects	377	754
	Hazard Ratio (95% CI)		0.757 (0.607, 0.944)
	Relative Risk Reduction		24%
	Cox model p-value		0.0134
Analysis description	**Secondary Endpoint Analysis: New and/or enlarging T2-hyperintense lesions**		
Analysis population and time point description	Intent to treat population, defined as all randomised participants according to the intervention group allocated by the randomisation, irrespective of the study intervention received. Data up to end of study (EOS)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Tolebrutinib 60 mg
	Number of subjects	377	754
	Average number of new and/or enlarging T2-hyperintense lesions per year		
	Estimate (95% CI)	2.948 (2.239, 3.880)	1.835 (1.441, 2.336)
	Relative risk (95% CI)		0.622 (0.432, 0.897)
	p-value		0.0110
Analysis description	**Secondary endpoint analysis: 9-HPT**		
Analysis population and time point description	Intent to treat population, defined as all randomised participants according to the intervention group allocated by the randomisation, irrespective of the study intervention received. Data up to end of study (EOS)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Tolebrutinib 60 mg
	Number of subjects	377	754
	Hazard Ratio (95% CI)		0.972 (0.735, 1.286)
	Cox model p-value		0.8428
Analysis description	**Secondary endpoint analysis: T25-FW**		
Analysis population and time point description	Intent to treat population, defined as all randomised participants according to the intervention group allocated by the randomisation, irrespective of the study intervention received. Data up to end of study (EOS)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Tolebrutinib 60 mg
	Number of subjects	377	754
	Hazard Ratio (95% CI)		0.767 (0.640, 0.919)

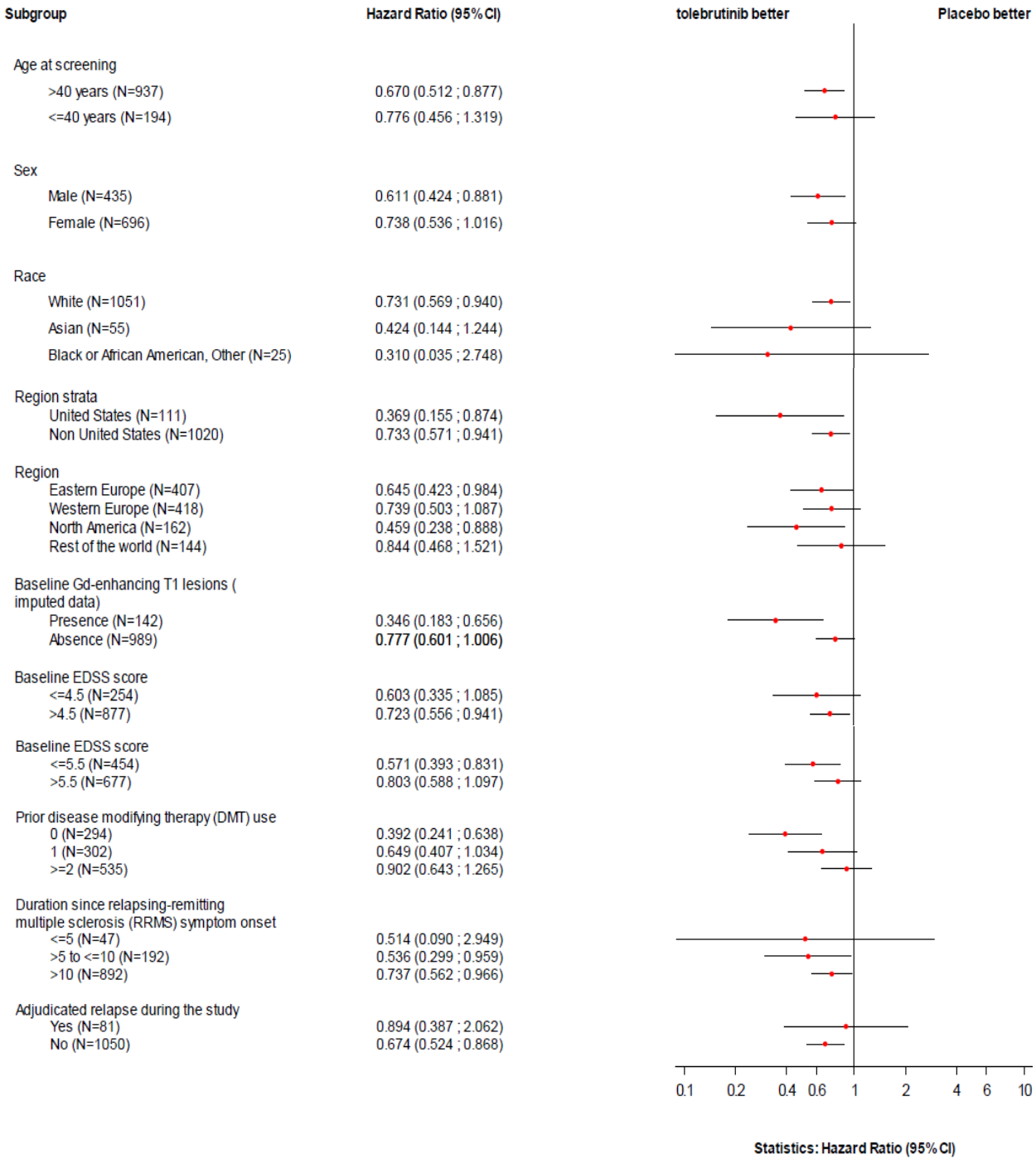
	Cox model p-value		0.0040 (nominal)
Analysis description	**Secondary endpoint analysis: 6-month CDI**		
Analysis population and time point description	Intent to treat population, defined as all randomised participants according to the intervention group allocated by the randomisation, irrespective of the study intervention received. Data up to end of study (EOS)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Tolebrutinib 60 mg
	Number of subjects	377	754
	Hazard Ratio (95% CI)		1.882 (1.102, 3.214)
	Cox model p-value		0.0206 (nominal)
Analysis description	**Secondary endpoint analysis: Brain Volume**		
Analysis population and time point description	Intent to treat population, defined as all randomised participants according to the intervention group allocated by the randomisation, irrespective of the study intervention received. Data up to end of study (EOS)		
	LS mean (95% CI)	-0.776 (-0.870, -0.681)	-0.694 (-0.760, -0.628)
	LS mean difference (95% CI)		0.082 (-0.034 to 0.197)
	p-value		0.1646

5.3.2.1.8.5. Pre-defined and *post hoc* subgroup analyses

Subgroup analyses of the primary endpoint (pre-defined):

Results of the analyses of the primary endpoint "time to onset of 6-month CDP" for tolebrutinib treatment vs. placebo across pre-defined subgroups are presented in Table 21.

Table 21 Forest plot of hazard ratios and corresponding 95% CIs comparing tolebrutinib to placebo for time to onset of 6-month CDP within each subgroup



Results for the subgroup analyses "baseline Gd+ lesions (present, absent)" and "prior disease modifying therapy use (0, 1, ≥2)" are in detail presented in Table 22 and results for the subgroup analysis "baseline number of PRL" are presented in Table 23.

Table 22 Analysis of time to onset of 6-month CDP using Cox model by subgroups (baseline Gd+ lesions (present, absent) and prior disease modifying therapy (0, 1, ≥2) (ITT population)

Subgroup		Statistic	Placebo (N=377)	tolebrutinib 60 mg (N=754)
Baseline Gd-enhancing T1 lesions (imputed data)	Presence	Number of participants	49	93
		Number of participants with 6-month CDP, n (%)	20 (40.8)	17 (18.3)
		Number of participants who were censored, n (%)	29 (59.2)	76 (81.7)
		Hazard ratio (95% CI)[a]		0.346 (0.183 ; 0.656)
	Absence	Number of participants	328	661
		Number of participants with 6-month CDP, n (%)	94 (28.7)	151 (22.8)
		Number of participants who were censored, n (%)	234 (71.3)	510 (77.2)
		Hazard ratio (95% CI)[a]		0.777 (0.601 ; 1.006)
	Overall	p-value for treatment by subgroup interaction[b]		0.0183
Prior disease modifying therapy (DMT) use	0	Number of participants	89	205
		Number of participants with 6-month CDP, n (%)	31 (34.8)	33 (16.1)
		Number of participants who were censored, n (%)	58 (65.2)	172 (83.9)
		Hazard ratio (95% CI)[a]		0.392 (0.241 ; 0.638)
	1	Number of participants	102	200
		Number of participants with 6-month CDP, n (%)	29 (28.4)	44 (22.0)
		Number of participants who were censored, n (%)	73 (71.6)	156 (78.0)
		Hazard ratio (95% CI)[a]		0.649 (0.407 ; 1.034)
	>=2	Number of participants	186	349
		Number of participants with 6-month CDP, n (%)	54 (29.0)	91 (26.1)
		Number of participants who were censored, n (%)	132 (71.0)	258 (73.9)
		Hazard ratio (95% CI)[a]		0.902 (0.643 ; 1.265)
	Overall	p-value for treatment by subgroup interaction[b]		0.0274

[a] Derived using Cox proportional-hazards model with treatment group, age at screening (>40, <=40 years), geographic region (US, non-US), baseline EDSS score and baseline Gd-enhancing T1 lesions (presence, absence) as covariates.
[b] Derived using Cox proportional-hazards model with treatment group, age at screening (>40, <=40 years), geographic region (US, non-US), baseline EDSS score and baseline Gd-enhancing T1 lesions (presence, absence), subgroup (if different than the aforementioned covariates) and treatment by subgroup interaction as covariates.

Post hoc subgroup analyses of the primary endpoint: participants with baseline phase rim lesions (PRL)

Table 23 Analysis of time to onset of 6-month CDP using Cox model by baseline number of phase rim lesions (PRL) (ITT population)

Subgroup		Statistic	Placebo (N=377)	tolebrutinib 60 mg (N=754)
Baseline number of phase rim lesions	0	Number of participants	56	119
		Number of participants with 6-month CDP, n (%)	12 (21.4)	30 (25.2)
		Number of participants who were censored, n (%)	44 (78.6)	89 (74.8)
		Hazard ratio (95% CI)[a]		1.171 (0.612 ; 2.242)
	1-3	Number of participants	54	105
		Number of participants with 6-month CDP, n (%)	19 (35.2)	30 (28.6)
		Number of participants who were censored, n (%)	35 (64.8)	75 (71.4)
		Hazard ratio (95% CI)[a]		0.846 (0.468 ; 1.531)
	4 or more	Number of participants	39	64
		Number of participants with 6-month CDP, n (%)	15 (38.5)	14 (21.9)
		Number of participants who were censored, n (%)	24 (61.5)	50 (78.1)
		Hazard ratio (95% CI)[a]		0.463 (0.210 ; 1.019)

CDP: confirmed disability progression
A Derived using Cox proportional-hazards model with treatment group, age at screening (> 40, ≤40 years), geographic region (US, non-US), baseline EDSS score and baseline Gd-enhancing T1 lesions (presence, absence) as covariates.

Further, the applicant provided analyses correlating disability progression based on the PIRA concept to the proportion of baseline chronic active lesions, i.e. the PRL load (0 PRL vs 1-3 PRLs vs ≥4 PRLs). In untreated patients, the proportion of patients with disability progression was higher in those with larger number of baseline PRL lesions. According to results in Table 22, the efficacy of Tolebrutinib was greater in those with baseline PRL. Comparing the proportion of events between the treated and untreated per group of markers, results support that efficacy of tolebrutinib appear to be greater in those with at least 4 PRL lesions at baseline.

No subgroup analyses were performed for any of the secondary endpoints.

5.3.2.1.8.6. Pre-defined and *post hoc* sensitivity analyses

Pre-defined sensitivity analyses:

Time to 6-month confirmed disability progression

Participants with disability progression but without confirmation: The percentage of participants with an event was 31.4% in the tolebrutinib group as compared to 39.3% in the placebo group. Tolebrutinib reduced the risk of 6-month CDP by 26% compared with placebo, with an HR of 0.735 (95% CI: 0.599 to 0.903, p=0.0034). *Participants with missing or incomplete 6-month CDP:* The percentage of participants with an event was 22.3% in the tolebrutinib group as compared to 30.2% in the placebo group. Tolebrutinib reduced the risk of 6-month CDP by 30% compared with placebo, with an HR of 0.696 (95% CI: 0.547 to 0.884, p=0.0030).

Total number of new and/or enlarging T2-hyperintense lesions

Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with the primary analysis of this endpoint [relative risk (95% CI) 0.627 (0.439, 0.896) p= 0.0103].

Time to onset of sustained 20% increase in the 9-Hole Peg Test for at least 3 months

Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with those of the primary analysis of this endpoint.

Time to onset of sustained 20% increase in the T25-FW for at least 3 months

Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with the primary analysis of this endpoint [HR of 0.760 (95% CI: 0.632 to 0.915, nominal p=0.0037].

Percent change in brain volume at the end of study compared to Month 6

Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with the primary analysis of this endpoint.

Post hoc sensitivity analysis of the primary endpoint

Analysis of 6-month CDP excluding participants with an adjudicated relapse during the study

In the subset of the ITT population with no adjudicated relapse during the study (N=700 tolebrutinib and N=350 placebo), the percentage of participants with 6-month CDP was 21% and 29.7% in the tolebrutinib and the placebo group, respectively. Tolebrutinib reduced the risk of 6-month CDP by 33% compared to placebo [HR of 0.674 (95% CI: 0.524 to 0.868, p=0.0022)].

Analysis of time to onset of 6-month CDP in non-active participants, i.e., with no relapse in the 2 years prior to screening and without Gd+ lesions

In the *post hoc* analysis of time to onset of 6-month CDP (with imputation) in the subgroup of non-active participants (with no relapse in the 2 years prior to screening and without Gd+ lesions at baseline), 152 (23.0%) participants in the tolebrutinib group had an event compared to 96 (29.2%) in the placebo group, with a relative risk reduction of 23% (HR [95% CI]: 0.767 [0.593 to 0.992]; unadjusted p=0.0433).

The analysis utilised the same approach as for the primary analysis of the primary endpoint, e.g. for participants who met 3-month CDP and continued to meet the EDSS criteria for disability progression through the final study assessment, but did not reach 6-month confirmation due to the end of study, the 6-month CDP event status was imputed via a multiple imputation.

5.3.2.1.8.7. Ancillary analyses

N/A

5.3.3. Clinical studies in special populations

No studies in adolescents or children have been started at the time of MAA. No separate studies were conducted in pregnant or lactating women, elderly, patients with renal impairment or patients with hepatic impairment.

5.3.4. *In vitro* biomarker test for patient selection for efficacy

Not applicable

5.3.5. Supportive studies

Two similarly designed Phase 3 studies in RMS have additionally been submitted:

5.3.5.1. ***Study EFC16033 (GEMINI 1): A Phase 3, randomised, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis***

Study initiation date: 30 June 2020, Date last subject last visit: 15 July 2024

5.3.5.2. ***Study EFC16034 (GEMINI 2): A Phase 3, randomised, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis***

Study initiation date: 11 June 2020, Date last subject last visit: 16 July 2024

Overview of methods

The two trials were similarly designed Phase 3 multi-center, randomised, double-blind, double-dummy, 2-arm, active-controlled, parallel-group, event driven (6-month CDW) trials with a variable treatment duration expected to range from approximately 18 to 36 months to evaluate the efficacy and safety of tolebrutinib in the treatment of subjects with RMS. The only difference in trial design was that EFC16033 (RMS) included routine PK sampling and lymphocyte phenotyping while EFC16034 (RMS) did not. The trials were conducted concurrently.

EFC16033 was a multicenter study conducted at 162 centers that screened at least 1 participant in 24 countries/regions worldwide (Austria, Belarus, Bulgaria, Canada, China, Czech Republic, Denmark, Estonia, Finland, Germany, Hong Kong Special Administrative Region, Italy, Japan, Lithuania, Mexico, Poland, Romania, Russian Federation, Spain, Sweden, Taiwan, Turkey, Ukraine, and US). A total of 158 centers randomised at least 1 participant.

EFC16034 was a multicenter study conducted at 154 centers that screened at least 1 participant in 25 countries/regions worldwide (Argentina, Belgium, Brazil, Canada, Chile, Croatia, Czech Republic, France, Germany, Greece, Hungary, India, Israel, Republic of Korea, Latvia, Portugal, Russian Federation, Serbia, Slovakia, Spain, Switzerland, Turkey, Ukraine, UK, and the US). A total of 150 centers randomised at least 1 participant. In addition, 3 centers in France, Netherlands, and Canada never randomised but treated relocated participants.

The studies consisted of the following study periods: 1) screening period: Day -28 to Day -1; 2) intervention period: double-blind, double-dummy, treatment period for the assessment of efficacy and safety. All participants were to be followed from randomisation to their EOS visit. Any participant who prematurely discontinued study intervention, regardless of the reason, were to be maintained in the study and were strongly encouraged to complete all remaining study visits and procedures, as originally scheduled, including the EOS visit; 3) safety follow-up period: 4 weeks after the last dose of study intervention (for participants completing IMP double-blind treatment only if not entering the LTS study and for participants who prematurely discontinued study intervention) to collect safety data.

Eligible participants were randomly assigned at a 1:1 ratio to receive: 60 mg oral, once daily tolebrutinib as well as placebo to match the oral, once daily teriflunomide tablet; OR 14 mg oral, once daily teriflunomide as well as placebo to match the oral, once daily tolebrutinib tablet. The study interventions were to be taken with a regular meal.

A participant was considered to have completed the study if he/she completed all periods of the study including the EOS visit, whether remaining on study intervention or not. Eligible participants completing the double-blind treatment period were offered enrolment in a separate Phase 3 safety extension study (LTS17043). For participants that completed double-blind treatment and did not enter LTS17043, a final follow-up visit to collect safety data was performed 4 weeks after their EOS visit.

Both trials were event-driven based on the pooled incidence of 6-month CDW with a variable treatment duration based on the time of participant randomisation into the study. A study end date was announced in advance by the Sponsor, when it was projected that approximately 162 events of 6-month CDW would have occurred in the pooled EFC16033 and EFC16034 studies (RMS). All participants still on study came in for a final efficacy assessment visit within -2 to +4 weeks of the announced study end date.

Randomisation was stratified by the EDSS score at screening (<4.0 versus ≥4.0) and geographic region (US versus non-US).

Table 24 Primary and secondary efficacy objectives and endpoints in pivotal Phase 3 studies in RMS

Objectives	Endpoints
Primary	
• To assess the efficacy of daily tolebrutinib compared to a daily dose of 14 mg teriflunomide (Aubagio®) measured by the annualized relapse rate (ARR) in participants with relapsing forms of multiple sclerosis (MS)	• ARR during the study period assessed by confirmed protocol-defined adjudicated relapses
Secondary	
• To assess the efficacy of tolebrutinib compared to teriflunomide (Aubagio) on disability progression, magnetic resonance imaging (MRI) lesions, cognitive performance, and quality of life	• Time to onset of confirmed disability worsening (CDW), confirmed over at least 6 months, defined as follows: - increase of ≥1.5 points from the baseline Expanded Disability Status Scale (EDSS) score when the baseline score is 0, OR - increase of ≥1.0 point from the baseline EDSS score when the baseline score is 0.5 to ≤5.5, OR - increase of ≥0.5 point from the baseline EDSS score when the baseline score is >5.5 • Time to onset of CDW, assessed by the EDSS score and confirmed over at least 3 months • Total number of new and/or enlarging T2-hyperintense lesions as detected by MRI, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline up to and including the end of study (EOS) visit and number of new and/or enlarging T2-hyperintense lesions by visit over time • Total number of new gadolinium (Gd)-enhancing T1-hyperintense lesions as detected by MRI, defined as the sum of the individual number of new Gd-enhancing T1-hyperintense lesions at all scheduled visits starting after baseline up to and including the EOS visit • Time to confirmed disability improvement (CDI), defined as a ≥1.0 point decrease on the EDSS from the baseline EDSS score confirmed over at least 6 months • Percent change in brain volume loss as detected by brain MRI scans at the EOS compared to Month 6 • Change in cognitive function at the EOS compared to baseline as assessed by the Symbol Digit Modalities Test (SDMT) • Change in cognitive function at the EOS compared to baseline as assessed by the California Verbal Learning Test Second Edition (CVLT-II), where available • Change in Multiple Sclerosis Quality of Life 54 (MSQoL-54) questionnaire score at the EOS compared to baseline

ARR refers to the adjudicated ARR, unless otherwise specified.

With regard to the requested inclusion criteria both studies enrolled male and female participants aged 18 to 55 years of age with RMS according to the 2017 revision of the McDonald diagnostic criteria.

Participants must have had at least 1 documented relapse within the previous year, or ≥2 documented relapses within the previous 2 years, or ≥1 active Gd+ brain lesion on an MRI scan in the year prior to screening and had to be ambulatory without assistance for >100 meters (i.e., EDSS score ≤5.5) at the first screening visit. Participants were excluded from the study if they had been diagnosed with PPMS or with nrSPMS or had previously been treated with certain MS DMTs within a protocol-specified period of time before any baseline assessment was taken. The following were also exclusionary: any screening laboratory values outside normal limits or abnormal electrocardiograms as per the Investigator's judgment; a history of infection or the risk for infection or conditions that could predispose the participant to excessive bleeding or that could adversely affect participation in the study or make the primary efficacy endpoint non-evaluable.

Efficacy analyses were performed on the ITT population, defined as all randomly assigned participants. All efficacy analyses were conducted according to the treatment group allocated by the randomisation schedule, irrespective of the treatment received.

The following efficacy measurements were used:

Adjudicated relapses: relapse confirmation and responsibilities were pre-defined.

Confirmed disability worsening (CDW) at 3 or 6 months is a confirmed, sustained increase from baseline in EDSS score (of **≥1.5** points when the baseline score is **0,** of **≥1.0** point when the baseline score is **1.0 to ≤5.5**, of **≥0.5** point when the baseline EDSS score is **>5.5**) over at least the specified number of months (3 or 6months).

The initial onset of increase from baseline in EDSS score can be from a scheduled or unscheduled assessment. All intermediate EDSS scores (EDSS scores obtained after onset of disability and before the confirmatory assessment), if any, had to maintain at least the minimum increase. A confirmatory EDSS assessment had to be obtained at least the specified number of months (3 or 6 months) after onset of disability worsening, at a routine scheduled quarterly visit, at least **30 days** after an onset of any confirmed clinical relapse and could not be associated with an ongoing relapse.

Confirmed disease improvement (CDI): Six-month CDI was defined as a decrease of ≥1.0 point from baseline in the EDSS score lasting for at least 6 months.

Moreover, efficacy assessments were based on MRI (radiographic measures of intra-cranial inflammation include detection of new Gd+ lesions and development of new and/or enlarging T2 lesions by MRI. Reduction in the number of Gd+ lesions has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in RMS. Cognitive tests (CVLT-II memory test and SDMT information processing speed test) and Patient-reported outcomes (MSQoL-54).

Statistical methods:
Details of the statistical methods used in the 2 Phase 3 studies in RMS were provided in the combined study SAP.

The primary efficacy population for each of the EFC16033 and EFC16034 studies was the ITT population, defined as all randomly assigned participants with a treatment kit number allocated and recorded in the Interactive Response Technology database. All efficacy analyses were conducted according to the intervention group allocated by the randomisation schedule, irrespective of the treatment received.

Analysis of primary efficacy endpoint

The primary endpoint in each of the 2 pivotal Phase 3 trials in RMS (EFC16033 and EFC16034) was the ARR based on protocol-defined adjudicated relapses (in this document, ARR refers to the adjudicated ARR, unless otherwise specified). The ARR was analysed using a negative binomial regression model

with robust variance estimation which included the total number of adjudicated relapses per participant occurring during the intervention period (i.e., from randomisation to the last study visit with or without study intervention) as the response variable. Treatment group, Gd+ at baseline (presence, absence), EDSS strata (<4.0, ≥4.0) and geographic region (US, non-US) were covariates. Log-transformed observation duration was the offset variable. A study was declared positive if the primary endpoint was significant at the 2-sided α=0.05 level. To include all participants in the analysis, the baseline Gd+ lesion presence or absence was imputed for a few participants with a missing baseline count.

Analysis of secondary endpoints

In order to have sufficient statistical power to detect relevant treatment differences, the pre-specified primary analysis population for time-to-onset of 3- and 6-month CDW, and time-to-onset of 6-month CDI, was the pooled ITT population of studies EFC16033 and EFC16034. In addition to the analysis using pooled data, time to onset of 6-month CDW was also defined to be analysed within each study separately using the same statistical methods as for the primary analysis, but without study included in the model and without any treatment-by-study interaction analysis. Analysis of other secondary endpoints were performed in each individual ITT study population separately.

Key secondary endpoint

Time to onset of 6-month CDW was defined as the time from randomisation to the onset of a confirmed, sustained increase from baseline in EDSS (of ≥1.5 points when the baseline score is 0, of ≥1.0 point when the baseline score is 0.5 to ≤5.5, of ≥0.5 points when the baseline EDSS score is >5.5) over at least 6 months that is not attributable to another aetiology (e.g., fever, concurrent illness, or concomitant medication). Note: 6-month confirmation must be ≥154 days after onset. Given that visits were scheduled every 12 weeks with a time window of ±7 days for conducting EDSS assessment, the minimum per protocol allowed time between 2 EDSS assessments scheduled 24 weeks apart was 154 days (6 months=24 weeks=168 days minus a 7-day window for each of the 2 visits, i.e., 168-14=154).

The time to onset of 6-month CDW for tolebrutinib versus teriflunomide was compared via a log-rank test stratified by EDSS strata (<4, ≥4), geographic region (US, non-US), and study (EFC16033, EFC16034). The HR (95% CI) was estimated by a Cox proportional hazards model with robust variance estimation. The covariates were intervention group, Gd+ lesions at baseline (presence, absence), EDSS strata (<4, ≥4), geographic region (US, non-US), and study (EFC16033, EFC16034). For participants with 3-month CDW, who continued to meet criteria for EDSS disability worsening through the final study assessment but did not reach 6-month confirmation due to end of study, the 6-month CDW event status was imputed via a multiple imputation method. An expanded model with a treatment-by-study interaction was fitted to the data, and between-study heterogeneity was tested (type-3). In the analysis of time to onset of 6-month CDW: For participants who completed the study without an initial onset of disability worsening, the participant was censored at the date of last EDSS assessment; for participants who had an initial onset of disability worsening but completed the study at the common study end date without a 3-month confirmation, the participant was censored at the date of last EDSS assessment. If a participant died due to MS, it was considered a confirmed disability worsening regardless of the baseline EDSS or the change in EDSS. A pre-planned sensitivity without imputation was performed.

Analysis of multiplicity-controlled secondary endpoints

A multiplicity procedure was used to strongly control the overall type I error rate for testing the primary and selected secondary efficacy endpoints at a 2-sided significance level of 0.05 at the level of the individual study and at the level of the pooled studies.

For categorical efficacy endpoints with count data (annualised rate of new and/or enlarging T2-hyperintense lesions and average number of new Gd+ lesions per scan), similar negative binomial regression analyses as those used for the primary analysis of ARR were performed in the ITT population. The response variable was the total number of the respective type of lesions across all scheduled MRI scans during the study period. The offset variable was the log-transformed duration from screening MRI to last available MRI scan for T2-hyperintense lesions and number of MRI scans for T1-hyperintense lesions.

Percent change in brain volume at the EOS compared to Month 6 and change from baseline in SDMT number of correct substitutions and CVLT-II total correct at the EOS were analysed using a mixed-effect model with repeated measures approach in the ITT population.

Subgroup analyses (pooled data only) were performed on observed confirmed 6-month CDW for the following prespecified subgroups: age (≤40, >40 years), sex (Male, Female), race (White, Black or African American, Asian, Other), EDSS strata (<4.0, ≥4.0), Gd+ lesions at baseline (presence, absence), geographic region (US, non-US), Region (Eastern Europe [European Union], Western Europe [European Union], North America, Rest of World), HAD at baseline (Yes, No), prior DMT use (Yes, No), relapses in the year prior to screening (<2, ≥2), and time since symptom onset in years (<5, 5 to <10, ≥10).There was no imputation for incomplete/missing data for these subgroup analyses.

An additional *post hoc* subgroup analysis was performed for 6-month CDW (pooled population; without imputation) in the subset of participants with PRL assessment to assess the relationship between MRI biomarkers and tolebrutinib treatment response (in participants with 0, 1-3, and ≥4 PRLs at baseline, respectively).

Results

Disposition of subjects

In study **EFC16033,** a total of 974 participants were randomised to study intervention: 486 in the tolebrutinib group and 488 in the teriflunomide group. All randomised participants were exposed to study intervention. In the randomised population, 727 (74.6%) participants completed the study intervention: 367 (75.5%) and 360 (73.8%) of the subjects in the tolebrutinib and the teriflunomide arm, respectively. The percentage of participants who permanently discontinued study intervention was similar between the tolebrutinib and teriflunomide groups (24.5% and 26.2%, respectively). The most frequently reason for permanent study intervention discontinuation was "withdrawal by subject" (62 [12.8%] and 66 [13.5%] in the tolebrutinib and the teriflunomide group, respectively. "Adverse event" was reported by the Investigator as the reason for permanent study intervention discontinuation for 23 (4.7%) and 24 (4.9%) participants in the tolebrutinib and the teriflunomide group, respectively. "Lack of efficacy" as the reason for permanent study intervention discontinuation was reported for 23 (4.7%) and 28 (5.7%) participants in the tolebrutinib and the teriflunomide group, respectively.

In study **EFC16034**, a total of 899 participants were randomised to study intervention: 447 in the tolebrutinib group and 452 in the teriflunomide group. 1 (0.2%) participant in the teriflunomide group was randomised but not exposed to the study intervention. In the randomised population, 662 (73.6%) participants completed the study intervention: 333 (74.5%) and 329 (72.8%) of the subjects in the tolebrutinib and the teriflunomide arm, respectively. The percentage of participants who permanently discontinued study intervention was similar between the tolebrutinib and teriflunomide groups (25.5% and 27.0%, respectively). The most frequently reported reason for permanent study intervention discontinuation was "withdrawal by subject" (52 [11.6%] and 67 [14.8%] in the tolebrutinib and the teriflunomide group, respectively. "Adverse event" was reported by the Investigator as the reason for permanent study intervention discontinuation for 19 (4.3%) and 19

(4.2%) participants in the tolebrutinib and the teriflunomide group, respectively. An imbalance in the percentage of participants that discontinued study intervention due to lack of efficacy (8.3% [tolebrutinib] versus 5.1% [teriflunomide]) was observed; however, the majority continued in the study to the end, and their data were included in the ITT efficacy analyses.

Demographic and disease characteristics at baseline

In study **EFC16033**, demographic and participant characteristics at baseline were generally balanced between both intervention groups. The mean age was 36.7 years, and the majority of participants were female (67.7%) and White (82.2%). Baseline disease characteristics were generally balanced between both intervention groups. All participants were diagnosed with RMS (963 [98.9%] with relapsing-remitting MS and 11 [1.1%] with relapsing SPMS) with a mean EDSS score of 2.39 (min 0.0, max 5.5), a median time since first symptoms of MS of 4.82 years, and a median time since first diagnosis of 1.629 years. Across intervention groups, the mean (SD) number of relapses was 1.18 (0.58) in the year prior to screening and 1.56 (0.88) in the 2 years prior to screening. Overall, 354 (36.5%) of participants had active lesions on the baseline MRI (as assessed by the presence of Gd+ lesions by a central reader): 186 (38.4%) subjects and 168 (34.7%) subjects in the teriflunomide and the tolebrutinib group, respectively. The overall mean (SD) number of GdE at baseline was 1.4 (4.0): 1.5 (4.2) and 1.3 (3.7) for subject in the teriflunomide and the tolebrutinib group, respectively. Overall, 491 (50.5%) participants had highly active disease. Participants with HAD were defined as having 1 relapse in the previous year AND one of the following: at least 1 Gd+ lesion; or ≥9 T2-hyperintense lesions at baseline for participants who were already treated with a DMT (any treatment with DMTs would be considered, if documented, during the prior year); or who had ≥2 relapses in the previous year, whether treated with DMTs or not. The intervention groups were balanced with respect to the prior use of DMTs. The most used prior DMTs were interferon beta-1a and glatiramer acetate in both intervention groups. 606 (62.2%) of the participants were DMT naïve.

In study **EFC16034**, demographic and participant characteristics at baseline were generally balanced between intervention groups. Overall, the mean age of the randomised population was 36.4 years, and the majority of participants were female (66.0%) and White (92.1%). Baseline disease characteristics were generally balanced between intervention groups and were representative of a population with relapsing forms of MS. All participants were diagnosed with RMS (894 [99.4%] with relapsing-remitting MS and 5 [0.6%] with relapsing SPMS) with a mean EDSS score of 2.37 at baseline (min 0.0, 5.5), a median time since first symptoms of MS of 3.28 years, and a median time since first diagnosis of 0.999 years. The mean (SD) number of relapses was 1.14 (0.55) in the year prior to screening and 1.47 (0.83) in the 2 years prior to screening. Disease-specific baseline characteristics were similar between intervention groups; 445 (49.5%) of participants had HAD. Participants with highly active disease were defined as having 1 relapse in the previous year AND one of the following: at least 1 Gd+ lesion; or ≥9 T2-hyperintense lesions at baseline for participants who were already treated with DMT (any treatment with DMTs would be considered, if documented, during the prior year); or who had ≥2 relapses in the previous year, whether treated with DMTs or not. Overall, 291 (32.5%) participants had active lesions in the baseline MRI (as assessed by the presence of Gd+ lesions by a central reader): 146 (32.6%) subjects and 145 (32.4%) subjects in the teriflunomide and the tolebrutinib group, respectively. The overall mean (SD) number of Gd+ lesions at baseline was 1.0 (2.8): 1.0 (3.2) and 1.0 (2.4) for subject in the teriflunomide and the tolebrutinib group, respectively. 601 (66.9%) of the participants were DMT naïve.

Efficacy results

Table 25 Primary and secondary efficacy objectives and endpoints in pivotal Phase 3 studies in RMS

			Comparison between teriflunomide 14 mg and tolebrutinib 60 mg		
Category	**Endpoint**		**EFC16033**	**EFC16034**	**EFC16033+EFC16034**
Primary Endpoint	ARR	Relative risk (95% CI)	1.061 (0.808, 1.393)	0.996 (0.754, 1.315)	
		p-value[a]	0.6691	0.9758	
		Adjusted significance level	0.05	0.05	
Secondary Endpoints	6-month CDW	Hazard Ratio (95% CI)			0.710 (0.529, 0.953)
		Stratified Log-Rank test p-value			0.0225
		Adjusted significance level			NA
	3-month CDW	Hazard Ratio (95% CI)			0.732 (0.571, 0.939)
		Stratified Log-Rank test p-value			0.0175
		Adjusted significance level			NA
	6-month CDI	Hazard Ratio (95% CI)			1.222 (0.935, 1.598)
		Stratified Log-Rank test p-value			0.1678
		Adjusted significance level			NA
	New Gd-enhancing T1-hyperintense lesions	Relative risk (95% CI)	1.860 (1.358, 2.548)	2.118 (1.502, 2.987)	
		p-value[a]	0.0001	<0.0001	
		Adjusted significance level	NA	NA	
	New and/or enlarging T2-hyperintense lesions	Relative risk (95% CI)	1.084 (0.876, 1.342)	1.165 (0.905, 1.502)	
		p-value[a]	0.4575	0.2362	
		Adjusted significance level	NA	NA	
	Change from baseline in SDMT Z-score for number of correct substitutions at EOS	LS Mean difference (95% CI)	0.035 (-0.053, 0.124)	-0.053 (-0.156, 0.050)	
		p-value for the difference between groups	0.4320	0.3100	
		Adjusted significance level	NA	NA	
	Change from baseline in standardized score of CVLT-II total correct at EOS	LS Mean difference (95% CI)	1.873 (-0.135, 3.880)	-0.612 (-2.493, 1.269)	
		p-value for the difference between groups	0.0675	0.5235	
		Adjusted significance level	NA	NA	

Percent change in brain volume at EOS compared to Month 6	LS Mean difference (95% CI)	0.196 (0.093, 0.298)	0.044 (-0.065, 0.153)
	p-value for the difference between groups	0.0002	0.4266
	Adjusted significance level	NA	NA

a Chi-square test for relative risk
All values in bold font are statistically significant according to the hierarchical testing procedure

Tolebrutinib did not meet the primary efficacy endpoint of reducing the ARR compared to teriflunomide in either of the EFC16033 or EFC16034 studies: the adjusted ARR was similar in both study intervention groups, i.e., study: EFC16033: 0.130 in the tolebrutinib group and 0.122 in the teriflunomide group (RR [95% CI]: 1.061 [0.808 to 1.393]; p=0.6691); study EFC16034: 0.108 in the tolebrutinib group and 0.109 in the teriflunomide group (RR [95% CI]: 0.996 [0.754 to 1.315]; p=0.9758).

Pre-specified, multiplicity-controlled, hierarchical testing was planned for the primary, key secondary, and other supportive secondary efficacy endpoints. The table above presents the results for each endpoint in the order of the hierarchy. However, since the null hypothesis for the primary efficacy endpoint was not rejected, all further testing is considered non-confirmatory, and p-values are nominal.

Multiplicity-controlled secondary endpoints

Time to onset of 6-month confirmed disability worsening *(key secondary endpoint)*

In the pooled ITT population of Studies EFC16033 and EFC16034, the percentage of participants with 6-month CDW was 8.3% in the tolebrutinib group compared to 11.3% in the teriflunomide group; representing a 29.0% risk reduction in favour of tolebrutinib (HR [95% CI]: 0.710 [0.529 to 0.953]; nominal p=0.0225 from the pre-specified stratified log-rank test). There was no evidence of a treatment-by-study interaction for the effect of tolebrutinib on 6-month CDW (p-value for heterogeneity >0.1).

The pre-specified sensitivity analysis for the key secondary endpoint (without imputation) was in line with the primary analysis.

In study EFC16033, the percentage of participants with 6-month CDW was 8.9% (43/486 subjects) in the tolebrutinib group compared to 10.4% (51/488 subjects) in the teriflunomide group; corresponding to a 15.0% risk reduction in favour of tolebrutinib (HR [95% CI]: 0.850 [0.565 to 1.278] p = 0.4888).

In participants free of adjudicated relapse in EFC16033, the percentage of participants with 6-month CDW was 6.5% (24/368 subjects) in the tolebrutinib group compared to 8.5% (32/377 subjects) in the teriflunomide group; corresponding to a 24% risk reduction in favour of tolebrutinib (HR [95% CI]: 0.758 [0.446 to 1.288] p = 0.3455).

In study EFC16034, the percentage of participants with 6-month CDW was 7.7% (34/447 subjects) in the tolebrutinib group and 12.3% (55/452 subjects) in the teriflunomide group; corresponding to a 41.8% risk reduction in favour of tolebrutinib (HR [95% CI]: 0.582 [0.380 to 0.891] p = 0.0114).

In participants free of adjudicated relapse in EFC16034, the percentage of participants with 6-month CDW was 7.0% (24/342) in the tolebrutinib group as compared to 10% (36/359) in the teriflunomide group; corresponding to a 33% risk reduction in favour of tolebrutinib (HR [95% CI]: 0.666 [0.399 to 1.112] p = 0.1193).

Time to onset of 3-month confirmed disability worsening

In the pooled ITT population for the EFC16033 and EFC16034 studies, the percentage of participants with 3-month CDW was 11.7% (109/933 subjects) in the tolebrutinib group and 15.3% (144/940 subjects) in the teriflunomide group, corresponding to a 26.8% % risk reduction in favour of tolebrutinib (HR [95% CI]: 0.732 [0.571 to 0.939]; nominal p=0.0175 from the prespecified stratified log-rank test).

In Study EFC16033, the percentage of participants with 3-month CDW was 12.6% (61/486 subjects) in the tolebrutinib group as compared to 15.0% (73/488 subjects) in the teriflunomide group (HR [95% CI]: 0.819 [0.582 to 1.151] p = 0.2991) corresponding to a 18.1% risk reduction in favour of tolebrutinib and in Study EFC16034 the percentage of participants with 3-month CDW was 10.7% (48/447 subjects) in the tolebrutinib group and 15.7% (71/452 subjects) in the teriflunomide group (HR [95% CI]: 0.641 [0.444 to 0.925] p = 0.0181) corresponding to a 35.9% in favour of tolebrutinib.

Time to onset of 6-month conformed disability improvement

In the pooled ITT population for the EFC16033 and EFC16034 studies, the percentage of participants with 6-month CDI was 12.6% (118/933 subjects) in the tolebrutinib group and 10.4% (98/940) in the teriflunomide group; a numerically higher rate was observed with tolebrutinib (HR [95% CI]: 1.222 [0.935 to 1.598] p = 0.1678).

In Study EFC16033, the percentage of participants with 6-month CDI was 8.8% (43/486 subjects) in the tolebrutinib group as compared to 10.7% (52/488 subjects) in the teriflunomide group (HR [95% CI]: 0.831 [0.554 to 1.245] p = 0.3584) in favour of teriflunomide whereas in Study EFC16034 the percentage of participants with 6-month CDI was 16.8% (75/447 subjects) in the tolebrutinib group and 10.2% (46/452 subjects) in the teriflunomide group (HR [95% CI]: 1.652 [1.145 to 2.383] p = 0.0079) in favour of tolebrutinib.

Magnetic resonance imaging: new Gd+ lesions and new and/or enlarging T2-hyperintense lesions

In study EFC16033, the adjusted mean number of new Gd+ lesions per scan was 0.530 in the tolebrutinib group as compared to 0.285 in the teriflunomide group (RR [95% CI]: 1.860 [1.358 to 2.548] p = 0.0001). The percentage of participants who did not develop any new Gd+ lesions during the study period was 52.5% in the tolebrutinib group as compared to 57.4% in the teriflunomide group. The adjusted mean number of new and/or enlarging T2-hyperintense lesions per year was 5.611 in the tolebrutinib group as compared to 5.175 in the teriflunomide group (RR [95% CI]: 1.084 [0.876 to 1.342] p = 0.4575).

In study EFC16034, the adjusted mean number of new Gd+ lesions per scan was 0.460 in the tolebrutinib group and 0.217 in the teriflunomide group (RR [95% CI]: 2.118 [1.502 to 2.987] p <0.0001). The percentage of participants who did not develop any new Gd+ lesions during the study period was 51.7% in the tolebrutinib group and 62.2% in the teriflunomide group. The adjusted mean number of new and/or enlarging T2-hyperintense lesions per year was 5.092 in the tolebrutinib group and 4.369 in the teriflunomide group (RR [95% CI]: 1.165 [0.905 to 1.502] p = 0.2362).

Subgroup analyses for 6-month CDW were conducted in the pooled ITT population of Studies EFC16033 and EFC16034. A consistent reduction in the risk of 6-month CDW with tolebrutinib versus teriflunomide was generally observed across all subgroups, with potentially higher efficacy in participants with no prior use of DMTs. Of note, the results in the race subgroup, including all races other than White or Asian, were based on 2 events as compared to 1 in a very small subgroup.

An additional *post hoc* subgroup analysis of 6-month CDW in the subset of participants with PRL assessment (34% of randomised participants), although impacted by small sample size, suggested that the impact of tolebrutinib treatment may be greater in those with higher number of PRLs (0 PRL:

RRR of 18%); HR [95% CI]: 0.815 [0.338 to 1.963]); 1-3 PRLs: RRR of 46%; HR [95% CI]: 0.540 [0.223 to 1.304]; ≥4 PRLs: RRR of 49%; HR [95% CI]: 0.513 [0.206 to 1.280]).

5.3.5.3. Study LTS16004

Long-term extension safety and efficacy study of SAR442168 in participants with relapsing multiple sclerosis

Overview of Methods

Study LTS16004 is a Phase 2 long-term, follow-up study to assess the safety and efficacy of tolebrutinib. Participants who completed treatment in the previous study DRI15928 were eligible for enrolment. Participants started the study intervention as soon as possible.

The study consists of 2 parts: Part A: Double-blind period of continued study intervention with the respective tolebrutinib dose regimen administered in study DRI15928 until selection of the Phase 3 dose regimen (60 mg once daily tolebrutinib with food). Cohort 1 of study DRI15928 that exited the trial receiving placebo from Weeks 13 to 16 received the active intervention dose assigned to them at randomisation and administered during Weeks 1 to 12. The double blind was maintained until the Phase 3 dose was selected based on study DRI15928 (implemented in Amended protocol 03). Part B: Open-label period of a single-group treatment with the Phase 3 dose regimen, 60 mg tolebrutinib once daily with food.

Dose groups 5/60, 15/60, 30/60, and 60/60 mg were defined as participants who received 5, 15, 30, or 60 mg tolebrutinib once daily during Part A, respectively, and then exposed to 60 mg once daily in Part B.

First participant enrolled: 23 September 2019, date of interim data cut-off: 27 September 2023

In Part A, participants continued to receive their previous tolebrutinib dose assigned in the parent study DRI15928 (2.5 or 15 mg film coated tablets). In Part B all participants formed a single dose group with the selected Phase 3 dose (15 or 60 mg film coated tablets; 60 mg once daily).

Primary objective: To determine the LTS and tolerability of tolebrutinib in RMS participants

Secondary objectives: To evaluate efficacy of tolebrutinib on disease activity, assessed by clinical and imaging methods. Secondary endpoints consisted of counts of brain lesions assessed by MRI (new and total Gd+ and new or enlarging T2), ARR, and change from baseline in EDSS score over time.

Analyses were primarily descriptive summaries of parameters by visit. ARR was estimated using a negative binomial model. All efficacy endpoints in this study were secondary or tertiary/exploratory endpoints.

Results

Of the 129 subjects who completed study DRI15928, a total of 125 subjects received tolebrutinib treatment in the extension study: in Part A, 31, 31, 32 and 31 subjects received tolebrutinib 5 mg, 15 mg, 30 mg and 60 mg, respectively. One participant in the tolebrutinib 5 mg group did not complete the Part A study intervention due to "progressive disease", and this participant prematurely discontinued from the study.

All 124 participants who completed Part A switched to Part B (60 mg tolebrutinib once daily). By the cut-off date, 96 participants were still receiving study intervention, and 28 participants prematurely discontinued the study intervention. The most common reason for study intervention discontinuation was "withdrawal by subject" with 12 out of 124 participants who received study intervention during Part B.

As of the cut-off date, 117 (93.6%) participants were treated for at least 2 years (>96 weeks) and 105 (84.0%) for at least 3 years (>144 weeks). The mean duration of IMP exposure in all participants was 1165.9 days (190.5 days in Part A and 983.2 days in Part B). During Part A, the maximal duration of IMP exposure was 271 days and the minimal duration was 87 days. Cumulative exposure to tolebrutinib in all participants was 434.40 participant-years.

Efficacy

New Gd+ lesions: The observed mean (SD) number of new Gd+ lesions at Week 144 (N=103) was 0.42 (1.01) in the overall mITT population with 0.50 (1.29), 0.48 (0.96), 0.20 (0.50) and 0.48 (1.15) in the tolebrutinib 5/60 mg, 15/60 mg, 30/60 mg and 60/60 mg group, respectively.

New or enlarging T2 lesions: The observed mean (SD) of new or enlarging T2 lesions per month at Week 144 (N=106) compared to Week 96 was 0.30 (0.54) in the overall mITT population with 0.43 (0.71), 0.38 (0.64), 0.18 (0.34) and 0.23 (0.36) in the tolebrutinib 5/60 mg, 15/60 mg, 30/60 mg and 60/60 mg group, respectively.

Total number of Gd+ lesions: The observed mean (SD) total number of Gd+ lesions at Week 144 (N=103) was 0.44 (1.03) in the overall mITT population with 0.54 (1.32), 0.48 (0.96), 0.24 (0.52) and 0.48 (1.15) in the tolebrutinib 5/60 mg, 15/60 mg, 30/60 mg and 60/60 mg group, respectively.

The ***adjusted ARR*** (95% CI) was 0.28 (0.15, 0.52) in the 5/60 mg group, 0.23 (0.12, 0.43) in the 15/60 mg group, 0.28 (0.18, 0.43) in the 30/60 mg group, and 0.24 (0.15, 0.40) in the 60/60 mg group. The 95% CI for the relative risk of relapse with continued tolebrutinib 60 mg compared to switching from a lower dose in Part B included 1 in all cases.

The overall ARR (95% CI) during treatment with once daily 60 mg tolebrutinib (N=124) was 0.25 (0.19 to 0.33).

As of the cut-off date, over 62.1% of participants remained relapse free: 19 (61.3%) participants in the 5/60 mg group, 18 (58.1%) in the 15/60 mg group, 16 (50.0%) in the 30/60 mg group, and 18 (58.1%) in the 60/60 mg group had no MS relapses. The ARR was analysed using only relapses with onset during treatment with tolebrutinib 60 mg once daily.

The mean (SD) change from baseline in ***EDSS*** score at Week 144 (N=104) was 0.09 (0.64) in the overall mITT population and remained stable across visits.

During the procedure (14th December 2025), the applicant provided topline results of the phase 3 study EFC1035 (PERSEUS) conducted in a PPMS population:

5.3.5.4. ***Study EFC16035 (PERSEUS): A Phase 3, randomised, double-blind, efficacy and safety study comparing SAR442168 to placebo in participants with primary progressive multiple sclerosis***

Study EFC16035 (PERSEUS) was a Phase 3, randomised, double-blind, 2-arm, placebo-controlled, parallel group, multicenter, event-driven [6-month composite confirmed disability progression (cCDP)] trial with a variable treatment duration ranging from approximately 12 to 60 months in participants with PPMS. The study was designed and conducted to evaluate the efficacy and safety of tolebrutinib compared to placebo in participants with PPMS. The primary endpoint was time to onset of 6-month composite confirmed disability progression (6M-cCDP) assessed via the EDSS, T25-FW test, or 9-HPT.

Initially, the study was designed with 6-month CDP based on EDSS as primary endpoint with a sample size of 990 participants (original protocol: 28th February 2020). With protocol amendment 12 (28th September 2023), the Sponsor changed the primary endpoint to the 3-month composite CDP (3M-cCDP) to reduce the sample size and to enable completion of the trial within a feasible time and

maintain trial integrity. According to the applicant, further participant enrollment and accumulation of events have made it possible to achieve adequate power on the 6-month composite CDP (6M-cCDP) within a similar estimated study duration while the primary endpoint was further changed (see amended clinical trial protocol 14, 31th October 2024).

Topline results:

A total of 767 participants were randomised to study intervention: 515 in the tolebrutinib group and 252 in the placebo group. In the randomised population, 1 participant in each group was randomized but not exposed to study intervention. A total of 588 (76.7%) participants completed the study, including 398 (77.3%) participants in the tolebrutinib arm and 190 (75.4%) participants in the placebo arm.

There was no difference between 60 mg daily tolebrutinib treatment and placebo in delaying the time to onset of 6McCDP during the study period, defined as an increase of: • ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.0, or an increase of ≥0.5 point when the baseline EDSS score is >5.5; OR • ≥20% from the baseline T25-FW test time; OR • ≥20% from the baseline 9-HPT time.

In the ITT population, the percentage of participants with 6-month cCDP as assessed by EDSS, T25FW, or 9HPT was 50.5% in the tolebrutinib group as compared to 48.4% in the placebo group: HR of 1.008 (95% CI: 0.809 to 1.257, p=0.9410).

Three pre-planned sensitivity analyses confirmed that the findings were statistically robust.

Given the primary endpoint did not reach statistical significance, the pre-specified, multiplicity controlled, hierarchical testing was stopped. No nominally significant treatment effect of tolebrutinib compared to placebo was observed for the time to event disability endpoints including 6M-CDP, 3M-cCDP or 6-month confirmed disability improvement (6M-CDI). Nominally significant treatment benefits with tolebrutinib compared to placebo were observed for the annualized rate of new/enlarging T2 lesions and % change in brain volume at end of study compared to month 6.

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

MS typically progresses along a continuum of increasing neurodegeneration (Dobson, 2019; Olek, 2021). Participants with RMS in EFC16033/EFC16034 are at an earlier point in the MS disease continuum as compared to participants with (nr)SPMS in EFC16645. Additionally, the RMS and (nr)SPMS pivotal Phase 3 trials had different comparators and primary endpoints. Accordingly, an integrated analysis of efficacy based on data pooled from all 3 pivotal Phase 3 trials has not been performed.

Integrated analysis of efficacy data from the two Phase 3 studies in RMS (EFC16033 and EFC1603)

(Date of ISE SAP 02 July 2024)

The efficacy results of the 2 similarly designed Phase 3 studies (EFC16033 and EFC16034) were compared with each other as well as with the efficacy results of the pooled analyses of these 2 studies.

The pooled EFC16033 and EFC16034 dataset in RMS (denominated as Pool E) was the basis for the integrated analyses of efficacy. Efficacy analyses were performed in the ITT population defined as all randomly assigned participants. All analyses were conducted according to the intervention group allocated by the randomisation schedule, irrespective of the intervention received.

Table 26 Clinical efficacy data Pool in Phase 3 RMS trials (EFC16033 and EFC16034)

Dataset Pool	Type	Studies	Average treatment duration	Participant numbers		Treatment comparison
				teriflunomide 14 mg	tolebrutinib 60 mg	
E	Active-controlled	Total	2.3 years	939	933	60 mg tolebrutinib daily vs 14 mg teriflunomide daily
		EFC16033 (GEMINI 1)	2.4 years	488	486	
		EFC16034 (GEMINI 2)	2.3 years	451	447	

The same statistical methods as specified for the analyses at the individual study level were used for the pooled RMS efficacy analyses, with some additional considerations such as using 'study' as a stratification factor or covariate. Except where stated, statistical hypotheses were tested at the 5% significance level (α=0.05) against two-sided alternatives. All specified endpoints were analysed, stratified, or adjusted by study (EFC16033 and EFC16034), geographical region (US, non-US), and EDSS strata (<4.0 versus ≥4.0). Further descriptions of the analyses of the pooled data are in the SAP for the ISE, dated 02 July 2024.

The primary analysis population for the 3 disability endpoints (time to onset of 6-month CDW, time to onset of 3-month CDW, and time to onset of 6-month CDI) was the pooled ITT population from studies EFC16033 and EFC16034. No additional analyses were planned for these endpoints except for subgroup analyses for 3-month CDW.

A summary of the breakdown of 6-month CDW events related to relapse (RAW) or not, (PIRA) was provided where:

- PIRA was defined as a 6-month CDW event with no onset of adjudicated relapse within the 90 days before or after the confirmed disability onset date (this includes events in participants with no adjudicated relapse during the study).
- RAW was defined as a 6-month CDW event with an onset of an adjudicated relapse within the 90 days before or after the confirmed disability onset date.

PIRA and RAW events were analysed separately in the Pool E ITT population using the same methods as for 6-month CDW, but without imputation.

A *post hoc* sensitivity analysis for 6-month CDW was performed (pooled population) where all participants with at least one adjudicated relapse during their respective study were excluded from the analysis set. The same statistical analysis methods as for the primary analysis were utilised, but without imputation.

Results:

In the pooled populations of studies EFC16033 and EFC16034 (RMS studies), a total of 1873 participants were randomised 1:1 to study intervention: 933 to tolebrutinib and 940 to teriflunomide. All randomised participants, except one, were exposed to study intervention.

The percentage of participants who permanently discontinued study intervention was similar between the tolebrutinib and teriflunomide groups (233 (25.0%) and 250 (26.6%), respectively). The most frequently reported reasons for permanent study intervention discontinuation were AEs 42 (4.5%), lack of efficacy 60 (6.4%) and withdrawal by subject 114 (12.2%) in the tolebrutinib group and AEs 43 (4.6%), lack of efficacy 51 (5.4%) and withdrawal by subject 133 (14.1%) in the teriflunomide group.

A total of 1586 (84.7%) of all participants completed the study into which they were randomised (EFC16033 or EFC16034), 793 (85.0%) in the tolebrutinib group and 793 (84.4%) in the teriflunomide group.

Demographic and participant characteristics at baseline were generally balanced across intervention groups and across both studies in RMS. In the pooled ITT population of Studies EFC16033 and EFC16034 (RMS studies), the mean age was 36.5 years, and the majority of participants were female (66.8%) and White (87%), similar to the individual studies. Demographic and participant characteristics at baseline were similar/comparable between intervention groups in the pooled ITT population.

Disease characteristics at baseline were generally balanced across intervention groups and across both studies in RMS. In the pooled ITT population of Studies EFC16033 and EFC16034, all participants had been diagnosed with relapsing forms of MS (i.e., RMS or active SPMS) with a median time since RMS diagnosis of 1.284 years; within the year prior to screening, the majority of participants had 1 (74.9%) or 2 (16.7%) relapse (s), similar to the individual studies. Disease characteristics at baseline were similar between intervention groups in the pooled ITT population.

MRI lesion counts for Gd+ lesions and T2 lesions at baseline were generally balanced across intervention groups and across both studies in RMS. Gd+ lesions and T2 lesions at baseline were generally balanced between intervention groups in the pooled ITT population of Studies EFC16033 and EFC16034.

Efficacy results:

Table 27 Summary of 6-month CDW events as progression independent of relapse activity or relapse associated worsening (EFC16033 + EFC16034)

	teriflunomide 14 mg (N=940)	tolebrutinib 60 mg (N=933)
Total 6M-CDW	105 (11.2)	77 (8.3)
PIRA	80 (76.2)	60 (77.9)
No adjudicated relapse	68 (64.8)	48 (62.3)
Disability onset not within +/- 90 days of an adjudicated relapse onset	12 (11.4)	12 (15.6)
RAW	25 (23.8)	17 (22.1)

Table 28 Analysis of time to onset of PIRA (ITT population) (EFC16033 + EFC16034)

	teriflunomide 14 mg (N=940)	tolebrutinib 60 mg (N=933)
Number of participants with PIRA, n (%)	80 (8.5)	60 (6.4)
Number of participants who were censored, n (%)	860 (91.5)	873 (93.6)
Time to onset of PIRA (months)		
Number	80	60
Mean (SD)	16.34 (9.17)	15.99 (10.45)
Median	16.32	15.09
Q1 ; Q3	8.95 ; 22.71	6.04 ; 24.04
Min ; Max	2.8 ; 38.9	2.6 ; 36.1
Kaplan-Meier estimates of proportion of participants with >= 1 event (95% CI)[a] at		
Month 12	0.031 (0.022, 0.045)	0.027 (0.018, 0.039)
Month 18	0.050 (0.037, 0.067)	0.038 (0.027, 0.053)
Month 24	0.069 (0.054, 0.089)	0.050 (0.038, 0.067)
Month 30	0.086 (0.069, 0.107)	0.062 (0.047, 0.080)
Month 36	0.096 (0.077, 0.118)	0.069 (0.053, 0.089)
Month 42	0.099 (0.080, 0.123)	0.076 (0.059, 0.098)
Month 48	0.099 (0.080, 0.123)	0.076 (0.059, 0.098)
Month 54	0.099 (0.080, 0.123)	0.076 (0.059, 0.098)
Hazard Ratio (95% CI)[b]		0.730 (0.522, 1.021)
Cox model p-value		0.0657
Stratified Log-Rank test p-value[c]		0.0694

PIRA=progression independent of relapse activity

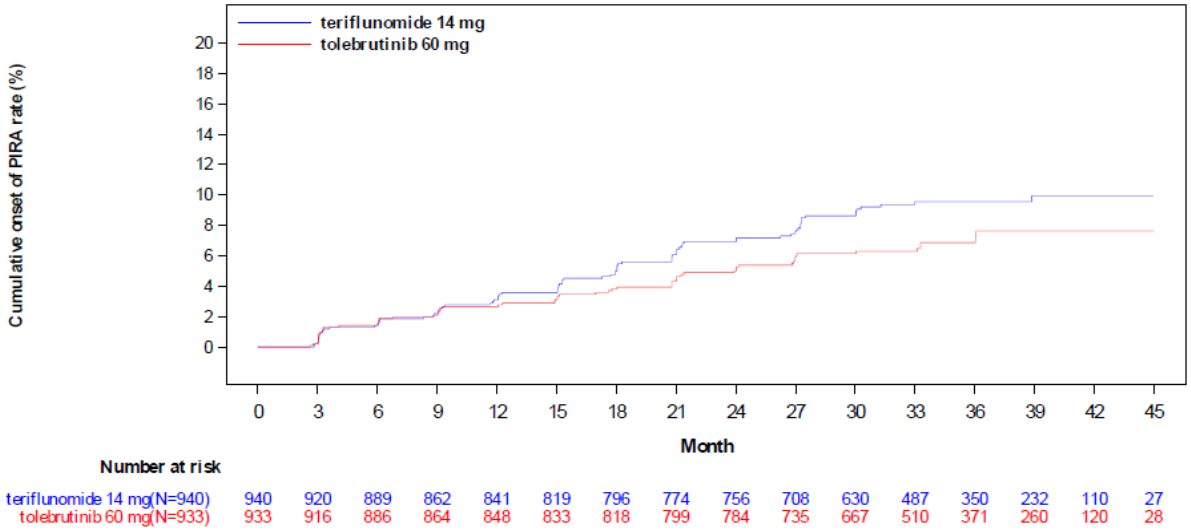
Note: Participants with missing PIRA are censored at their last EDSS assessment.

[a] Derived from Kaplan-Meier estimates.

[b] Derived using Cox proportional-hazards model with robust variance estimation. Covariates are treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4, >=4), geographic region (US, non-US) and study (EFC16033, EFC16034).

[c] Derived from log-rank test with stratification of EDSS strata (<4, >=4), geographic region (US, non-US) and study (EFC16033, EFC16034).

Figure 8 Kaplan-Meier plot of cumulative incidence rate of onset of PIRA - EFC16033 + EFC16034 (ITT population)



PIRA=progression independent of relapse activity

Table 29 Analysis of time to onset of RAW - Pool E (EFC16033 + EFC16034) (ITT population)

	teriflunomide 14 mg (N=940)	tolebrutinib 60 mg (N=933)
Number of participants with RAW, n (%)	25 (2.7)	17 (1.8)
Number of participants who were censored, n (%)	915 (97.3)	916 (98.2)
Time to onset of RAW (months)		
Number	25	17
Mean (SD)	12.53 (8.62)	14.45 (9.24)
Median	11.71	12.39
Q1 ; Q3	4.29 ; 17.96	7.18 ; 21.00
Min ; Max	1.4 ; 29.9	2.0 ; 32.8
Kaplan-Meier estimates of proportion of participants with >= 1 event (95% CI)[a] at		
Month 12	0.016 (0.009, 0.026)	0.008 (0.004, 0.016)
Month 18	0.021 (0.014, 0.033)	0.011 (0.006, 0.021)
Month 24	0.024 (0.016, 0.036)	0.017 (0.010, 0.028)
Month 30	0.029 (0.020, 0.043)	0.019 (0.011, 0.030)
Month 36	0.029 (0.020, 0.043)	0.020 (0.013, 0.033)
Month 42	0.029 (0.020, 0.043)	0.020 (0.013, 0.033)
Month 48	0.029 (0.020, 0.043)	0.020 (0.013, 0.033)
Month 54	0.029 (0.020, 0.043)	0.020 (0.013, 0.033)
Hazard Ratio (95% CI)[b]		0.683 (0.368, 1.265)
Cox model p-value		0.2250
Stratified Log-Rank test p-value[c]		0.2220

RAW=relapse associated worsening
Note: Participants with missing RAW are censored at their last EDSS assessment.
[a] Derived from Kaplan-Meier estimates.
[b] Derived using Cox proportional-hazards model with robust variance estimation. Covariates are treatment group, Gd-enhancing T1 lesions at baseline (presence, absence), EDSS strata (<4, >=4), geographic region (US, non-US) and study (EFC16033, EFC16034).
[c] Derived from log-rank test with stratification of EDSS strata (<4, >=4), geographic region (US, non-US) and study (EFC16033, EFC16034).

New Gd+ lesions: In the pooled ITT population of Studies EFC16033 and EFC16034 (RMS studies), the number of new Gd+ lesions per scan was higher in the tolebrutinib group as compared to the teriflunomide group (relative risk, 95% CI: 1.94 [1.52 to 2.47] p <0.0001). New and/or enlarging T2-hyperintense lesions: In the pooled ITT population of Studies EFC16033 and EFC16034 (RMS studies), the adjusted mean number of new and/or enlarging T2-hyperintense lesions per year was similar in the tolebrutinib group as compared to the teriflunomide group (relative risk, 95% CI: 1.12 [0.95 to 1.31]; p=0.1893).

Additional *post hoc* sensitivity analysis (without imputation) excluding any participants with an adjudicated relapse during study from the analysis set: In the subset of the pooled ITT population with no adjudicated relapse during the study (N=710 tolebrutinib and N=736 teriflunomide) 48 (6.8%) subjects in the tolebrutinib group and 68 (9.2%) in the teriflunomide group had a 6-month CDW [HR of 0.716 (95% CI: 0.495 to 1.036) p = 0.0765]), representing a 28% risk reduction of 6-momth CDW in favour of tolebrutinib.

5.3.7. Patient experience data (PED)

EMA has invited **European Multiple Sclerosis Platform (EMSP)** to share patients' perspectives on behalf of its patient/carer members. Their response is included below:

There is an urgent need for treatments that effectively slow or halt MS progression, particularly in progressive forms such as PPMS and SPMS, where current options are limited. A brain-penetrating BTKi offers promise by targeting both inflammatory and neurodegenerative processes across the

blood-brain barrier, showing potential to significantly reduce disability accumulation. However, ensuring safety remains critical, and both short- and long-term side effects must be carefully monitored. Establishing a patient registry is essential to track long-term outcomes and improve safety surveillance. Given the lack of effective therapies for relapsing-remitting SPMS *(CHMP's comment: It is assumed that non-relapsing is meant),* this new treatment represents a valuable opportunity to address an important gap. Patients with progressive MS, who often feel overlooked, urgently seek treatments that prevent further decline without exacerbating symptoms like fatigue or cognitive impairment. Making such therapies available should be a priority to meet these unmet needs and improve patient quality of life.

5.3.8. Healthcare professional engagement

EMA has invited the **European Committee for Treatment and Research in Multiples Sclerosis (ECTRIMS)** to share perspectives on behalf of healthcare professionals' organisations.

Their views are summarised below.

Being able to stop or slow disability progression independent of relapse activity (PIRA) in patients with multiple sclerosis is a very relevant unmet need at present, particularly in those patients without concomitant radiological activity.

Tolebrutinib could be prescribed in patients non-relapsing secondary progressive multiple sclerosis without radiological activity, that are not covered under any indication. Of note that in the HERCULES trial, 12.5% of patients in the tolebrutinib arm, and 13.1% in the placebo arm, had Gd+ lesions at baseline. Hence, information on real impact on this group of patients is lacking. It is unclear whether the future indication will include non-relapsing SPMS patients without MRI activity.

What benefits you would hope for in new medicines; as well as what level of side-effects you would be considered manageable?

As mentioned above, a clear beneficial impact on PIRA is the major hope in any new medicine to be used in patients with multiple sclerosis. Excellent short-term tolerability coupled with an appropriate dosing scheme is needed, as existing drugs already provide a good balance of both. An acceptable and manageable impact on the immune system is required from any new medicine, as existing drugs already provide highly acceptable safety profiles with regards to immunosuppressive features.

The pursued indication is non-relapsing secondary progressive multiple sclerosis (SPMS). How is this subtype of multiple sclerosis diagnosed/defined in the clinical practice?

Abundant literature exists on the search for appropriately clinical and paraclinical tools to achieve a prompt and accurate diagnosis/definition of SPMS. Unfortunately, no consensus has been reached on the best approach to diagnose SPMS and, in most cases, such approaches involve a retrospective assessment of previous disease evolution.

In simple terms, non-relapsing SPMS is defined as a continuous worsening of disability independent of relapses and without recent relapses, but there is no consensus on how long a patient should be free of relapses to be defined as non-relapsing SPMS.

It is possible that patients with non-relapsing SPMS show asymptomatic new lesions on MRI scans (i.e., they are non-relapsing SPMS with active MRI).

Considerations for pregnant people/people of child-bearing potential, where applicable.

Multiple Sclerosis is a disease that affects predominantly women of childbearing age. Therefore, greater benefits and wider usability are expected from drugs that can be used in young women without

an impact on pregnancy and lactation. With regards to the pursued indication, SPMS tends to be more prevalent in older ages, with a lower female predominance.

Under the pursued indication tolebrutinib would be the only drug to be prescribed in non-relapsing SPMS without radiological activity (it is unclear whether those with MRI activity would be included or excluded in the future indication).

Of note that, in spite of abundant research, important difficulties exist in prospectively achieve an accurate diagnosis of SPMS.

During the procedure, **ECTRIMS** was further consulted to share perspectives on behalf of a healthcare professional organisation on the following four questions:

Background - Characterisation of the studied population

In 2013, the classic MS phenotypes (CIS, RRMS, PPMS, SPMS) were redefined to include considerations of two key aspects: (acute and focal) inflammatory activity and disease progression. Disease inflammatory activity is determined by clinical relapses and/or MRI activity (Gd+ lesions; new or unequivocally enlarging T2 lesions) assessed at least annually. Progression - i.e. accrual of disability independent of any relapse activity- should be measured by clinical evaluation and assessed at least annually in patients who have a progressive disease course (PPMS or SPMS). In short, a patient with SPMS could fall within four categories: active and with progression, active but without progression, inactive and with progression and inactive and without progression. To illustrate this classification, the article by Lublin[1] states a patient with SPMS who has gradually worsened and has Gd+ lesions on MRI would be classified as SPMS–active and progressing.

[1]The 2013 clinical course descriptors for multiple sclerosis: A clarification - PMC Defining the clinical course of multiple sclerosis

Question 1: The CHMP would like to understand how the SPMS phenotypes are diagnosed, monitored and treated in the clinical practice.

Summary of ECTRIMS Response:

ECTRIMS indicated that SPMS is diagnosed clinically and retrospectively, based on sustained disability worsening for at least 6 months independent of relapses. In clinical practice, SPMS is commonly described using two modifiers, that are activity (relapses and/or MRI evidence of new inflammatory lesions) and progression (ongoing disability worsening). In this framework, SPMS can be described as:

(1) SPMS with relapses (superimposed relapses), (2) SPMS without relapses but with MRI activity (e.g., new and/or enlarging T2 lesions and/or Gd+ lesions), (3) SPMS without relapses and without MRI activity (no new inflammatory lesions).

In the Lublin classification[1], groups (1) and (2) would be considered active SPMS (ongoing relapses and/or MRI activity), whereas group (3) would be non-active SPMS (no relapses and no MRI activity).

Monitoring is based on clinical and radiological assessment, including outcomes such as: relapse identification, EDSS evolution and appearance of new T2 lesions. Clinical follow-up tend to be annually or semi-annually, and radiological monitoring tends to occur annually or biennially.

People with relapsing SPMS (group 1), and people with non-relapsing SPMS AND evidence of MRI activity (group 2) are mostly eligible for ocrelizumab, cladribine and siponimod. Patients with non-relapsing SPMS **without** evidence of MRI activity (group 3) are not eligible for any treatment.

Question 2: The CHMP would like to understand how patients with SPMS without recent relapses are monitored in terms of MRI imaging in the clinical practice and to which extent the information on acute and focal inflammatory activity drives the therapeutic decision in this SPMS subpopulation.

Summary of ECTRIMS Response:

ECTRIMS stated that people with SPMS (either relapsing or not) are monitored clinically and by MRI.

Patients with recent inflammatory activity (either relapses or new MRI lesions) tend to have an increased frequency of clinical and MRI monitoring as compared to those without recent clinical or radiological activity, although this may show profound variations across centres.

Presence of acute and focal inflammation (defined as relapses or MRI activity) clearly drives therapeutic decisions in non-relapsing SPMS, as such patients will have a formal indication to start an approved therapy as mentioned above.

In general, if the SPMS without recent relapses is on DMT, the clinical and MRI follow-up visits are more regular and frequent than SPMS without relapses who are not on treatment, because the MRI scan is less likely to change management if there is no treatment plan.

ECTRIMS further noted that MRI activity may represent the only objective marker of treatable inflammation in non-relapsing SPMS and may lead to classification as active SPMS, with subsequent initiation, switch or escalation of DMT according to product characteristics, safety considerations and local eligibility rules.

Background - Interpretation of efficacy in the context of the mechanism of action

Acute and focal inflammatory activity together with compartmentalized inflammation cause neurodegeneration in multiple sclerosis. There is evidence that these mechanisms are present from the beginning in MS although the relative contribution to the overall disability accumulation varies throughout the disease course. In particular, compartmentalized inflammation is considered more relevant in the progressive phenotype. In 2013, Lublin consensus criteria[2] argued that *PPMS should remain a separate clinical course because of the absence of exacerbations prior to clinical progression, but it likely does not have pathophysiologically distinct features from relapsing forms of MS that have entered a progressive course (SPMS).* According to the new MC Donald 2024 criteria[3], a single, unified framework of diagnostic criteria should be used to diagnose relapsing and primary progressive MS. It is stated that *pathological and imaging studies have identified quantitative, not qualitative differences between the various clinical forms, suggesting that the disease course should be considered as a continuum*.

[2]The 2013 clinical course descriptors for multiple sclerosis: A clarification - PMC Defining the clinical course of multiple sclerosis

[3]Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria

Question 3

The CHMP would like to understand where the current evidence stands with respect to the considerations about MS being a continuum vs. disease with discrete subtypes.

Summary of ECTRIMS Response:

ECTRIMS considered that current evidence supports MS as a disease continuum rather than a set of discrete subtypes. Pathophysiological studies indicate that the mechanisms driving neurodegeneration—acute and focal inflammation alongside compartmentalized inflammation—are present from disease onset across phenotypes, with focal inflammation predominating earlier and compartmentalized inflammation becoming more prominent during progression. Importantly, imaging

and pathological studies show quantitative, not qualitative, differences between RRMS, SPMS, and PPMS, suggesting that all forms share a common underlying pathology.

This is also reflected in the 2024 McDonald revisions propose a unified diagnostic framework for both relapsing and primary progressive MS. These criteria recognize that disease progression occurs along a spectrum and that clinical manifestations reflect varying degrees of the same pathological processes rather than fundamentally distinct mechanisms.

For regulatory evaluation, this continuum model implies that therapies targeting inflammation and neurodegeneration may have benefits across all stages of MS. The magnitude of effect may vary depending on disease stage, but efficacy should be interpreted in the context of shared mechanisms rather than limited to specific clinically-driven subtypes. Overall, the current evidence supports a mechanism-based approach to treatment and a conceptualization of MS as a single disease with a spectrum of clinical manifestations. It is also important to understand that important heterogeneity exists across subjects in the contribution of such mechanisms to the clinical and radiological presentation.

Question 4

The CHMP would like to understand to which extent efficacy and safety results obtained for a disease modifying treatment can be extrapolated from one of the PMS populations to the other one (PPMS to SPMS and vice versa).

Summary of ECTRIMS Response:

ECTRIMS stated that efficacy outcomes in progressive MS are more likely to depend on the predominant pathogenic mechanisms and the level of baseline inflammatory activity in the enrolled population than on the nominal phenotype alone. *Post hoc* analyses of randomized clinical trials consistently support this, showing greater benefit from immunomodulatory therapies in patients with ongoing inflammatory activity. This mostly concerns current immunomodulatory approaches that target the peripheral immune system.

The differing results of the EUSPMS and NASPMS trials of interferon-beta-1b in SPMS were presented as classic example. While the European trial demonstrated a significant delay in confirmed disability progression, the North American study failed to replicate this effect. Such striking differences in efficacy outcomes can be traced to baseline characteristics: the EUSPMS cohort had a higher percentage of patients with relapses in the preceding two years, a higher mean number of relapses, and more Gd+ lesions at baseline compared to NASPMS. These differences suggest that the presence of active inflammation, rather than the nominal SPMS designation, drove treatment responsiveness. Direct extrapolation between SPMS and PPMS was considered limited, including because siponimod has shown efficacy in SPMS but has not been formally investigated in PPMS, whereas ocrelizumab has shown efficacy in PPMS but has not been specifically studied in SPMS populations without inflammatory activity.

ECTRIMS further noted that treatments primarily targeting peripheral immune mechanisms have generally not demonstrated meaningful efficacy in progressive disease in the absence of clinical or radiological activity, as illustrated by the natalizumab and fingolimod development programmes, whereas safety findings appear broadly consistent across SPMS and PPMS.

5.3.9. Overall discussion and conclusions on clinical efficacy

5.3.9.1. Discussion

Tolebrutinib (60 mg film-coated tablets) is intended as a disease modifying oral therapy for the treatment of MS.

The initially proposed indication was:

"CENRIFKI is a brain penetrant Bruton's tyrosine kinase inhibitor (BTKi) indicated for the treatment of non-relapsing secondary progressive multiple sclerosis (nrSPMS) in adults".

During the procedure, the statement "*a brain penetrant Bruton's tyrosine kinaser inhibitor (BTKi)*" was removed from the wording of the indication. Different wording of indications were discussed and the final agreed indication is "*Cenrifki is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (see section 5.1)".*

The applicant submitted one pivotal study (study EFC16645) in (nr)SPMS, two supportive phase 3 studies (studies EFC16033 and EFC16034) in RMS, one placebo-controlled, dose-finding phase 2b study (study DRI15928) in RMS and its ongoing long-term extension study (study LTS16004).

There are two additional phase 3 studies, i.e., a double-blind, placebo-controlled study EFC16035 in patients with PPMS and a long-term study LTS17043 including those patients previously enrolled in one of the aforementioned MS tolebrutinib studies (i.e., EFC16645, EFC16033 and EFC16034, LTS16004 and EFC16035) that were ongoing at the time of the initial MAA application. Meanwhile, during the procedure, the applicant provided on 14th December 2025 topline results of the phase 3 study EFC1035 (PERSEUS) conducted in PPMS.

Dose finding

Rationale for dose selection to be tested in study DRI15928

The investigated doses in study DRI15928 were selected taking non-clinical data and the BTK occupancy in human peripheral blood mononuclear cells *in vitro* into account (see also Clinical Pharmacology (PK/PD) and non-clinical sections).

In the single ascending dose/multiple ascending doses (SAD/MAD) study in healthy volunteers, the BTK occupancy was dose-dependently increased by ≥90 % at 4h after a single dose of 60 mg tolebrutinib or above and at day7 after repeated daily doses of 15 to 90mg tolebrutinib. More than 90% BTK occupancy was maintained at 24 h post single 60 mg tolebrutinib and returned towards low levels around 16% after one week following the last multiple 60 mg dose. These clinical data are corroborated by PK/PD modelling in rat and mouse splenocytes, which revealed >90% BTK occupancy at 6 h post oral tolebrutinib doses of 2 or 5 mg/kg, respectively (see non-clinical section). This high BTK occupancy correlated with average tolebrutinib plasma concentrations of 4.4 – 9.5 ng/ml in rats and 4.7 – 27 ng/ml in mice. In fact, the peak plasma level of tolebrutinib in RMS patients in study DRI15928 receiving the 60 mg dose is in the same range (15.9 ng/ml), hence, confirming the rationale for the dose selection. A dose range between 5 and 60 mg once daily has been set to provide the best chance of capturing the optimal dose for tolebrutinib in RMS. Overall, the rationale for dose selection for the dose finding study DRI15928 is plausible but with respect to higher doses also limited due to safety aspects (reference is made to section 5.4 Clinical safety).

One double-blind phase 2b study has been conducted:

Study DRI15928 was a phase 2b, double-blind, randomised, multi-center, placebo-controlled, cross-over study evaluating 4 doses of tolebrutinib in 130 subjects with RMS. The study served as a dose-

finding study based on MRI measures in patients with RMS to inform the Phase III programme. For details of the study, refer to section 5.3.1. of this report.

For data analysis in this study a model-based dose-response analysis was applied. Application of the MCP-Mod procedure to test for a dose response allowed to use a wider range of doses with more dose levels compared to a standard parallel group design. The MCP-model used baseline Gd+ lesions (presence or absence for new Gd+ lesions and the total number of Gd+ lesions) as covariate. The MCP-method used is overall endorsed.

The primary endpoint was met demonstrating a dose-response relationship for tolebrutinib as evidenced by a higher reduction in the number of new Gd+ brain lesions after 12 weeks of treatment detected by MRI with higher doses (60 mg vs 5 mg to 30 mg). Results regarding the first secondary endpoint, the number of new or enlarging T2 lesions at the end of 12 weeks, were in line with those obtained for the primary endpoint.

The final indication for tolebrutinib in the current MAA is "*SPMS without relapses in the last 2 years*", whereas the examined dose-response effects in phase IIb were based on markers of focal and acute inflammatory activity in subjects with high chance of showing an effect (i.e. predominantly RRMS patients, reference is made to the baseline characteristics). Although the study indicates at which dosages some effects on MS disease activity can be expected, effects on MRI outcome measurements in RRMS do not necessarily predict an effect on disability progression in SPMS. However, assessment of neurological function, i.e., worsening of disability does not provide useful information in the context of this short 12-week phase II trial. It is noted that there is no comparable validated MRI biomarker to predict clinical efficacy on disability progression. However, the pathophysiological mechanisms driving disease progression are likely to be conserved, at least in part, across all MS diagnostic phenotypes, supporting the hypothesis that the mechanism of action of the medicinal product could be effective in RMS, PPMS, and (nr)SPMS. In this regard, the chosen primary endpoint can be accepted, even if the duration of three months in relation to the assessment of the primary endpoint is not in line with the recommendations of the multiple sclerosis guideline for a longer duration of an exploratory trial in SPMS. Moreover, the approach to justify the 60 mg dose to be carried forward to phase III based on study DRI15928 regardless of MS subtype i.e. RMS, PPMS and (nr)SPMS had been agreed in the former scientific advice in 2020 (EMA/CHMP/SAWP/266275/2020) although it could not be excluded that higher doses than 60 mg once daily may achieve better efficacy. Study DRI15928 was a study in a patient population diagnosed with RMS and a diagnosis of nrSPMS or PPMS was an exclusion criterion. The selected dose for the pivotal Study EFC16645 was not based on a biological rational for the optimal dose in patients with (nr)SPMS specifically, but rather based on assumptions that the dose with established benefit-risk attributes in RMS would also be the optimal dose in progressive forms of MS. In other words, based on the study's concept including inclusion criteria and the chosen endpoints (i.e., reduction in new active brain MRI lesions), this proof-of-concept study is considered of most relevance for the efficacy of tolebrutinib on active acute inflammatory lesions and to define a dose for a corresponding patient population to be tested in phase III. Overall, effects needed subsequently be confirmed in phase III based on relevant endpoints for (nr)SPMS.

According to provided PK data (reference is made to section 5.2.2) food intake did alter the exposure of tolebrutinib, and this has also been described in the SmPC. However, at the time Study DRI15928 has been conducted, no specific instruction was given to take the IMP with food, although it was recommended to take it always under the same conditions. Data obtained from the study indicate that this recommendation was difficult to follow throughout the entire study. There was a significant number of missing recordings of mealtimes relative to IMP administration at study visits with PK sampling, i.e. fed status was properly documented only in 35% (135/389) of the total visits with collection of meal status. 60% (78/130) of participants had at least 1 documented visit and of these 78

participants, the intake of the IMP with or without food was adequately balanced across the different dosage arms

The dosing regimen, 60 mg tolebrutinib orally once daily, that has been evaluated in phase II and was further used in the pivotal study is reflected in the labelled dose regimen of the Product Information. These results were supported by food-effect studies (reference is made to section 5.2). According to these studies, tolebrutinib must be taken with food, which is also described in the SmPC.

Study LTS16004 is an ongoing phase 2 long-term, follow-up study to assess the safety and efficacy of tolebrutinib. Participants who completed treatment in the previous study DRI15928 were eligible for enrolment. For details of the study, see section 5.3.5.3. of this report.

Analyses are primarily descriptive summaries of parameters by visit. ARR is estimated using a negative binomial model. All efficacy endpoints in this study are secondary or tertiary/exploratory endpoints.

Of the 129 subjects who completed study DRI15928, a total of 125 subjects received tolebrutinib treatment in the extension study. By the cut-off date, 96 participants were still receiving study intervention, and 28 participants prematurely discontinued the study intervention. As of the cut-off date, 117 (93.6%) participants were treated for at least 2 years (>96 weeks) and 105 (84.0%) for at least 3 years (>144 weeks).

Although the study was blinded with regard to dose in study Part A, the results of the extension study nevertheless need to be interpreted with caution, as all participants received tolebrutinib during this study. Further, blinded efficacy endpoints for the extension part were not formally defined in the Statistically Analysis Plan. Taking these limitations into consideration, results of the extension study appear indicative of maintenance of effect with regard to the reduction in the number of new Gd+ lesions, new or enlarging hyperintense T2 hyperintense lesions and total number of Gd+ lesions with an ARR of 0.25 during the treatment with 60 mg daily dose, and stable disability status. Separation for the 60/60 mg dose group from the lower dosages based on MRI derived endpoints was not clearly demonstrated in the ongoing extension study.

Pivotal phase 3 study EFC16645

Methodology

The single pivotal phase 3 study was a randomised, double-blind, placebo-controlled, two-arm, parallel-group, multicentre, event-driven [(based on 6-month CDP] study with a variable treatment duration to evaluate the efficacy and safety of tolebrutinib in participants with nrSPMS. For details of the study, see section 5.3.2.1. of this report.

The chosen placebo control is considered appropriate since no drug is currently approved for the treatment of patients with (non-relapsing) SPMS or for SPMS patients with low or absent clinical or MRI activity. It is worth mentioning, that in the EU, only Mayzent (Siponimod) and Betaferon (interferon beta-1b) are specifically indicated for SPMS with disease activity. Further, there are several medicinal products for the treatment of relapsing forms of multiple sclerosis with active disease which can be used for the the treatment of SPMS with relapses. However, these products were not appropriate comparators for the tolebrutinib trial, in which the absence of active disease as evidenced by relapses (i.e., absence of clinical relapses for at least 24 months) was defined as an inclusion criterion.

While the primary analysis was event-driven, all subjects were followed in the study until the common study end, which occurred when 288 events of 6 months confirmed disability progression (CDP, primary endpoint) were observed. Considering the long treatment period of an estimated mean duration of 33 to 36 months of double-blind treatment, challenges with adherence of subjects might be expected. The use of placebo as comparator for such long duration in patients who according to the underlying disease pathology might further progress also bears the risk that subjects may not be

willing to enter the study. The possibility to switch to open-label tolebrutinib treatment or to another DMT (if available for nrSPMS in their country) in case of disease progression (6-month CDP) is therefore supported.

Overall, the study design of the single pivotal study is considered adequate for the finally agreed indication.

Key inclusion criteria encompassed a previous diagnosis of RRMS in line with the 2017 revised McDonald criteria and a current diagnosis of SPMS in accordance with the clinical course criteria revised in 2013 (Lublin, 2014). According to Lublin, SPMS is usually diagnosed retrospectively and is characterised by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course. Included subjects were defined to be 18 to 60 years of age and had an EDSS score at screening from 3.0 to 6.5 points, inclusive. Patients must have had documented evidence of disability progression observed during the 12 months before screening and should not have had clinical relapses for at least 24 months. The 2 years relapse-free period appears adequate for a patient population with a low likelihood of relapses also during treatment.

The inclusion criterion for the pivotal study limited enrolment to patients under 60 years of age at baseline. The applicant´s argumentation to limit the upper age to 60 years to reduce confounding neurological conditions prevalent in older individuals (e.g., degenerative pathology of the spine, vascular disorders, other neurodegenerative processes) is considered acceptable. However, since participants were further enrolled in the long-term study, some may be 65 years old at the day of the evaluation. During the procedure the applicant stated that based on descriptive statistics on observed PK concentrations, no dose adjustment is required for subjects aged 65 years and above. This has been implemented in the SmPC.

Regarding disease activity based on radiological activity, no limitations were defined for the study. Thus, SPMS patients with certain activity based on MRI - month or weeks before, baseline status inclusive – could be enrolled into the study. Overall, a total of 12,7 % of participants (142/1131) had Gd+ lesions at baseline.

The allowed baseline EDSS score from 3.0 to 6.5 points inclusive, spans from patients with a moderate disability (but still fully ambulatory) to an advanced disability population, characterised by the need for bilateral walking aids with an ability to walk 20 meters without resting. Although the EDSS is still the most frequently used assessment tool for defining disability, it also has some limitations, e.g. focusing on ambulation and physical disability, while upper limb function or cognition are not sufficiently considered. However, these aspects are also relevant for patients with SPMS, e.g. patients with SPMS have more frequent and more severe cognitive impairment than subjects with RRMS (Brochet, 2022).

In principle, any increase in EDSS score was considered sufficient to confirm the requested evidence of disability progression observed during the 12 months before screening. Eligibility was analysed by an Adjudication Committee before randomisation consisting of MS experts who evaluated anonymised data of participants to endorse the (nr)SPMS diagnosis and confirm disability progression during the last 12 months and absence of clinical relapses for at least 24 months. Documented evidence of EDSS progression prior to study entry was defined as follows: in case, no documentation on increased EDSS scores was available, further modalities to justify disability progression, e.g. disability progression explained by a functional systems assessment or objective neurologic findings were to be used for proof of eligibility. Annually determination of progression by history or objective measures in progressive disease courses (PPMS or SPMS) is in line with the criteria proposed by Lublin (Lublin, 2014). Overall, the chosen pragmatic definition of disability progression is generally considered acceptable. Upon request, the applicant clarified that out of the 1131 enrolled subjects, 547 were included based on documented increase (any increase) in EDSS score in the previous year and 578

were included due to documented evidence of disability progression other than EDSS score increase, i.e. based on other functional domains mainly indicative of walking impairment, mostly representing gait/motor (96%) or coordination/balance problems (81%). Of these 578 subjects, there were a small number of 58 (10%) participants with a less well-defined functional systems assessment of "progression detected by other MS functional scale". Despite the overall high number of subjects included based on evidence of disability progression other than a documented EDSS score increase, progression of disability in the last year had to be confirmed by the Independent Adjudication Committee and therefore, the included patient population is considered adequate to represent a progressing SPMS population. With regard to the chosen definition for on-study disability progression (i.e., EDSS score ≥ 1.0 point from baseline when the baseline score was ≤ 5.0, or ≥ 0.5 points from baseline when the baseline EDSS score was > 5.0), that with respect to the chosen cut-offs for worsening differs from those recommended in the EMA MS guideline but however has been properly defined in the clinical study protocol, the applicant could demonstrate that, based on a sensitivity analyses, there were no significant differences in effects compared to the definitions described in the MS guideline (i.e., increase ≥ 1.0 point from baseline when the baseline score is ≤ 5.5, or ≥ 0.5 points from baseline when the baseline score is > 5.5). In this context the applicant also argued that the later definitions are more driven by reproducibility data than by clinical relevance data (van Munster, 2017). Moreover, they already have been used to define disability progression in former MS clinical trials.

Subjects could be MS-treatment naïve or could have had received prior DMT with an appropriate defined wash-out period. Exclusion of systemic corticosteroid treatment only pertained to the last month prior to screening MRI.

While several of the inclusion criteria are in line with those selected for the definition of SPMS e.g. in the siponimod study (e.g. age range, baseline EDSS scores or no restriction with respect to MRI activity), it is noted that there were other criteria that significantly differed, e.g., with respect to relapse history and disability progression based on EDSS: - documented evidence of disability progression observed during the 12 months before screening (24 months for siponimod); - absence of clinical relapses for at least 24 months (3 months for siponimod) (reference is made to the EPAR of Mayzent).

However, diagnosing SPMS is generally considered challenging and as highlighted by the input of the healthcare providers (see section 5.3.8) is made retrospectively as there are no established clinical, imaging, immunological, or pathological criteria that clearly define the progression. According to Brieva (Brieva, 2025) the definition of SPMS described by Lorscheider (Lorscheider, 2016) is currently the most widely used to identify SPMS that includes a disability progression by 1 EDSS step in patients with EDSS ≤5.5 or 0.5 EDSS steps in patients with EDSS ≥6 in the absence of a relapse, a minimum EDSS score of 4.0 and Pyramidal Functional System score of 2 and confirmed progression over at least 3 months. Brieva states, this definition does not capture all patients transitioning to SPMS, as some may experience a progressive course without reaching the specified EDSS threshold. In this context it is noted that some national consensus supports identification of progression without setting a specific minimum EDSS score (Ciron, 2022).

Overall, the inclusion criteria of the pivotal study appear adequate to evaluate a patient population with SPMS without relapses.

Measures to reduce bias in the efficacy assessment, i.e. standardised procedures to be followed by trained and certified staff, were in place. The Relapse Adjudication Committee evaluated all suspected relapses reported during the study using blinded data. Relapses, as adjudicated by the committee, had to meet protocol-defined criteria. While blinding processes overall appear acceptable, potential development of thrombocytopenia, increased liver enzymes and also temporary treatment interruptions and/or increases in scheduled visits due to adverse events, carry the risk of unblinding.

The study site personnel who collected the primary and secondary efficacy data such as data from functional tests and MRI was different from the personnel who reviewed subjects' safety results. Moreover, safety results were not to be shared with the personnel responsible for the functional tests and MRI. Blinding has sufficiently been maintained during the study and was not affected by the safety profile, e.g. in case of elevated liver enzymes.

Randomisation was stratified by age at screening (>40 versus ≤40 years) and geographic region (US versus non-US). Randomisation was not stratified according to disease focal acute inflammatory activity as recommended by CHMP scientific advice (EMEA/H/SA/4302/1/2019/II), even though analyses for subgroups defined by disease activity at baseline were conducted. This is considered a design deficiency but does not appear to have a relevant influence on the interpretation of the results.

Tolebrutinib (60 mg) or placebo once daily was administered as film-coated tablets under fed conditions with consistent meals throughout the study whenever possible.

Short-term use (3 to 5 days) of glucocorticoids (e.g., for MS relapse treatment or an acute illness) and local corticosteroids (e.g., topical, nasal, ocular, otic, intra-articular) were allowed. In the case of MS relapse, treatments were allowed as per local routine practice (e.g., high dose IV methylprednisolone for 3 to 5 days). Medications for treatment of MS symptoms (e.g., walking impairment, fatigue, spasticity, incontinence, pain) had to be maintained at a stable dose prior to screening and for the duration of the treatment period, if clinically feasible.

Endpoints, trial objectives and estimands

The primary endpoint was the time to 6-m CDP in patients with (nr)SPMS. It was defined as an increase on the EDSS score of ≥ 1.0 point from the baseline EDSS score when the baseline score was ≤ 5.0, or an increase of ≥ 0.5 point from the baseline EDSS score when the baseline score was > 5.0 sustained for 6 months. These cut-offs for worsening in the EDSS score differ from those recommended in the EMA MS Guideline but are acceptable as discussed above.

Prevention or delaying the accumulation of permanent disability is a relevant goal of treatment of patients with SPMS. The primary endpoint, time to 6-m CDP, is therefore considered appropriate and in line with Guideline recommendations.

In the pivotal study the confirmation of disability progression relied on the PIRA concept, i.e., confirmation of disability accumulation independently of relapse activity. PIRA relied on the following criteria: Only EDSS assessments measured more than 90 days after the onset of an adjudicated relapse, if present, were used to determine onset of disability progression. In addition, for the purpose of confirmation, only EDSS scores measured more than 90 days after the onset of an adjudicated relapse, if present, were used. In case of such MS relapse, the next quarterly EDSS assessment > 90 days after relapse onset was used for CDP confirmation. The minimum increase in score required for progression must have been maintained for any non-confirmatory (i.e., intervening) EDSS assessment(s) between the initial onset of CDP and confirmation EDSS scores. In sum, PIRA is a clinical concept that represents insidious disability accrual not influenced by relapses, including preceding, concurrent, and succeeding relapses. The underlying mechanisms of PIRA are thought to be mainly chronic inflammation and neurodegeneration, more pronounced in progressive MS, but also present in RMS (Ciccarelli, 2024), however, there are various definitions of PIRA. Based on the outcome of the Phase II trial DRI15928, tolebrutinib can be expected to be efficacious for the treatment of RMS patients based on MRI imaging endpoints. It is therefore assumed that tolebrutinib also affects relapse activity, consequently also reducing disability accumulation associated with relapses, relapse associated worsening (RAW). For the purpose of this trial intended to demonstrate a treatment effect of tolebrutinib on disability progression independent of an effect on relapses, the chosen approach to evaluate disability progression is supported.

As stated in Ciccarelli *et al* the current definition of PIRA assumes that acute inflammation, which can manifest as a relapse, and neurodegeneration, manifesting as progressive disability accrual, can be disentangled by introducing specific time windows between the onset of relapses and the observed increase in disability. Instead, the PIRMA concept, i.e. progression independent of relapses and brain and spinal cord MRI focal acute inflammatory activity, would have been more useful to gaining insights into disability progression independent of acute and focal inflammatory activity, i.e. regardless of clinical relapses and activity based on MRI acute inflammatory lesions. However, basic MRI assessments in parallel to the EDSS scores evaluated for the assessment of sustained disability progression have not been pre-defined. Therefore, correlation of disability progression independent of acute inflammatory MRI activity was not possible. Accordingly, it is not possible to conclude that the effect on disability progression is due to the effect of tolebrutinib on the chronic neuroinflammation.

Further, the pre-specified subgroup analyses on MRI activity based on Gd+ lesions at baseline (present, absent) are useful to more specifically characterise the obtained effect of tolebrutinib in at baseline non-relapsing SPMS subjects, i.e., with and without focal acute inflammatory activity.

There was both a Basic- and an Expanded MRI protocol. The Basic MRI sequences was performed at all sites and consist of T2- and T1-weighted sequences before and after administering a Gd-contrast agent. An Expanded MRI protocol was conducted at selected sites using additional MRI sequences such as MTR (all centres) and SWI, (subset of centres with capacity of 3T MRI). A blinded MRI central review was performed for all MRI-derived endpoints.

Six secondary endpoints were defined to be tested following a hierarchical testing procedure: the time to onset of 3-month CDP; the total number of new and/or enlarging T2 hyperintense lesions as detected by MRI; the time to onset of sustained 20% increase in the 9-HPT for at least 3 months; the time to onset of sustained 20% increase in the T25-FW for at least 3 months, the time to onset of CDI defined as a ≥1.0 point decrease on the EDSS score from baseline confirmed over at least 6 months and the percent change in brain volume loss as detected by MRI at the EOS compared to Month 6.

The number of new and/or enlarging T2 hyperintense lesions indicates focal and acute inflammatory activity.

The T25FW, 9HPT and the SDMT as single variable or in combination with each other were included as secondary endpoints in comparison to functional scales for measurement of disability:

The T25W (also part of the Multiple Sclerosis Functional Composite (MSFC)) is capable of detecting changes in ambulation, specifically walking speed, and any lack of further deterioration on the T25W or even improvement in time to perform this test is valuable in patients with MS. However, the T25FW is not universally applicable across the MS spectrum, as it might have ceiling effects for those patients with an EDSS score above 6.5 (i.e. not able to walk 25 feet; Motl et al. 2017).

Upper limb function is often affected in subjects with progressive MS. The 9-HPT measures capacity of upper limb function, is objective and the most frequently test used in clinical trials and practice for measuring upper limb function.

Worsening on the =T25FWT (walking) and the 9HPT (hand dexterity) as secondary endpoints was defined as an increase of ≥ 20% compared to baseline. The results of literature reviews indicate that a 20% change in T25FW performance represents a meaningful change in walking performance in MS. The 20% threshold for 9HPT is less clear, however it has been often used in clinical trials in MS (i.e. natalizumab in SPMS (Kapoor et al 2018), fingolimod in PPMS (Lublin et al 2016), ocrelizumab in PPMS (Montalban et al 2017).

The loss of neurons and glial cells presents a progressive loss of brain volume across the different MS subtypes but the impact is thought to be especially relevant in SPMS where diffuse neurodegeneration

plays a more prominent pathophysiological role (Lassmann, 2018). Brain volume loss is a slow process that develops over years to decades (Koch, 2022). However, the assessment of changes in brain volume in this trial is endorsed.

The study further addressed the need for cognitive outcome measures (secondary endpoints) as stipulated by the MS guideline. 55%-86% of patients with SPMS are affected by cognitive deficits (Mistri, 2022). Cognitive function was tested with the oral version of the SDMT. The SDMT is considered a valid measure of processing speed, however, it does not measure other aspects of cognitive function. While speed of information processing is important for cognitive function, it is not clear whether it sufficiently covers cognitive function in multiple sclerosis. Aspects of memory and learning are also important. Therefore, the additional use of the CLVT-II is endorsed since CVLT-II also includes other cognitive aspects, e.g., visuoperception (EMEA/H/SA/4302/2/2020/III).

Patient-reported outcomes to measure quality of life, i.e., MSQoL-45 (secondary endpoint) and EQ-5D-5L (tertiary endpoint) are appropriate.

The choice of the secondary endpoints is overall supported. However, the current MS guideline also recommends the assessment of clinical global impression of change as a secondary endpoint. Unfortunately, no such endpoint was defined although recommended during Scientific Advice.

Further tertiary and exploratory efficacy endpoints comprised clinical outcomes.

In the MS guideline, the MSFC as a whole testing battery is proposed as a secondary endpoint measure to fill the gap of deficiencies known for the EDSS (i.e. assessing upper limb function and cognitive deficits). In this study it has been evaluated as tertiary/exploratory endpoint.

The primary objective of study EFC16645 was to determine the efficacy of tolebrutinib compared to placebo in delaying disability progression in nrSPMS. The corresponding endpoint was time to onset of 6-month CDP. Comparison was made of the tolebrutinib group to the placebo group, with the hypothesis that there is superiority of tolebrutinib over placebo on the primary endpoint.

The estimand of the primary endpoint referred to the treatment policy strategy with respect to the ICE treatment discontinuation, i.e. the effect regardless of discontinuation. Other ICE than treatment discontinuation as death or switch to another treatment, i.e., change to OL tolebrutinib treatment or change in background medication were not considered. Death was considered to be an event without precisely specifying death as an ICE to be treated by a composite estimand strategy. It is acknowledged that as per the instructions for measuring EDSS, death due to MS implies an EDSS of 10. Thus, it is acceptable. All other potential ICEs not considered by the applicant were hence implicitly be handled by a treatment policy strategy. Estimands were not defined for secondary or tertiary endpoints. The applicant confirmed that the implicit estimand strategy for the 3-month CDP is in accordance to that used for the time to 6-month CDP. Regarding the secondary endpoint "number of new and/or enlarging T2 lesions", a negative binomial model was chosen. The analysis model includes the total lesion count across all MRI scans at all scheduled post-randomisation visits.

Statistical methods

The ITT population was defined to be the primary efficacy population. The ITT analysis set used for the primary efficacy analysis consisted of all patients, using all available efficacy assessments irrespective of the treatment received. Efficacy data collected while patients were receiving treatment other than the originally assigned (open-label tolebrutinib or other MS treatment) were also included in the primary analysis. However, planned treatment switches to open-label tolebrutinib or other disease modifying MS treatments were only allowed after 6-m CDP and therefore did not influence 3-month and 6-month CDP analyses.

Analysis of the ***primary efficacy endpoint***

The time to onset of 6-month CDP was analysed by a Cox proportional hazards model with terms for intervention group, age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline Gd+ lesions (0, ≥1). The HR, its 95% CI and the p-value for comparing tolebrutinib to placebo were estimated from this model. A log-rank test stratified by age at screening (>40, ≤40 years) and geographic region (US, non-US) was also used to compare tolebrutinib to placebo. To include all participants in the analysis, the baseline Gd+ lesion (presence or absence) was imputed for a few participants with a missing baseline count.

The following *sensitivity analyses*, without any imputation, were performed to evaluate the impact of missing data on the results of the main analytical approach to the primary analysis: Participants with a potential onset of disability progression but without 6-month confirmation due to missing data, regardless of reason, were considered to have confirmed progression with the time to onset being the time to the initial EDSS increase. Of note, a potential onset is invalidated if there is any non-confirmatory EDSS in the confirmation period that does not meet the minimum change required for progression; participants with missing or incomplete 6-month CDP were treated as censored at the last EDSS assessment date.

For the above analyses, the same Cox proportional hazards model as described for the primary endpoint were performed without imputation.

An additional *post hoc sensitivity analysis* for 6-month CDP was performed where all participants with at least one adjudicated relapse during the study were excluded from the analysis set. The same statistical analysis methods as for the primary analysis were utilised but without imputation.

Analyses of ***secondary endpoints***

Time to onset of 3-month CDP, 3-month sustained increase in T25-FW and 9-HPT, and 6-month CDI were analysed using similar methods as for the primary endpoint, but without imputation.

Continuous efficacy endpoints (percent change in brain volume, change in cognitive function, and change in MSQoL-54 at EOS) were analysed using a mixed model repeated measures approach in the ITT population. The model included change/percent change values for the respective endpoint at each scheduled visit as response variables, and treatment, age at screening (>40, ≤40 years), geographic region (US, non-US), visit, treatment by-visit interaction, baseline value for the endpoint being assessed and baseline value-by-visit interaction as covariates. For brain volume change, the Month 6 value serves as the reference value rather than baseline.

Categorical efficacy endpoints with count data (new and/or enlarging T2 hyperintense over the study period after baseline) were analysed using a negative binomial regression model in the ITT population. The model included the total count of lesions across all scheduled MRI scans during the study period as the response variable, with treatment group, age at screening (>40, ≤40 years), geographic region (US, non-US), baseline EDSS score, and baseline T2 lesion count as covariates. Log-transformed time from screening MRI to the last available scheduled MRI scan was the offset variable.

Missing data were not replaced for the secondary endpoint "number of new and/or enlarging T2 lesions". Upon request, the applicant provided sensitivity analyses using missing not at random-based imputations supporting robustness of results.

To control the Type 1 error rate for the study, a hierarchical testing procedure was applied at a 2-sided 5% significance level. If statistical significance was achieved for the primary endpoint, a selected set of secondary endpoints were tested using a pre-specified hierarchical testing order.

The original study protocol was dated 28 February 2020. The study protocol was revised multiple times throughout the study, i.e. 10 global amendments, with the most notable changes referring to liver enzyme elevation (e.g., update of liver related exclusion criteria or liver function monitoring requirements to mitigate the risk of DILI, starting with protocol amendment 6 (dated 23 May 2022). Overall, protocol changes with respect to potential relevance on efficacy were performed before the first participant was enrolled, thus, protocol amendments overall are not considered to have any relevant impact on the outcome of efficacy.

Participants who interrupted the study intervention due to the partial hold (within first 60 days) but remained in trial, could reinitiate the study intervention, and this might have affected blinding of these subjects and the corresponding investigators. The applicant clarified that the partial hold did only affect participants in the United States. Only 11 participants were put on hold due to being on study treatment for less than 60 days: 7 were treated with tolebrutinib and 4 were treated with placebo. Blinding was maintained for these participants and their Investigators. Regardless, due to the very limited number impact of these interruptions is negligible.

Efficacy data and additional analyses

Patient disposition

The date first participant enrolled was 24 September 2020 and the date last participant completed was 29 August 2024. A total of 1131 screened participants were enrolled and randomised as follows: 754 to tolebrutinib and 377 to placebo. Overall, 869 (76.8%) participants completed the study: 580 (76.9%) participants in the tolebrutinib arm and 289 (76.7%) participants in the placebo arm. Overall, the discontinuation rate of 23% (262 subjects) was not insignificant.

626 (55.3%) participants completed the DB study period: 434 participants in the tolebrutinib group (57.6% of those randomised) and 192 in the placebo group (50.9% of those randomised). 501 (44.3%) participants discontinued permanently double-blind treatment: 318 participants in the tolebrutinib group (42.2% of those randomised) and 183 in the placebo group (48.5% of those randomised). Overall, the number of subjects who discontinued prematurely DB treatment was high, but not unexpected in the context of the studied patient population. In addition, the primary endpoint used a treatment policy strategy considering data after treatment discontinuation: discontinuation of DB treatment was considered an ICE and occurred in 42% of the tolebrutinib and 48% patients. Apparently, a part of these treatment discontinuations occurred before the primary endpoint event. Also, due to the application of a treatment policy strategy and the lower proportion in the active treatment group the large number of treatment discontinuation does not appear to be a major issue.

The most frequently reported reason for permanent DB study intervention discontinuation was "progressive disease" [116 (15.4%) in the tolebrutinib group and 76 (20.2%) in the placebo group]. There were 16.2% and 17.8% subjects who did not completed the DP phase in the tolebrutinib and placebo arms, respectively due to reason "withdrawal by participant" with the occurrence of "adverse events", "study procedure" and "other" designated as potential (sub)reasons. There were ten participants in the tolebrutinib group and 12 in the placebo group who switched over to another DMT after study intervention discontinuation due to the reasons "withdrawal by participant, other" or "other" reason. Overall, these switches are not considered to have impacted the efficacy results in favour of tolebrutinib.

Participants with progressive disease (6-month CDP) were given the option to switch to OL tolebrutinib or to switch to some other marketed treatment if available. 196 participants switched over to OL tolebrutinib treatment: 120 (15.9%) participants in the tolebrutinib group and 76 (20.2%) in the placebo group, including 5 participants from the DB tolebrutinib group without disability progression but who erroneously switched to OL treatment. The low number of patients that switched to OL

treatment without 6-month CDP was treated as non-censored at the time of switch and was censored at the last available EDSS assessment. A sensitivity analysis censoring these patients at time of switching was provided with essentially identical results.

The percentage of participants who permanently discontinued OL study intervention was similar between the tolebrutinib/tolebrutinib and placebo/tolebrutinib groups (25 and 9 subjects, 3.3% and 2.4%, respectively). All randomised subjects were analysed for the primary outcome: 754 participants in the tolebrutinib group and 377 participants in the placebo group (including those subjects, who started the DB study intervention period on tolebrutinib or placebo but switched over to OL tolebrutinib).

Overall, 100 subjects have been treated during the study with systemic corticosteroids due to relapses, i.e., 34 (9.0%) in the placebo group and 66 (8.8%) under tolebrutinib treatment. Four participants in each treatment group switched to another DMT after 6-month CDP. The number of participants taking a DMT after study intervention discontinuation is around 14 in the tolebrutinib group and 9 in the placebo group. Some medications were considered post study intervention start but are likely prior due to incomplete dates (reporting issue), and others reflected periods of treatment during the FDA clinical hold.

Demographics and disease characteristics including MRI parameters and prior DMT were adequately balanced across the two groups and representative for a SPMS population.

In line with the intended patient population, the study targeted an overall older MS population as evidenced by a mean age of 48.9 years (range: 20 to 60 years). Most participants had a history of prior DMT, i.e., 535 (47.3%) participants used ≥2 prior DMTs and 302 (26.7%) participants used 1 prior DMT. 294 (26.0%) of all participants did not receive MS DMT at any time prior to baseline, which is in accordance with other SPMS trial populations (i.e. 23% in the ASCEND trial). The most used prior DMTs were interferon beta-1a (31.8%), glatiramer acetate (23.8) and interferon beta-1b (19.2%) in both intervention groups. Exclusion of systemic corticosteroid treatment only covered the last month prior to screening MRI while systemic corticosteroid use in the 2 years prior randomisation only occurred in a small number of participants that was balanced across the treatment groups, i.e. 19 (5.0%) and 33 (4.4%) in the placebo and the tolebrutinib group, respectively. In this context, the applicant clarified that the most common reason for systemic corticosteroid-use was due to MS, i.e. 15 (4.0%) and 21 (2.8%) in the placebo and the tolebrutinib group, respectively, excluding treatment of relapses.

According to clinical course criteria revised in 2013, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course. With respect to the provided baseline disease characteristics, subjects had a median time since first RRMS symptoms of about 16.15 years (min: 1.0, max: 43.9) and of about 5.487 years (min: 0.00, 41.33) since SPMS diagnosis. There were 3 participants in Study EFC16645 for which RRMS symptom onset has erroneously been estimated to be ≤1 year from the screening date as in reference to a review of the eCRF and the eligibility adjudication checklist, for these participants the applicant could justify a longer MS history than the one documented in the eCRF. Further, the applicant clarified that in reference to the study's inclusion criteria, the (nr)SPMS eligibility adjudication criteria have been fulfilled by all participants, including the 158 subjects with SPMS diagnosis less than one year: since the requirement for disability progression included evidence of such within the year prior to randomisation but without a minimum time requirement at the respective disability level, i.e. disability progression while being SPMS, participants with an SPMS diagnosis <1 year were also eligible to participate. Overall, it is considered that subjects with SPMS had adequately been included into the study based on pre-defined inclusion criteria.

Inclusion criteria required an EDSS of 3.0 to 6.5 points, inclusive. The included SPMS population had rather advanced disability based on a mean EDSS baseline score of 5.53 (median EDSS score of 6.0). The proportion of participants with baseline EDSS >5.5 was 59.9%, indicating that the majority required assistance with ambulation at baseline. The mean time since the most recent relapse was 7.50 (min: 2.0, max: 36.0) years.

Baseline MRI disease characteristics indicate a low disease activity with Gd+ lesions being present in only 12.7 % of patients. The mean number of Gd+ lesions was generally low (0.5 (82.6)). Information regarding the number of GD+ lesions at baseline was missing for 4 subjects randomised to placebo and for 12 subjects randomised to tolebrutinib. In the SAP Version 3 a rule was defined on how to treat subjects with missing baseline Gd+ lesions (to be used as covariates). Due to the low number of subjects with missing baseline Gd+ lesions, a relevant impact was not expected. However, since according to the rule absence or presence was assigned randomly if not all non-missing postbaseline values for a participant are 0, the uncontrolled random attribution may be prone to bias if potential results could have been taken into account. Out of the 4 placebo and 12 tolebrutinib treated patients with missing amount of Gd+ lesions at baseline, 1 (PBO) and 7 (tolebrutinib) patients were randomly assigned as "absence". An analysis of the primary endpoint assigning "presence" for the single placebo patient and an analysis removing the covariate of baseline Gd+ lesions in the primary analysis yield basically identical results to the primary analysis.

To conclude, the studied patient population represented a SPMS population in a progressive disease stage, relapse-free (for at least 24 months) - but with some acute focal inflammatory MRI activity.

In this study, 22.6% (171/754 participants) in the tolebrutinib arm and 30.7% (116/377 subjects) in the placebo arm experienced a 6-month CDP based on the EDSS, resulting in a net difference of 8.1%. The study met its primary objective, based on the pre-specified primary analysis, e.g. the **primary endpoint**, time to 6-month CDP, was achieved when tolebrutinib was compared to placebo (HR 0.693 (95% CI: 0.546 to 0.880), p=0.0026), representing a 31% risk reduction of 6-month CDP in favour of tolebrutinib. The magnitude of the treatment effect is in the range of what was assumed as clinically relevant based on the sample size calculation to detect a 30% risk reduction in 6-month CDP with tolebrutinib compared to placebo.

The Kaplan-Meier curves of cumulative incidence rate for the onset of 6-month CDP showed a sustained effect with an early separation with a lower proportion of patients in the tolebrutinib group with 6-month CDP events throughout the treatment period. Based on Kaplan-Maier estimates the absolute treatment difference for subjects free of 6-month CDP was 5.1% at month 12 and reached 10.3% at month 48 in favour of tolebrutinib. Pre-specified sensitivity analyses were performed 1) without imputation and 2) assuming events for all sustained disability onsets, with or without confirmation, that were in line with the results received in the primary analysis.

However, given the challenges with respect to the diagnosis of SPMS in general and specifically with regard to the claimed indication, non-relapsing SPMS, namely 1) to identify an adequate patient population that has not only been relapse-free in the past but is expected to be also relapse-free in the future, and 2) to show a convincing treatment effect on disability progression independent of relapse activity, it is inevitable to also consider the existing MRI focal acute inflammatory activity (reference is made to subgroup analyses based on MRI focal acute inflammatory activity based on Gd+ lesions). Given these prerequisites and the limitations stated to be derived from these subgroup analyses, the claimed indication "nrSPMS" which does imply no disease activity was not sufficiently justified even though the ARR in the placebo group of the pivotal study was low (0.032).

It was agreed that the discrepancy between relapsing and non-relapsing course of disease has been considered relevant by the MS community across Europe and it has been used to characterise MS for decades. Mostly, because DMTs until recently have been limited to treatment of relapsing forms of MS. Overall, the depiction of the clinical spectrum of MS was supported.

As recently emphasised by Brownlee et al., 2025 *"there are calls for a disease classification linked to biological mechanisms that considers MS as a continuum with inflammation and neurodegeneration present at disease onset in all MS patients".* And further *"…there is increasing consensus that the pathophysiology of RRMS and PPMS share greater similarities than differences. Acute inflammatory demyelinating lesions on MRI (manifesting clinically as acute relapses* [in some cases]) *occur in PPMS, and neurodegeneration, the main determinant of clinical progression, reflected by brain atrophy, begins early in RRMS"*.

"The new 2024 McDonald criteria provide a unified approach for diagnosing multiple sclerosis in individuals with relapsing or progressive courses throughout the lifespan" and the "secondary progressive" terminology has been edited out (Montalban, 2025 (20)).

Overall, active/no-active SPMS are considered more useful terms than "relapsing SPMS"/"non-relapsing SPMS" to characterise a patient population in the context of an indication for a DMT. This approach is also supported by Ciccarelli O, 2024, who describes that *"MRI reflects the MS pathogenic mechanisms better than purely clinical descriptors."* *"…- the recent recommendation of characterizing MS based on disease-driving pathogenic mechanisms, rather than the traditional clinical descriptors".*

When taking the by Lublin (Lublin, 2020) revised clinical course descriptions of MS into account *active SPMS* is evidenced by imaging: (Gd+ lesions and/or new T2 lesions **or** at least one relapse while *inactive (or "non-active") SPMS* is defined by no Gd+ lesions and no new T2 lesions **and** no relapses.

Based on these criteria, the studied patient population consisted according to the current state of the individuals of both, active and non-active SPMS showing positive effects in both groups. According to the inclusion criteria for study EFC16645 patients had to be free of clinical relapses for two years but patients with acute focal inflammatory MRI lesions (i.e. Gd+ lesions) were included as discussed above.

It is well acknowledged that study EFC16645 included a patient population with generally low baseline disease activity: with respect to clinical activity, enrolled patients were SPMS patients without relapses in the 2 years prior to screening and also in the study, analyses assessing the adjusted annualised adjudicated relapse rate (evaluated as tertiary/exploratory endpoint) showed a very low on-study ARR in patients randomly assigned to placebo (0.032).

Regarding MRI inflammatory activity, characterisation of acute focal inflammatory disease activity per MRI was not included in the pre-requisites for study inclusion. However, the mean number of Gd+ lesions at baseline was generally low (0.5 (82.6)). While most of the participants did not have acute MRI based activity at baseline, only 142 (12.7%) participants showed Gd+ lesions at baseline (49 (13.1%) and 93 (12.5 %) in the placebo and the tolebrutinib treatment arm, respectively). During the study period, there was a slight increase of acute MRI based focal acute inflammatory disease activity with 96 (25.5%) and 144 (19.1%) of the subjects in the placebo and the tolebrutinib arm, respectively experiencing ≥ 1 new Gd+ lesion. It is worth mentioning that it was not possible to characterise the study population in terms of the appearance of new and/or enlarging FLAIR/T2 lesions at baseline or while on trial. The proportion of active SPMS patients within the overall study population might therefore have been underestimated and some patients in the non-active SPMS group might have been misclassified as inactive although being active.

While the individual patients' study duration was planned to be variable, the estimated mean treatment duration was 33 to 36 months of double-blind treatment.

In this context it is worth mentioning, that in the cohort study published by Pontieri the cumulative probability for an initially diagnosed nrSPMS patient (defined by a diagnosis of SPMS according to the treating physician and absence of relapses in the previous 2 years) after ~15 years since SPMS diagnosis to never relapse was 60.6%, whereas the cumulative probability to ever relapsing was 26.5%". Although patients with (clinically) nrSPMS rarely change their phenotype these findings confirm that MS patients could still relapse after several years of a relapse-free status.

Overall, on the basis of the applicant's provided arguments including the referenced literature, the definition and use of "nrSPMS" was still not justified to sufficiently characterise the entire study population (encompassing both, clinical course and current disease state) and consequently the applicant's intended target indication was not supported.

With regard to the *unmet medical need* the applicant justified the chosen study design for study EFC16645 to demonstrate an effect on disability progression that occurs independent of relapses; this is endorsed. It is further agreed with the applicant, that the obtained effects on disability progression on the basis of the chosen PIRA concept address the mechanism associated with disability progression in MS independent of relapses but not necessarily independent of acute focal inflammatory clinical disease activity.

However, as outlined above, an indication of "non-relapsing SPMS" could, from a pathophysiological perspective, be misinterpreted as if benefit was observed to those subjects being "non-active". While it is agreed with the applicant that *per se* the included subjects were free of clinical (relapse) activity, 12.7% of the included study population additionally showed Gd+ lesions at baseline, a marker of focal acute inflammatory activity, also clearly benefitting from treatment. According to the published literature (see Pontieri) it cannot be excluded, that several of these subjects would again relapse in future. Therefore, restricting the indication to an effect on disability progression solely in "nrSPMS" was also not supported/not considered reasonable from a clinical decision-making perspective. Moreover, the applicant admitted the effect on disability progression in those subjects with focal and acute inflammatory activity. This has also been supported by the findings described by the applicant, where based on *post hoc* analyses similar to the SPMS study EFC16645 also in the RMS studies EFC16033 and EFC16034 tolebrutinib showed an effect on the risk of disability accumulation associated with the proportion of PRL formation.

Moreover, restricting the indication to nrSPMS, which is associated with a "late/more advanced" disease stage, and excluding subjects from treatment at an active disease stage, which is associated with an earlier disease stage, would limit the possibility for timely treatment. Early treatment is necessary from the perspective of the scientific MS community.

To assess the homogeneity of the treatment effect across various subgroups, the following pre-defined subgroup analyses on the primary endpoint were performed:

Geographic region (US, non-US; Eastern Europe, Western Europe, North America, rest of the world [ROW]); age at screening (>40, ≤40 years); sex (Male or Female); race (White, Black or African American, Asian, Other); baseline Gd+ lesions (present, absent); baseline EDSS score (≤4.5, >4.5; ≤5.5, >5.5); prior disease modifying therapy use (0, 1, ≥2); duration since relapsing-remitting multiple sclerosis (RRMS) symptom onset (≤5, >5 to ≤10, >10 years) and adjudicated relapse during the study (yes, no).

Regarding subgroup analyses, the applicant claimed a cautious interpretation of subgroup analyses referring to the EMA Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013). This is generally agreed and also has been considered by CHMP in earlier assessment. As already stated earlier, despite differences in magnitude of the treatment effects obtained, results across the subgroups were overall consistent with results from the primary analysis, favouring tolebrutinib over placebo.

However, it remains worth mentioning, that for subgroups of baseline Gd+ lesions and for subgroups of prior DMT use a significant treatment-by-subgroup interaction has been shown. It is acknowledged that this interaction is quantitative in nature.

While a positive effect was observed for both subgroups according to *baseline Gd+ lesions* (absence and presence), tolebrutinib exhibited a more pronounced treatment effect in the subgroup of patients with MRI Gd+ lesions at study entry (baseline Gd+ lesions (risk reduction 65%, HR 0.35 [95% CI 0.183, 0.656])) as compared to subjects without Gd+ lesions (risk reduction 22%, HR 0.78 [95% CI 0.601, 1.006]) (the interaction p-value being 0.018).

As already mentioned, this difference needs to be interpreted in the context of the overall positive treatment effect obtained for the entire studied patient population. Moreover, it is acknowledged, that the respective subgroups were not the primary analysis population, and the study was not powered for these subgroups. However, as initially has been submitted, a *post hoc* analysis in *non-active* participants (i.e. no relapse in the 2 prior years and no Gd+ lesions at baseline in this study) for the time to onset of 6-month CDP using Cox Model (imputed data) has also been performed, obviously to fulfil the pre-defined requested evaluation of possible qualitative interactions in case of the observed quantitative treatment by subgroup interaction (p-value <0.1). Results showed a relative risk reduction of 23% (HR [95% CI]: 0.767 [0.593 to 0.992]; unadjusted p=0.0433) with borderline statistical significance while the corresponding subgroup analyses as described above showed similar results (HR of 0.78 [95% CI 0.601, 1.006]).

The applicant further argued against an additional benefit in patients with Gd+ lesions based on the results for younger age and on-study relapse (both no subgroup interaction) as well as non-significant effects on ARR and Gd+ lesions. However, as already discussed, since the subgroup with on-study relapse is defined by a post-randomisation event, treatment groups within each subgroup may not be comparable and no causal effect can be attributed to the treatment difference within the subgroup of patients with an adjudicated relapse during the study. According to the underlying mechanism of action tolebrutinib considered to also affect the probability of relapses it is not possible to estimate the effect outside relapses by studying patients without on-study relapses. Hence, the analysis cannot provide further evidence with respect to the treatment effect. This is in line with the EMA Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) *Post-baseline covariates may be affected by treatment received and will not usually be appropriate to define subgroups for the investigation of a treatment effect.* With respect to the endpoint ARR, that has been assessed as tertiary/exploratory endpoint, no significant effect has been expected on the basis of the study's defined inclusion criteria with no relapses in the past 24-month prior study start. The same relates to the endpoint Gd+ lesions, both evaluated in a rather non-active study population.

In sum, despite taking the above discussed *post hoc* aspect of this analysis into consideration as a limitation, a positive effect has been shown for tolebrutinib in subjects with active SPMS and non-active SPMS, i.e. subjects without relapses but with/without Gd+ MRI lesions although the subgroup of active patients with Gd+ lesions showed better results and probably contributed substantially to the effect in the analysis of the primary endpoint, supporting at least a claim for SPMS patients without specific characterisation of MRI based disease activity at baseline.

It is noted that results for analyses for subgroups according to *prior disease modifying therapy* were generally in favour of tolebrutinib, even though better results were noted for those subjects being treatment naïve compared to those who have been treated with DMTs in the past. The applicant provided a justification why interpretation of these results is difficult, e.g., the existence of variability across regions, possible confounders known to correlate with the numbers of DMTs tried (e.g. age, disease duration or baseline disability status) as well as various caveats, e.g., the time when the treatment has been used or the types of DMTs in different regions including their availability.

Upon request, the applicant provided analyses correlating disability progression based on the PIRA concept to the proportion of baseline chronic active lesions, i.e. the PRL load (0 PRL vs 1-3 PRLs vs ≥4 PRLs), a potential marker of chronic and active inflammation, in the subset of patients with PRL assessment at baseline from the studies EFC16645 (tolebrutinib: n=288; placebo: n=149) and EFC16033/EFC16034 tolebrutinib: n=325; teriflunomide: n=306). The current evidence supports that the number of PRL lesions is a prognostic marker, results in the placebo arm also supports this notion: i.e. in the untreated patients, the proportion of patients with disability progression is also higher in those with larger number of baseline PRL lesions. At the same time, it should be recognised that the current data support that the number of PRL lesions at baseline may be a predictive marker of response. According to results, the efficacy of tolebrutinib is greater in those with baseline PRL. Comparing the proportion of events between the treated and untreated per group of markers, results support that efficacy of tolebrutinib appears to be greater in those with at least 4 PRL lesions at baseline. However, given the *post hoc* nature of these analyses- which were conducted in a subset of patients studied using SWI imaging and only performed at a subset of centres with capability of 3T MRI- these results should be interpreted with caution and no firm conclusion on a treatment effect of tolebrutinib on PRL can be drawn.

The mean plasma neurofilament light (p-NfL) concentrations at baseline were close to normal. Considering p-NfL as a marker of neuronal injury, the applicant was asked to provide further subgroup analyses for the primary endpoint according to p-NfL value at baseline, e.g. by separating the patient population according to either a higher (≥30 pg/mL) or lower (<30 pg/mL) p-NfL. Only 13/377 patients in the placebo group and 14/754 patients in the tolebrutinib group had p-NfL levels ≥30 pg/mL at baseline. Also, subgroup analysis according to baseline z-score values would be explorative of nature.

Secondary endpoints:

The selected set of secondary endpoints were tested following a statistical testing hierarchy:

The result on the first secondary endpoint "time to 3-month CDP" was overall in line with the primary endpoint and therefore supporting the obtained effect. The percentage of patients with 3-month CDP was 27.6% in the tolebrutinib group and 34.2% in the placebo group. Tolebrutinib significantly reduced the risk of 3-month CDP by 24% compared with placebo, with an HR of 0.757 (95% CI: 0.607 to 0.944, p=0.0134). The stratified Log-Rank test p-value was p=0.0106. However, a less pronounced treatment effect was demonstrated with regard to 3-month CDP compared to 6-month CDP, the latter being considered a more robust outcome measure, and it is accepted that patients risk of achieving 3-month CDP is higher compared to 6-month CDP.

The second secondary endpoint based on MRI parameter "total number of new and/or enlarging T2-hyperintense lesions" was also met. The adjusted mean number of new and/or enlarging T2-hyperintense lesions per year was statistically significantly lower in the tolebrutinib group (1.835) as compared to the placebo group (2.948), corresponding to a 38% relative reduction in favour of tolebrutinib (RR [95% CI]: 0.622 [0.432 to 0.897]; p=0.0110). The percentage of participants who did not develop any new and/or enlarging T2-hyperintense lesions during the study period was greater in the tolebrutinib group as compared with the placebo group (58.2% versus 49.1%).

The difference between tolebrutinib and placebo in the third secondary endpoint "time to onset of sustained 20% increase in the 9-Hole Peg Test for at least 3 months" failed to show statistical significance. The percentage of participants with sustained 20% increase (worsening) in the 9-HPT confirmed over at least 3 months was similar in the tolebrutinib group (19.0%) as compared to the placebo group (19.6%) (HR 0.972 (95% CI: 0.735 to 1.286, p=0.8428). Probably due to the fact that based on the EDSS scores at baseline (mean EDSS score of 5.53, median EDSS score of 6.0), the recruited population was more likely to have disability driven by ambulation compared to upper limb function as measured by the 9-HPT and that therefore the 9-HPT was less sensitive in the studied population.

Given that the null hypothesis was not rejected, the hierarchical testing stopped at this endpoint. None of the results for the subsequent secondary endpoints contribute to the confirmatory efficacy strategy.

A number of further clinical and paraclinical secondary and exploratory endpoints not included into the hierarchical testing were evaluated that lacked significant results, e.g., NEDA; the ARR; change from baseline in volume of T2-hyperintense lesions at Months 18, 24, and the EOS; total number of new Gd+ lesions. The change from baseline in the number of PRL in SWI and in the Slowly Evolving Lesions (SEL) was similar between groups.

Considering the rational outlined in the dossier, it is noted that MRI results are not consistently supporting a treatment effect of tolebrutinib and not confirmed by change from baseline in A) MTR recovery in new MTR lesions and B) Normalized T1 intensity evolution in SELs. The MTR outcome is considered an exploratory measure of remyelination. The SELs outcome is an exploratory measure of smouldering inflammation and chronic active lesions. Both SELs and PRLs are associated with Progression Independent of Relapse Activity and PMS (Brieva et al). It is agreed that both the MTR and SELs outcomes are exploratory of nature and lack validation.

While it is acknowledged that cognitive function endpoints (SDMT and CVLT-II) were implemented in line with the MS guideline requirements, no benefit on cognitive impairment was observed on these tests. The same relates to the outcome on the change in the MSQoL-54.

However, the "proportion of participants with confirmed disability improvement confirmed over at least 6 months" and the "proportion of participants with confirmed disability improvement confirmed over at least 6 months and maintained until the EOS" were in support of the primary endpoint ([RR (95% CI) 1.913 (1.139 to 3.214)] and [RR (95% CI) 2.999 (1.360 to 6.612)], respectively).

The adjusted annualised adjudicated relapse rate was 0.033 in the tolebrutinib group and 0.032 the placebo group (relative risk of 1.036 (95% CI: 0.628 to 1.708). The applicant also provided an analysis of the annualized reported relapse rate, including relapses not confirmed by the Committee. The adjusted annualised adjudicated relapse rate was 0.050 in the tolebrutinib group and 0.059 the placebo group (relative risk of 0.849 (95% CI: 0.566 to 1.274), showing also comparable results for both treatment arms.

78 (10.3%) participants in the tolebrutinib and 50 (13.3%) in the placebo group had EDSS ≥7 at the end of study. Overall, the percentage of subjects with an EDSS ≥7 at the end of study was almost comparable across the treatment arms.

Supportive Studies

Two similarly designed Phase 3 studies in relapsing multiple sclerosis have additionally been submitted:

Study EFC16033 (GEMINI 1): A Phase 3, randomised, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis (Study initiation date: 30 June 2020, Date last subject last visit: 15 July 2024)

Study EFC16034 (GEMINI 2): A Phase 3, randomised, double-blind efficacy and safety study comparing SAR442168 to teriflunomide (Aubagio®) in participants with relapsing forms of multiple sclerosis (Study initiation date: 11 June 2020, Date last subject last visit: 16 July 2024)

The two phase III studies EFC16033 and EFC16034 evaluated the effect of tolebrutinib in comparison to teriflunomide in subjects with RMS. For details of the studies, see sections 5.3.5.1. and 5.3.5.2. of this report.

Overall, both studies included a RMS population with defined disease activity, characterised by relapses and MRI based activity. Inclusion criteria significantly differed from those of the pivotal study EFC16645, e.g. in studies 033 and 034 subjects had to be able to walk without assistance for >100 meters (i.e., EDSS score ≤5.5) while in study EFC16645 the EDSS was defined to be 3 - ≤ 6.5; the RMS studies also included pre-requisites for existing disease activity criteria while study EFC16645 focused on none disease activity.

Tolebrutinib did not meet the primary efficacy endpoint of reducing the ARR compared to teriflunomide in either of the EFC16033 or EFC16034 studies: the adjusted ARR was similar in both study intervention groups, i.e., study: EFC16033: 0.130 in the tolebrutinib group and 0.122 in the teriflunomide group (RR [95% CI]: 1.061 [0.808 to 1.393]; p=0.6691); study EFC16034: 0.108 in the tolebrutinib group and 0.109 in the teriflunomide group (RR [95% CI]: 0.996 [0.754 to 1.315]; p=0.9758).

Formally, both studies are failed studies. Although the pooled analyses for the key secondary endpoint 6-month CDW of the two studies were properly pre-specified in the ICE SAP, it is noted that both single studies failed in their primary endpoint, ARR.

Nominally significant differences between tolebrutinib and teriflunomide were reached for the key secondary 6-month CDW and the secondary endpoint 3-month CDW in the pooled population. However, according to the hierarchical multiplicity procedure, the results in the secondary endpoints (e.g. 6-month or 3-month CDW) cannot be used as a confirmatory proof of efficacy in the given context. It should further be noted that the key secondary endpoint also nominally failed in study EFC16033. Hence, the results of the secondary endpoints, especially the 6-months CDP/CDW, can only be considered as descriptive.

Nevertheless, the study results of the two studies in RMS (EFC16033 and EFC16034) support that also patients with disease activity would benefit from treatment. Therefore, inclusion of information on study design and the most relevant results on disability progression into the SmPC is considered justified**.**

During the procedure, the applicant provided topline results of the phase 3 study performed in PPMS:

Study EFC16035 (PERSEUS): A Phase 3, randomised, double-blind, efficacy and safety study comparing SAR442168 to placebo in participants with primary progressive multiple sclerosis

Study EFC16035 evaluated the effect of tolebrutinib compared to placebo in a PPMS population.

Topline results: The primary endpoint was time to onset of 6-month composite confirmed disability progression (6M cCDP) assessed via the EDSS, T25-FW test, or 9-HPT and did not reach statistical significance. In the ITT population, the percentage of participants with 6-month cCDP as assessed by EDSS, T25FW, or 9HPT was 50.5% in the tolebrutinib group as compared to 48.4% in the placebo group: HR of 1.008 (95% CI: 0.809 to 1.257, p=0.9410).

Analysis performed across trials (pooled analyses and meta-analysis)

Integrated analysis of efficacy data from the two Phase 3 studies in RMS (EFC16033 and EFC16034)

Demographic and baseline characteristics, including relapse history, MRI baseline lesion counts, and prior DMT use were overall balanced across intervention groups and across both studies in RMS. Accordingly, the EFC16033 and EFC16034 ITT populations are considered suitable for pooling. For the pooled ITT population of EFC16033 and EFC16034, demographic and disease characteristics at baseline were comparable/similar between intervention groups.

Additional analysis of the disability data from EFC16033 and EFC16034 (RMS studies) were performed by the applicant to show an effect of tolebrutinib on disability progression independent of relapse activity in RMS. In this context, observed 6-month CDW events were further divided into PIRA: defined as a 6-month CDW event with no onset of adjudicated relapse within the 90 days before or after the confirmed disability onset date (this includes events in participants with no adjudicated relapse during the study) and RAW: defined as onset of an adjudicated relapse within the 90 days before or after the confirmed disability onset date.

In reference to the provided analyses, the majority of 6-month CDW events in the pooled EFC16033 and EFC16034 population (RMS trials) constituted PIRA/were PIRA events and thereof occurred in participants without any adjudicated relapse during the trial.

Of the 140 PIRA events, 60 (43%) occurred in the tolebrutinib group and 80 (57%) in the teriflunomide group.

The percent of participants with a PIRA event was 6.4% on tolebrutinib compared to 8.5% on teriflunomide [(HR (95% CI) 0.730 (0.522, 1.021) p = 0.0657] indicating a 27% relative risk reduction in favour of tolebrutinib.

Overall, these analyses support the effect of tolebrutinib on PIRA in participants with RMS, suggesting an impact on disability progression independent of an effect on relapses. However, it needs to be considered that the two studies were failed studies. According to the hierarchical testing on disability worsening (6-month CDW) derived from the pooled analyses of these studies the key secondary endpoint therefore can only be considered as descriptive.

During the procedure, the applicant revised the proposed indication to *"Cenrifki is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses and with signs of disability progression (see section 5.1)."*

In response to the major objection regarding benefit/risk the applicant provided a detailed justification in favour of a positive benefit/risk balance for tolebrutinib in participants with SPMS and without relapses.

The applicant's justification was mainly based on the following considerations:

1 Analysis of Differential Treatment Responses to Tolebrutinib Between the PERSEUS (PPMS) and HERCULES (nrSPMS) Phase 3 studies: Pathophysiological and Clinical Rationale

The applicant provided a detailed discussion on the expected differences between PPMS and SPMS, i.e. with respect to different treatment responses and pathophysiological mechanisms, including the characterisation of the PPMS population studied in the PERSEUS study.

According to the applicant, the differential responses between HERCULES and PERSEUS could be explained by three principal factors: (1) precedent from previous clinical trials demonstrating differential treatment responses between these two progressive MS populations, (2) the influence of baseline inflammatory activity on treatment outcomes in previous PPMS trials, with the PERSEUS population characterized by particularly low inflammatory burden and (3) qualitative and quantitative differences in the pathophysiology and clinical characteristics of PPMS versus SPMS.

It is agreed with the applicant that prior data from other therapeutic agents evaluated in progressive MS are limited. To justify the differential outcomes between the PERSEUS and the HERCULES studies the applicant referred amongst others to PPMS studies of ocrelizumab, glatiramer acetate and rituximab, indicating that different rates of progression and treatment response might depend on the degree of baseline inflammatory activity present in the study population. This observation "*to interpret efficacy in the context of shared mechanisms rather than limited to specific clinically-driven subtypes"* (ECTRIMS feedback*)* is also supported by the results obtained for betaferon (interferon-beta-1b) in SPMS:

"*Two controlled clinical trials with Betaferon involving a total of 1,657 patients with secondary progressive multiple sclerosis (baseline EDSS 3 to 6.5, i.e. patients were able to walk) were performed. ……. The two studies showed inconsistent results for the primary endpoint time to confirmed progression, representing delay of disability progression:*

One of the two studies demonstrated a statistically significant delay in the time to disability progression. …….

In the second trial of Betaferon in secondary progressive multiple sclerosis, no delay in the time to disability progression was observed. There is evidence that the patients included in this study had overall less active disease than in the other study in secondary progressive multiple sclerosis.".

While in the HERCULES trial, the mean (SD) time since most recent relapse was 7.50 (5.37) years [median time since most recent relapse 5.76 years (min: 2.0, max: 36.0)] and the mean (SD) Gd+ lesions at baseline were 0.5 (2.6) [median 0.0 (0;54)], most patients in the HERCULES study had never experienced any relapse, i.e., 634 out of 767 included subjects. For those 133 subjects with a relapse history, the mean (SD) time since most recent relapse of 37.64 (52.61) years [median time since most recent relapse was 14.75 years (min: 0.1, max: 303.0)] and mean (SD) Gd+ lesions at baseline of 0.4 (2.4) [median 0.0 (0;52)]. Unfortunately, the number of new/and or enlarging T2 lesions as an additional criterion for disease activity has not been evaluated in these two studies.

As stressed by input from ECTRIMS "*efficacy outcomes for disease-modifying treatments in progressive MS are likely to reflect the pathogenic mechanisms predominant in the enrolled population, rather than the clinical phenotype used for trial inclusion. Specifically, baseline MRI features (such as the proportion of patients with gadolinium-enhancing lesions or recent new T2 lesions) can strongly influence observed treatment effects.".*

It is agreed with the applicant that from a pathophysiological perspective, while PPMS shares certain disease mechanisms with other types of MS, there exist both qualitative and in particular quantitative differences that distinguish this population. Regarding extrapolation between SPMS and PPMS, it is acknowledged that direct comparative evidence is limited. For instance, siponimod demonstrated efficacy in SPMS but has not been formally investigated in PPMS, whereas ocrelizumab showed efficacy in PPMS but has not been specifically studied in SPMS populations without inflammatory activity. According to ECTRIMS "*one consistent observation across programmes, however, is that treatments*

primarily targeting peripheral immune mechanisms have not demonstrated meaningful efficacy in progressive disease in the absence of clinical or radiological activity, as illustrated by the natalizumab and fingolimod development programmes."

The CHMP considers that the negative findings in PPMS challenged the proposed treatment effect of tolebrutinib on disability progression via a mechanism of action independent of an effect on acute and focal inflammatory activity. However, it is acknowledged that the negative outcome of the PERSEUS study does not allow to conclude that there is no effect of tolebrutinib in the SPMS population.

2 Clinical Efficacy of Tolebrutinib in HERCULES: Corroboration by GEMINI RMS data and mechanistic interpretation

The studied population in the HERCULES study was a SPMS population without clinical disease activity evidenced by relapses at study entry and efficacy of tolebrutinib has been observed in these subjects according to the primary endpoint. Treatment with tolebrutinib led to a 31% reduction in the risk of 6-month CDP compared with placebo (HR 0.693 (95% CI: 0.546 to 0.880), p=0.0026). The magnitude of the treatment effect is in the range of what was assumed as clinically relevant based on the sample size calculation to detect a 30% risk reduction in 6-month CDP with tolebrutinib compared to placebo. The Kaplan-Meier curves of cumulative incidence rate for the onset of 6-month CDP showed a sustained effect with an early separation with a lower proportion of patients in the tolebrutinib group with 6-month CDP events throughout the treatment period.

Results for the primary endpoint were consistently supported by all sensitivity analyses results, and by a number of relevant secondary endpoints, assessing lower limb function.

Overall, the mean (SD) change from baseline in PRL at EOS was 0.2 (0.9) and 0.4 (1.8) in the tolebrutinib and the placebo group, respectively. [The EOS mean (SD) was 3.1 (5.3) and 3.2 (5.7) compared to the baseline mean (SD) 2.6 (4.5) and 3.1 (5.3) for tolebrutinib and placebo respectively]. Therefore, it is agreed with the applicant that these data do not depict a resolution of PRLs as measured by lesion counts. Moreover, PRLs tend to persist and are therefore not considered to be PD biomarkers to assess treatment effects.

Post hoc subgroup analyses assessing the treatment effect of the primary endpoint according to the number of baseline PRL suggested that the effect of tolebrutinib is more pronounced in the subgroup of patients with 4 or more PRL (HR 0.463 [95% CI 0.210, 1.019]), compared to 0 PRL (HR 1.171 [95% CI 0.612, 2.242]), and 1-3 PRL (HR 0.846 [95% CI 0.468, 1.531]). The results suggested that although tolebrutinib had no effect on resolution of PRL, tolebrutinib might have a greater effect on the risk of disability progression in those with PRL.

Overall, the analyses provided for the risk of 6-month CDP in relation to the proportion of PRLs in the SPMS and the two RMS studies can be considered indicative to further support the proposed mechanism of action of tolebrutinib in MS. In this context, the additional subgroup analysis based on PRLs (existence/ no existence) and T2 lesion volume (>15 cc/≤15cc; the median baseline T2 lesion volume in the HERCULES study) is acknowledged.

The two RMS studies (GEMINI I and II) also showed an effect on the time to sustained disability progression supporting the overall effect of tolebrutinib on disability progression in MS and on acute focal inflammatory activity in MS.

3 Unmet need in SPMS highlighted through distinct HERCULES study population and paradigm shift in understanding of MS pathophysiology

The unmet medical need in SMPS is undisputably given. While approved medical products for SPMS, e.g., siponimod, are approved "*for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity"*, the studied patient population in the HERCULES study was at a more advanced stage of the disease. While for siponimod patients had to be relapse-free for 3 months prior randomization, patients in the HERCULES study were at least 2 years relapse-free. No products are explicitly licensed for this population.

4 Indication Statement

Overall, the indication needed to reflect the studied patient population. The applicant's proposal for a revised indication *"for the treatment of SPMS without relapses and with signs of disability progression"* was acknowledged. To better reflect the studied patient population the indication "*for the treatment of SPMS without relapses in the last 2 years"* is considered more adequate, "with signs of disability progression" is rather vague, considered to be a prerequisite as inclusion criterion also for former SPMS studies and therefore not agreed. For example, in the siponimod SPMS study patients had to have documented disability progression in the 2 years prior to study, while for tolebrutinib, documented evidence of disability progression had to be observed during the 12 months before screening. Details of the population characteristics are described in SmPC section 5.1.

5 *Additional sub-populations – Not Recommended*

Reference is made to topic 4 above. The CHMP considers an indication for tolebrutinib "*Cenrifki is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (see section 5.1)"* adequate. Such indication includes those subjects with and without MRI based disease activity while also highlighting the more advanced disease stage, e.g. being relapse free for 2 years, in line with the study´s inclusion criteria.

5.3.9.2. Conclusions on the clinical efficacy

In study EFC16645 (HERCULES), that included patients with (non-relapsing) SPMS and 18-60 years of age 22.6% (171/754 participants) in the tolebrutinib arm and 30.7% (116/377 subjects) in the placebo arm experienced a 6-month CDP based on the EDSS. The **primary endpoint**, time to 6-month CDP, was met when tolebrutinib was compared to placebo (HR 0.693 (95% CI: 0.546 to 0.880), p=0.0026), representing a 31% risk reduction of 6-month CDP in favour of tolebrutinib. The magnitude of the treatment effect is in the range of what was assumed as clinically relevant based on the sample size calculation to detect a 30% risk reduction in 6-month CDP with tolebrutinib compared to placebo. The Kaplan-Meier curves of cumulative incidence rate for the onset of 6-month CDP showed a sustained effect with an early separation with a lower proportion of patients in the tolebrutinib group with 6-month CDP events throughout the treatment period. Based on Kaplan-Maier estimates the absolute treatment difference for subjects free of 6-month CDP was 5.1% at month 12 and reached 10.3% at month 48 in favour of tolebrutinib. Several secondary endpoints supported a treatment effect in line with the primary endpoint.

Subgroup analyses for the primary endpoint defined by focal (Gd+ lesions)/no focal active inflammatory (without Gd+ lesions) activity on MRI showed a more pronounced effect in the smaller active group but effects in the non-active group were still positive. Overall, these non-powered subgroup analyses should be interpreted cautiously also in line with the EMA Guideline on the investigation of subgroups in confirmatory clinical trials. In addition, subgroup analyses defined by prior DMT use were also not consistent with better results for those subjects being treatment naïve compared to those subjects who have been treated with DMTs in the past.

Although tolebrutinib as a brain penetrant BTK inhibitor was expected to act on peripheral and central inflammatory pathways, it was not possible to conclude that the effect on disability progression is due to the effect on chronic neuroinflammation since basic MRI assessment in parallel to EDSS scores were not predefined and a correlation of disability progression independent of acute focal inflammatory MRI activity was not possible. In addition, the negative findings in PPMS challenged the proposed treatment effect of tolebrutinib on disability progression via a mechanism of action independent of an effect on acute and focal inflammatory activity. This uncertainty for the first product from a substance class, i.e. BTK-inhibitors, claimed to have a new mechanism of action for the treatment of MS, together with the less clear efficacy observed in the non-active SPMS group, was originally questioned by the CHMP.

Several indications were discussed during the procedure and based on the applicant's justification and further input from ECTRIMS (reference is made to section 5.3.9) it was considered sufficiently justified that the differential responses between the PERSEUS study and the HERCULES trial are not sufficient to question the obtained benefit in the studied SPMS population in the HERCULES trial. In addition, the results from the GEMINI studies have been taken into account. Overall, it was agreed that efficacy has been shown in the entire studied SPMS population (i.e. including both, active and non-active SPMS subjects based on focal inflammatory disease activity), being relapse free for 2 years at baseline. It was finally agreed that the indication is best reflected in the following wording: *"treatment of adult patients with SPMS without relapses in the last 2 years (see section 5.1)"*. Results for the subgroups regarding baseline disease activity are described in the SmPC section

5.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Safety evaluation for tolebrutinib is based on the following clinical studies/ Pools as of 11 September 2024:

- Completed pivotal Phase 3 Study **EFC16645** in nrSPMS: safety data are presented individually with the primary analysis for the DB study intervention. Participants with progressive disease (i.e., having experienced 6-month CDP) who were given the option to switch to OL tolebrutinib are described separately, as supportive data. Both DB and OL participants were included in Pool B.

- **Pool A** including the 2 completed pivotal Phase 3, pivotal, active (teriflunomide)-controlled studies in RMS (Study EFC16033 and Study EFC16034), providing an integrated analysis with the same dosing regimen and comparator, and approximately the same study intervention duration (Table 30),

- **Pool B** including all participants in Phase 2b (Study DRI15928 and Study LTS16004) and Phase 3 studies (in nrSPMS [Study EFC16645] and RMS [pool A]), who received tolebrutinib 60 mg QD (Table 31).

Table 30 Primary safety pool (Pool A)

			Average	Participant numbers		
Dataset pool	**Type**	**Study**	**Treatment duration**	**teriflunomide 14 mg**	**tolebrutinib 60 mg**	**Treatment comparison**
pool A	Active-controlled	EFC16033	2.4 years	488	486	60 mg tolebrutinib QD versus 14 mg teriflunomide QD
		EFC16034	2.3 years	451	447	
		Total	2.3 years	939	933	

Table 31 60 mg tolebrutinib exposed safety pool (Pool B)

Dataset pool	**Type**	**Study**	**Phase**	**Number treated with 60 mg tolebrutinib**	**Participant-years on 60 mg tolebrutinib[b]**
Pool B	tolebrutinib 60 mg QD	DRI15928+LTS16004[a]	2b	125	363.0
		EFC16033	3	486	1163.1
		EFC16034	3	447	1036.5
		EFC16645	3	828	1738.6
		Total	2b/3	1886	4301.2

a Participants receiving tolebrutinib 60 mg in DRI15928 and those switching from a lower dose (5, 15, or 30 mg) to 60 mg in Part B LTS16004.

b exposure calculated as last administration of tolebrutinib 60 mg-first administration of tolebrutinib 60 mg + 1, including any gaps between DRI15928 and LTS16004 and OL treatment in EFC16645.

- **ongoing Phase 3 studies in MS**: nrSPMS and RMS (Study LTS17043, a LTS and efficacy extension for participants coming from LTS16004, EFC16033, EFC16034, EFC16035, or EFC16645), and PPMS (Study EFC16035 [PERSEUS; still blinded]): cases of deaths, SAEs, TEAEs leading to study intervention discontinuation, AESIs, and other hepatic events of interest (ALT >3 × ULN with TBILI >2 × ULN, ALP >2 × ULN, or AST >5 × ULN) for ongoing Study EFC16035 (blinded) for PPMS and ongoing Study LTS17043 up to 11 September 2024 are presented individually.

- completed **clinical pharmacology studies**: A total of 278 healthy participants, 7 participants with mild hepatic impairment, and 12 participants with severe renal impairment were exposed to tolebrutinib. Safety data from clinical pharmacology studies were not pooled.

- early terminated Phase 3 study (Study **EFC17262**; early terminated/ completed) in generalised myasthenia gravis (**gMG**).

Safety assessment for each study was based on the monitoring of AEs, clinical laboratory parameters, physical examination, vital signs, and ECGs. AESIs were prospectively identified based on the

pharmacological properties and mechanism of action of tolebrutinib and data from other BTKis. Safety analyses were primarily descriptive and performed on the safety population.

5.4.2. Patient exposure

Table 32 Patient exposure (11 September 2024)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	1261	882	784	700/639
Blinded studies (active -controlled)	1873	933	933	874/838
Open studies	125	125	124	123/121
Post marketing	NA	NA	NA	NA
Compassionate use	NA	NA	NA	NA

NA: not applicable
* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Study EFC16645 (nrSPMS population)

A total of 1127 participants were randomised and treated. The cumulative exposure to study intervention during the DB was higher in the tolebrutinib group than in the placebo group (1519.00 PY versus 743.65 PY) during the DB period due to the 2:1 randomisation. Of the 752 participants exposed to tolebrutinib 60 mg QD and 375 participants exposed to placebo during the DB period, 85.0% and 84.5% were exposed for at least 48 weeks, and 61.7% and 61.3% for at least 96 weeks.

42.2% of participants in the tolebrutinib group and 48.5% of participants in the placebo group permanently discontinued study intervention, with the main reason for not completing the DB period being "progressive disease" (15.4% and 20.2% of participants in the tolebrutinib and in the placebo group). Participants with progressive disease (i.e., having experienced 6-month CDP) were given the option to switch to OL tolebrutinib (or to switch to another DMT). A total of 15.9% of participants in the tolebrutinib group and 20.2% of participants in the placebo group switched to OL tolebrutinib. Other relevant reasons for premature discontinuation in the DB period were withdrawal by subject (16.2% and 17.8% in the tolebrutinib and the placebo group, respectively) and AE (3.8% and 3.4% in the tolebrutinib and the placebo group, respectively).

Pool A (RMS population [Studies EFC16033 and EFC16034])

A total of 933 participants were exposed to tolebrutinib 60 mg and 939 participants were exposed to teriflunomide 14 mg. 25% and 26.6% of participants in the tolebrutinib and teriflunomide group, respectively, permanently discontinued study intervention, with the main reason being "withdrawal by subject" (12.2% and 14.2% of participants in the tolebrutinib and in the teriflunomide group). "Adverse event" was reported by the Investigator as the reason for permanent DB study intervention discontinuation for 4.5% of participants in the tolebrutinib group and 4.6% of participants in the teriflunomide group. Overall, 89.5% participants in the tolebrutinib group and 88.2% in the teriflunomide group were exposed for at least 48 weeks and 80.8% and 78.4% for at least 96 weeks.

Pool B (60 mg tolebrutinib exposure)

In Pool B safety population, 1886 participants were exposed to tolebrutinib 60 mg. Of those, 87.0% were exposed for at least 48 weeks and 75.6% for at least 96 weeks. A total of 26.2% of participants in the tolebrutinib group permanently discontinued study intervention with the main reason being "withdrawal by subject" (14.4%).

Ongoing studies:

The numbers of participants randomised/ enrolled in ongoing studies as of 11 September 2024 and evaluated for safety were: 125 patients in study LTS16004, 767 patients in study EFC16035 (PPMS; blinded tolebrutinib 60 mg or placebo), and 1761 patients in study LTS17043.

Clinical pharmacology studies

A total of 278 healthy participants were exposed to tolebrutinib during clinical pharmacology studies: 6 at 5 mg, 24 at 7.5 mg, 14 at 15 mg, 29 at 30 mg, 155 at 60 mg, 8 at 90 mg, 35 at 120 mg, 9 at 180 mg, 17 at 240 mg and 8 at 300 mg. In addition, 7 participants with mild hepatic impairment and 12 participants with severe renal impairment were exposed to tolebrutinib 60 mg.

5.4.3. Adverse events

An overview of adverse events reported during **study EFC16645** is presented in Table 33. The percentages of participants with treatment-emergent SAEs, treatment-related TEAE, and any treatment-emergent AESI were higher in the tolebrutinib group compared to the placebo group. These differences were mainly driven by the SOC of Infections and Infestations.

Table 33 Overview of adverse event profile – TEAEs during EFC16645 DB period

n (%)	Placebo (N=375)	tolebrutinib 60 mg (N=752)
Participants with any TEAE	293 (78.1)	613 (81.5)
Participants with any treatment-emergent SAE	39 (10.4)	113 (15.0)
Participants with any TEAE leading to death	1 (0.3)	2 (0.3)
Participants with any TEAE leading to permanent study intervention discontinuation	11 (2.9)	29 (3.9)
Participants with any treatment-emergent AESI	20 (5.3)	75 (10.0)
Participants with any treatment-related TEAE	83 (22.1)	209 (27.8)

DB: double-blind; TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest; n (%) = number and percentage of participants with at least one TEAE

The SOCs with the highest proportion of participants with TEAEs (≥20% of participants in either study intervention group) were: *Infections and infestations, Musculoskeletal and connective tissue disorders, Injury, poisoning and procedural complications, and Nervous system disorders*.

The incidence of TEAEs at the SOC level was similar between the tolebrutinib and placebo groups, with the exception of the following SOCs for which a ~5% difference was observed.

- Infections and infestations: 54.4% of patients in the tolebrutinib group versus 49.3% in the placebo group, mainly driven by Coronavirus infections (27.0% and 23.5%), and upper respiratory tract infections (16.9% and 14.1%).
- Skin and subcutaneous tissue disorders: 16.6% of patients in the tolebrutinib group versus 9.6% in the placebo group, with the imbalance mainly driven by petechiae (2.7% and 0.3%).
- Investigations: 14.4% of patients in the tolebrutinib group versus 9.6% in the placebo group, mainly driven by PT of ALT increased (4.4% and 1.6%).

A < 5% higher incidence in the tolebrutinib group as compared to the placebo group was observed in the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) (4.1% versus 2.4%). Reference is made to section 5.4.4.

TEAEs that occurred with a frequency of ≥2% in either study intervention group by primary SOC and PT in the EFC16645 DB period are presented in Table 34.

Table 34 EFC16645 Number (%) of participants with TEAE(s) that occurred in at least 2% of all participants in either group by primary SOC and PT during DB period - Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	**Placebo (N=375)**	**tolebrutinib 60 mg (N=752)**
Any event	293 (78.1)	613 (81.5)
INFECTIONS AND INFESTATIONS	185 (49.3)	409 (54.4)
COVID-19	85 (22.7)	192 (25.5)
Urinary tract infection	49 (13.1)	85 (11.3)
Nasopharyngitis	26 (6.9)	70 (9.3)
Influenza	13 (3.5)	42 (5.6)
Cystitis bacterial	15 (4.0)	31 (4.1)
Upper respiratory tract infection	18 (4.8)	31 (4.1)
Cystitis	14 (3.7)	29 (3.9)
Viral upper respiratory tract infection	12 (3.2)	28 (3.7)
Bronchitis	5 (1.3)	19 (2.5)
Pharyngitis	4 (1.1)	17 (2.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	19 (5.1)	64 (8.5)
Anaemia	2 (0.5)	16 (2.1)
Neutropenia	8 (2.1)	12 (1.6)
PSYCHIATRIC DISORDERS	30 (8.0)	65 (8.6)
Depression	2 (0.5)	17 (2.3)
Insomnia	11 (2.9)	16 (2.1)
NERVOUS SYSTEM DISORDERS	77 (20.5)	176 (23.4)
Headache	27 (7.2)	54 (7.2)
Dizziness	7 (1.9)	17 (2.3)
Muscle spasticity	6 (1.6)	17 (2.3)
VASCULAR DISORDERS	16 (4.3)	57 (7.6)
Hypertension	11 (2.9)	38 (5.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	22 (5.9)	55 (7.3)
Cough	9 (2.4)	16 (2.1)
Oropharyngeal pain	5 (1.3)	15 (2.0)
GASTROINTESTINAL DISORDERS	59 (15.7)	150 (19.9)
Diarrhoea	14 (3.7)	33 (4.4)
Constipation	12 (3.2)	22 (2.9)
Abdominal pain upper	2 (0.5)	19 (2.5)
Nausea	8 (2.1)	17 (2.3)
Dyspepsia	7 (1.9)	15 (2.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	36 (9.6)	125 (16.6)
Petechiae	1 (0.3)	20 (2.7)
Alopecia	6 (1.6)	18 (2.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	94 (25.1)	186 (24.7)
Arthralgia	19 (5.1)	49 (6.5)
Back pain	24 (6.4)	47 (6.3)
Muscular weakness	10 (2.7)	18 (2.4)
Pain in extremity	9 (2.4)	18 (2.4)
Neck pain	9 (2.4)	9 (1.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	54 (14.4)	128 (17.0)
Fatigue	11 (2.9)	35 (4.7)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	Placebo (N=375)	tolebrutinib 60 mg (N=752)
Oedema peripheral	12 (3.2)	27 (3.6)
Pyrexia	17 (4.5)	25 (3.3)
INVESTIGATIONS	36 (9.6)	108 (14.4)
Alanine aminotransferase increased	6 (1.6)	33 (4.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	88 (23.5)	179 (23.8)
Fall	41 (10.9)	72 (9.6)
Contusion	4 (1.1)	29 (3.9)
Accidental overdose	19 (5.1)	25 (3.3)
Ligament sprain	7 (1.9)	15 (2.0)
Rib fracture	9 (2.4)	7 (0.9)

DB: double-blind; TEAE: treatment-emergent adverse event, SOC: System organ class, PT: Preferred term; MedDRA 27.0; n (%) = number and percentage of participants with at least one TEAE
Note: Table sorted by SOC and by decreasing frequency of PT in tolebrutinib 60 mg group.

An overview of adverse events in **Pool A** is presented in Table 35. The percentages of participants with TEAEs, SAEs, TEAEs leading to death, TEAEs leading to study intervention discontinuation, and AESI were similar between the tolebrutinib and teriflunomide groups. The percentages of participants with TEAEs related to study intervention by the Investigator were higher in the teriflunomide compared to the tolebrutinib group.

Table 35 Overview of adverse event profile - Pool A (EFC16033 + EFC16034) safety population

n (%)	teriflunomide 14 mg (N=939)	tolebrutinib 60 mg (N=933)
Participants with any TEAE	810 (86.3)	792 (84.9)
Participants with any treatment-emergent SAE	77 (8.2)	91 (9.8)
Participants with any AE leading to death	2 (0.2)	1 (0.1)
Participants with any TEAE leading to study intervention discontinuation	41 (4.4)	42 (4.5)
Participants with any treatment-emergent AESI	97 (10.3)	99 (10.6)
Participants with any TEAE considered related to study intervention	367 (39.1)	302 (32.4)
Participants with at least one TEAE by maximal toxicity grade	808 (86.0)	789 (84.6)
1	235 (25.0)	208 (22.3)
2	455 (48.5)	454 (48.7)
3	110 (11.7)	114 (12.2)
4	8 (0.9)	12 (1.3)
5	0	1 (0.1)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest, IMP: Investigational medicinal product; n (%) = number and percentage of participants with at least one TEAE

The SOCs with the highest proportion of participants with TEAEs (≥ 20% of participants in either study intervention group) by decreasing frequency in the tolebrutinib group were: *Infections and infestations, Skin and subcutaneous tissue disorders, Nervous system disorders, Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, and Investigations*.

There were no SOCs for which TEAEs were more frequently (with a difference ≥5%) reported for tolebrutinib compared to teriflunomide.

Similar to study EFC16645, a < 5% higher incidence was observed for tolebrutinib versus teriflunomide in the SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* (5.8% vs. 2.7%). In a majority of patients, the TEAEs in this SOC were benign in nature, mainly uterine myomas, in

participants with prior medical history of myoma or presenting with menstrual abnormalities or abnormal vaginal bleeding.

TEAEs that occurred in ≥2% of participants in either intervention group are presented in Table 36.

Table 36 Number (%) of participants with TEAE(s) that occurred in at least 2% of all participants in either treatment group by primary SOC and PT - Pool A (EFC16033 + EFC16034) safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	**teriflunomide 14 mg (N=939)**	**tolebrutinib 60 mg (N=933)**
Any class	810 (86.3)	792 (84.9)
INFECTIONS AND INFESTATIONS	546 (58.1)	554 (59.4)
COVID-19	252 (26.8)	225 (24.1)
Nasopharyngitis	105 (11.2)	119 (12.8)
Upper respiratory tract infection	82 (8.7)	77 (8.3)
Urinary tract infection	57 (6.1)	59 (6.3)
Viral upper respiratory tract infection	59 (6.3)	50 (5.4)
Influenza	52 (5.5)	46 (4.9)
Tonsillitis	19 (2.0)	31 (3.3)
Sinusitis	22 (2.3)	30 (3.2)
Cystitis	20 (2.1)	28 (3.0)
Pharyngitis	19 (2.0)	26 (2.8)
Oral herpes	18 (1.9)	24 (2.6)
Bronchitis	14 (1.5)	22 (2.4)
Gastroenteritis	26 (2.8)	17 (1.8)
Rhinitis	21 (2.2)	12 (1.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	25 (2.7)	54 (5.8)
Uterine leiomyoma	3 (0.3)	19 (2.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	142 (15.1)	122 (13.1)
Anaemia	16 (1.7)	37 (4.0)
Iron deficiency anaemia	12 (1.3)	29 (3.1)
Neutropenia	92 (9.8)	24 (2.6)
Increased tendency to bruise	3 (0.3)	20 (2.1)
PSYCHIATRIC DISORDERS	154 (16.4)	130 (13.9)
Anxiety	35 (3.7)	36 (3.9)
Insomnia	34 (3.6)	34 (3.6)
Depression	41 (4.4)	26 (2.8)
NERVOUS SYSTEM DISORDERS	262 (27.9)	247 (26.5)
Headache	98 (10.4)	117 (12.5)
Paraesthesia	37 (3.9)	31 (3.3)
Dizziness	22 (2.3)	26 (2.8)
Hypoaesthesia	22 (2.3)	21 (2.3)
VASCULAR DISORDERS	77 (8.2)	62 (6.6)
Hypertension	62 (6.6)	29 (3.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	106 (11.3)	108 (11.6)
Cough	29 (3.1)	31 (3.3)
Oropharyngeal pain	8 (0.9)	22 (2.4)
GASTROINTESTINAL DISORDERS	261 (27.8)	208 (22.3)
Diarrhoea	85 (9.1)	44 (4.7)
Nausea	37 (3.9)	30 (3.2)
Abdominal pain upper	24 (2.6)	26 (2.8)
Constipation	12 (1.3)	19 (2.0)
Dyspepsia	19 (2.0)	19 (2.0)
Vomiting	24 (2.6)	15 (1.6)
Abdominal pain	25 (2.7)	14 (1.5)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	teriflunomide 14 mg (N=939)	tolebrutinib 60 mg (N=933)
Toothache	19 (2.0)	13 (1.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	261 (27.8)	248 (26.6)
Alopecia	146 (15.5)	73 (7.8)
Petechiae	3 (0.3)	42 (4.5)
Dermatitis allergic	20 (2.1)	24 (2.6)
Pruritus	23 (2.4)	13 (1.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	210 (22.4)	199 (21.3)
Back pain	55 (5.9)	58 (6.2)
Arthralgia	44 (4.7)	41 (4.4)
Pain in extremity	44 (4.7)	29 (3.1)
Neck pain	13 (1.4)	21 (2.3)
Muscular weakness	11 (1.2)	19 (2.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	64 (6.8)	87 (9.3)
Heavy menstrual bleeding	9 (1.0)	24 (2.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	140 (14.9)	143 (15.3)
Fatigue	36 (3.8)	46 (4.9)
Pyrexia	34 (3.6)	34 (3.6)
Influenza like illness	21 (2.2)	20 (2.1)
INVESTIGATIONS	189 (20.1)	172 (18.4)
Alanine aminotransferase increased	64 (6.8)	44 (4.7)
Blood creatine phosphokinase increased	33 (3.5)	22 (2.4)
Neutrophil count decreased	20 (2.1)	7 (0.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	146 (15.5)	176 (18.9)
Accidental overdose	27 (2.9)	34 (3.6)
Fall	25 (2.7)	18 (1.9)

Only PTs at least 2% incidence in either treatment group are presented.

5.4.3.1. Adverse drug reactions

The identification of potential ADRs was based on the following criteria: The PTs or cluster of PTs (identified based on medical concept consisting of similar medical terms at PT and HLT levels in the Study EFC16645 or Pool A safety population) reported in ≥ 2% of participants in the tolebrutinib group and with a higher incidence compared to placebo or teriflunomide, respectively, were reviewed for potential causal relationship.

As a result, the following PTs in **Study EFC16645** are proposed by the applicant as ADRs:

ALT increased (>3 × ULN based on laboratory abnormalities); HLT coronavirus infections (reported PTs in the tolebrutinib group include COVID-19, COVID-19 pneumonia, suspected COVID-19); Influenza; viral upper respiratory tract infections; HLT upper respiratory tract infections (reported PTs in the tolebrutinib group include acute sinusitis, laryngitis, laryngopharyngitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection); HLT Lower respiratory tract and lung infections (reported PTs in the tolebrutinib group include bronchitis, pneumonia); petechiae; HLT Gastrointestinal and abdominal pains, excl. oral and throat (reported PTs include abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain).

As a result, the following PTs in **Pool A** are proposed by the applicant as ADRs:

ALT increased (>3 × ULN based on laboratory abnormalities); HLT Coronavirus infections (reported PTs in the tolebrutinib group include COVID-19, COVID-19 pneumonia, coronavirus infection, suspected

COVID-19); Influenza; viral upper respiratory tract infections; HLT upper respiratory tract infections (reported PTs in the tolebrutinib group include acute sinusitis, chronic tonsillitis, laryngitis, laryngopharyngitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection); HLT lower respiratory tract and lung infections (reported PTs in the tolebrutinib group include bronchitis, pneumonia, lower respiratory tract infection); petechiae; increased tendency to bruise; heavy menstrual bleeding.

The following PTs with ≥2% of participants in the tolebrutinib group and with a higher incidence compared to placebo or teriflunomide were not considered as ADRs by the applicant:

In Study EFC16645:

- *contusion*: all TEAEs of contusion with tolebrutinib were nonserious, non-severe, and did not lead to treatment interruption or permanent discontinuation. In 3 participants, the events were assessed as related to the study intervention. In a majority of events, alternative aetiologies were reported including co-reported falls, trauma, or prior history of increased tendency to bruise.
- *anaemia and iron deficiency anaemia*: all TEAEs of anaemia in the tolebrutinib group were nonserious and none led to permanent treatment discontinuation. A total of 32 participants on tolebrutinib reported anaemia, all were nonserious and did not lead to treatment interruption or permanent discontinuation. Five participants experienced severe TEAEs (Grade 3); none was > Grade 3. Five participants experienced TEAEs that were assessed as related to tolebrutinib. 4 of 32 participants had a medical history of anaemia. 5 of 32 participants had a potential confounder of bleeding. Given that the majority of observed anaemia cases are in female participants of reproductive age, and that heavy menstrual bleeding can be underdiagnosed, anaemia is not proposed as an ADR. Anaemia is considered a potential complication of bleeding events already proposed as ADRs. There is no biological plausibility for tolebrutinib to directly cause anaemia.
- *Hypertension*: a majority of the TEAEs of hypertension with tolebrutinib were nonserious and non-severe. Two participants had TEAEs assessed as severe (Grade 3) of which 1 was serious, and none was > Grade 3. No participants in the tolebrutinib group withdrew treatment due to hypertension. 16 of 38 participants in the tolebrutinib group with hypertension had confounders or predisposing factors, including preexisting hypertension, obesity, hyperlipidaemia, dyslipidaemia, or hypertriglyceridemia. In addition, based on the PCSA (potentially clinically significant abnormality) values, there were no clinically meaningful changes over time observed for SBP and DBP, throughout the treatment-emergent period in the tolebrutinib group. Focusing on the events ≥ Grade 2, which meet the definition of hypertension (blood pressure ≥ 140/90 mmHg), and after excluding participants with a medical history of hypertension, there was no imbalance between the tolebrutinib and placebo groups for ≥ Grade 2 events.
- *arthralgia*: all TEAEs of arthralgia with tolebrutinib were nonserious, non-severe, and did not lead to treatment interruption or permanent discontinuation. Four TEAEs were assessed as related to tolebrutinib. No action was taken with tolebrutinib for the events. Arthralgia may be related to underlying MS disease and therefore is not considered an ADR.
- *fatigue*: all TEAEs of fatigue with tolebrutinib were nonserious and non-severe except 1 participant who had nonserious Grade 3 TEAE that resolved with ongoing treatment. One participant with nonserious Grade 2 fatigue, interrupted treatment and later resumed; the participant did not recover and finally discontinued treatment. Five of 35 events were assessed as related to tolebrutinib. Fatigue is a commonly reported non-specific symptom and is not considered to be an ADR.

For the remaining individual PTs, there was no significant imbalance observed (incidence rate was 1% higher in the tolebrutinib group than in the placebo group) and are therefore not proposed as ADRs.

In Pool A:

- *anaemia and iron deficiency anaemia*: all TEAEs of anaemia with tolebrutinib were nonserious and none led to treatment interruption/ discontinuation. Three events were severe. 13 of 71 patients in the tolebrutinib group had a medical history of anaemia. A potential confounder of bleeding was identified/reported in 13 participants.
- *headache*: In the tolebrutinib group, all but 1 TEAEs of headache were non-severe and nonserious, and did not lead to interruption/permanent discontinuation. 21 of 117 participants had TEAEs assessed as related to tolebrutinib. Due to the similar rate of headache seen across the tolebrutinib and placebo groups in Study EFC16645, a causal association between tolebrutinib and headache is unlikely. The prevalence of primary headaches in patients with MS is estimated to be about 57%.

For the remaining individual PTs, there was no significant imbalance observed (incidence rate was 1% higher in tolebrutinib group than teriflunomide group) and are therefore not proposed as ADRs: cystitis, cystitis bacterial, oral herpes, uterine leiomyoma, vitamin D deficiency, dizziness, oropharyngeal pain, epistaxis, constipation, gastroesophageal reflux disease, dermatitis allergic, urticaria, rash pruritic, neck pain, muscular weakness, myalgia, fatigue, accidental overdose, and ligament sprain. The majority of these TEAEs were non-serious, mild to moderate in intensity, and no action was taken with tolebrutinib.

Table 37 Summary of ADRs proposed for inclusion by the applicant in the SmPC

Infections and infestations	
COVID-19[2]	Very common
Upper respiratory tract infections[3]	Very common
Influenza	Common
Lower respiratory tract and lung infections[4]	Common
Skin and soft tissue disorders	
Petechiae	Common
Gastrointestinal disorders	
Abdominal pain	Common
Investigations	
ALT elevation [6]	Common
Blood and lymphatic system disorders	
Increased tendency to bruise	Common
Reproductive system and breast disorders	
Heavy menstrual bleeding[1]	Common

1 Observed only in the active-controlled pooled CENRIFKI dataset.
2 COVID-19 includes preferred terms COVID-19, COVID-19 pneumonia, suspected COVID-19, coronavirus infection, and post-acute COVID-19 syndrome. The studies were conducted during the COVID-19 pandemic.
3 Upper respiratory tract infections include preferred terms acute sinusitis, sinusitis, tonsillitis, chronic tonsillitis, nasopharyngitis, pharyngitis, laryngitis, laryngopharyngitis, pharyngotonsillitis, rhinitis, tracheitis, chronic sinusitis, croup infections, viral upper respiratory tract infection, and upper respiratory tract infection.
4 Lower respiratory tract and lung infections include preferred terms bronchitis, pneumonia, pleural infection, pneumonia aspiration, and lower respiratory tract infection.
5 Abdominal pain includes preferred terms abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
6 ALT greater than 3-fold ULN.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Table 38 Number (%) of participants with treatment-emergent AESI(s) by AESI category, primary SOC and PT - EFC16645 safety population

AESI Category **PRIMARY SYSTEM ORGAN CLASS** **Preferred Term n (%)**	**Placebo (N=375)**	**tolebrutinib 60 mg (N=752)**
Any AESI	20 (5.3)	75 (10.0)
Pregnancy/Partner pregnancy	0	1 (0.1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	1 (0.1)
Pregnancy	0	1 (0.1)
Symptomatic overdose	0	0
Increased ALT > 3xULN	5 (1.3)	27 (3.6)
INFECTIONS AND INFESTATIONS	0	2 (0.3)
Hepatitis C	0	1 (0.1)
Hepatitis E	0	1 (0.1)
HEPATOBILIARY DISORDERS	1 (0.3)	3 (0.4)
Drug-induced liver injury	1 (0.3)	1 (0.1)
Hepatic failure	0	1 (0.1)
Hepatitis toxic	0	1 (0.1)
INVESTIGATIONS	4 (1.1)	22 (2.9)
Alanine aminotransferase increased	4 (1.1)	20 (2.7)
Transaminases increased	0	2 (0.3)
Atrial arrythmia	0	3 (0.4)
CARDIAC DISORDERS	0	3 (0.4)
Atrial fibrillation	0	3 (0.4)
Severe infection	11 (2.9)	39 (5.2)
INFECTIONS AND INFESTATIONS	11 (2.9)	39 (5.2)
COVID-19 pneumonia	1 (0.3)	8 (1.1)
COVID-19	0	6 (0.8)
Pneumonia	2 (0.5)	5 (0.7)
Urinary tract infection	1 (0.3)	4 (0.5)
Pyelonephritis	0	3 (0.4)
Bacterial pyelonephritis	0	1 (0.1)
Cellulitis	0	1 (0.1)
Cystitis	1 (0.3)	1 (0.1)
Cystitis bacterial	2 (0.5)	1 (0.1)
Erysipelas	0	1 (0.1)
Gastroenteritis	0	1 (0.1)
Gastroenteritis viral	0	1 (0.1)
Hepatitis C	0	1 (0.1)
Herpes zoster	1 (0.3)	1 (0.1)
Influenza	0	1 (0.1)
Periodontitis	0	1 (0.1)
Pharyngitis	0	1 (0.1)
Pneumonia bacterial	1 (0.3)	1 (0.1)
Pneumonia pneumococcal	0	1 (0.1)
Sepsis	0	1 (0.1)
Sinusitis	0	1 (0.1)
Varicella zoster pneumonia	0	1 (0.1)
Viral upper respiratory tract infection	0	1 (0.1)
Wound infection	0	1 (0.1)
Appendicitis	1 (0.3)	0
Pneumonia viral	1 (0.3)	0
Urosepsis	3 (0.8)	0
Moderate or severe hemorrhagic event	5 (1.3)	6 (0.8)

AESI Category PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	Placebo (N=375)	tolebrutinib 60 mg (N=752)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.1)
Increased tendency to bruise	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	1 (0.3)	1 (0.1)
Haemorrhage intracranial	0	1 (0.1)
Subarachnoid haemorrhage	1 (0.3)	0
GASTROINTESTINAL DISORDERS	2 (0.5)	1 (0.1)
Haematemesis	0	1 (0.1)
Haemorrhoidal haemorrhage	1 (0.3)	0
Upper gastrointestinal haemorrhage	1 (0.3)	0
RENAL AND URINARY DISORDERS	1 (0.3)	0
Haematuria	1 (0.3)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.3)	2 (0.3)
Heavy menstrual bleeding	1 (0.3)	1 (0.1)
Intermenstrual bleeding	0	1 (0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.3)	1 (0.1)
Traumatic haemothorax	0	1 (0.1)
Brain contusion	1 (0.3)	0
Extradural haematoma	1 (0.3)	0
Subcutaneous haematoma	1 (0.3)	0
Thrombocytopenia (platelet count < 75*10^9/L)	0	1 (0.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.1)
Thrombocytopenia	0	1 (0.1)

AESI: Adverse event of special interest, SOC: System organ class, PT: preferred term

MedDRA 27.0

n (%) = number and percentage of participants with at least one AESI

Note: Table sorted by AESI category (protocol order), SOC internationally agreed order, and decreasing frequency of PT in tolebrutinib 60 mg group within category

Pregnancy includes in female participant or female partner of male participant. Symptomatic overdose includes of IMP. Atrial arrythmia refers to ECG observation including atrial fibrillation and atrial flutter, for example.

Severe infection includes grade 3 or above, including opportunistic infection. Moderate or severe hemorrhagic events include grade 2 or above, including symptomatic bleeding, in a critical area or organ, such as CNS, or intraocular bleeding.

Table 39 Number (%) of participants with treatment-emergent AESI(s) by AESI category, primary SOC and PT - pool A (EFC16033 + EFC16034) safety population

AESI Category PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	teriflunomide 14 mg (N=939)	tolebrutinib 60 mg (N=933)
Any AESI	96 (10.2)	99 (10.6)
Pregnancy/Partner pregnancy	14 (1.5)	15 (1.6)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	11 (1.2)	11 (1.2)
Pregnancy	11 (1.2)	11 (1.2)
SOCIAL CIRCUMSTANCES	3 (0.3)	4 (0.4)
Pregnancy of partner	3 (0.3)	4 (0.4)
Symptomatic overdose	3 (0.3)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (0.3)	0
Accidental overdose	3 (0.3)	0
Increased ALT > 3xULN	49 (5.2)	51 (5.5)
INFECTIONS AND INFESTATIONS	1 (0.1)	1 (0.1)
Cytomegalovirus hepatitis	0	1 (0.1)
Hepatitis C	1 (0.1)	0
HEPATOBILIARY DISORDERS	4 (0.4)	5 (0.5)
Drug-induced liver injury	0	3 (0.3)

AESI Category PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	teriflunomide 14 mg (N=939)	tolebrutinib 60 mg (N=933)
Hepatic steatosis	0	1 (0.1)
Hepatitis acute	0	1 (0.1)
Bile duct stone	1 (0.1)	0
Cholecystitis chronic	1 (0.1)	0
Hepatic cytolysis	1 (0.1)	0
Hepatic function abnormal	2 (0.2)	0
Hepatitis	1 (0.1)	0
INVESTIGATIONS	44 (4.7)	46 (4.9)
Alanine aminotransferase increased	39 (4.2)	33 (3.5)
Transaminases increased	2 (0.2)	10 (1.1)
Aspartate aminotransferase increased	0	1 (0.1)
Hepatic enzyme increased	2 (0.2)	1 (0.1)
Liver function test increased	0	1 (0.1)
Hepatic enzyme abnormal	1 (0.1)	0
Atrial arrythmia	0	1 (0.1)
CARDIAC DISORDERS	0	1 (0.1)
Atrial flutter	0	1 (0.1)
Severe infection	18 (1.9)	21 (2.3)
INFECTIONS AND INFESTATIONS	18 (1.9)	21 (2.3)
COVID-19 pneumonia	2 (0.2)	4 (0.4)
Appendicitis	3 (0.3)	3 (0.3)
COVID-19	0	2 (0.2)
Enteritis infectious	0	2 (0.2)
Pneumonia	3 (0.3)	2 (0.2)
Acute sinusitis	0	1 (0.1)
Bronchitis	1 (0.1)	1 (0.1)
Chronic tonsillitis	0	1 (0.1)
Cytomegalovirus hepatitis	0	1 (0.1)
Gastroenteritis norovirus	0	1 (0.1)
Herpes zoster	0	1 (0.1)
Pyelonephritis	0	1 (0.1)
Pyelonephritis acute	0	1 (0.1)
Salpingo-oophoritis	0	1 (0.1)
Subcutaneous abscess	0	1 (0.1)
Tonsillitis	0	1 (0.1)
Bone abscess	1 (0.1)	0
Cystitis	1 (0.1)	0
Dengue fever	1 (0.1)	0
Diverticulitis	1 (0.1)	0
Escherichia pyelonephritis	1 (0.1)	0
Gastroenteritis	2 (0.2)	0
Influenza	1 (0.1)	0
Mastitis bacterial	1 (0.1)	0
Pleural infection	1 (0.1)	0
Pneumonia aspiration	1 (0.1)	0
Viral upper respiratory tract infection	1 (0.1)	0
Moderate or severe hemorrhagic event	16 (1.7)	20 (2.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.1)
Spontaneous haematoma	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	0	1 (0.1)
Subarachnoid haemorrhage	0	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.3)	0

AESI Category PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	teriflunomide 14 mg (N=939)	tolebrutinib 60 mg (N=933)
Epistaxis	3 (0.3)	0
GASTROINTESTINAL DISORDERS	1 (0.1)	1 (0.1)
Duodenal ulcer haemorrhage	0	1 (0.1)
Gastric haemorrhage	1 (0.1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	4 (0.4)
Petechiae	0	2 (0.2)
Ecchymosis	1 (0.1)	1 (0.1)
Purpura	0	1 (0.1)
RENAL AND URINARY DISORDERS	1 (0.1)	0
Cystitis haemorrhagic	1 (0.1)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	9 (1.0)	10 (1.1)
Heavy menstrual bleeding	2 (0.2)	4 (0.4)
Abnormal uterine bleeding	1 (0.1)	2 (0.2)
Intermenstrual bleeding	3 (0.3)	2 (0.2)
Menometrorrhagia	0	1 (0.1)
Uterine haemorrhage	2 (0.2)	1 (0.1)
Vulval haematoma	0	1 (0.1)
Vaginal haemorrhage	1 (0.1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	5 (0.5)
Post procedural haemorrhage	0	2 (0.2)
Contusion	0	1 (0.1)
Hyphaema	0	1 (0.1)
Traumatic haematoma	0	1 (0.1)
Post procedural haematoma	1 (0.1)	0
Thrombocytopenia (platelet count < 75*10^9/L)	0	0

AESI: Adverse event of special interest, SOC: System organ class, PT: preferred term

MedDRA 27.0

n (%) = number and percentage of participants with at least one AESI

Note: Table sorted by AESI category (protocol order), SOC internationally agreed order, and decreasing frequency of PT in tolebrutinib 60 mg group within category

Pregnancy includes in female participant or female partner of male participant. Symptomatic overdose includes of IMP. Atrial arrythmia refers to ECG observation including atrial fibrillation and atrial flutter, for example.

Severe infection includes grade 3 or above, including opportunistic infection. Moderate or severe hemorrhagic events include grade 2 or above, including symptomatic bleeding, in a critical area or organ, such as CNS, or intraocular bleeding.

5.4.4.1. AESI – Pregnancy of a female participant or a female partner of a male participant

Pregnant or lactating females were excluded from the tolebrutinib clinical development program. Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study were considered AESI and had to be followed-up until the outcome (including offspring information) had been determined.

Overall, there were 48 pregnancies (36 in female participants and 12 in female partners of participants). In total, there were 16 live births, 11 elective termination, 6 spontaneous abortions, and 4 abortions. Eleven pregnancies are ongoing.

In total, 36 pregnancies were reported in female participants during the treatment-emergent period. In the tolebrutinib group, there were 3 live birth, 6 elective termination, 4 spontaneous abortion and 4 ongoing pregnancies. In the teriflunomide group, there were 7 live birth, 2 abortions, 5 elective termination, 1 spontaneous abortion and 3 ongoing pregnancies. In the blinded group, there is 1 ongoing pregnancy. Among the pregnancies with live birth, there were no malformations identified.

Four post-treatment pregnancies were reported in Study EFC16033, all in the teriflunomide group. The outcomes were as follows: 1 live birth delivering a healthy baby, 2 induced abortions, and 1 pregnancy still ongoing at the time of dossier cut-off.

Five post-treatment pregnancies were reported in Study EFC16034: 2 participants in the tolebrutinib group and 3 in the teriflunomide group. The outcomes were as follows: live birth delivering a healthy baby for 2 participants (both in the teriflunomide group), spontaneous abortion for 1 participant in the tolebrutinib group, induced abortion for 1 participant in the teriflunomide group, and 1 pregnancy ongoing at the time of dossier cut-off for 1 participant in the tolebrutinib group.

A total of 12 pregnancies in the female partners of male participants were reported in the tolebrutinib clinical development program. In the tolebrutinib group, there were 3 live birth, 2 abortions, and 2 ongoing pregnancies. In the teriflunomide group, there were 3 live birth and 1 ongoing pregnancy. In the blinded group, there was 1 spontaneous abortion.

Among the pregnancies with live birth in participant's partners, there was 1 major congenital abnormality reported (trisomy 14) in the teriflunomide group in EFC16034.

5.4.4.2. AESI – Symptomatic overdose (serious or non-serious)

In Study EFC16645, Pool A, and Pool B, there were no participants with treatment-emergent AESIs of symptomatic overdose with IMP in the tolebrutinib group.

5.4.4.3. AESI – increase of ALT >3 × ULN

Monthly monitoring of liver function tests (LFTs) and associated AESI designation for ALT increase were included in the initial Phase 3 program based on data from the evobrutinib phase 2 clinical trial in MS and the known increased risk of liver injury in MS patients. While there were no significant liver injury findings in preclinical studies or in the early clinical development of tolebrutinib including the phase 2 clinical trial, liver injury emerged as an identified risk in the Phase 3 tolebrutinib program.

Protocols were amended across the Phase 3 programme in May of 2022 to include increased frequency of LFT monitoring (addition of Weeks 6 and 10), mandatory ALT algorithm for cases above 5 × ULN and creation of the HAC, i.e. a panel of independent hepatologists to review key cases of liver injury and advise on the pattern and risk mitigation strategies.

The program was put on partial clinical hold in June of 2022 with conditions that prohibited tolebrutinib initiation in all study patients and stoppage of drug for patients within the first 60 days of administration. In September 2022, protocols were further modified to include LFT monitoring at Week 2, and weekly between Weeks 4 and 12. In October of 2023, the partial clinical hold was modified to resume enrolment due to unmet need in EFC16645 and EFC16035 and subsequent protocol amendments including Week 3 monitoring and further revisions to the ALT algorithm were included.

Overall, in both Study EFC16645 (including participants exposed to OL tolebrutinib in Study EFC16645) and pool A, PCSAs of ALT >3 × ULN were observed in 4.8% of tolebrutinib exposed participants (84 out of 1761).

In Study EFC16645, the percentage of participants with treatment-emergent AESI of increase of ALT >3 × ULN was higher in the tolebrutinib group compared to the placebo group (3.6% versus 1.3%, respectively), while in pool A the incidence was comparable between study intervention group (5.5% in the tolebrutinib group and 5.2% in the teriflunomide group). The summary of AESIs of increase of ALT >3 × ULN is provided in Table 40 for Study EFC16645 and in Table 41 for pool A.

The PCSAs of ALT >3 × ULN trended similarly to the AESI of increased ALT >3 × ULN (4.0% in the tolebrutinib group and 1.6% in the placebo group in Study EFC16645; 5.6% in the tolebrutinib group and 6.3% in the teriflunomide group in pool A). The differences in the numbers observed between the laboratory values and AESI designation are due to the protocol requirement to confirm ALT >3 × ULN by retesting to meet criteria for AESI (6 participants had ALT <3 × ULN upon retest), occurrence outside of the treatment-emergent period (2 participants), Investigator discretion (ALT increase attributed to cholecystitis), and/or laboratory errors (1 participant). All but 1 case resolved.

In pool B, the EAIR of AESI of ALT increase >3× ULN was 2.0 participants per 100 PY.

Upon review of the individual AESIs of increase of ALT >3× ULN from ongoing studies, the characterisation of liver events was consistent with what was observed in completed studies.

ALT increased (>3× ULN based on laboratory abnormalities) was rated an ADR for Study EFC16645 and pool A.

Table 40 Summary of increased ALT > 3 × ULN - EFC16645 safety population

ALT > 3xULN	**Placebo (N=375)**	**tolebrutinib 60 mg (N=752)**
Participants with any TEAE	5 (1.3)	27 (3.6)
Participants with any grade 3 or above TEAE	3 (0.8)	12 (1.6)
Participants with any treatment-emergent SAE	1 (0.3)	3 (0.4)
Congenital anomaly or birth defect	0	0
Significant disability	0	0
Death	0	1 (0.1)
Hospitalization	1 (0.3)	1 (0.1)
Life threatening	0	0
Other medically important	1 (0.3)	3 (0.4)
Participants with any AE leading to death	0	1 (0.1)
Participants with any TEAE leading to study intervention discontinuation	2 (0.5)	5 (0.7)
Participants with any treatment related TEAE	3 (0.8)	14 (1.9)
Number of AEs (Number of AEs per 100 participant-years)	5 (0.7)	28 (1.8)
PRIMARY SYSTEM ORGAN CLASS/ Preferred Term n (%)		
INFECTIONS AND INFESTATIONS	0	2 (0.3)
Hepatitis C	0	1 (0.1)
Hepatitis E	0	1 (0.1)
HEPATOBILIARY DISORDERS	1 (0.3)	3 (0.4)
Drug-induced liver injury	1 (0.3)	1 (0.1)
Hepatic failure	0	1 (0.1)
Hepatitis toxic	0	1 (0.1)
INVESTIGATIONS	4 (1.1)	22 (2.9)
Alanine aminotransferase increased	4 (1.1)	20 (2.7)
Transaminases increased	0	2 (0.3)
Maximum severity grade		
1	1 (0.3)	3 (0.4)
2	1 (0.3)	12 (1.6)
3	3 (0.8)	8 (1.1)
4	0	3 (0.4)
5	0	1 (0.1)
Corrective treatment [a]		
Yes	2 (0.5)	7 (0.9)

ALT > 3xULN	Placebo (N=375)	tolebrutinib 60 mg (N=752)
Final outcome		
Recovered or resolved	5 (1.3)	25 (3.3)
Recovered or resolved with sequelae	0	0
Recovering or resolving	0	0
Not recovered or not resolved	0	1 (0.1)
Fatal	0	1 (0.1)
Unknown	0	0
Time to onset of first AE (days)		
Number	5	27
Mean (SD)	239.0 (255.6)	223.4 (313.6)
Median	118.0	58.0
Q1 ; Q3	112.0 ; 225.0	56.0 ; 337.0
Min ; Max	57 ; 683	1 ; 1094
Average duration of TEAEs (days)[c]		
Number	4	25
Mean (SD)	155.8 (141.5)	58.3 (84.2)
Median	136.0	36.9
Q1 ; Q3	59.5 ; 252.0	22.0 ; 57.0
Min ; Max	6 ; 345	10 ; 438
Average duration of TEAEs [n(%)]		
>0 to ≤2 days	0	0
>2 to ≤7 days	1 (0.3)	0
>7 days to ≤4 weeks	0	10 (1.3)
>4 weeks to ≤8 weeks	0	7 (0.9)
>8 weeks to ≤12 weeks	0	5 (0.7)
>12 weeks to ≤24 weeks	2 (0.5)	2 (0.3)
>24 weeks	1 (0.3)	1 (0.1)

a For multiple occurrences of the same event, summarize as Yes if any occurrence required corrective treatment

b Time to first event in the TEAE period

c Average duration is the average over all occurrences that resolved

Table 41 Summary of increased ALT > 3 × ULN - pool A (EFC16033 + EFC16034) safety population

ALT > 3xULN	teriflunomide 14 mg (N=939)	tolebrutinib 60 mg (N=933)
Participants with any TEAE	49 (5.2)	51 (5.5)
Participants with any grade 3 or above TEAE	17 (1.8)	25 (2.7)
Participants with any treatment-emergent SAE	3 (0.3)	6 (0.6)
Congenital anomaly or birth defect	0	0
Significant disability	0	0
Death	0	0
Hospitalization	2 (0.2)	2 (0.2)
Life threatening	0	0
Other medically important	1 (0.1)	4 (0.4)
Participants with any AE leading to death	0	0
Participants with any TEAE leading to study intervention discontinuation	12 (1.3)	17 (1.8)
Participants with any treatment related TEAE	28 (3.0)	30 (3.2)
Number of AEs (Number of AEs per 100 participant-years)	53 (2.4)	54 (2.5)

ALT > 3xULN	teriflunomide 14 mg (N=939)	tolebrutinib 60 mg (N=933)
PRIMARY SYSTEM ORGAN CLASS/ Preferred Term n (%)		
INFECTIONS AND INFESTATIONS	1 (0.1)	1 (0.1)
Cytomegalovirus hepatitis	0	1 (0.1)
Hepatitis C	1 (0.1)	0
HEPATOBILIARY DISORDERS	4 (0.4)	5 (0.5)
Drug-induced liver injury	0	3 (0.3)
Hepatic steatosis	0	1 (0.1)
Hepatitis acute	0	1 (0.1)
Bile duct stone	1 (0.1)	0
Cholecystitis chronic	1 (0.1)	0
Hepatic cytolysis	1 (0.1)	0
Hepatic function abnormal	2 (0.2)	0
Hepatitis	1 (0.1)	0
INVESTIGATIONS	44 (4.7)	46 (4.9)
Alanine aminotransferase increased	39 (4.2)	33 (3.5)
Transaminases increased	2 (0.2)	10 (1.1)
Aspartate aminotransferase increased	0	1 (0.1)
Hepatic enzyme increased	2 (0.2)	1 (0.1)
Liver function test increased	0	1 (0.1)
Hepatic enzyme abnormal	1 (0.1)	0
Maximum severity grade		
1	4 (0.4)	5 (0.5)
2	28 (3.0)	21 (2.3)
3	17 (1.8)	20 (2.1)
4	0	5 (0.5)
5	0	0
Corrective treatment [a]		
Yes	18 (1.9)	17 (1.8)
Final outcome		
Recovered or resolved	45 (4.8)	48 (5.1)
Recovered or resolved with sequelae	0	0
Recovering or resolving	2 (0.2)	1 (0.1)
Not recovered or not resolved	2 (0.2)	2 (0.2)
Fatal	0	0
Unknown	0	0
Time to onset of first AE (days)		
Number	49	51
Mean (SD)	284.2 (331.5)	206.3 (292.3)
Median	111.0	59.0
Q1 ; Q3	50.0 ; 429.0	29.0 ; 341.0
Min ; Max	16 ; 1110	1 ; 1100
Average duration of TEAEs (days)[c]		
Number	46	49
Mean (SD)	76.6 (95.3)	70.8 (94.3)
Median	50.5	51.0
Q1 ; Q3	27.0 ; 84.0	26.0 ; 76.0
Min ; Max	8 ; 567	3 ; 583
Average duration of TEAEs [n(%)]		
>0 to ≤2 days	0	0
>2 to ≤7 days	0	3 (0.3)
>7 days to ≤4 weeks	12 (1.3)	12 (1.3)

ALT > 3xULN	teriflunomide 14 mg (N=939)	tolebrutinib 60 mg (N=933)
>4 weeks to ≤8 weeks	12 (1.3)	13 (1.4)
>8 weeks to ≤12 weeks	11 (1.2)	13 (1.4)
>12 weeks to ≤24 weeks	6 (0.6)	4 (0.4)
>24 weeks	5 (0.5)	4 (0.4)

a For multiple occurrences of the same event, summarize as Yes if any occurrence required corrective treatment

b Time to first event in the TEAE period

c Average duration is the average over all occurrences that resolved

Eight participants met criteria for biochemical Hy's law from Study EFC16645 and pool A (7 in the tolebrutinib group, 1 in the teriflunomide group, and 0 in the placebo group).

In addition, there was 1 participant in the tolebrutinib group in Study LTS16004 and 3 participants in ongoing studies as of 11 September 2024 (1 unblinded to tolebrutinib in Study EFC16035, 1 in the teriflunomide group in Study LTS17043, and 1 remains blinded in Study EFC16035).

In both Study EFC16645 and pool A, in 4 out of 7 participants in the tolebrutinib group with concurrent elevation of ALT >3 × ULN and TBILI >2 × ULN, no alternative etiology was found. These cases were assessed by HAC as meeting criteria for Hy's law. One of the 4 participants developed liver failure requiring a liver transplant and died due to postoperative complications. This case occurred when monitoring frequency was every 2 weeks from Weeks 4 to 12 and prior to implementation of Week 2, Week 3 and weekly from Week 4 to Week 12. In the remaining 3 participants, the events spontaneously resolved without sequelae after permanent study intervention discontinuation. In addition, in ongoing studies, 1 participant in Study EFC16035 (unblinded to tolebrutinib) had an elevation of ALT >3 × ULN with concurrent TBILI >2 × ULN without alternative etiology.

Five confirmed Hy's law cases in the tolebrutinib group had time to onset within the first 90 days of tolebrutinib exposure and these cases occurred prior to implementation of weekly LFTs monitoring through Week 12:

- A participant with SPMS and obesity presented on Day 44 with severe acute hepatitis (peak ALT 65.0 × ULN, peak TBILI 31.4 × ULN), underwent liver transplantation on Day 97, and died on Day 153 after post-operative complications including Klebsiella bacteraemia.
- A participant with RMS presented on Day 57 with severe acute hepatitis (peak ALT 98.7 × ULN, AST 49.4 × ULN, TBILI 13.7 × ULN). The participant was hospitalized, study intervention discontinued, and liver parameters returned to baseline by Day 112. Potential confounders included baseline transaminase elevations (1.7 x ULN), elevated iron parameters, and alcohol use.
- A participant with SPMS self-discontinued study intervention on Day 47 due to worsening generalized weakness and mild jaundice presented on Day 54 with ALT 51.1 × ULN, AST 30 × ULN, and TBILI 5.4 × ULN. Transaminases peaked on Day 57: ALT 65.7 × ULN, and AST 31.5 × ULN; TBILI peaked on Day 61 (10.0 × ULN), with all reaching normal values by Day 113. The participant was managed as an outpatient. The participant has had a negative workup and a positive dechallenge.
- A participant with RMS presented on Day 49 with complaints of mild nausea, mild scleral icterus, and ALT 17.9 × ULN, AST 8.4 × ULN (peak values), and TBILI 7.5 × ULN, which later peaked on Day 52 at 10.6 × ULN. The study intervention was permanently discontinued on Day 49, and the participant was managed as an outpatient. Transaminases and TBILI returned to baseline by Day 79 and 147, respectively. Potential confounders included elevated iron studies, mild iron overload on imaging, and HFE C282Y carrier status.

- A participant with PPMS, and prior liver dysfunction presented on Day 85 with nausea, vomiting, and elevated transaminases following a COVID-19 mRNA booster on Day 63. Study intervention was discontinued on Day 86. Peak ALT (25.7× ULN) and AST (25.4× ULN) occurred by Day 92, with TBILI peaking at 2.7× ULN on Day 106. The participant was hospitalized on Day 99 and fully recovered by Day 155. Confounders included prior liver injury from PPIs, recent vaccination, ursodiol use, and a mixed-to-idiosyncratic hepatocellular injury pattern.

In addition, a participant with RMS and obesity presented on Day 550 with symptomatic liver injury (ALT >3× ULN, TBILI >2× ULN). Although the event met Hy's law criteria, the HAC determined it was due to concomitant medications and not related to the study intervention. Potentially confounding factors included recently initiated hepatotoxic medications (antidepressants, metformin, NSAIDs) and positive anti-smooth muscle antibodies. The participant recovered following permanent discontinuation.

In both Study EFC16645 and pool A, there were 48 participants with liver events of interest reviewed by the HAC (ALT >3 × ULN with concurrent TBILI >2 × ULN or ALT >8 × ULN). Seventeen out of 30 in the tolebrutinib group were assessed as possibly or probably related to the study intervention by the HAC. In the blinded ongoing Study EFC16035, in addition to the participants with Hy's law, 10 participants had liver events of interest of ALT >8 × ULN reviewed by the HAC. Nine of these events were noted to be possibly or probably related to the study intervention by the HAC. These cases remain blinded and all participants have recovered following discontinuation of the study intervention.

The time to onset and time to recovery of the liver events were analyzed for liver events of interest for both Study EFC16645 and pool A. In 16 out of 17 participants with liver events of interest assessed as possibly or probably related to tolebrutinib, time to onset of ALT increase occurred within the first 90 days after treatment initiation. Mean time to onset was 55.1 days. Mean time to recovery was 56.6 days for these 16 participants. One participant) had a peak ALT increase of 9.5× ULN on Day 757 with potential confounders (Hashimoto thyroiditis and use of hepatotoxic medication brivudine). This case was rated as possibly related to study intervention by the HAC. In the other 7 participants, the events were assessed as unlikely related to the study intervention by the HAC and had confounders.

In total, 15 of 48 participants with liver events of interest had a rechallenge following event resolution. Two participants in the tolebrutinib group had a positive rechallenge. These participants had study intervention restarted prior to the formation of the HAC and therefore the HAC determination of the relationship to the study intervention considered the positive rechallenge as a factor in their assessment. Following formation of the HAC, the applicant consulted with the HAC prior to rechallenge and endorsement was limited to cases with a clear alternative aetiology. While the number of rechallenged participants were low, cases rated as unlikely related to the study intervention had no ALT increase following restart of study intervention (negative rechallenge).

Significant risk mitigation measures were implemented in ongoing Phase 3 studies including weekly liver monitoring for the first 3 months following initiation of tolebrutinib and guidance for stopping study intervention when transaminase elevations occur. In the ongoing studies, liver events of interest were detected in 4 participants after initiation of weekly LFTs. In Study EFC16035, 2 participants had liver events of interest observed in the first 90 days after study intervention initiation with initial ALT increase of 3.8 × ULN and 6.2 × ULN detected at Week 5 and Week 6, respectively. These 2 participants remain blinded, fully recovered after study intervention discontinuation, and were assessed as probably related to study intervention by the HAC.

Liver events of interest assessed as probably or possibly related to tolebrutinib by the HAC were found time delimited, with a greater risk within the first 90 days of tolebrutinib exposure. HAC assessments of severity of the liver events were mild in a majority of cases except those with confirmed Hy's law.

Proposed guidance for frequent LFTs monitoring within the first 3 months of tolebrutinib exposure, therapy modifications due to elevated transaminases, and rechallenge/reinitiation of therapy based on above data and FDA recommendations are included in the dosage and administration section of the product information. Label guidance also includes that periodic monitoring after Month 12 may be performed as warranted to align with BTKi class recommendations. Additional guidance is included to require ALT <1.5× ULN at treatment start, exclude patients with moderate to severe hepatic impairment, and to use caution with concomitant use of hepatotoxic medications.

Since the start of weekly liver monitoring, no cases of confirmed Hy's law have occurred in tolebrutinib treated participants.

Table 42 Tolebrutinib therapy modifications and monitoring for elevated transaminases

Laboratory abnormalities	Tolebrutinib therapy modification
• ALT/AST >3 × and ≤5 × ULN with clinical symptoms[a] OR with concurrent total bilirubin >2 × ULN • ALT/AST >5 × ULN	• Withhold tolebrutinib treatment • Repeat laboratory testing every 2 to 3 days until ALT/AST down trending and monitor weekly until ALT/AST <1.5 ×ULN
	If an alternative cause other than drug-induced liver injury (DILI) is identified, reinitiation of tolebrutinib can be considered when ALT/AST decreases to <1.5 × ULN. Upon reinitiation of tolebrutinib, if ALT/AST ≥3 ×ULN, permanently discontinue tolebrutinib treatment
	If no alternative cause to DILI is identified, permanently discontinue tolebrutinib treatment if any of the following occurred as initial event: ALT/AST >8 × ULN ALT/AST >5 × ULN for greater than 2 weeks ALT/AST >3 × ULN and total bilirubin >2 × ULN

ULN = upper limit of normal; [a] fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, jaundice, and/or eosinophilia (>5%)

5.4.4.4. AESI – ECG observation of atrial fibrillation/atrial flutter

Atrial fibrillation and atrial flutter were observed in clinical trials and post-marketing with approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib). The pathological mechanism of atrial arrhythmia is possibly linked to off-target cardiac binding of BTK inhibitors (HER2, HER4, Tec, or tyrosine kinase).

The selection criteria for tolebrutinib Phase 3 studies excluded participants with abnormal ECG values that were judged to be of clinical significance.

In both Study EFC16645 and pool A, there were 4 participants in the tolebrutinib group (3 in Study EFC16645 and 1 in pool A) with AESI of ECG observation of atrial fibrillation/atrial flutter, two of them serious, 0 in the teriflunomide group, and 0 in the placebo group:

In study EFC16645, one patient was reported with serious Grade 3 atrial fibrillation.) on Day 249, requiring hospitalisation and corrective treatment. Lab results showed mildly elevated TSH (a potential confounder for cardiac electrical abnormalities, particularly atrial fibrillation), lactate, and glucose. The SAE recovered the same day and was rated as related to tolebrutinib. Tolebrutinib was not interrupted due to the event. Another patient) was reported with Grade 2 atrial fibrillation after Day 844 and Apixaban was initiated. Medical history included atrial standstill and bladder disorders for many years. Tolebrutinib was temporarily interrupted and not restarted. Cardioversion was cancelled after spontaneous resolution of atrial fibrillation on Day 975. The event was not rated as related to tolebrutinib. In a third patient (treated with OL tolebrutinib in the tolebrutinib/ tolebrutinib group),

Grade 1 atrial fibrillation was reported and not rated as related to IMP, while the patient did not recover from the event.

In Pool A, one participant developed atrial flutter Grade 2, 4 days after initiation of tolebrutinib. The atrial flutter was treated and resolved the same day, and study intervention was continued. The event was considered not related to the IMP.

An analysis of SMQ Cardiac arrhythmia terms (incl. bradyarrhythmias and tachyarrhythmias) in both Study EFC16645 and Pool A was conducted. The number of participants with TEAEs was similar between tolebrutinib and placebo in Study EFC16645 (2.9% and 2.7%), and slightly higher in the tolebrutinib group compared to the teriflunomide group in Pool A (3.2% and 2.2%).

In ongoing studies, there was 1 serious AESI of atrial fibrillation in blinded Study EFC16035.

5.4.4.5. AESI - Severe infection (NCI CTCAE grade 3 or above), that may or may not meet seriousness criteria (eg, a grade 3 opportunistic infection) - Infections and Infestations

Infection is an important identified risk for all approved BTK inhibitors due to expected immunosuppression.

In both Study EFC16645 and Pool A, the SOC Infections and infestations was reported with the highest proportion of participants with TEAEs, treatment-emergent SAEs, and AESI of severe infection. The incidence of TEAEs, SAEs, and AESIs of severe infection was higher in the tolebrutinib group versus placebo group in Study EFC16645, and comparable between the tolebrutinib and the teriflunomide group for Pool A. The most frequently reported PTs were within the HLT Coronavirus infections and HLT upper respiratory tract infections, with similar incidences in the tolebrutinib groups in Study EFC16645 and Pool A.

Study EFC16645 and Pool A

The incidence rate of treatment-emergent serious and severe infection was higher in the tolebrutinib group as compared to placebo in Study EFC16645 (39 [5.2%] and 39 [5.2%] in the tolebrutinib group and 13 [3.5%] and 11 [2.9%] in the placebo group, respectively) and comparable between tolebrutinib and teriflunomide in Pool A (2.5% and 2.3%, respectively in the tolebrutinib group and 2.2% and 1.9%, respectively in the teriflunomide group). In the majority of participants in Study EFC16645 and Pool A the event of severe infection was assessed as serious, mainly due to hospitalisation.

In Study EFC16645 and Pool A, there were no participants with TEAEs of infection with fatal outcome.

The most frequently reported PTs for treatment-emergent SAEs were: COVID-19 pneumonia and COVID-19. Of the participants with SAEs, the Investigator assessed 11 participants (8 in the tolebrutinib group and 3 in the placebo group) as having events related to the study intervention. The PTs in the tolebrutinib group were pneumonia in 2 participants, bacterial pyelonephritis, cystitis, pneumonia bacterial, pyelonephritis, urinary tract infection, and viral upper respiratory tract infection.

In Pool A, the most frequently reported PT for SAEs was COVID-19. The Investigator assessed treatment emergent SAEs in 7 participants (4 in the tolebrutinib group and 3 in the teriflunomide group) related to the study intervention. The PTs in the tolebrutinib group were COVID-19 (also leading to study intervention discontinuation), COVID-19 pneumonia, pyelonephritis acute, and bronchitis.

An analysis of the relationships between exposure (tolebrutinib, metabolite M2, and tolebrutinib + metabolite M2, respectively) AEs in participants in Study EFC16645 and Study EFC16033 showed a similar risk across all exposure quartiles for tolebrutinib and metabolite M2 for severe infections.

In ongoing studies, 1 participant in Study EFC16035 died due to septic shock secondary to aspiration pneumonia under blinded treatment. The death was assessed as not related to the study intervention.

A fatal case of pneumonia leading to sepsis, assessed as related to tolebrutinib, was reported in Study LTS17043 after the data cut-off: a participant with a history of hypertension, smoking, and suspected urinary tract infection was hospitalised with weakness and possible MS relapse after 642 days of treatment with tolebrutinib (last dose 65 days prior). The participant developed severe respiratory symptoms, hypoxia, and fever. Initial treatment focused on MS and UTI, but pneumonia was missed early due to delayed testing. The condition of the participant rapidly worsened to septic shock and cardiac arrest. Legionella and other pathogens were later identified. The participant died due to sepsis and respiratory failure.

One participant in the gMG study EFC17262 had a SAE of COVID-19 pneumonia leading to death in the tolebrutinib group assessed as not related.

COVID-19 (Other AE grouping)

In Study EFC16645, there was a higher number of participants with COVID-19 ≥ Grade 3 TEAEs and treatment emergent SAEs and in the tolebrutinib group as compared to placebo (5.2% and 4.8% versus 2.9% and 2.9%). Most of the events led to hospitalisation. Two participants in the tolebrutinib group had serious Grade 4 COVID-19 pneumonia. Both events resolved and were assessed as not related to the study intervention by the Investigator.

In Pool A, there were no imbalances between tolebrutinib and teriflunomide groups for ≥ Grade 3 TEAEs and SAEs of COVID-19.

Opportunistic Infections (*post hoc* assessment)

Post hoc assessment of opportunistic infections was performed using the SMQ opportunistic infections.

In Study EFC16645 and Pool A, there was no imbalance observed for TEAEs of opportunistic infections.

In Study EFC16645, in the SMQ opportunistic infection, there were 2 (0.3%) participants in the tolebrutinib group and 0 in the placebo group. One of these participants had serious Grade 3 varicella zoster pneumonia (after coming in close contact with the grandchild who had active varicella infection) that resolved after study intervention interruption and the second had a nonserious Grade 2 Herpes zoster oticus that resolved without study intervention discontinuation.

In Pool A, in the SMQ opportunistic infection there were 3 (0.3%) participants in the tolebrutinib group and 1 (0.1%) participant in the teriflunomide group. All events were non-serious. Two events (Grade 2 Ophthalmic herpes zoster and Grade 1 Herpes ophthalmic) resolved without study intervention interruption or permanent discontinuation while 1 event (Grade 3 Cytomegalovirus hepatitis) resolved after study intervention interruption. The participant with Grade 1 herpes ophthalmic had steroid treatment for MS relapse prior to the event.

There were 2 participants with fatal outcome for whom opportunistic infection was identified on autopsy report:

A participant (study EFC16645) in the tolebrutinib group experienced a SAE of hepatic failure with fatal outcome. Study intervention was discontinued on Day 43 and the participant eventually underwent liver transplant on Day 97. The participant was later diagnosed with disseminated aspergillosis probably attributed to increased immunosuppression following liver transplantation and concomitant use of anti-rejection drugs. The participant was also tested positive for cytomegalovirus attributed to the donor liver. The participant has been off study drug for 2 months when infections occurred.

A participant (ongoing Study EFC16035) receiving blinded study intervention, experienced convulsions and loss of consciousness with hospitalisation complicated by severe aspiration pneumonia, later developed ventricular tachycardia and died due to brain oedema. The autopsy report showed the presence of "Drusen actinomycetes" in lung tissue indicative of pulmonary actinomycosis. The role of blinded study intervention in the development of pulmonary actinomycosis cannot be ruled out.

Hepatitis reactivation

In the completed Phase 3 MS studies no cases of hepatitis B reactivation were observed. The HLT Hepatitis virus infections in Study EFC16645 and Pool A, retrieved 3 participants with tolebrutinib (1 participant with hepatitis E and 2 participants with hepatitis C), 2 participants in the teriflunomide group (1 participant with chronic hepatitis C and 1 participant with hepatitis C) and 0 participants on placebo. Hepatitis observed in the tolebrutinib participants were new infections and not related to reactivation of preexisting infections.

Neutropenia

The number of TEAEs of neutropenia was balanced between the tolebrutinib and placebo groups in Study EFC16645 (1.6% and 2.1% of participants) and lower in the tolebrutinib group versus teriflunomide group in Pool A (2.6% versus 9.8%). No participants on tolebrutinib 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. Neutropenia is not expected aggravate the risk of infection with tolebrutinib.

5.4.4.6. AESI – Thrombocytopenia, platelet count < 75 x 10^9/L

A single patient on tolebrutinib in study EFC16645 presented with nonserious Grade 2 thrombocytopenia (without associated symptoms) 421 days after starting study intervention that resolved after study intervention interruption without corrective treatment. The event was assessed as not related to the study intervention by the Investigator. There were no participants with thrombocytopenia in the placebo group.

In addition, thrombocytopenia with platelet count of $<75 \times 10^9$/L has neither been reported in Pool A, Pool B, in ongoing MS studies, other participant population (EFC17262), nor in clinical pharmacology studies (1 participant in PRN2246-001 Part B [60 mg] had mild reduced platelet count [$<150 \times 10^9$/L but $>100 \times 10^9$/L] leading to study intervention discontinuation.

5.4.4.7. AESI – Moderate or severe haemorrhagic events (NCI CTCAE grade 2 or above), including, but not limited to, symptomatic bleeding, bleeding in a critical area or organ such as the CNS, or intraocular bleeding

In both Study EFC16645 and Pool A, the percentages of participants with TEAEs, SAEs, and TEAEs leading to permanent study intervention discontinuation were similar between study intervention groups. Grade 3 or above TEAEs (SAEs) were reported in 0.1% and 0.8% (0.3% and 0.8%) of participants treated with tolebrutinib and placebo in study EFC16645. In Pool A, Grade 3 or above TEAEs (SAEs) were reported in 0.5% and 0.4% (0.3% and 0.4%) of participants treated with tolebrutinib and teriflunomide. One death occurred in the Pool A teriflunomide group (subarachnoid haemorrhage). None of the participants in study EFC16645 and in Pool A had concurrent thrombocytopenia.

The percentage of participants with TEAEs assessed as related to the study intervention by the investigator was balanced between the tolebrutinib and the placebo group in Study EFC16645 (0.4%

and 0.3%) and higher in the tolebrutinib group as compared to the teriflunomide group in Pool A (0.9% and 0.2%).

In Study EFC16645, individual PTs that were reported once in the tolebrutinib group were: increased tendency to bruise, haemorrhage intracranial, haematemesis, heavy menstrual bleeding, intermenstrual bleeding, and traumatic haemothorax. In the placebo group, it was subarachnoid haemorrhage, haemorrhoidal haemorrhage, upper gastrointestinal haemorrhage, haematuria, heavy menstrual bleeding, brain contusion, extradural haematoma, and subcutaneous haematoma. In Pool A, the number of participants with TEAEs was balanced at the SOC level and most individual PTs were reported once.

In Pool A, the SOC with the highest frequency of participants with AESI of moderate to severe haemorrhage was *Reproductive system and breast disorders*, mainly driven by menstrual/ uterine bleeding, and with similar frequency between study intervention groups (1% teriflunomide and 1.1% tolebrutinib). More patients on tolebrutinib as compared to teriflunomide had AESI from the injury, poisoning and procedural complications SOC (0.5% vs. 0.1%), and skin and subcutaneous tissue disorders SOC (0.4% vs. 0.1%). Single PTs of spontaneous haematoma, subarachnoid haemorrhage, and duodenal ulcer haemorrhage have been reported in the tolebrutinib group, while PTs of gastric haemorrhage, cystitis haemorrhagic, and epistaxis (3 events) were only reported in the teriflunomide group.

An analysis of the relationships between exposure (tolebrutinib, metabolite M2, and tolebrutinib + metabolite M2, respectively) and AESIs of moderate to severe haemorrhage in participants in Study EFC16645 and Study EFC16033 showed a similar risk across all exposure quartiles for tolebrutinib and metabolite M2. The relationship between the combined AUC of tolebrutinib + metabolite M2 and the severity (grade) of haemorrhage showed a similar AUC regardless of the severity of haemorrhage.

One participant in the ongoing blinded Study EFC16035 had a suspected unexpected serious adverse reaction (SUSAR) of epistaxis) on Day 370 that was Grade 3 and rated as related to IMP. At the same time, pneumonia aspiration (Grade 4) was reported as SAE (AESI: severe infection).

In studies in other participant population (gMG, Study EFC17262), there was 1 participant with an AESI of increased tendency to bruise (nonserious, Grade 2) in the tolebrutinib group, determined as secondary to long-term steroid use and resolved upon dose reduction, and assessed as not related to the study intervention.

Mild haemorrhagic events (not a designated AESI; Grade 1 events)

There was a higher incidence of mild haemorrhagic events with tolebrutinib as compared to placebo in Study EFC16645 (12.8% vs. 5.3%) due to nonserious and Grade 1 events. The same imbalance was found for the tolebrutinib and teriflunomide group in Pool A (16.8% for tolebrutinib vs. 8.2% for teriflunomide).

The most frequently reported PTs in Study EFC16645 were contusion (3.9% in the tolebrutinib group and 1.1% in the placebo group) and petechiae (2.7% and 0.3%) and in Pool A petechiae (4.5% with tolebrutinib and 0.3% with teriflunomide), heavy menstrual bleeding (2.6% and 1%), increased tendency to bruise (2.1% and 0.3%), epistaxis (1.7% and 1%), and ecchymosis (1.1% and 0.4%).

5.4.4.8. Anaemia

Anaemia has been evaluated as a consequence of bleeding events. For both Study EFC16645 and Pool A the percentage of participants with TEAEs of anaemia was higher in the tolebrutinib group than in the placebo group (2.1% vs. 0.5%) or the teriflunomide group (4% vs. 1.7%). The trend was similar in

participants with normal or missing value at baseline for PCSAs values of haemoglobin ≤115 g/L in male (≤95 g/L in female) and PCSAs of haematocrit ≤0.37 in male (≤0.32 in female): 6.2% versus 2.7% and 10.8% versus 4.4%, respectively in Study EFC16645; 6.5% versus 3.2% and 14.9% versus 7.9%, respectively in Pool A.

A majority of events was reported in female participants <45 years of age (of reproductive age) and likely related to other factors including the ADR of heavy menstrual bleeding.

5.4.4.9. Suicidal ideation and behaviour

Since tolebrutinib crosses the BBB and considering the suicide risk for people with MS, precautionary measures for suicidal ideation and behaviour were taken by excluding participants from the clinical studies with psychiatric disturbance or substance abuse.

The C-SSRS was used to assess suicidal ideation and behaviour/ treatment-emergent suicidal ideation and behaviour were monitored during Phase 3 studies.

In addition, the Sponsor conducted an assessment of AE grouping of suicidal behaviour using SMQ Suicide/self-injury.

In both Study EFC16645 and Pool A, there was no imbalance observed between groups in the C-SSRS questionnaire. Since a numerical imbalance was observed in the number of participants with any TEAE in the AE grouping of suicidal behaviour in Study EFC16645 (9 participants with tolebrutinib vs. 0 with placebo) and Pool A (7 with tolebrutinib vs. 1 with teriflunomide), a comprehensive assessment of suicidal ideation and behaviour based on data collected via the C-SSRS questionnaire (suicidal ideation and suicidal behaviour) and SMQ Suicide/self-injury TEAEs across Study EFC16645 and Pool A was performed:

Suicidal ideation (based on participants who were administered C-SSRS):

- In Study EFC16645, 33 out of 718 (4.6%) participants receiving tolebrutinib and 15 of 364 (4.1%) participants receiving placebo had suicidal ideation during the treatment emergent period.
- In Pool A, 28 out of 909 (3.1%) participants receiving tolebrutinib and 27 out of 907 (3.0%) receiving teriflunomide had suicidal ideation during the treatment-emergent period.

Suicidal behaviour (based on AE grouping of suicidal behaviour and C-SSRS)

- In Study EFC16645, 3 out of 752 (0.4%) participants receiving tolebrutinib and 0 out of 375 (0.0%) participants receiving placebo had suicidal behaviour during the treatment emergent period:
    - 1 participant with 2 suicide attempts reported as TEAEs and also recorded on C-SSRS,
    - 1 participant with TEAE of suicide attempt (incorrectly recorded as death in C-SSRS), and
    - 1 participant with suicide attempt reported in C-SSRS only.

One participant receiving tolebrutinib underwent a medically assisted suicide recorded only as TEAE. The latter included a comprehensive psychiatric evaluation that determined the participant had capacity and did not have any underlying psychiatric conditions. The event was assessed as not related to tolebrutinib.

- In Pool A, 4 out of 933 (0.4%) participants receiving tolebrutinib and 3 out of 939 (0.3%) participants in the teriflunomide group experienced suicidal behaviour during the treatment emergent period:

- In the tolebrutinib group, 3 suicide attempts were reported as TEAEs and also recorded on C-SSRS and 1 suicide attempt was reported as TEAE only.

- In the teriflunomide group, 3 participants attempted suicide which were recorded on C-SSRS only.

During the post-treatment period, there was 1 suicide attempt in the tolebrutinib group and 1 completed suicide in the teriflunomide group; both approx. 1 year after study intervention discontinuation and both assessed as not related to study intervention. None of the participants receiving tolebrutinib in Study EFC16645 or Pool A was on concomitant medications that may be linked to suicidal behaviour.

5.4.4.10. Neoplasm benign, malignant and unspecified (incl. cysts and polyps)

An increased incidence of TEAEs in the SOC Neoplasm benign, malignant and unspecified (incl. cysts and polyps) was observed in the tolebrutinib group as compared to placebo in Study EFC16645 (4.1% vs. 2.4%) and as compared to teriflunomide in Pool A (5.8% vs. 2.7%).

For BTK inhibitors approved for blood malignancies including chronic lymphocytic leukaemia, the risk of second primary malignancy is identified. A pre-planned analysis was conducted based on the malignancy AE grouping using SMQ "Malignant or unspecified tumors".

Study EFC16645 and Pool A

In Study EFC16645, a numerical imbalance in malignancies was observed with 12 [1.6%] participants in the tolebrutinib group and 1 [0.3%] participants in the placebo group. Malignancies in the tolebrutinib group were: breast cancer (2), basal cell carcinoma, bladder cancer, bladder cancer stage 0 with cancer in situ, chronic myeloid leukaemia, endometrial adenocarcinoma, invasive breast carcinoma, lung cancer metastatic, prostate cancer, rectal cancer, renal cell carcinoma stage I, squamous cell carcinoma.

In Pool A, the incidence of malignancies was similar for tolebrutinib and teriflunomide (0.9% and 0.7%).

Malignancies in the tolebrutinib group were: breast cancer, breast cancer stage II, intraductal proliferative breast lesion, invasive breast carcinoma, invasive ductal breast carcinoma, plasma cell myeloma, renal cancer, and squamous cell carcinoma of skin.

Malignancies in the teriflunomide group were: adenocarcinoma of colon, bladder transitional cell carcinoma, malignant melanoma in situ, oligodentroglioma, prostate cancer, and soft tissue sarcoma.

In both Study EFC16645 and Pool A, the time-to-onset of malignancy ranged from 15 days to over 2 years after starting study intervention.

In Study EFC16645 and Pool A combined, the number of malignancies observed in at least 2 participants in the tolebrutinib group included female breast cancer (n=7), skin cancer (n=3), bladder cancer (n=2), and kidney cancer (n=2), with incidence rates of 1.63, 0.70, 0.46, and 0.46, per 1000 patient-years, respectively. The remaining malignancies were single occurrences.

An evaluation of the individual cases with breast cancer was conducted in participants with tolebrutinib in Study EFC16645 (2 patients; none on placebo) and Pool A (5 [0.5%] participants in the tolebrutinib group and 2 [0.2%] in the teriflunomide group) to determine a possible relation with the study intervention:

In study EFC16645, one participant with extensive family history of breast and endometrial cancer was found to have a SAE of breast cancer (Grade 3; invasive breast cancer; not rated as related to study drug) 1.5 years after initiation of tolebrutinib. Tolebrutinib was permanently discontinued. The other participant, with smoking history of 10 cigarettes per day, was diagnosed with a SAE of breast cancer (Grade 3) 2 years and 2 months after study start , which was not rated as related to tolebrutinib. Study intervention was temporarily interrupted and later permanently discontinued.

In Pool A, two participants were found to have stage 2 breast cancer at 3 months and 1 year and 4 months after the start of study intervention, respectively (SAE of invasive breast carcinoma, Grade 3; not rated as related to tolebrutinib) and (SAE of breast cancer stage II, Grade 2; not rated as related to tolebrutinib). Another 2 participants had known breast lesions prior to study start that were diagnosed as malignant during study on Day 20 and after 1 year and 5 months, respectively (SAE of Intraductal proliferative breast lesion, Grade 3; not rated as related to tolebrutinib; medical history of benign breast neoplasm and meningioma benign) and (SAE of breast cancer, Grade 3; not rated as related to tolebrutinib). The last participant was found to have breast carcinoma at 2 years and 3 months after the start of the study intervention (SAE of Invasive ductal breast carcinoma; Grade 3; not rated as related to tolebrutinib).

The majority of breast malignancy cases include confounding factors (previous breast lesion, extensive family history, and/or lifestyle factors with a known association to cancer). Time to onset for the cases were variable ranging from two weeks to 2.5 years after first dose of tolebrutinib.

In the ongoing open-label LTS17043 study, 1 participant on tolebrutinib during Study EFC16645 had a SAE of malignant melanoma after crossing over to LTS17043 (Grade 3; family history of melanoma and other skin cancers; not related to tolebrutinib) and 1 participant from the tolebrutinib group in Pool A had a SAE of germ cell tumor after crossing over to LTS17043 (Grade 3; rated as related to tolebrutinib).

In the ongoing blinded Study EFC16035, there were 4 SAEs of cancer: 1 participant with colon cancer ~ 10 months after starting the study intervention (Grade 3; medical history includes morbid obesity. Diabetes mellitus type II, hypercholesterolaemia, and hypertension; occasional alcohol consumption; not related to IMP), 2 participants with breast malignancies ~ 1 year and 9 months (intraductal proliferative breast lesion Grade 3, not related to IMP) and ~2 years after starting the study intervention , and 1 participant with malignant melanoma ~ 2 years and 10 months after starting the study intervention (Grade 3, not related to IMP). One of the 2 participants with breast malignancy had a grade 2 ductal carcinoma of the left breast reported on Day 633 and resected on Day 668. Further details for this participant including case narrative will be included in the safety update.

The incidence rate of malignancies across tolebrutinib participants in Pool B was 0.5 participants per 100 PY (20 participants with events / 4311.8 participant-years), which is similar to the incidence rate observed in the MS reference population (0.5 people with MS per 100 PY, Source: Grytten et al., 2021).

5.4.4.11. Benign conditions

Benign neoplasms in Study EFC16645 in the SOC Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps) occurred in 18 of 31 participants in the tolebrutinib and 8 of 9 participants in the placebo group (mainly involving the breast, skin, bone, uterus, and colon). There was 1 pre-malignant condition of polycythaemia vera in the tolebrutinib group. Benign neoplasms in Pool A within the same SOC were reported in 46 of 54 participants in the tolebrutinib and 18 of 25 participants in the teriflunomide group, mainly of the breast, uterus and skin. The time to onset with tolebrutinib ranged from 25 to 1063 days.

Across studies, a numerical imbalance was observed for participants with uterine leiomyoma, leiomyoma, or uterine leiomyoma necrosis (1.4% of participants with tolebrutinib vs. 0.3% participants in the teriflunomide group, 1.1% participants in the placebo group). Of the 23 participants (24 events) experiencing uterine leiomyoma, 2 were in Study EFC16645 and 21 were in Pool A. The higher occurrence in Pool A was explained by the younger population more likely to experience menstrual bleeding. The majority of events of uterine leiomyoma presented with bleeding. 14 of 23 study participants with uterine leiomyomas had prior history of uterine myoma and/or simultaneously reported/antecedent bleeding.

In summary, the applicant considers it unlikely that malignancy is a risk associated with tolebrutinib exposure. No additional pharmacovigilance and/or risk minimization activities are proposed for the risk of malignancy, while cases of malignancy will be followed up as a monitored event for further characterisation.

5.4.4.12. Deaths

In Study EFC16645, there were no AEs leading to death in the tolebrutinib group in addition to the two fatal cases described above in detail:

- A participant experienced a treatment-emergent SAE of hepatic failure resulting in a fatal outcome.
- A participant underwent a medically assisted suicide.

In the placebo group, 1 participant with traumatic brain injury had cerebral oedema and subarachnoid haemorrhage leading to death during the DB period, assessed as not related to the study intervention.

There were no AEs leading to death in the participants receiving OL tolebrutinib.

In Pool A, there were 3 participants with AEs leading to death, one of which in the tolebrutinib group (TEAE of gunshot wound [non-self-inflicted]) was assessed as not related to the study intervention. In the teriflunomide group, during the post-treatment period, 1 participant completed suicide with a firearm and 1 participant had subarachnoid haemorrhage leading to death, both events assessed as not related to the study intervention.

In the blinded Study EFC16035 for PPMS, there were 5 reports of death, all assessed as not related to the study intervention: one participant with convulsions and loss of consciousness, whose hospitalisation was complicated by severe aspiration pneumonia, later developed ventricular tachycardia and died due to brain oedema. One participant had bronchoaspiration and died due to septic shock secondary to aspiration pneumonia. One participant died due to brain oedema and multiorgan failure. The cause of death in these 3 participants was attributed to MS disease progression/ complication.

In the fourth participant, the cause of death was unknown and most likely due to myocardial dysfunction secondary to coronary artery disease/myocardial infarction. One participant committed suicide leading to death and the family reported that the patient had been depressed since diagnosis of PPMS.

After the cut-off, one participant was identified with sepsis due to pneumonia with fatal outcome in Study LTS17043 for which, based on the information provided, causal association with tolebrutinib cannot be ruled out. Potential contributing factors included 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 hospitalisation .

In Study EFC17262 (gMG population), there was 1 participant with a treatment-emergent SAE of COVID-19 pneumonia leading to death in the tolebrutinib group, assessed as not related to the study intervention by the Investigator.

5.4.4.13. Serious adverse events

In Study EFC16645 DB period, treatment-emergent SAEs were higher for tolebrutinib than for placebo (15.0% vs. 10.4%). Individual PTs had a frequency <1% (most of the PTs were observed once or twice), except COVID-19 pneumonia (1.1% with tolebrutinib and 0.5% for placebo) and multiple sclerosis relapse 1.1% in the tolebrutinib group and 0 in the placebo group). The number of participants with treatment-emergent SAEs assessed as related to the study intervention by the Investigator (1.9% with tolebrutinib and 1.3% with placebo) were balanced between study intervention groups, mainly in SOC Infections and infestations, and with individual PTs observed once or twice by study intervention group.

Among the participants with SAEs assessed as related to study intervention, there were:

- 11 participants (8 in the tolebrutinib group and 3 in the placebo group) with SAEs in the SOC Infections and infestations,
- 3 participants (2 in the tolebrutinib group and 1 in the placebo group) with SAE in the SOC Hepatobiliary disorders,
- 1 participant with atrial fibrillation in the tolebrutinib group (SOC Cardiac disorders),
- 1 participant with ischaemic stroke in the tolebrutinib group (SOC Nervous system disorders),
- 1 participant with squamous cell carcinoma (SOC Neoplasm benign, malignant and unspecified (incl. cysts and polyps)) in the tolebrutinib group.

In the participants receiving OL tolebrutinib, the SAE profile was similar to the DB period.

In Pool A, the percentage of participants with SAEs was comparable between tolebrutinib and teriflunomide (9.8% and 8.2%). All individual PTs had a frequency <1% and most were reported once or twice. SAEs that were assessed as related to the study intervention were reported in a comparable number of participants in both study intervention groups, mainly in SOC Infections and infestations, and most individual PTs were observed once or twice by study intervention group (12 participants on tolebrutinib and 9 participants on teriflunomide). Among participants with SAEs assessed as related to the study intervention, there were:

- 7 participants (4 in the tolebrutinib group, 3 in the teriflunomide group) with SAEs in the SOC Infections and infestations,
- 3 participants (2 in the tolebrutinib group, 1 in the teriflunomide group) with SAEs in the SOC Hepatobiliary disorders,
- 3 participants (2 in the tolebrutinib group, 1 in the teriflunomide group) with SAEs in the SOC Investigations. In the tolebrutinib group, PTs were transaminases increased, and ALT increased.

There were 19 participants with SUSARs in ongoing studies (14 participants in Study EFC16035 and 5 in Study LTS17043). In 11 out of 19 participants infectious events were reported (PTs of COVID-19, urosepsis, pneumonia, cellulitis, respiratory syncytial virus infection, pyelonephritis acute, and urinary tract infection). All of the participants recovered or are recovering except 1 participant in Study LTS17043:

A participant was diagnosed with a Grade 3 extragonadal germ cell tumor and pulmonary embolism, requiring hospitalisation. Biopsy confirmed Stage 3A testicular cancer with lung metastases. Treatment with tolebrutinib was interrupted, and the participant was readmitted due to worsening pulmonary embolism requiring anticoagulation adjustment. Both events of pulmonary embolism and extragonadal primary germ cell tumor were rated as related to tolebrutinib.

In 9 out of 19 participants the time to onset was more than 1 year from the first dose of study intervention. The study intervention was withdrawn in 11 out of 19 participants.

5.4.5. Discontinuation due to adverse events

Study EFC16645, permanent study discontinuation due to TEAEs in the DB period was comparable between intervention groups (3.9% for tolebrutinib vs. 2.9% for placebo). There was a numerical imbalance observed for the SOC Neoplasm benign, malignant, and unspecified (incl. cysts and polyps) (0.7% of patients in the tolebrutinib group [breast cancer, lung cancer metastatic, rectal cancer, renal cell carcinoma stage I, and squamous cell carcinoma] and none in the placebo group).

TEAEs leading to permanent study intervention discontinuation reported in 2 patients each in the tolebrutinib group were MS relapse, ALT increased, and rash. All other TEAEs were reported only once. Noteworthy (single) TEAEs in the tolebrutinib group were: *suicide attempt, parkinsonian gait, myocardial infarction, oesophagitis ulcerative, cholelithiasis, DILI, hepatic failure, platelet count decreased, transaminases increased, and assisted suicide*.

Among participants receiving OL tolebrutinib, there was 1 participant in the placebo/ tolebrutinib group and 0 in the tolebrutinib/ tolebrutinib group with PT *purpura* leading to permanent study intervention discontinuation.

In Pool A, the overall incidence of TEAEs leading to treatment discontinuation was similar between groups (4.5% in the tolebrutinib group and 4.4% in the teriflunomide group).

The most frequently reported TEAEs that led to permanent treatment discontinuation

- in the tolebrutinib group were *ALT increased (1.4%), pregnancy, suicide attempt (0.3% each), DILI, and urticaria (0.2% each),*

- in the teriflunomide group were *neutropenia (1%), ALT increased (0.9%), and pregnancy (0.5%)*.

Other individual PTs were reported once or twice.

A noteworthy numerical imbalance was observed for suicide attempt (3 participants in the tolebrutinib group and 0 in the teriflunomide group).

In Pool B, the EAIR of TEAEs leading to treatment discontinuation in participants exposed to tolebrutinib 60 mg was 1.7 participant per 100 PY.

TEAEs leading to treatment discontinuation in the ongoing studies were consistent with completed studies.

TEAEs leading to treatment discontinuation in the clinical pharmacology studies (in 5 participants) were ALT increased (Grade 2; after a single dose of 60 mg tolebrutinib with pantoprazole), mild reduced platelet count (after multiple 60 mg doses of tolebrutinib), symptomatic hypotension (Grade 3), drug eruption (Grade 1; during itraconazole alone administration), creatinine phosphokinase increased (7 days after a single dose of 60 mg tolebrutinib).

5.4.6. Safety in special populations

Table 43 AE by special population

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	None	12/24[a]
Hepatic impairment** patients (Subjects number /total number)	None	None
Paediatric patients <18 years (Subjects number /total number)	None	None
Older patients; Age 65-74 (Subjects number /total number)	None	14/36[b]
Age 75-84 (Subjects number /total number)	None	1/24[a]
Age 85+ (Subjects number /total number)	None	None
Other (Subjects number /total number)	None	None

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

a Phase 1 study POP16399

b Phase 1 study POP16398 (2/10), Phase 1 study POP16399 (11/24) and Phase 1 study PKM17308 (1/12)

The incidence rate and RR ratio of TEAEs (all TEAEs, treatment-emergent SAEs, TEAE leading to permanent study intervention discontinuation, treatment -emergent AESI, and other selected AE groupings) by subgroup for tolebrutinib compared to placebo in Study EFC16645 and compared to teriflunomide in Pool A have been evaluated.

Based on popPK analyses, age, sex, race/ ethnicity, weight, and BMI were not identified as covariates on the PK of tolebrutinib.

The following intrinsic factors have been predefined: age group (≤ 40, ≥40 years old; strata for Study EFC16645), sex (female, male), race (White, Black or African American, Asian, Other), weight (<70, ≥ 70 to <90, ≥90 kg), BMI (<25, ≥25 to <30, ≥30 kg/m2), EDSS strata (<4, ≥4; baseline value for EFC16645), and HAD at baseline (Yes/ No; only for pool A. Defined as 1 relapse in the previous year AND one of the following: at least 1 Gd+ lesion; or 9 or more T2-hyperintense lesions at baseline for participants who were already treated with DMT (any treatment with DMTs would be considered, if documented, during the prior year) or who had 2 or more relapses in the previous year, whether treated with DMTs or not).

The following extrinsic factors have been predefined: region 1 (US, non-US), region 2 (Eastern EU, Western EU, North America, ROW), and prior DMT use (Yes, No).

The subgroup analyses of TEAEs (and also for treatment-emergent SAEs, TEAEs leading to study intervention discontinuation, AESIs, and other selected AE groupings) for intrinsic factors (age group, sex, race, weight, BMI, EDSS strata, and HAD at baseline [for pool A]) as well as for extrinsic factors (regions and prior DMT use) were generally consistent with analyses in Study EFC16645 and Pool A. There were no unique patterns or trends identified in any of the subgroups examined and results in the subgroups were generally consistent with the results in the overall population. However, data should be interpreted with caution given the small number of events per subgroup.

Hepatic function

The effect of hepatic impairment on the tolebrutinib PK profile was investigated only in participants with mild hepatic impairment at 60 mg with a meal compared to matched participants with normal hepatic function (Study POP16398). The changes in the tolebrutinib and metabolite M2 exposures in participants with mild hepatic impairment were not clinically significant.

A single oral dose of 60 mg tolebrutinib taken with a meal was generally safe and well tolerated in both groups of participants with mild hepatic impairment and of matched control participants with normal hepatic function. Following a single oral dose of 60 mg tolebrutinib under fed conditions, total and unbound tolebrutinib C_{max}, AUC, and $t_{1/2z}$ in participants with mild HI compared to matched participants with normal HF were similar or slightly lower/ shorter by a maximum of 20%.

Based on Applicant's study results, neither a contraindication in patients with mild hepatic impairment nor a dose adjustment is deemed necessary. In contrast, tolebrutinib was not evaluated in participants with moderate and severe hepatic impairment in this study since PBPK modeling predictions led to higher exposure than the highest dose of tolebrutinib (240 mg) administered in the study. Therefore, the use of tolebrutinib 60 mg is contraindicated in patients with moderate and severe hepatic impairment.

Renal function

Since tolebrutinib undergoes very minor renal excretion, the effect of renal impairment on tolebrutinib and metabolite M2 PK was assessed only in participants with severe renal impairment not requiring dialysis.

The study showed that in participants with severe renal impairment, following a single oral dose of 60 mg tolebrutinib with a meal, total and unbound tolebrutinib C_{max} and AUC were slightly higher by a maximum of 1.6-fold compared to matched participants with normal renal function; while total and unbound metabolite M2 C_{max} were similar, and AUC were slightly higher by a maximum of 1.2-fold.

A single oral dose of 60 mg tolebrutinib taken with a meal was generally safe in both groups of participants with severe renal impairment and of matched-control participants with normal renal function. There were no SAEs, severe TEAEs, AESIs, or TEAEs leading to permanent study discontinuation reported during the study. Safety findings identified based on vital signs, ECG parameters, or laboratory values were absent.

Based on the study results, a contraindication of tolebrutinib 60 mg in any degree of renal impairment is not considered warranted. Participants with severe renal impairment and requiring dialysis were not evaluated.

Use in pregnancy

Reference is made to section 5.4.4.

Food effect

The pivotal food effect study with the to-be-marketed tablet 1C3 administered with a high-fat meal showed a positive food effect on tolebrutinib exposures (by 1.8-fold) and no food effect on M2 exposure.

Accordingly, the Phase 3 studies were conducted with the instruction that participants should always take tolebrutinib with a meal.

5.4.7. Immunological events

N/A

5.4.8. Safety related to drug-drug interactions and other interactions

Recommendations for concomitant use of potential perpetrator drugs with tolebrutinib 60 mg once daily with a meal are based on: 1) tolebrutinib and metabolite M2 PK results from DDI clinical studies (Study INT16385, Study INT16726, and PKM17308), 2) their safe and tolerable exposures of tolebrutinib and metabolite M2 in the multiple ascending dose study up to 240 mg (the highest repeated dose tested) QD under fed conditions (Study TDR16862), 3) complementary PBPK simulations, and 4) the exposure and safety relationship from Phase 3 studies. The recommendations are:

- Coadministration of any CYP3A inhibitors is allowed as tolebrutinib and metabolite M2 exposures at the intended therapeutic dose of 60 mg remained below exposures at 240 mg once daily.
- Potent and moderate CYP2C8 inhibitors should be avoided as they may increase tolebrutinib exposure with a risk of exceeding its exposure at 240 mg once daily. Weak CYP2C8 inhibitors are allowed.
- Potent and moderate CYP3A inducers (being also CYP2C8 inducers) should be avoided as they may decrease the exposures of tolebrutinib and metabolite M2.

The possibility of interaction from tolebrutinib and its main metabolites exhibiting similar to higher exposures to parent drug as CYP and/or transporter perpetrator towards other drugs was investigated using a tiered approach: *in vitro*, static predictions, and PBPK predictions. It was predicted that tolebrutinib and its metabolites are unlikely to interact with any other drugs *in vivo*. Therefore, there was no specific recommendations for coadministration of tolebrutinib as a perpetrator drug towards other drugs.

5.4.9. Vital signs and laboratory findings

Laboratory findings - Study EFC16645 (nrSPMS population) and Pool A (RMS population [Studies EFC16033 and EFC16034])

Haematology

Laboratory values over time

Descriptive statistics across visits for RBCs (haemoglobin, haematocrit, erythrocytes) in study EFC16645 and in Pool A indicated slight mean changes (decreases) from baseline in the tolebrutinib group (and neither in the placebo nor the teriflunomide group) within the first 3 months of treatment that did not worsen over time and were not found clinically meaningful.

A decrease in mean platelet counts from baseline was evident in the tolebrutinib group compared to placebo in study EFC16645 within the first 4 weeks of treatment and remained roughly stable thereafter (reference is also made to section 4.4). In Pool A, a decrease in mean platelet counts from baseline was evident also in the teriflunomide group.

Descriptive statistics across visits for WBCs in EFC16645 and in Pool A indicated slight mean changes (increases) from baseline in the tolebrutinib group (no changes in the placebo group) for leucocytes, neutrophils, lymphocytes within the first months of treatment that did not worsen over time and were not found clinically meaningful. In Pool A, there were slight decreases in WBCs in the teriflunomide

group. No clinically meaningful mean changes from baseline were noted for monocytes, basophils, and eosinophils.

Potentially clinically significant abnormality

Among participants with normal or missing values at baseline, the number of participants with PCSAs of haemoglobin ≤115 g/L in male (≤ 95 g/L in female) and PCSAs of haematocrit ≤ 0.37 in male (≤ 0.32 in female) was higher in the tolebrutinib group than in the placebo group in study EFC16645 (6.2% versus 2.7% and 10.8% versus 4.4%, respectively, see AESI section 'anaemia'), and the teriflunomide group in Pool A studies (3.2% and 7.9%). The number of participants with PCSAs for other (WBC) haematology parameters was similar between study groups in study EFC16645.

In Pool A studies, among participant with normal or missing value at baseline, the number of participants with PCSAs of leukocyte count <3 x 10^9/L and PCSAs of neutrophil count <1.5 x 10^9/L was lower in the tolebrutinib group than in the teriflunomide group (3.4% vs. 13.3% and 5.3% vs. 16.0%, respectively). More patients in the tolebrutinib group as compared to teriflunomide had a PCSA for lymphocytes >4 x 10^9/L (5.9% vs. 1.2%).

Clinical Chemistry

Laboratory values over time

No clinically meaningful changes in mean values of metabolic parameters (glucose, protein, albumin, creatine kinase, and lipase) and electrolytes parameters (sodium, potassium, chloride, calcium, and bicarbonate) were observed throughout the treatment-emergent period in either study intervention group in study EFC16645 and Pool A.

Potentially clinically significant abnormality

The overall number of participants with PCSAs for metabolic and electrolytes parameters during treatment emergent periods according to the baseline status was low and similar for treatment groups in study EFC16645 and Pool A. However, a higher frequency of total protein below lower limit of normal was reported in the tolebrutinib group (15.7%) compared to placebo (7.8%) in Study EFC16645, while in Pool A, the incidences were similar between tolebrutinib and teriflunomide (12.7% vs. 13.1%).

Liver function

For detailed assessment of increase in ALT >3 × ULN (AESI), biochemical Hy's law and ALT <8 × ULN reference is made to section 5.4.4.

In both, Study EFC16645 and Pool A, no clinically meaningful changes over time in mean ALT, AST, ALP, or TBILI values were observed. However, in Study EFC16645, some extreme values were observed at earlier timepoints, resulting in peaks in the mean values and large SEs. During the DB period of Study EFC16645, among participants with normal or missing value at baseline, a higher number of PCSA in the tolebrutinib group than in the placebo group was observed for ALT elevations, AST elevations, and ALT >3 × ULN with TBILI >2 × ULN (Table 44). In Pool A, among participants with normal or missing value at baseline, the number of participants with PCSAs of liver parameters was balanced between study intervention groups.

Table 44 Liver Function Number (%) of participants with abnormality (PCSA) during EFC16645 DB treatment period according to baseline PCSA status - Safety population (amended by the Rapporteur)

Laboratory parameter **Baseline** **PCSA criteria n/N1 (%)**	**Placebo** **(N=375)**	**tolebrutinib 60 mg** **(N=752)**
Alanine Aminotransferase (ALT)		

Laboratory parameter Baseline PCSA criteria n/N1 (%)	Placebo (N=375)	tolebrutinib 60 mg (N=752)
Normal/Missing		
> 3 ULN	6/372 (1.6)	30/741 (4.0)
> 5 ULN	3/372 (0.8)	15/741 (2.0)
> 10 ULN	1/372 (0.3)	7/741 (0.9)
> 20 ULN	0/372	4/741 (0.5)
Aspartate Aminotransferase (AST)		
Normal/Missing		
> 3 ULN	3/372 (0.8)	15/741 (2.0)
> 5 ULN	1/372 (0.3)	8/741 (1.1)
> 10 ULN	0/372	5/741 (0.7)
> 20 ULN	0/372	3/741 (0.4)
Alkaline Phosphatase		
Normal/Missing		
> 1.5 ULN	8/372 (2.2)	20/738 (2.7)
Total Bilirubin		
Normal/Missing		
> 1.5 ULN	6/371 (1.6)	15/739 (2.0)
> 2 ULN	3/371 (0.8)	8/739 (1.1)
> 1.5 ULN and ≤ 2 ULN		
> 2 ULN	0/0	0/2
ALT and Total Bilirubin		
Normal/Missing		
Alanine Aminotransferase > 3 ULN and Bilirubin > 2 ULN*	0/372	3/741 (0.4)

DB: double-blind, PCSA: Potentially clinically significant abnormality (2014-05-24 v1.0)

For ALT, AST and Total Bilirubin, categories are cumulative.

Note: The number (n) represents the subset of the total number of participants who met the criterion in question at least once during DB treatment period.

The denominator (/N1) for each parameter within a treatment group is the number of participants for the treatment group who had that parameter assessed post-baseline (not missing) during DB treatment period

Only the worst case during the DB treatment period for each participant with worsening from baseline is presented. If there is no participant with worsening in a baseline category, the row is not presented

*This is based on the maximum on-treatment ALT and TBILI values as multiples of ULN. They may not be concurrent, ie, the increase in ALT > 3 ULN may not be at the same, or similar, time point as the increase in TBILI > 2 ULN.

Renal function

In both Study EFC16645 and Pool A, no clinically meaningful changes in mean values of creatinine, creatinine clearance, and blood urea nitrogen were observed throughout the treatment-emergent period in either study intervention groups. The overall number of participants with PCSAs for renal function parameters during the treatment emergent period according to the baseline status was overall low and without clinically meaningful difference in the study intervention groups. Of note, in Pool A, there were more patients in the tolebrutinib group as compared to the teriflunomide group, who had a ≥30% change from (normal at) baseline in creatinine (13% vs. 6.4%) corresponding to a change in creatinine clearance from normal at baseline to ≥60 - <90 ml/min post-baseline (22.8% vs. 16.1%).

Vital signs - Study EFC16645 (nrSPMS population) and Pool A (RMS population [Studies EFC16033 and EFC16034])

Blood pressure and orthostatic changes

In Study EFC16645, systolic hypertension (defined as ≥160 mmHg and increase from baseline ≥20 mmHg) occurred in a similar number of patients treated with tolebrutinib and placebo (2.2% and 1.9%). In Pool A, systolic hypertension was reported in 1.5% and 3.7% of patients treated with tolebrutinib and teriflunomide.

No clinically meaningful changes over time were observed regarding systolic hypotension, DBP abnormalities, heart rate abnormalities (bradycardia or tachycardia), or body temperature throughout the treatment-emergent period in the tolebrutinib groups as compared to placebo and teriflunomide.

In Study EFC16645, a ≥ 5% increase in body weight was reported in 32.2% of patients treated with tolebrutinib compared to 25.8% of patients in the placebo group. In Pool A, weight increases of ≥5% occurred in 38.7% versus 25.4% of tolebrutinib and teriflunomide-treated patients.

Weight decreases of ≥ 5% were observed in 25.5% of patients with tolebrutinib compared to 28.6% of patients with placebo in Study EFC16645, and in 30.3% versus 44.7% of tolebrutinib and teriflunomide -treated patients in Pool A. No clinically relevant differences in body temperature were reported.

Electrocardiogram

No clinically meaningful changes over time were observed for ECG parameters (heart rate, PR, QRS, QT, and QTcF) throughout the treatment-emergent period in the tolebrutinib groups as compared to placebo and teriflunomide.

5.4.10. Post marketing experience

Not applicable

5.4.11. In vitro biomarker test for patient selection for safety

N/A

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

Safety database and exposure:

The completed pivotal Phase 3 Study **EFC16645** in nrSPMS serves as the primary source of safety data and is the only double-blind placebo-controlled trial in the intended patient population allowing assessment of the background adverse event rate of tolebrutinib 60 mg once daily. Additional safety data for tolebrutinib 60 mg once daily are available from the two similarly designed Phase 3, active-controlled studies EFC16033 and EFC16034 (forming **Pool A**) in RMS patients, as well as from the broader dataset including all participants treated with tolebrutinib 60 mg QD across Phase 2b and Phase 3 trials (**Pool B**). LTS data derive from the ongoing OLEs of the three Phase 2b/3 studies with tolebrutinib in participants with nrSPMS, RMS, and PPMS (LTS17043; as well as LTS16004 [only RMS] and EFC16035 [only PPMS]). In total, 1,886 participants were exposed to tolebrutinib 60 mg QD during Phase 2 and Phase 3 studies as of the data cut-off 11 September 2024. The size of the safety database is considered adequate to support the evaluation of tolebrutinib for chronic use in the intended indication. In study EFC16645, 752 patients were exposed to tolebrutinib 60 mg. The mean (SD) of treatment was 737.8 (340.3) days. 700 nrSPMS patients were treated with tolebrutinib for at least 6 months (24 weeks), 639 patients were treated with tolebrutinib for at least 1 year (48 weeks) and 464 were treated with tolebrutinib for at least 2 years (96 weeks).

In Pool A, 933 RMS patients were exposed to tolebrutinib 60 mg. 873 RMS patients were treated with tolebrutinib for at least 6 months (24 weeks), 835 patients were treated with tolebrutinib for at least 1 year (48 weeks) and 754 were treated with tolebrutinib for at least 2 years (96 weeks). The discontinuation rate in Study EFC16645 was rather high, with 42.2% of participants in the tolebrutinib group and 48.5% in the placebo group discontinuing treatment, predominantly due to progressive disease, while lower discontinuation rates were reported for the RMS studies in Pool A (25.0%) and Pool B (26.2%), which is to be seen in the context of the studied patient population in study EFC16645. Discontinuations due to TEAEs in Study EFC16645 were reported in 51 participants (6.6%) in the tolebrutinib group and 18 (4.8%) in the placebo group. In Pool A, the rate of TEAE related discontinuations was similar: 55 participants (5.9%) in the tolebrutinib group and 65 (6.9%) in the teriflunomide group. Patients in Study EFC16645 were generally older, more disabled, and had a higher prevalence of prior MS DMT use, comorbidities, and concomitant medications, while patients in Pool A were younger, less disabled, and largely treatment-naïve regarding MS DMTs. These differences need to be taken into consideration when comparing the safety outcomes in the two study populations of Multiple Sclerosis. Overall, the extent of exposure and the available safety data are considered adequate for assessing the clinical safety of tolebrutinib in the intended indication nrSPMS.

In Study EFC16645, 3 events of contusion were assessed by the Investigator as related to tolebrutinib, and the incidence was higher as compared to placebo (4% vs. 1%). Although, none of the events were rated as serious, contusion is included as ADR in the product information of the approved BTKi, thus, constituting a class effect, and appears to be related to the bleeding risk of these drugs as referenced by Li et al. (2025). Reflecting the observed imbalance, class experience, and biological plausibility contusion has been included as an ADR in section 4.8 of the SmPC with a frequency of common.

Anaemia occurred at a higher incidence in the tolebrutinib group (32 participants in Study EFC16645 vs. 2 with placebo; 71 in Pool A vs. 31 with teriflunomide). Events were reported predominantly in females of reproductive age (83.7%) and were frequently associated with heavy menstrual bleeding, which is already labelled as an ADR of tolebrutinib. No imbalance was observed among male participants, suggesting that the observed signal is largely driven by bleeding-related events in women of reproductive age.

Petechiae were more frequently observed in the tolebrutinib group (42 participants in Study EFC16645 vs. 3 with placebo group; 20 in Pool A vs. 1 with teriflunomide). Based on these findings, petechiae are listed as ADR under the SOC "vascular disorders", reflecting the bleeding-related nature of the event and its association with BTKi-induced platelet dysfunction, consistent with other approved BTKi.

The difference in the Vascular disorders SOC in study EFC16645 is driven by the PT hypertension (5.1% vs. 2.9%), which is not included in the ADR table in the SmPC, since a high proportion of patients with hypertension in the tolebrutinib group had confounders or predisposing factors identified. Furthermore, there were no clinically meaningful changes over time observed for SBP and DBP in the tolebrutinib group. Focusing on the events ≥ grade 2 (blood pressure ≥140/90 mmHg), and after excluding patients with a medical history of hypertension, no imbalance between the tolebrutinib and placebo group was found for ≥ grade 2 TEAEs.

With regard to the Gastrointestinal disorders SOC, the imbalance in study EFC16645 was mainly driven by the PT Abdominal pain upper (2.5% vs. 0.5%), which is included in the ADR table with the frequency "common". Diarrhoea was the most frequent reported gastrointestinal TEAE, occurring in 33 patients (4.4%) compared to 14 patients (3.7%) in the placebo group. Most events were mild and none patients discontinued treatment due to diarrhoea. The majority of events were assessed as not related to treatment. The applicant states that diarrhoea was not observed in nonclinical studies with tolebrutinib. This is not fully agreed, since non-formed liquid faeces were apparent following prolonged dosing ≥1 mg/kg/day tolebrutinib in the 39 weeks toxicity study in dogs. However, it is acknowledged

that the difference to placebo is minor and therefore accepted not to include diarrhoea as an ADR in the SmPC section 4.8.

In Pool A, the difference in the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) is mainly driven by the PT uterine leiomyoma (2.0% vs. 0.3%). As the imbalance is likely related to underlying conditions and increased detection due to bleeding events (see below), and heavy menstrual bleeding is already listed in section 4.8, inclusion of uterine leiomyoma in the SmPC is not considered warranted.

The difference in the SOC Reproductive system and breast disorders in Pool A is mainly driven by the PT Heavy menstrual bleeding (3% vs. <1%) which is included in the ADR table in the SmPC. In Study EFC16645, 6 patients experienced heavy menstrual bleeding (5 in the tolebrutinib group [0.7%] and 1 [0.3%] in the placebo group). The proposed ADR was primarily supported by safety data from the RMS population in Pool A. However, these findings are relevant for women in the reproductive age with nrSPMS.

AEs of special interest, serious adverse events and deaths, other significant events

The following adverse events of special interest have been predefined for tolebrutinib based on its pharmacological properties and mechanism of action and data from other BTK inhibitors:

Pregnancy of a female participant or female partner of a male participant; symptomatic overdose (serious or non-serious); increase of ALT >3 × ULN (confirmed); ECG observation of atrial fibrillation/atrial flutter; severe infection (NCI CTCAE ≥ Grade 3), that may or may not meet seriousness criteria (e.g., Grade 3 opportunistic infection); moderate or severe haemorrhagic events (NCI CTCAE ≥ Grade 2), including, but not limited to, symptomatic bleeding, bleeding in a critical area or organ such as the CNS, or intraocular bleeding; thrombocytopenia, platelet count $<75 \times 10^9$/L.

In addition, other AE groupings of interest pre-planned were COVID-19, suicidal behaviour, and malignancy, while depression, cardiac arrhythmia, opportunistic infections and haemorrhage were evaluated *post hoc*.

Pregnancy: in the clinical program, participants of reproductive potential were required to use contraception. Overall, there were 48 pregnancies (36 in female patients and 12 in female partners of patients). In total, there were 16 live births, 11 elective termination, 6 spontaneous abortions and 4 abortions. There are 11 ongoing pregnancies. Among female participants treated with tolebrutinib, there were 3 live births (no malformations), 6 elective terminations, 4 spontaneous abortions, and 4 ongoing pregnancies. In partners of male participants, there were 3 live births (no malformations), 2 abortions, 2 ongoing pregnancies, and 1 spontaneous abortion in the blinded group. Three post-treatment pregnancies were reported (1 spontaneous abortion, 2 ongoing). While no congenital abnormalities were observed, the number of exposures is limited, and outcomes include spontaneous abortions and ongoing pregnancies. The safety of tolebrutinib during pregnancy has not been established. Reference is made to the nonclinical assessment for further details.

No symptomatic overdoses were reported with tolebrutinib in Study EFC16645, Pool A, or Pool B. Therefore, it is agreed with the applicant that symptomatic overdose is not considered an identified risk.

Characterisation of the liver injury risk

ALT increases >3 × ULN as AESI were observed in 4.8% of tolebrutinib-treated participants across Study EFC16645 and Pool A (84 out of 1761 participants), with a higher incidence compared to placebo in Study EFC16645 (3.6% vs. 1.3%) and comparable rates to teriflunomide in Pool A (5.5% vs. 5.2%). Weekly liver monitoring during the first 12 week was implemented to mitigate the risk of DILI. The majority of participants in Study EFC16645 (95%) and all participants in Pool A were enrolled prior to

implementation of weekly LFTs; thus, evaluation of effectiveness of weekly LFTs relies mainly on Study LTS17043. In LTS17043, ALT elevations >3×ULN occurred in 26/643 newly initiated participants (4.0%) **under weekly LFTs**, including ten cases >8×ULN (1.6%). One case fulfilled Hy's law criteria. In this participant, ingestion of a traditional Chinese medicinal preparation ("swim bladder pills") shortly before the marked ALT rise was identified; the preparation consists of fish maw combined with various herbal supplements including yam and Radix polygonae. *In vitro* testing demonstrated concentration-dependent hepatocellular toxicity, supporting a potential contributory role while not excluding a drug-related effect. An additional case showed a Hy's-law-like pattern in the context of baseline hyperbilirubinaemia due to Gilbert's syndrome and was therefore not classified as Hy's law by the HAC. As in the Phase 3 programme, events displayed an early-onset (typically Weeks 4–8), steep ALT increases, and were largely asymptomatic. Among the ten ALT >8×ULN cases, four occurred without identifiable confounders. The remaining six cases involved potential confounding factors. All affected participants had recovered or were recovering at last follow-up. A temporal analysis conducted by the applicant indicated shorter recovery times in participants monitored weekly compared with those monitored less frequently (mean 39.6 days with weekly compared to 56.6 days prior to weekly), suggesting reduced magnitude of the liver injury due to weekly monitoring and earlier treatment discontinuation. In response to these findings, the applicant has added specific precautions in section 4.4 regarding concomitant hepatotoxic medicinal products, particularly early in treatment, and has advised against the use of hepatotoxic herbal or dietary supplements during tolebrutinib therapy.

Participants with elevated liver parameters at baseline (ALT or AST >1.5 × ULN, ALP >2 × ULN, or total bilirubin >1.5 × ULN) were excluded from the clinical development programme. Consistent with these criteria, tolebrutinib is contraindicated in patients with pre-existing acute or chronic liver disease or with baseline ALT or AST >1.5 × ULN, ALP >2 × ULN (unless explained by a stable chronic liver disorder), or total bilirubin >1.5 × ULN (unless due to Gilbert syndrome or a non-hepatic disorder). This restriction has been appropriately implemented in section 4.3 of the SmPC.

The following Hy's law cases occurred **before the introduction of weekly LFTs:** Five participants developed liver injury fulfilling Hy's law criteria assessed as possibly or probably related to tolebrutinib by the HAC. One of these cases progressed to acute liver failure requiring liver transplantation with fatal outcome. All of these cases had a time to onset within the first 90 days of tolebrutinib exposure and occurred before the implementation of weekly LFTs monitoring (between Weeks 2 and 12), including the fatal case. This suggests that limited monitoring frequency might delay detection of rapidly developing liver injury and underlines the need for strict compliance with the weekly monitoring schedule. In Study EFC16034, one additional participant developed liver injury consistent with Hy's law criteria on Day 550. This case was assessed as unlikely related to tolebrutinib by two HAC members due to confounding hepatotoxic co-medications initiated shortly before the event, while one member noted a weak potential association. Although causality was not established, this case raises concern about the potential for delayed-onset hepatotoxicity, particularly in the presence of concomitant hepatotoxic medication, and a contributory role of tolebrutinib cannot be fully excluded. In Study EFC16645 and Pool A, there were 48 patients with liver events of interest reviewed by the HAC (ALT >3 × ULN with concurrent TBILI >2 × ULN or ALT >8 × ULN), with 30 events in the tolebrutinib group. In total, 17 out of 30 liver-related TEAEs in the tolebrutinib groups across study EFC16645 and Pool A were considered by the HAC as possibly or probably related (including 4 of the Hy's law cases). Of the 30 patients with liver events of interest in the tolebrutinib group, 9 had a rechallenge in which study intervention was restarted following event resolution. Seven of these cases had a negative rechallenge. Therefore, in cases where a clear alternative aetiology is found, rechallenge can be acceptable. Although, the majority of the 30 events occurred within the first 90 days of treatment, cases were also observed at later time points, including those with more frequent monitoring. One participant experienced a marked ALT increase to 17.5 × ULN by Day 29 despite ALT levels being normal at screening and Week 2. Furthermore, the occurrence of two liver events of interest beyond Day 90,

both in participants with hepatotoxic co-medication, underlines that the risk for liver-related TEAEs cannot be completely restricted to early time points. In five of the 17 liver events of interest considered related to tolebrutinib, participants were receiving one or more concomitant medications with known hepatotoxic potential at the time of the event. Documented co-medications included NSAIDs (n=3), metformin (n=1), antidepressants (n=1), and proton pump inhibitors (n=2), with some participants exposed to more than one of these medications. Although, no clear association with a specific class of drug could be identified, the repeated presence of hepatotoxic co-medication in several cases raises concern that concomitant use may have contributed to the development or worsening of liver injury. This is further supported by the observation that two of the liver events of interest, including one fulfilling Hy's law criteria, occurred beyond Day 90 (Day 550 and Day 757, respectively) in participants with hepatotoxic co-medication. Furthermore, idiosyncratic DILI has also been reported for zanubrutinib after 30 months of treatment (Atallah et al., 2021).

In the pooled Phase 3 dataset (EFC16033, EFC16034, EFC16645), the applicant's relative risk analysis, however, did not show a trend for increased frequency of ALT >3×ULN events, including late-onset cases, among participants receiving hepatotoxic co-medication, though interpretation is limited by the low event numbers and a contributory role of individual agents cannot be excluded. In LTS17043, four late-onset ALT elevations were reported, three not meeting AESI criteria and one attributed to intercurrent infection; these numbers are too small for a meaningful assessment of late-onset risk under hepatotoxic co-medication. Based on the current evidence, the existing SmPC warning on concomitant use with potentially hepatotoxic medicinal products is considered adequate.

The introduction of weekly LFTs in LTS17043 enabled earlier identification of hepatic events and treatment interruption. However, the updated data also show that weekly monitoring does not fully prevent the occurrence of hepatic events, including high-magnitude ALT increases. As a consequence of the liver injury risk, the applicant added a boxed text in the SmPC section 4.4. ('Safety measures to be taken to mitigate the risk of severe liver injury'), outlining the required blood testing for ALT, AST, ALP, and bilirubin prior to initiation and then weekly in the first 3 months, monthly between months 4 to 12, and every 6 months between Months 12 and 24, with guidance to discontinue treatment if liver injury is suspected. Periodic monitoring thereafter may be performed as warranted. Further, a table with recommendations for dose adjustment and monitoring for patients who develop elevated transaminases during therapy is included in section 4.2 of the SmPC. In view of the frequency and severity of the reported cases, liver injury is an important identified risk in the tolebrutinib RMP, where it is described as "drug-induced liver injury". Moreover, the applicant has proposed a PASS study (ToleAdhere) to evaluate the adherence to liver function monitoring. In addition, the applicant proposed a patient card, patient guide, and the use of a prescriber guide, together with voluntary prescriber education and continued HAC review in the post-marketing period, which is supported by the CHMP.

Data from Study EFC16035 (PERSEUS) showed that, among 234 tolebrutinib-treated participants with scheduled LFTs at Week 2 and Weeks 4 through 12, ALT elevations >3× ULN were observed in 12 participants (5.1%), including four participants with ALT elevations >8× ULN. Of the four participants with ALT >8× ULN, three were considered probably related to tolebrutinib by the HAC, while one case with confounding factors was considered unlikely related. The narratives consistently show an early-onset hepatocellular injury pattern, most often between weeks 4 and 8 after treatment initiation, frequently asymptomatic and characterised by steep ALT increases that continued transiently following treatment interruption. Overall, the clinical safety data show that clinically relevant ALT elevations continue to occur in patients treated with tolebrutinib despite the implementation of weekly liver function monitoring during the first 12 weeks of treatment In total, six cases fulfilling Hy's law criteria have occurred in the tolebrutinib clinical development programme, including one despite the proposed weekly monitoring strategy (5/2006 prior to weekly monitoring vs 1/920 with weekly monitoring).

Beyond these Hy's law cases, several participants experienced high-magnitude ALT elevations (>8×ULN), with substantial aminotransferase increases in the absence of identifiable alternative aetiologies. No additional Hy's law cases have been reported since the previous data cut-off. Updated analyses indicate that weekly monitoring allows earlier detection of transaminase elevations (mean time to onset 40 vs 60 days) and facilitates earlier clinical management, which is reflected in a shorter mean time to recovery (44 vs 57 days). Most ALT elevations occurred early after treatment initiation, frequently between Weeks 4 and 8.

In summary, the data indicate that weekly LFTs during the first 12 weeks enable earlier detection and management of hepatic events and represent a necessary risk minimisation measure, while recognising that a residual risk cannot be fully excluded.

Atrial fibrillation/ atrial flutter was reported in 3 participants treated with tolebrutinib in Study EFC16645 and in 1 tolebrutinib-treated participant in Pool A. No such events occurred in the placebo group in Study EFC16645 or in the teriflunomide group in Pool A. In Study LTS17043 (cut-off 11 September 2025), five participants experienced atrial fibrillation; all events were assessed by the investigator as not related, given the presence of confounding factors. Atrial fibrillation/ atrial flutter has also been associated with other BTKi (Gambril et al., 2024), likely attributed to off-target effects (reference is made to the non-clinical section). Moreover, the major metabolite M8 is metabolised by CYP2J2, which is responsible for epoxidation arachidonic acid. CYP2J2 is predominantly expressed in cardiac tissues, see OC in the Clinical pharmacology/Metabolism section. Based on these findings, atrial arrhythmias (atrial fibrillation/ atrial flutter) remains an important potential risk in the tolebrutinib RMP. Accordingly, the applicant has included a general warning on atrial fibrillation/atrial flutter in section 4.4 of the SmPC.

In Study EFC16645, serious and severe infections occurred more frequently in the tolebrutinib group (5.2% for both) than in the placebo group (3.5% and 2.9%, respectively). In Pool A, rates were lower and comparable between tolebrutinib (2.5% and 2.3%) and teriflunomide (2.2% and 1.9%, respectively). Most events were respiratory tract infections, mainly COVID-19, consistent with the timing of study conduct during the pandemic. No fatal infections were reported in EFC16645 or Pool A. However, three fatal cases were documented in ongoing studies. In Study EFC16035, one participant died from sepsis; the event was assessed by the Investigator as not related to study drug, though, full evaluation is not possible since the study is still blinded. In Study LTS17043, a fatal pneumonia progressing to sepsis was assessed as related to tolebrutinib. In Study EFC17262 (gMG population), one fatal case of COVID-19 pneumonia was assessed by the Investigator as unrelated to tolebrutinib. Overall, the events confirm serious infection as an identified risk and are consistent with observations reported for other BTKi (Pilmis et al., 2023). This risk is addressed through a warning in Section 4.4 of the SmPC. Section 4.4 of the proposed SmPC also states that tolebrutinib is not recommended in patients with severe immunodeficiency, bone marrow disease, or uncontrolled infections. In view of the events described, the applicant has revised Section 4.3 of the SmPC to include "patients with severe immunodeficiency (e.g. acquired immunodeficiency syndrome, bone marrow disease, or severe, uncontrolled active infections)" as a contraindication.

When comparing infection rates with or without concomitant medications, the infection rates were higher in patients who received tolebrutinib with concomitant immunosuppressive treatment. In Study EFC16645 the incidence with concomitant immunosuppressive treatment was 62.7% and without 52.2%. In Pool A the incidence with concomitant immunosuppressive treatment was with 66.1% and without 56.1%. The same pattern was seen for the different categories of immunosuppressive treatment. Consequently, a warning on concomitant use with immunosuppressants is included in the SmPC section 4.4 and 4.5.

Across Study EFC16645 and Pool A, **opportunistic infections** were reported in six participants receiving tolebrutinib compared to 0 participants in placebo group and 1 participant receiving teriflunomide, respectively. In EFC16645, one case of varicella zoster pneumonia (Grade 3) and one case of herpes zoster oticus (Grade 2) occurred; both resolved, in one case with temporary treatment interruption. A fatal case of disseminated aspergillosis and cytomegalovirus infection occurred in a participant who had undergone liver transplantation two months after discontinuing tolebrutinib. This case was confounded by immunosuppressive therapy. In Pool A, three participants in the tolebrutinib group developed opportunistic infections (ophthalmic herpes zoster, herpes ophthalmic following steroid use, and cytomegalovirus hepatitis); all events were non-fatal and resolved, including two without treatment interruption. One case of herpes ophthalmic (Grade 1) was reported in the teriflunomide group. In addition, in Study EFC16035, a fatal case of pulmonary actinomycosis was identified at autopsy following severe aspiration pneumonia. While a causal relationship with the study intervention cannot be excluded, a full evaluation is not possible due to the blinded study status. Across Study EFC16645 and Pool A, the overall incidence of opportunistic infections among tolebrutinib-treated participants was ≤0.3%. In several cases, potential contributing factors such as immunosuppressive therapy, corticosteroid use, or aspiration were present. However, such factors were not consistently documented across all events, and a role of tolebrutinib in increasing susceptibility to opportunistic infections cannot be excluded. Based on the mechanism of actions and the small imbalance in opportunistic infections in Study EFC16645 and the opportunistic infection in ongoing Study EFC16035, Section 4.4 of the SmPC has been updated to include a warning on opportunistic infections.

Haemorrhages, albeit no major bleedings, were reported in nonclinical studies with tolebrutinib in rats and dogs in line with the pharmacological characteristics and mode of action of licensed BTK inhibitors, which imply a complex and still not fully elucidated mechanism to cause bleedings, basically thought to be due to on- and off-target kinase inhibition. In platelets, BTK and other related TEC family kinases contribute to platelet activation and aggregation mediated via the collagen receptor glycoprotein VI (Lipsky et al., 2020). As a result, treatment with therapeutic doses of irreversible BTK inhibitors is thought to lead to complete inhibition of GPVI signalling, which is expected to cause only mild bleedings (Jamasbi et al., 2017).

Tolebrutinib was found to reduce platelet counts only to a small extent, i.e. an approximate 10% reduction from baseline values over the first 6 to 12 weeks of treatment without further deterioration. Evaluation of the AESI thrombocytopenia; platelet count $<75 \times 10^9/L$ revealed a single patient fulfilling this criterion after ~15 months of treatment; the event resolved after study intervention interruption without corrective treatment, and was assessed by the Investigator as not related to tolebrutinib. In summary, it is agreed that thrombocytopenia is not considered as a risk of tolebrutinib exposure.

Evaluation of the AESI moderate or severe haemorrhagic events (NCI CTCAE Grade ≥2) revealed similar low incidences in the treatment groups in study EFC16645 (placebo: 1.3%; tolebrutinib: 0.8%), while a slightly higher incidence was reported for tolebrutinib in Pool A (2.1%), probably in line with the longer treatment duration. Two discontinuations in Pool A were due to haemorrhagic events: one case of spontaneous haematoma, assessed as related to tolebrutinib, and one case with heavy menstrual bleeding and uterine haemorrhage, also considered related. Importantly, none of the AESI events was associated with thrombocytopenia. Moderate to severe haemorrhagic events with tolebrutinib occurred with a maximum severity Grade ≤3, with Grade 3 being reported in a single patient in study EFC16645 and in 5 patients in Pool A (0.5%) contrasting the experience with other BTK inhibitors, e.g. ibrutinib (4%) acalabrutinib (3%), zanubrutinib (2%) (von Hundelshausen, 2021). Single haemorrhages affecting the brain were reported as PTs in EFC16445 and Pool A but occurred in a similar small number across treatment groups. Compared to study EFC16645, there were more events in Pool A related to the reproductive system and breast disorders SOC in line with menstrual/

uterine bleeding, which might be explained by the younger patient population in the RMS trials including female patients in the reproductive age. In total, six participants with tolebrutinib in EFC16645 and 20 in Pool A experienced moderate to severe haemorrhagic events, of which three and eight events, respectively, were assessed as related to treatment. Two discontinuations occurred in Pool A, and concomitant NSAID use was documented in several cases. Altogether, eleven haemorrhagic events were considered related to tolebrutinib. A warning on haemorrhage has been included in SmPC sections 4.4 and potential interactions in section 4.5.

Mild (Grade 1) haemorrhagic events in study EFC16645 as well as in Pool A occurred with a 2-fold higher incidence in the tolebrutinib group as compared to placebo and teriflunomide, mainly due to contusion and petechiae in study EFC16645 and petechiae, heavy menstrual bleeding, increased tendency to bruise, and epistaxis in Pool A. Petechiae, heavy menstrual bleeding and increased tendency to bruise is included in the ADR table in the section 4.8 of the SmPC.

Based on the non-clinical findings of haemorrhage in CNS and intraocular bleeding, the applicant was asked to provide an overview of AEs and SAEs related to haemorrhages in CNS and intraocular bleeding in the clinical studies. Overall, there was few events of haemorrhage in CNS and intraocular bleeding and no significant imbalance observed between treatment arms for haemorrhagic events under the SOCs Eye Disorders and Nervous System Disorders. Most events were mild in severity, non-serious, assessed as unrelated to tolebrutinib and associated with identifiable risk factors.

Taken together, given the recognised class effect, the exclusion of patients with bleeding risk factors, and the involvement of concomitant NSAID use in several cases, support the need for clear bleeding-risk information in the SmPC. A warning on bleeding risk, including guidance for patients with underlying risk factors or concomitant medications that affect coagulation or platelet function, has therefore been included in the SmPC. Haemorrhages are included in the RMP as an important potential risk with appropriate measures reflected in the RMP.

While second primary malignancies (SPM) with approved BTK inhibitors have been described, the mechanism for their development is not readily clear and they are also often associated with haematologic malignancies for which these BTKi are licensed. SPM without non-melanoma skin cancer or SPM non-melanoma skin cancer is either an important identified or potential risk in the RMPs for the approved BTK inhibitors.

Malignancies have not been rated as an identified risk for tolebrutinib by the applicant and have thus not been prespecified as AESI. However, a 2:1 imbalance of TEAEs was reported in the Neoplasm benign, malignant and unspecified (incl. cysts and polyps) SOC at the expense of tolebrutinib both in study EFC16645 and Pool A (4.1% vs. 2.4% [placebo] and 5.8% vs. 2.7% [teriflunomide]). A preplanned SMQ analysis (malignant and unspecified tumours) revealed a clear difference between tolebrutinib and placebo, i.e. 1.6% vs. 0.3%, but not between tolebrutinib and teriflunomide (0.9% vs. 0.7%). In both Study EFC16645 and Pool A, the highest number of malignancies observed in the tolebrutinib group included female breast cancer (7 patients), skin cancer (3 patients), bladder cancer (2 patients), and kidney cancer (2 patients). The remaining malignancies were single occurrences. In study EFC16645 there were numerically more malignancy events despite the slightly shorter treatment duration in this study as compared to Pool A. However, the patient population with nrSPMS in study EFC16645 was older as compared to patients with RMS included in Pool A (mean age of 49 years versus 36.5 years), and importantly, almost 50% of patients in study EFC16645 were treated with at least 2 DMTs prior to the study, as compared to 10% of patients in Pool A. A correlation between at least two switches of DMTs and an increased risk for cancer development has been reported in the literature, which is thought to be a consequence of exposure to different molecules with different mechanisms of action that negatively influence the innate and adaptive immune system (D'Amico et

al., 2019). These factors might have contributed to the numerically higher incidence of malignancies in study EFC16645.

While no specific cancer type prevailed in the tolebrutinib group in study EFC16645, breast cancer dominated the malignancies in Pool A (5 of 8 patients with events). Upon review, it is agreed that these patients had confounding factors, i.e. family history of breast cancer, lifestyle habits, and preexisting breast lesions. Moreover, all breast cancer cases were reported between 2 weeks and 2.5 years after initiation of tolebrutinib, which is far below published latency periods for solid cancers in general and specifically for breast cancer, i.e. > 4 to 5 years (Little et al., 2024; Howard 2015). Two additional breast cancer cases have been reported in the ongoing blinded study EFC16035 (PPMS). The higher number of breast cancer cases in Pool A versus study EFC16645 (despite the younger age of the patients and the lower number of previous DMT use in Pool A) and the fact that only two breast cancer cases have been reported in the teriflunomide group cannot be neglected. In total, 10 breast cancer cases have been identified across Study EFC16645 and Pool A, 8 in patients treated with tolebrutinib and 2 in patients treated with teriflunomide. All but two patients had predisposing risk factors, including pre-existing lesions, family history of breast or endometrial cancer, obesity, or smoking, which may have contributed to the occurrence of these events. It is agreed with the applicant that a causal relation of breast malignancies in patients treated with tolebrutinib is not plausible in the vast majority of cases. There were two more malignancy SAEs with tolebrutinib in the ongoing open-label study LTS17043, malignant melanoma and germ cell tumor. The latter occurred in a patient with a family history of cancer and was diagnosed with stage 3AM1A testicular cancer with lung metastasis. As the diagnosis was raised with latency, a causal relationship with tolebrutinib cannot be established, although a contributory role also cannot be excluded.

Further clarification of the malignancy risk was provided by comparing incidence rates observed in the clinical programme with background rates reported in epidemiological studies of MS populations. In total, 27 patients with 28 malignancy events were identified in the tolebrutinib groups, compared with 9 events in 8 patients on teriflunomide and 2 cases on placebo. The incidence rate was numerically highest with tolebrutinib (5.49/1000 PY), followed by teriflunomide (3.69/1000 PY) and placebo (2.69/1000 PY). Reported background rates in MS cohorts ranged from 4.0 to 8.0/1000 PY. Standardised incidence ratios (SIRs) were calculated using nine epidemiological datasets. Four studies yielded SIRs >1 for tolebrutinib, but confidence intervals in most comparisons included 1, limiting firm conclusions. In contrast, based on the largest dataset (Pierret, 2024), the SIR was statistically <1 (0.69 [95% CI 0.45–0.97]). The analyses are, however, not adjusted for age, which restricts interpretability. For teriflunomide and placebo, SIRs were generally below 1, but the low number of cases and wide confidence intervals preclude meaningful comparison. Albeit being benign in nature, there was a striking imbalance of uterine leiomyoma reported in the tolebrutinib group in Pool A as compared to the teriflunomide group (21 vs. 3 patients). On review, several of these patients had a history of leiomyoma, abnormal uterine bleeding, or other gynaecological conditions that may have contributed, while in 6 patients no such history was identified. In Study EFC16645, no imbalance was observed versus placebo. The applicant attributed the higher reporting rate in Pool A to bleeding tendencies associated with BTK inhibition, leading to more frequent detection of coinciding conditions. As heavy menstrual bleeding is already listed in section 4.8, uterine leiomyoma does not need to be added as an ADR.

While there is no strong evidence for a relation of tolebrutinib to the reported malignancies (including breast, skin and other malignancies), a contribution cannot be excluded given its mechanism of action as a BTK inhibitor and the calculated incidence rates against background incidences for malignancies in the MS population. Therefore, the applicant has included a warning in section 4.4 of the SmPC, and has added “Malignancies” in the RMP as an important potential risk.

Patients with MS are known to have an increased risk for suicidality, partly due to higher rates of depression and anxiety (Kalb et al., 2019, as referenced by the applicant). As with any brain penetrant drug, a potential for suicidal ideation and suicidality cannot be excluded. Accordingly, structured assessments using C-SSRS and MedDRA SMQ groupings were conducted in Study EFC16645 and Pool A, showing comparable rates of suicidal ideation and behaviour across treatment groups. In Study EFC16645, based on the C-SSRS/SMQ-derived dataset, suicidal ideation was reported in 4.6% of participants receiving tolebrutinib and 4.3% receiving placebo, while suicidal behaviour occurred in 0.4% of participants in the tolebrutinib group and none in the placebo group. In Pool A, suicidal behaviour was reported in 0.4% of tolebrutinib-treated participants and 0.3% of those treated with teriflunomide. Although the applicant concluded that suicidality rates were balanced across treatment groups, the TEAE data in the grouping of suicidal behaviour suggest a numerical imbalance favouring placebo and teriflunomide: in Study EFC16645, 9 tolebrutinib-treated participants (1.2%) experienced such events compared to none on placebo. In Pool A, the incidence was 7 participants in the tolebrutinib group (0.8%) and only 1 participant in the teriflunomide group (0.1%). Events included suicide attempts, suicidal ideation, and one medically assisted suicide. Among tolebrutinib-treated participants, two required hospitalisation and three discontinued treatments. None of the affected participants had a history of suicidality or received medications known to increase suicide risk. The median time to onset was 292 days in Study EFC16645 and 418 days in Pool A. The applicant attributes the discrepancy between C-SSRS assessments and TEAE reporting to reporting variability, data entry errors, and external triggers, and considers C-SSRS the more reliable source. However, this explanation does not fully account for the consistent imbalance observed in TEAE data, particularly as no such signal was observed in comparator groups. Moreover, psychiatric comorbidities were excluded from the clinical programme, which may underestimate risk in real-world practice. Across LTS17043, 17 participants experienced suicidality events (two suicide attempts and 15 cases of suicidal ideation). Psychiatric comorbidity was documented in six participants, and five were receiving concomitant antidepressant or anxiolytic medication. Psychosocial stressors were reported in several cases. All events were assessed by the investigators as not related to tolebrutinib. However, as a treatment-related risk cannot be fully excluded, the applicant has included suicidal behaviour in section 4.4 of the SmPC as a warning. Further risk minimisation measures are planned post-marketing (see section 6.4).

A total of 12 deaths were reported up to the DCO (4 with tolebrutinib, 1 with placebo, 2 with teriflunomide, and 5 in the blinded Study EFC16035). Of these, one death was assessed as related to tolebrutinib by the investigator, i.e. hepatic failure in Study EFC16645, and for one fatal pneumonia progressing to sepsis occurring after the DCO, a relation to tolebrutinib could not be ruled out in the ongoing Study LTS17043. In addition, one medically assisted suicide occurred in Study EFC16645, one fatal TEAE (non-self-inflicted gunshot wound) was reported in Pool A, and one fatal case of COVID-19 pneumonia in Study EFC17262 (gMG population); all were assessed as unrelated to tolebrutinib. No imbalance in fatal TEAEs was observed between treatment arms in Study EFC16645 or Pool A. In general, with regard to the cases of death associated with infections, a possible causality to the tolebrutinib treatment cannot be fully excluded, considering the mechanism of action. Serious infections are a known class effect of BTKi inhibitors, which is further addressed in the AESI section.

In Study EFC16035, five fatal cases have been reported (completed suicide, pneumonia aspiration, cardiomyopathy, brain oedema, and sudden death with supraventricular tachycardia)). All were assessed by investigators as unrelated to tolebrutinib, with alternative medical explanations identified in each case.

Serious adverse events

The SAE incidence was consistently higher with tolebrutinib across both, Study EFC16645 and Pool A. In Study EFC16645, the frequency of patients with treatment-emergent SAE was higher in the tolebrutinib group compared with the placebo group (15.0% vs. 10.4%).

The SOCs with the highest proportion of patients with treatment-emergent SAEs were Infections and infestations (5.2% vs. 3.5%), Nervous system disorders (4.0% vs. 2.7%), Injury, poisoning, and procedural complications (2.7% vs. 3.2%) and Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (1.6% vs. 0).

The imbalance in the SOC Infections and infestations SOC is mainly driven by the PTs COVID-19 pneumonia (1.1% vs. 0.5%), COVID-19 (0.9% vs. 0), pneumonia (0.7% vs. 0.8%), and pyelonephritis (0.4% vs. 0). Other PTs were observed once or twice. In eight patients, the treatment emergent SAEs in the SOC Infections and infestations were assessed as related to tolebrutinib. Serious infections are an important identified risk in the RMP, and a warning is included in section 4.4 of the SmPC.

The imbalance in the SOC Nervous system disorders is mainly driven by MS relapse (1.1% vs. 0). The overall relapse rate in the EFC16645 study was 0.033 for tolebrutinib and 0.032 for placebo. There were 8 (1.1%) participants in the tolebrutinib group who had an "MS relapse" reported as an SAE and none in the placebo group. Of the 8 cases, 2 were not consistent with a protocol-defined relapse as 1 had no change in the EDSS score and the other had a concomitant infection. Of the remaining 6 cases, 4 were treated immediately prior to study start with MS DMTs that are lymphocyte sequestering agents with a known risk of rebound reactivation of disease activity (fingolimod, siponimod and natalizumab). The other 2 cases occurred within 1 month of study start, suggesting the influence of prior MS DMT discontinuation. All 6 cases were deemed by the Investigator as not related to the IMP. Taken together, all of the MS relapse cases in the tolebrutinib group could be related to a risk of rebound reactivation with other MS DMTs and it is agreed with the applicant that there is no evidence of increase in relapse severity with tolebrutinib.

One ischemic stroke case was reported, assessed as related to tolebrutinib. This finding aligns with previous reports of stroke as a potential adverse effect of BTKi therapy, likely related to an increased risk of atrial fibrillation (Quartermaine et al., 2023).

The majority of SAEs were considered not related to the study intervention. The number of patients with SAEs assessed as related to the study intervention was 1.9% in the tolebrutinib group and 1.3% in the placebo group. Within the SOC Hepatobiliary disorders 2 patients with SAE were considered related to tolebrutinib (1 patient experienced an SAE of hepatic failure leading to death and 1 patient developed drug-induced liver injury). Furthermore, there was 1 patient with Grade 4 ALT increased assessed as probable related by the HAC. In the SOC Cardiac disorders, 1 case of atrial fibrillation was assessed as related to tolebrutinib.

In pool A, the incidence of SAEs was similar between tolebrutinib and teriflunomide (9.8% and 8.2%).

The most frequently reported SOCs with treatment-emergent SAEs were infections and infestations (2.5% vs. 2.2%), neoplasms benign, malignant, and unspecified (incl cysts and polyps) (1.5% vs. 0.9%), injury, poisoning, and procedural complications (1.6% vs. 0.9%), and Nervous system disorders (1.0% vs. 1.3%). treatment-emergent SAEs that were assessed as related to tolebrutinib by the Investigator were all in the SOC Infections and infestations, SOC Hepatobiliary disorders, and SOC Investigations: COVID-19, COVID-19 pneumonia, pyelonephritis acute, bronchitis, DILI (Hy's law confirmed by HAC), transaminases increased, and ALT increased. All cases occurred in 1 patient except for DILI in 2 patients.

Overall, serious adverse events were mostly related to serious infections, liver injury and malignancies in tolebrutinib treated patients.

In ongoing studies EFC16035 and LTS17043, 19 SUSARs have been reported, including 11 infections. As of the data cut-off (11 September 2025), narratives have been submitted for eight cases. Among these, four events (Grade 3 urinary tract infection, urosepsis, microscopic colitis, and supraventricular tachycardia) and one case of serious infections were assessed by investigators as related, while the

diabetes insipidus case remains unresolved and two further events (extragonadal germ cell tumour and a urinary tract infection with musculoskeletal symptoms) were assessed as not related. Infection-related events are already reflected in the product information, and the remaining events are isolated and do not indicate a new safety concern.

TEAEs leading to treatment discontinuation were generally consistent with predefined AESI, including hepatobiliary disorders, infections and infestations, and pregnancy. In Pool A, an increased incidence of discontinuation due to suicide attempt was observed in the tolebrutinib group compared to teriflunomide (3 vs. 0). Discontinuations associated to malignancies occurred more frequently in the tolebrutinib group in both Study EFC16645 (5 vs. 0) and Pool A (5 vs. 3).

Safety analyses were conducted across predefined subgroups (intrinsic and extrinsic factors), including comparative data from placebo and teriflunomide groups, enabling differentiation of drug-related effects from disease-related events. In Study EFC16645 and Pool A, the safety profile of tolebrutinib remained consistent across subgroups, with no clinically meaningful differences observed.

In the study including participants with severe renal impairment not requiring dialysis, tolebrutinib exposure increased up to 1.6-fold (parent drug) and 1.2-fold (M2 metabolite), with no safety concerns observed after a single 60 mg dose. Clinical data are very limited, with only three participants with severe renal impairment and none on dialysis included in Phase 3 studies. The applicant has revised section 4.2 of the SmPC to state that patients with severe renal impairment should only be treated if the anticipated benefit outweighs the potential risk and should be monitored closely, which is acceptable.

Tolebrutinib is mainly metabolised by CYP2C8, and to a lesser extent by CYP3A4. Based on PK DDI studies, the MAD Study, complementary PBPK simulations, and the exposure and safety relationship from Phase 3 studies, the applicant proposed the following recommendations:

- Coadministration of any CYP3A inhibitors is allowed as tolebrutinib and metabolite M2 exposures at the intended therapeutic dose of 60 mg remained below exposures at 240 mg once daily.
- Potent and moderate CYP2C8 inhibitors should be avoided as they may increase tolebrutinib exposure with a risk of exceeding its exposure at 240 mg once daily. Weak CYP2C8 inhibitors are allowed.
- Potent and moderate CYP3A inducers (being also CYP2C8 inducers) should be avoided as they may decrease the exposures of tolebrutinib and metabolite M2.

The applicant revised the SmPC wording in section 4.5 and added a warning in section 4.4 to state that the clinical relevance on the interaction between tolebrutinib and moderate or strong CYP2C8 inhibitors is uncertain, and as a precaution, co-administration should be avoided. The updated wording in the SmPC section 4.4. and 4.5. is considered acceptable.

In section 4.4 of the SmPC, it is mentioned that the use of live (attenuated) vaccines may carry a risk of infections and must therefore be avoided. Live (attenuated) vaccines (including but not limited to varicella zoster, oral polio, and nasal influenza) within 2 months before the first treatment visit was an exclusion criterion in Study EFC16645. The applicant has included information on vaccination in the SmPC section 4.5 and included a guidance on use of other vaccines during treatment in section 4.4 as requested.

No clear safety signal derived from the provided descriptive haematology and chemistry evaluations. A small decrease in mean platelet counts from baseline was evident in the first 4 weeks of treatment with tolebrutinib in study EFC16645 and Pool A (but also in the teriflunomide group), which did not exceed 10% from baseline values and which remained roughly stable thereafter. Slightly increased

incidences of PCSA values of low haemoglobin and low haematocrit in patients treated with tolebrutinib as compared to placebo and teriflunomide is in line with findings of more frequent TEAEs of anaemia in patients with tolebrutinib as a consequence of (mild) bleeding events.

While serious infection is an important identified risk associated with tolebrutinib, this risk appears not to be accompanied by a decrease in laboratory parameters on WBCs. With regard to liver function, there were no clinically meaningful changes over time in mean ALT, AST, ALP, or TBILI values throughout the course of study EFC16645. However, there were some extreme values in some of the first timepoints, resulting in peaks in the mean values. A higher number of PCSA in the tolebrutinib group than in the placebo group was observed for ALT elevations, AST elevations, and ALT >3 × ULN with TBILI >2 × ULN. This is related to the risk of liver injury (see AESI section above).

With respect to vital signs, in both Study EFC16645 and Pool A, no clinically relevant differences were observed between tolebrutinib as compared to placebo or teriflunomide for SBP or DBP or heart rate. No ECG abnormalities were observed with tolebrutinib in Study EFC16645 or Pool A compared to placebo or teriflunomide. This is in line with nonclinical findings, which showed no significant inhibition of the hERG channel and low risk of hERG-mediated cardiotoxicity.

A higher proportion of patients with ≥5% weight gain was observed with tolebrutinib vs. placebo (32.2% vs. 25.8%) and teriflunomide (38.7% vs. 25.4%). Most cases had early onset or relevant confounders (concomitant medication, comorbidities, female predominance). Overall, while a numerical imbalance was observed, the evidence does not support a causal association with tolebrutinib.

5.4.12.1.2. Adverse drug reactions in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 5.4.3 above.

Table 45 *ADRs proposed for inclusion in the SmPC by the CHMP*

Infections and infestations	
COVID-19	Very common
Upper respiratory tract infections	Very common
Influenza	Common
Lower respiratory tract and lung infections	Common
Gastrointestinal disorders	
Abdominal pain	Common
Investigations	
ALT elevation	Common
Reproductive system and breast disorders	
Heavy menstrual bleeding	Common
Vascular disorders	
Increased tendency to bruise	Common
Petechiae	Common
Contusion	Common

5.4.12.2. Conclusions on clinical safety

Overall, 1,886 participants were exposed to tolebrutinib in the clinical programme. The clinical safety evaluation, which informs the product information, is based on the pivotal study EFC16645 in nrSPMS patients and supportive studies in RMS patients from Pool A, including 1,685 patients who received at

least one dose of tolebrutinib at the recommended daily dose of 60 mg, with a mean exposure of 806.3 days. Of these, 1,474 patients (87.5%) received tolebrutinib for ≥ 12 months as of the data cut-off (11 September 2024). LTS from study LTS17043 is expected to add an additional 3 years of data upon completion. The size of the safety database is considered adequate at the time of potential marketing authorisation.

The ADRs identified by the applicant are COVID-19 and upper respiratory tract infections, each with very common frequency, and influenza, lower respiratory tract and lung infections, petechiae, contusion abdominal pain, ALT elevation, increased tendency to bruise, and heavy menstrual bleeding, each with common frequency are endorsed by the CHMP.

The main safety concern with tolebrutinib treatment in the clinical programme relates to liver injury. While no hepatic toxicity was identified in nonclinical studies or Phase 2 clinical trials, ALT elevations >3 × ULN were reported in Phase 3 studies including five confirmed cases fulfilling Hy's law, one of which resulted in a fatal outcome. These cases occurred prior to the implementation of weekly liver function monitoring, at a time when LFTs were performed less frequently.

Following the introduction of weekly liver function monitoring during treatment initiation, as implemented in Study LTS17043, earlier detection and management of hepatic events were observed. However, one additional Hy's law case was identified by the HAC and assessed as possibly related to tolebrutinib; this case was confounded by the ingestion of a traditional herbal preparation known to contain hepatotoxic ingredients. Beyond this case, several participants experienced high-magnitude ALT elevations (>8×ULN), including substantial aminotransferase increases in the absence of identifiable alternative aetiologies.

Liver injury is therefore considered an important identified risk with tolebrutinib treatment in the RMP and is addressed through a comprehensive set of risk minimisation measures, including frequent liver function monitoring, defined thresholds for treatment interruption or discontinuation, contraindications in patients with pre-existing liver disease, and warnings regarding hepatotoxic co-medications and herbal products. Additional measures include a PASS study (ToleAdhere), as well as a patient card, patient guide, and prescriber guide, and continued HAC review in the post-marketing setting.

Cross-program safety analyses support that weekly liver function monitoring enables earlier recognition of hepatic events and faster recovery following treatment interruption. Nevertheless, these measures do not fully prevent the occurrence of hepatic events. Across the tolebrutinib clinical development programme, six cases fulfilling Hy's law criteria have been identified, including one under the weekly monitoring strategy, and clinically relevant ALT elevations have continued to be observed. Overall, these findings indicate improved risk mitigation through weekly monitoring, while a residual hepatic risk remains.

Beyond liver injury, post marketing measures are in place for serious infections (important identified risk), atrial arrhythmias, haemorrhages and malignancies (important potential risks), in line with other approved BTK inhibitors, and corresponding information have been added to the SmPC. Suicidality has likewise been included as warning in the product information, based on observed imbalances.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP (version 0.7, signed off on 01 April 2026):

Table 46 Summary of safety concerns in the proposed RMP

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

6.1.2. Discussion on proposed safety specification

The CHMP endorsed the above described important identified risks, important potential risks and missing information as appropriate.

The potential safety concerns "Suicidal behaviour and attempts" and "Reproductive toxicity" which were not considered warranted for inclusion in the RMP should be followed up in PSURs. Similarly, "Use in breast-feeding" are included as missing information for the purpose of PSUR reporting.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

The safety profile of tolebrutinib will continue to be further characterized in real clinical conditions of use through routine pharmacovigilance activities, such as postmarketing safety surveillance, including periodic safety update reports, monitoring of product technical complaints relating to adverse events, and signal detection.

In addition, the following routine pharmacovigilance activities will be implemented:

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

Furthermore, the applicant has proposed the **additional pharmacovigilance activities** (Table 47 and Table 48).

Table 47 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

Table 48 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
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.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

A specific event follow-up questionnaire for atrial arrhythmias has been included as part of routine pharmacovigilance.

However, routine pharmacovigilance activities are not considered sufficient to address data on safety concerns and additional pharmacovigilance activities are warranted.

6.2.2.2. Additional pharmacovigilance activities

The following 2 additional Category 3 pharmacovigilance activities are required:

1) ongoing clinical trialLTS17043 - A Study to Investigate LTS and Tolerability of Tolebrutinib in Participants with Multiple Sclerosis.
   The LTS17043 study is a Phase 3 extension global, multicenter, interventional, open label study to assess LTS and tolerability of tolebrutinib in participants with relapsing multiple sclerosis, primary progressive multiple sclerosis, or non-relapsing secondary progressive multiple sclerosis who participated in the Phase 2b LTS16004 study or 1 of the 4 Phase 3 pivotal tolebrutinib studies (GEMINI 1 [EFC16033], GEMINI 2 [EFC16034], HERCULES [EFC16645], or PERSEUS [EFC16035]).
   The study sample is determined by parent study population.
   The final study report is foreseen in 2031. The study duration per participant is up to 3 years and the overall study is expected to be 5 years. The first participant was enrolled on 16 April 2024 and the last patient enrolled will depend on the completion of Study EFC16035, therefore the final completion date is not fixed.
   No standalone interim report for study LTS17043 will be submitted; safety data will be provided through periodic safety data updates within the PSUR. The final study report will be submitted to Health Authority within 12 months after the end of the trial.
   The Study will address the following safety concerns: DILI, serious Infections, atrial Arrhythmias (Atrial Fibrillation and Atrial Flutter), malignancy and haemorrhages. All safety endpoints are included in the primary objectives of the study, while secondary and tertiary objectives are exclusively related to efficacy aspect. The LTS17043 protocol, with safety as its primary objective, allows assessment of adverse events patterns and risk estimation by parent study treatment, including *ad hoc* analyses for unexpected events, also to evaluate risk factors associated with specific adverse events.
2) a post-authorization safety study (PASS). ToleAdhere, linked to Additional Risk Minimization Activities to measure the effectiveness of the additional risk minimization measures, focusing on adherence to liver function monitoring. The study will be conducted using routinely collected data from multiple European MS registries that participate in the Big MS Data Network:
   The objective is to evaluate the adherence to the recommended liver function monitoring (ALT, AST, ALP and TBILI) in patients initiating treatment with tolebrutinib for MS in routine clinical practice.
   The primary objectives are:
   - Describe characteristics of MS patients who are initially exposed to tolebrutinib
   - Assess the adherence to liver function monitoring before the initiation of tolebrutinib
   - Assess the adherence to weekly liver function monitoring in the first 12 weeks after the initiation of tolebrutinib
   - Assess the adherence to monthly liver function monitoring in months 4-12 after the initiation of tolebrutinib
   - Assess the adherence to every 6 months liver function monitoring in months 13-24 after the initiation of tolebrutinib

   The secondary objective is to assess the incidence of DILI among MS patients who are initially exposed to tolebrutinib. The exploratory objective is to assess the severity of DILI in the same cohort, in data sources where this information is available.
   Patients will be accrued for up to 5 years following the European Commission decision on marketing authorisation and will be followed after first exposure to tolebrutinib, from the date of first exposure to tolebrutinib (cohort entry date) for 24 months or to the earliest date of one the followings: discontinuation of tolebrutinib (gap between refills exceeds days of supply plus a grace period), abnormal LFTs, liver injury, death, last update of data source, emigration, or end of study period. The proposed data sources for the PASS include MS registries from Denmark, Sweden, and Finland, as well as the GePaRD claims database from Germany. Over 6,000 participants will be enrolled over a 5-year accrual period, enabling a robust assessment.

The full study protocol of ToleAdhere effectiveness study, including a feasibility assessment will be submitted within 6 months after marketing authorization.

6.3. Plans for post-authorisation efficacy studies

No imposed post-authorization efficacy studies as a condition of the marketing authorization are considered needed for this application.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

The applicant has proposed routine and additional risk minimisation measures (Table 49 and Table 50).

Table 49 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:**

Safety concern	Routine risk minimization activities
	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. **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.

Table 50 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

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

Part V of RMP is in line with safety concerns and the product information.

6.4.2.2. Additional risk minimisation measures

The following additional risk minimization measures are included in the Annex 6 of the RMP and in the annex IID of the SmPC:

- Prescriber Guide
- Patient Guide
- Patient Card

Prescriber Guide include the following updated 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.

The **Patient Guide** includes the following key elements:
- A recommendation to read the package 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.

Patient Card is designed as a portable tool, including a summary of monitoring schedule, a remind of signs and symptoms of liver problems and some advice to contact the doctor before starting any new treatment, as well as prescribers name and contacts:

a. The card should include an instruction for the patient "Carry with you at all times",
b. The card should be part of the PI and should be included in the package of the medicinal product to ensure that the Patient card is handled to the patient together with the medicinal product.
c. The following key elements for patient card should be included in Annex 6 of the RMP and in Annex II of the PI:
    - 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.

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 0.7 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list, and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21 July 2025.

8. Product information

8.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical trial, i.e. adult patients with SPMS without relapses in the previous two years. As the overall effect is positive, the differences in effect sizes for relevant subgroups, i.e. active, non-active, are only described in section 5.1 to provide valuable information for HCPs. A reference is made to section 5.1.

8.1.2. SmPC section 5.1 justification

Study design as well as results for the most important endpoints of the pivotal study in SPMS have been described. Moreover, efficacy outcomes in subgroups defined by disease activity (e.g. active versus non-active disease, with a more pronounced effect observed in patients with active disease) were included as this will provide useful information to prescribers.

Most important results for the two phase 3 studies in RMS have also been included as they were considered supportive.

8.1.3. SmPC section 4.3 justification

Tolebrutinib is contraindicated in patients with moderate to severe hepatic impairment or abnormal baseline liver parameters due to the identified risk of clinically significant liver injury with tolebrutinib. As patients with pre-existing liver disease or relevant baseline liver test abnormalities were excluded from the clinical studies, safety in this population has not been established.

The contraindication in patients with severe immunodeficiency or severe, uncontrolled active infections is justified by the identified risk of serious infections, including opportunistic infections, and by the mechanism of action of BTK inhibition.

8.2. Labelling

8.2.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Cenrifki (tolebrutinib) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

MS is a chronic immune-mediated condition, characterised by neuroinflammation, demyelination and neurodegeneration within the CNS. Disability accumulation is the result of both inflammatory and neurodegenerative processes.

The most common form (relapsing-remitting MS, RRMS) is characterised by acute episodes of neurological dysfunction named relapses followed by variable recovery and periods of clinical stability. Within 15-20 years approximately 50% of patients who suffer from a relapsing-remitting form develop sustained disability with or without superimposed relapses; this form is called SPMS.

With the consensus update of clinical MS phenotypes in 2013 (Lublin, 2014) MS subtypes are to be classified according to the presence of acute and focal inflammatory activity (active or non-active) and disease progression (progressing or non-progressing) independent of any relapse activity. Acute and focal inflammatory activity together with compartmentalised inflammation cause neurodegeneration in MS. There is evidence that these mechanisms are present from disease onset in any disease phenotype. However, the relative contribution to the overall disability accumulation varies throughout the disease course. In particular, compartmentalised inflammation becomes more prominent during progression. As per the underlying differences between PMS phenotypes, Lublin consensus 2013 criteria recommended that *PPMS should remain a separate clinical course because of the absence of exacerbations prior to clinical progression, but it likely does not have pathophysiologically distinct features from relapsing forms of MS that have entered a progressive course (SPMS)*. The new McDonald 2024 criteria provide a single, unified framework of criteria to diagnose relapsing or progressive MS. It is stated that *pathological and imaging studies have identified quantitative, not qualitative differences between the various clinical forms, suggesting that the disease course should be considered as a continuum* (Montalban, 2025).

The aim of treatment with tolebrutinib is to delay disability progression independent of relapses.

The finally agreed indication is:

"*CENRIFKI is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (see section 5.1)"*.

9.1.2. Available therapies and unmet medical need

Tolebrutinib (also termed SAR442168 in the dossier) is a CNS-penetrant small molecule with nanomolar potency, that binds irreversibly to and inactivates BTK.

The exact mechanism of action of tolebrutinib in MS therapy has not been completely unravelled. However, the covalent binding of the acryloyl moiety of tolebrutinib to cysteine 481 near the ATP-binding site of BTK is thought to inhibit the inflammatory BTK activity in B cells, macrophages and microglia in the periphery and CNS.

The currently available treatments for MS are primarily focused on relapsing phenotypes. There remains a significant unmet need for effective treatments in progressive forms of MS, e.g., to slow disability progression across the spectrum of MS. To date, only interferon beta-1b (*"Betaferon"*, EMEA/H/C/81) and siponimod (*"Mayzent"*, EMEA/H/C/4712) are specifically licensed for SPMS; however, their approval is limited to SPMS with active disease as evidenced by relapses or imaging features of inflammatory activity. Further, there are several medicinal products for the treatment of RMS with active disease which can be used for the treatment of SPMS with relapses. At present, there are no approved DMT in non-active SPMS or SPMS encompassing both, active and non-active SPMS. In the pivotal HERCULES trial SPMS patients were at least 2 years relapse-free at study baseline. No products are explicitly licensed for this population.

9.2. Main clinical studies

For a detailed description of the main clinical study supporting this application, please refer to section 5.3.2 of this document.

One phase 2 dose-finding study in RMS (DRI15928) and one pivotal study in nrSPMS (EFC16645, HERCULES) were submitted.

Study EFC16645 was a Phase 3, randomised, double-blind, placebo-controlled, two-arm, parallel-group, event-driven (based on the primary endpoint) study with a variable treatment duration to evaluate the efficacy and safety of tolebrutinib in participants with SPMS being relapse free for at least 24 months.

Adult subjects 18 to 60 years of age, inclusive with a history of RRMS and a current diagnosis of SPMS as well as documented accrual of disability during the last 12 months in the absence of clinically evident relapses for at least 2 years and an EDSS score 3.0 to 6.5 point inclusive were included. Regarding baseline disease activity based on MRI activity, the mean number of Gd+ lesions was generally low (0.5 (82.6)). While the majority of the participants did not have acute MRI based activity, only 142 (12.7%) participants showed Gd+ lesions at baseline.

In total 1131 subjects (435 (38.5%) males and 696 (61.5 %) females) were enrolled and randomised 2:1 to either tolebrutinib or placebo. 4/1131 participants were randomised but not exposed to study intervention but included in the ITT primary analysis population.

Assuming a recruitment period of approximately 24 months and 48 months study duration, the study was projected to have an estimated mean treatment duration of 33 to 36 months. As pre-specified, a

study end date was announced when approximately 288 events of 6-month CDP (primary endpoint) were projected to have occurred, after which all participants still on study had a final EOS efficacy assessment visit within -2 to +4 weeks of the announced date. A participant was considered to have completed the study if he/she had completed all periods of the study including the EOS visit, whether remaining on IMP or not.

Participants with 6-month CDP were eligible to receive OL treatment (tolebrutinib) or offered the possibility to switch to some other marketed treatment if available.

Subjects who completed the study and were taking the IMP treatment until the end of the trial (double-blind or open-label) were eligible to enrol in the open-label extension study LTS17043 where open-label tolebrutinib was provided.

The primary endpoint was the time to onset of 6-month CDP. Secondary endpoints were tested following a statistical testing hierarchy and included time to 3-month CDP; total number of new and/or enlarging T2-hyperintense lesions; time to onset of sustained 20% increase in the 9-HPT for at least 3 months; time to onset of sustained 20% increase in the T25-FW for at least 3 months; time to onset of 6-month confirmed disability improvement; percent change in brain volume at the end of study compared to month 6.

Two additional phase 3 studies in RMS were submitted (EFC16033 or GEMINI 1 and EFC16034 or GEMINI 2). However, since the GEMINI studies failed their primary endpoint and did not show superiority in ARR versus Teriflunomide, the data on CDP from these studies can only be considered supportive. An additional phase 3 study in PPMS (EFC16035) had been finalised during the MA application and the topline results were provided during the procedure on 14th December 2025. The study failed its primary endpoint 6-month cCDP and did not show superiority in the 6-months cCDP versus placebo.

9.3. Favourable effects

In the pivotal study EFC16645 the confirmation of disability progression relied on the PIRA concept, i.e., confirmation of disability as accumulation of disability based on progression independent of relapse activity. The study population consisted of patients with SPMS, as evidenced by worsening of disability in the 12 months prior screening and without clinical relapses, in the 24 months preceding study entry. Efficacy of tolebrutinib regarding disability progression independent of relapse activity has been observed in these subjects. The studied population comprises a patient population with high unmet medical need.

Study EFC16645 met its primary endpoint (time to event). Treatment with tolebrutinib led to a 31% reduction in the risk of 6-month CDP compared with placebo (hazard ratio 0.693 (95% CI: 0.546 to 0.880), p=0.0026). The proportions of 6-month CDP were 22.6% (171/754 pts) and 30.7% (116/377 pts), for tolebrutinib and placebo, respectively.

The magnitude of the treatment effect is in the range of what was assumed as clinically relevant based on the sample size calculation to detect a 30% risk reduction in 6-month CDP with tolebrutinib compared to placebo. The Kaplan-Meier curves of cumulative incidence rate for the onset of 6-month CDP showed a sustained effect with an early separation with a lower proportion of patients in the tolebrutinib group with 6-month CDP events compared to those on placebo throughout the treatment period. All pre-defined sensitivity analyses and *post hoc* analyses showed statistically significant differences in the treatment effect in favour of tolebrutinib over placebo in line with the results for the primary analysis.

A hierarchical statistical testing procedure for the key secondary endpoints was applied. The results for the first secondary endpoint "time to 3-month CDP" were consistent with the primary endpoint. Tolebrutinib led to a statistically significant difference compared with placebo showing a risk reduction of 24% (HR of 0.757 (95% CI: 0.607 to 0.944, p=0.0134). The Kaplan-Meier curves of cumulative incidence rate for the onset of 3-month CDP for tolebrutinib and placebo separated early with a lower proportion of subjects on tolebrutinib compared to those on placebo with 3-month CDP events throughout the treatment period.

The second secondary endpoint was also met. Tolebrutinib demonstrated a relative reduction of 38% in the "total number of new and/or enlarging T2-hyperintense lesions" (RR [95% CI]: 0.622 [0.432 to 0.897]; p=0.0110). Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with the primary analysis of this endpoint [relative risk (95% CI) 0.627 (0.439, 0.896) p= 0.0103]. The percentage of participants who did not develop any new and/or enlarging T2-hyperintense lesions during the study period was greater in the tolebrutinib group as compared with the placebo group (58.2% versus 49.1%).

The fourth secondary endpoint showed a 23% risk reduction in the "time to onset of sustained 20% increase in the T25-FW for at least 3 months" for tolebrutinib when compared to placebo (HR 0.767, 95% CI: 0.640 to 0.919, nominal p=0.0040). Sensitivity analyses excluding data after initiation of OL tolebrutinib treatment were in line with the primary analysis of this endpoint [HR of 0.760 (95% CI: 0.632 to 0.915, nominal p=0.0037].

With respect to the fifth secondary endpoint "time to onset of 6-month confirmed disability improvement" the percentage of participants achieving 6-month CDI was 8.6% in the tolebrutinib group and 4.5% in the placebo group (4.5%) (HR [95% CI]: 1.882 [1.102 to 3.214]; nominal p=0.0206).

Analyses assessing the adjusted annualised adjudicated relapse rate (evaluated as tertiary/exploratory endpoint) showed a very low on-study ARR in patients randomly assigned to placebo (0.032), indicating a studied SPMS population with overall low clinical disease activity.

Subgroup analyses of the primary endpoint 6-month CDP showed on the basis of a treatment-by-subgroup interaction that the treatment effect of tolebrutinib was more pronounced in the smaller subgroup of patients with Gd+ lesions at baseline (HR 0.346 [95% CI 0.183, 0.656]) as compared to the subgroup without baseline Gd+ lesions (HR 0.777 [95% CI 0.601, 1.006]) and in the subgroup of subjects naïve to disease modifying treatment (HR 0.392 [95% CI 0.241, 0.638]) as compared to those patients who have previously been treated with 1 DMT (HR 0.649 [95% CI 0.407, 1.034]) or with ≥ 2DMTs (HR 0.902 [95% CI 0.643, 1.265]).

Post hoc subgroup analyses assessing the treatment effect on the primary endpoint according to the number of baseline PRL load (chronic active lesions) suggest that the effect of tolebrutinib was more pronounced in the subgroup of patients with 4 or more phase rim lesions (HR 0.463 [95% CI 0.210, 1.019]), compared to 0 PRL (HR 1.171 [95% CI 0.612, 2.242]), and 1-3 PRL (HR 0.846 [95% CI 0.468, 1.531]).

The two identically designed phase III studies EFC16033 and EFC16034 in patients with RMS (around 99 % diagnosed with RRMS) to evaluate the superiority of tolebrutinib over teriflunomide included a population with RMS with documented disease activity as evidenced by relapse or Gd+ lesion(s) on MRI. It is noted that tolebrutinib did not meet the primary endpoint of reducing the ARR compared to teriflunomide but showed nominally significant differences between tolebrutinib and teriflunomide for the key secondary 6-month CDW and the secondary 3-month CDW (EFC16033 and EFC16034 pooled population) endpoint. The majority of 6-month CDW events in the pooled analysis were PIRA events and occurred in participants without any adjudicated relapse during the trial. Of the 140 PIRA events,

60 (43%) occurred in the tolebrutinib group and 80 (57%) in the teriflunomide group. The percent of participants with a PIRA event was 6.4% on tolebrutinib compared to 8.5% on teriflunomide [(HR (95% CI) 0.730 (0.522, 1.021)] indicating a 27% relative risk reduction in favour of tolebrutinib. It is therefore agreed with the applicant that these analyses of the two RMS studies support the effect of tolebrutinib on PIRA in participants with RMS, suggesting an impact on disability progression independent of an effect on relapses. Considering a SPMS indication, covering "active" and "non active" disease, the two studies in RMS (EFC16033 and EFC16034) are both considered supportive for active SPMS, i.e., patients with disease activity would benefit from treatment with regard to disability progression independent of relapses (PIRA).

In the phase 2b dose-response study in RMS participants (128 diagnosed with RRMS and 2 diagnosed with active SPMS) the primary endpoint was met demonstrating a dose – response relationship for tolebrutinib as evidenced by a higher reduction in the number of new Gd+ brain lesions after 12 weeks of treatment with higher doses (60 mg vs 5 mg to 30 mg).

9.3.1. Uncertainties and limitations about favourable effects

Indication

Overall, the indication wording was discussed during the procedure with the objective to adequately reflect the patient population studied in the pivotal SPMS trial. The applicant´s initial proposal "*CENRIFKI is a brain penetrant Bruton's tyrosine kinase inhibitor (BTKi) indicated for the treatment of non-relapsing secondary progressive multiple sclerosis (nrSPMS) in adults*." was revised to "*for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses and with signs of disability progression (see section 5.1).* However*,* the criterion "*with signs of disability progression"* was regarded as insufficiently specific by CHMP, as it represents a general prerequisite and inclusion criterion applied across SPMS studies rather than a distinguishing characteristic of the studied population.

In order to ensure alignment with the pivotal trial population, the CHMP considered that specifying "SPMS without relapses in the last 2 years" more accurately reflects the studied population. The applicant subsequently agreed to revise the indication accordingly. The final agreed indication therefore refers to adult patients with SPMS without relapses in the previous 2 years.

Further characterisation of the study population and treatment effects, including efficacy outcomes in subgroups defined by disease activity (e.g. active versus non-active disease, with a more pronounced effect observed in patients with active disease), is considered acceptable to be described in section 5.1 of the SmPC in order to appropriately inform prescribers.

Inclusion criteria

While disease activity or non-disease activity at baseline in study EFC16645 was determined solely by the presence or absence of Gd+ lesions at baseline, the number of new and/or enlarging T2 hyperintense lesions at baseline in comparison to previous MRIs, was not determined. Therefore, the proportion of active SPMS patients within the overall study population might therefore have been underestimated and some patients in the non-active SPMS group might have been misclassified as inactive although being active. In addition, due to the lack of these data, correlation of disability progression independent of acute and focal inflammatory MRI activity was not possible.

Study outcomes and estimation

With respect to the primary endpoint, it cannot be decided whether the differences for subgroup analyses based on the existence/non-existence of Gd+ lesions at baseline occurred by chance or not

since the respective subgroups were not the primary analysis population, and the study was not powered for these subgroups. However, results need to be interpreted in the context of the overall positive treatment effect. Moreover, an additionally performed *post hoc* analysis in non-active participants (no relapse in the 2 prior years and no Gd+ lesions at baseline) for the time to onset of 6-month CDP using Cox Model (imputed data) showed similar results with a relative risk reduction of 23% (HR [95% CI]: 0.767 [0.593 to 0.992]; unadjusted p=0.0433) with borderline statistical significance. Overall, it needs to be considered that a consistent treatment effect of tolebrutinib was demonstrated across the entire study population, which included patients with SPMS regardless of the presence/absence of focal acute inflammatory disease activity as evidenced by Gd+ lesions on baseline MRI.

No benefit on cognitive impairment was observed based on cognitive function tests (SDMT and CVLT-II). The same relates to the outcome on quality of life, assessed by the change in the MSQoL-54.

As stated in Ciccarelli et al. the current definition of PIRA assumes that acute inflammation and neurodegeneration can be disentangled by introducing specific time windows between the onset of relapses and the observed increase in disability. Instead, the PIRMA concept, i.e. progression independent of relapses and brain and spinal cord MRI activity, would have been more useful to gain insight in disability progression independent of focal and acute inflammatory disease activity, i.e. clinical relapses and focal and acute inflammatory activity based on MRI lesions. However, basic MRI assessments in parallel to the EDSS scores evaluated for sustained disability progression have not been pre-defined. As correlation of disability progression independent of acute inflammatory MRI activity is not possible, it cannot be concluded that effect on disability progression is due to the effect of tolebrutinib on the chronic neuroinflammation.

Mechanism of action

The postulated dual mechanism of action, i.e. the inhibition of the inflammatory BTK activity in B cells, macrophages and microglia in the periphery and CNS, has not been comprehensively established. In this context, the smaller effect in the subgroup of SPMS patients without Gd+ lesions at baseline, i.e. non-active SPMS, might be explained by a predominant mechanism of action against acute and focal inflammation. However, the results of *post hoc* analyses assessing the treatment effect on the primary endpoint according to the PRL load at baseline suggest that although tolebrutinib had no effect on resolution of PRL, tolebrutinib might have a greater effect on the risk of disability progression in those with more PRL, a potential marker of focal chronic inflammation. Nevertheless, PRLs tend to persist (mean (SD) change from baseline in PRL at EOS of 0.2 (0.9) and 0.4 (1.8) in the tolebrutinib and the placebo group, respectively) and are not considered to be PD biomarkers.

Results from the two GEMINI studies in RMS are overall supportive with respect to an effect on disability progression independent of relapse activity but do not necessarily implicate supportive evidence for the proposed dual treatment effect of tolebrutinib on disability progression via a mechanism of action independent of an effect on acute and focal inflammatory activity.

The negative findings of the PERSEUS study (PPMS) do not contradict the postulated mechanism of action of tolebrutinib as obviously quantitative differences for patient characteristics between the two studied patient populations, defined as SPMS and PPMS population, exist. Therefore, the negative outcome in the PERSEUS study does not allow to conclude that there is no effect of tolebrutinib in the SPMS population. During the procedure, the applicant argues, supported independently by ECTRIMS, that efficacy outcomes in progressive MS depend more on the underlying disease mechanisms of the study population than on the clinical phenotype. The HERCULES and PERSEUS trials differed markedly in patient characteristics: HERCULES included mainly female patients with more recent relapses, whereas PERSEUS included mostly male patients, the majority without any relapse history or with very long time since last relapse. Overall disease activity was low in both studies, and additional activity

measures (e.g., T2 lesions) were not assessed. Efficacy of tolebrutinib in the studied SPMS patient population is therefore sufficiently justified.

9.4. Unfavourable effects

The safety of tolebrutinib has been evaluated in the pivotal study EFC16645 in nrSPMS patients and in two supportive studies in RMS patients from Pool A, including 1,685 patients, who received at least one dose of tolebrutinib at the recommended daily dose of 60 mg, with a mean exposure of 737.8 days in study EFC16645 and 861.1 days in Pool A. Across Phase 2b and Phase 3 studies (Pool B), 1,886 participants were exposed to tolebrutinib 60 mg QD as of the data cut-off 11 September 2024 with a mean exposure of 833.0 days.

In Study EFC16645, 42.2% of patients in the tolebrutinib group and 48.5% in the placebo group discontinued treatment; the most common reason was disease progression. Discontinuations due to TEAEs occurred in 6.6% of tolebrutinib-treated participants and in 4.8% with placebo. In Pool A, 25.0% of patients in the tolebrutinib group and 26.6% of patients in the teriflunomide-group discontinued treatment, with TEAE-related discontinuations reported in 5.9% of tolebrutinib-treated and 6.9% of teriflunomide-treated patients. The overall incidence of TEAEs in Study EFC16645 was similar between groups, despite higher frequencies of infections in the tolebrutinib-group versus placebo (54.4% vs. 49.3%) and skin disorders (16.6% vs. 9.6%), the latter mainly including petechiae (2.7%). SAEs, treatment-related TEAEs, and AESIs were more frequently reported in the tolebrutinib group. In Pool A, rates of TEAEs, SAEs, discontinuations, and deaths were comparable between groups; treatment-related TEAEs were more frequent in the teriflunomide group.

In Study EFC16645, a total of 2 **deaths** occurred in the tolebrutinib group, one of which was assessed as related to tolebrutinib (hepatic failure). This case occurred prior to the implementation of weekly liver monitoring. The second case (medically assisted suicide) was assessed as unrelated to treatment. In addition, 1 fatal case assessed as unrelated to tolebrutinib was reported in Pool A (non-self-inflicted gunshot wound), and 1 fatal case assessed as unrelated to treatment was reported in Study EFC17262 in the gMG population (COVID-19 pneumonia). In the blinded Study EFC16035, 5 fatal cases were reported, including completed suicide, pneumonia aspiration, cardiomyopathy, and two cases of brain oedema. All cases were assessed as unrelated to tolebrutinib. Updated data from Study LTS17043 (cut-off 20 January 2026) report 4 deaths (community-acquired pneumonia, sepsis due to pneumonia, pneumonia, and chronic cerebrovascular failure). The case of sepsis due to pneumonia was assessed by the investigator as related to tolebrutinib, whereas the remaining cases were considered unrelated.

In Study EFC16645 and Pool A, the overall frequency of **common TEAEs** was comparable between the treatment groups, with the most frequently reported events (≥10%) in Study EFC16645 being COVID-19 (25.5% for tolebrutinib vs. 22.7% placebo), urinary tract infection (11.3% vs. 13.1%), and fall (9.6% vs. 10.9%); and in Pool A being COVID-19 (24.1% for tolebrutinib vs. 26.8% teriflunomide), nasopharyngitis (12.8% vs. 11.2%), and headache (12.5% vs. 10.4%).

Adverse drug reactions with tolebrutinib were based on events reported in ≥2% of the tolebrutinib-treated participants with a higher incidence than placebo or teriflunomide, causal relationship considering biological plausibility, potential confounders, alternative explanations, and exposure relationship, i.e. infections and infestations of the upper respiratory tract and COVID-19 (each with very common frequency), lower respiratory tract infections, influenza, petechiae, abdominal pain, ALT increase, increased bruise tendency, heavy menstrual bleeding, and contusion (each with common frequency).

ALT increases >3 × ULN were observed in 4.8% of tolebrutinib-treated participants across Study EFC16645 and Pool A (84 out of 1761 participants), with a higher incidence compared to placebo in

Study EFC16645 (3.6% vs. 1.3%) and comparable rates to teriflunomide in Pool A (5.5% vs. 5.2%). Across Study EFC16645 and Pool A, five participants developed liver injury fulfilling Hy's law criteria, assessed as possibly or probably related to tolebrutinib by the HAC. One of these cases progressed to acute liver failure requiring liver transplantation with fatal outcome. These cases occurred prior to the implementation of weekly liver function monitoring, at a time when LFTS were scheduled every two weeks. A sixth Hy's law case was reported on Day 550, also prior to weekly monitoring; however, this case was assessed by the HAC as not related to tolebrutinib in light of recent initiation of antidepressants, metformin, and NSAIDs.

Across Study EFC16645 and Pool A, a total of 17 liver-related TEAEs were considered by the HAC as possibly or probably related to tolebrutinib (including 4 of the Hy's law cases). Except for one event, all of them occurred within the first 90 days of treatment and prior to the implementation of weekly liver function monitoring. Among the 17 cases, five participants were receiving concomitant medications with known hepatotoxic potential at the time of the liver event. One liver-related TEAE, which was assessed as possibly related to tolebrutinib by the HAC, occurred on Day 757. This case, along with the Hy's law case occurring on Day 550, involved concomitant use of potentially hepatotoxic medications. In the ongoing blinded Study EFC16035, 10 participants experienced ALT elevations >8× ULN reviewed by the HAC, with 9 events assessed as possibly or probably related to the study intervention. Based on these findings, section 4.4 of the SmPC specifies weekly liver monitoring during the first 3 months, monthly up to Month 12 – and, to account for late-onset events – every 6 months between Months 12 and 24, and periodic monitoring thereafter.

In Study LTS17043, ALT elevations >3×ULN occurred in 26/643 newly initiated participants (4.0%) and ALT >8×ULN in 10/643 participants (1.6%) under weekly monitoring as of the cut-off date of 15 November 2025. One case fulfilled Hy's law criteria, and one further case showed a Hy's-law-like pattern but was not assessed as such due to elevated baseline bilirubin consistent with Gilbert's syndrome. In the confirmed Hy's law case, the participant had concomitantly ingested a traditional Chinese medicinal preparation ("swim bladder pills") and the case was assessed by the HAC as possibly related to tolebrutinib. All participants had recovered or were recovering at last follow-up. Participants with ALT >8×ULN recovered earlier under weekly monitoring (mean 39.6 days) compared with those monitored less frequently (56.6 days). The applicant has added precautions in section 4.4 of the SmPC regarding concomitant hepatotoxic medicinal products, particularly early in treatment, and has advised against the use of hepatotoxic herbal or dietary supplements during tolebrutinib therapy. This represents the only Hy's law case identified under the weekly liver function monitoring strategy.

In Study EFC16035 (PERSEUS), 234 tolebrutinib-treated participants had scheduled LFTs at Week 2 and at Weeks 4 through 12 after treatment initiation. ALT elevations >3×ULN occurred in 12 of 234 tolebrutinib-treated participants (5,1%). Four participants (1.7%) experienced ALT elevations >8×ULN. In addition, one case that fulfilled Hy's law criteria had already been identified in earlier reporting periods. Of the four ALT >8×ULN cases, no alternative aetiology was identified in three cases. These events showed a hepatocellular pattern, were largely asymptomatic, and occurred within the first 12 weeks of exposure; the HAC considered these cases probably related to tolebrutinib. In the remaining ALT >8×ULN case, confounding factors were present, including concomitant NSAID and paracetamol exposure, with liver enzyme worsening occurring during treatment interruption. In this case, the HAC considered a causal relationship to tolebrutinib unlikely.

Cross-programme analyses (data cut-off: 20 January 2026) of weekly liver function monitoring across the Phase 3 programme (GEMINI, PERSEUS, HERCULES and LTS17043) included 2,926 participants exposed to tolebrutinib who completed the first 12 weeks of monitoring, of whom 920 were monitored weekly. ALT elevations >3×ULN within the first 12 weeks occurred in 4% of participants under weekly monitoring and in 2.8% of those enrolled prior to its implementation. Across the clinical development programme, 35 participants experienced ALT elevations >8×ULN assessed by HAC as possibly or

probably related to tolebrutinib. Six cases fulfilled Hy's law criteria, comprising five cases identified prior to implementation of weekly monitoring (including one fatal case) and one case occurring under the weekly monitoring strategy.

In Study EFC16645, **serious and severe infections** occurred more frequently with tolebrutinib (5.2% for both) compared to placebo (3.5% and 2.9%, respectively). In Pool A, rates were lower and comparable for tolebrutinib (2.5% and 2.3%) and teriflunomide (2.2% and 1.9%, respectively). Most events were respiratory tract infections, mainly COVID-19. No fatal infections were reported in EFC16645 or Pool A. Two fatal cases were reported in ongoing studies (LTS17043 and Study EFC16035), one of which was assessed as related to tolebrutinib (LTS17043). An additional fatal case was reported in the gMG population in Study EFC17262, which was assessed as unrelated to tolebrutinib. Across Study EFC16645 and Pool A, six opportunistic infections were reported in participants receiving tolebrutinib (≤0.3%), compared to none in the placebo group and one in the teriflunomide group. One of these cases with tolebrutinib was fatal (disseminated aspergillosis/CMV post-liver transplant in Study EFC16645) as already mentioned above, while the remaining infections resolved, two requiring discontinuations of treatment. In the blinded Study EFC16035, a fatal case of pulmonary actinomycosis was identified post-mortem following aspiration pneumonia, assessed as possibly related to study drug. Overall, several opportunistic infections occurred in the presence of contributing factors such as immunosuppressive therapy, corticosteroid use, or aspiration. When comparing infection rates by concomitant immunosuppressive treatment, incidences were higher in patients receiving tolebrutinib with concomitant immunosuppressive agents. In Study EFC16645, infection rates were 62.7% with and 52.2% without immunosuppressive treatment. In Pool A, the respective rates were 66.1% versus 56.1%, with similar patterns observed across different categories of immunosuppressive agents. Consistent with these observations, section 4.3 of the SmPC has been revised to contraindicate use in patients with severe immunodeficiency (e.g. acquired immunodeficiency syndrome, bone marrow disease, or severe, uncontrolled active infections), and section 4.4 has been updated to include a warning on opportunistic infections.

Atrial fibrillation/atrial flutter was reported in 3 participants treated with tolebrutinib in Study EFC16645 and in 1 tolebrutinib-treated participant in Pool A. No such events occurred with placebo or teriflunomide. Based on the available data and class effect with other BTKis, atrial fibrillation and atrial flutter have been included as a warning in the SmPC and as an important potential risk in the RMP.

Bleeding events are very commonly reported for ibrutinib, zanubrutinib, acalabrutinib and pirtobrutinib, and thus, **haemorrhages** are an identified risk for the licensed BTK inhibitors. The underlying mechanisms of the bleeding risk - apart from disease-specific susceptibilities - are not fully understood. Prolonged administration of ≥2 mg/kg/day tolebrutinib over 26 weeks in rats and ≥1 mg/kg/day over 39 weeks in dogs increased the risk for bleeding events in multiple organs. Nevertheless, thrombocytes, red blood cell and coagulation parameters were not affected in both rats and dogs. Only a small mean platelet count reduction was found for tolebrutinib in the clinical Phase 2/3 studies (10% reduction from baseline values over the first 6 to 12 weeks of treatment). A single patient fulfilled the criterion of a platelet count $<75 \times 10^9$/L after ~15 months of treatment. Moderate or severe haemorrhagic events (NCI CTCAE Grade ≥2) occurred with a similar incidence in the treatment groups in study EFC16645 (placebo: 1.3%; tolebrutinib: 0.8%), while a slightly higher incidence was reported for tolebrutinib in Pool A (2.1% [1.7% with teriflunomide]). Few of these events were reported as SAEs or with ≥Grade 3 severity, and approximately half of the events were rated as treatment related. None of the events in the tolebrutinib group was fatal. PTs related to moderate or severe haemorrhagic events in study EFC16645 occurred only once and included - amongst others - bleeding events in the brain and traumatic haemothorax. In Pool A, some PTs occurred in >1 participant, i.e. bleedings related to skin (petechiae), and bleedings related to reproductive system and breast disorders (heavy menstrual/uterine bleeding). None of the events was

associated with thrombocytopenia. In total, six participants with tolebrutinib in EFC16645 and 20 in Pool A experienced moderate to severe haemorrhagic events, of which three and eight events, respectively, were assessed as related to treatment. Two discontinuations occurred in Pool A, and concomitant NSAID use was documented in several cases. Altogether, eleven haemorrhagic events were considered related to tolebrutinib. A 2:1 imbalance in mild (Grade 1) haemorrhagic events was reported in study EFC16645 as well as in Pool A at the expense of tolebrutinib (compared to placebo and teriflunomide), mainly contusion and petechiae in study EFC16645 and petechiae, heavy menstrual bleeding, increased tendency to bruise, and epistaxis in Pool A. Consequently, anaemia was reported more frequently with tolebrutinib as compared to placebo in study EFC16645 (2.1% versus 0.5%) and teriflunomide in Pool A (4.0% versus 1.7%). Given the biological plausibility, mild haemorrhagic events are considered a risk of tolebrutinib exposure and information has been added to the description of selected adverse reactions in section 4.8 of the SmPC. In addition, the applicant has included a warning in SmPC sections 4.4 and 4.5. "Haemorrhages" has been included as an important potential risk in the RMP.

Second primary malignancies (cancers developing either simultaneously or metachronously in the same individual who has been diagnosed with and survived one primary cancer) are rated as potential risk with approved BTK inhibitors. TEAEs in the SOC Neoplasm benign, malignant and unspecified (incl. cysts and polyps) were more frequently reported for tolebrutinib as compared to placebo in Study EFC16645 (4.1% vs. 2.4%) and as compared to teriflunomide in Pool A (5.8% vs. 2.7%). A pre-planned SMQ analysis on 'malignant and unspecified tumors' retrieved a higher incidence of **malignancies** in the tolebrutinib group as compared to placebo (1.6% vs. 0.3%) including breast cancer (2 cases), basal cell carcinoma, bladder cancer, bladder cancer stage 0 with cancer *in situ*, chronic myeloid leukaemia, endometrial adenocarcinoma, invasive breast carcinoma, lung cancer metastatic, prostate cancer, rectal cancer, renal cell carcinoma stage I, squamous cell carcinoma. A similar incidence of malignancies was reported for tolebrutinib and teriflunomide in Pool A (0.9% and 0.7%). Breast cancer was the prevailing malignancy in the tolebrutinib group in Pool A (5 of 8 malignancies), and none of them weas rated as related to tolebrutinib. An evaluation of the individual cases with breast cancer revealed confounding factors in some of them. In total, 10 breast cancer cases were identified across Study EFC16645 and Pool A, including 8 in patients treated with tolebrutinib and 2 in patients treated with teriflunomide. In both Study EFC16645 and Pool A, the time-to-onset of malignancy ranged from 15 days to over 2 years after starting study intervention. In the ongoing Study LTS17043, one SAE of malignant melanoma was not rated as related to tolebrutinib in a patient with a family history, while a malignant germ cell tumor was rated as related to tolebrutinib. Four additional malignancies, including two cases of breast cancer, were reported in the blinded study EFC16035. Across the clinical programme, 27 patients with 28 malignancy events were identified in the tolebrutinib groups, compared with 9 events in 8 patients on teriflunomide and 2 cases on placebo. The incidence rate was numerically highest with tolebrutinib (5.49/1000 PY), followed by teriflunomide (3.69/1000 PY) and placebo (2.69/1000 PY). Reported background rates in MS cohorts ranged from 4.0 to 8.0/1000 PY. SIRs were calculated using nine epidemiological datasets: four yielded SIRs >1 for tolebrutinib, although confidence intervals in most comparisons included 1, whereas in the largest dataset (Pierret, 2024) the SIR was <1 (0.69 [95% CI 0.45–0.97]).

Benign neoplasms were reported for 2.4% and 2.1% of participants in the tolebrutinib and the placebo group (mainly involving the breast, skin, bone, uterus, and colon) in EFC16645 and for 4.9% and 1.9% of participants in the tolebrutinib and teriflunomide group in Pool A. There was a higher incidence of uterine leiomyoma cases in the tolebrutinib as compared to the teriflunomide group in Pool A (21 vs. 3 patients), while no imbalance was observed in Study EFC16645 versus placebo. The applicant has included a warning on malignancies in section 4.4 of the SmPC and malignancies is included as important potential risk in the RMP.

Based on C-SSRS and SMQ-derived data from Study EFC16645, suicidal ideation was reported in 4.6% of tolebrutinib-treated and 4.3% of placebo-treated participants, while **suicidal behaviour** was observed in 0.4% and 0%, respectively. In Pool A, suicidal ideation occurred in 3.1% of tolebrutinib-treated and 3.0% of teriflunomide-treated participants, and suicidal behaviour in 0.4% and 0.3%, respectively. However, TEAE data in the AE grouping of suicidal behaviour showed a higher incidence of suicidal behaviour events with tolebrutinib: in Study EFC16645, 1.2% of patients treated with tolebrutinib vs. none on placebo, and in Pool A, 0.8% vs. 0.1%. These events included 4 cases of suicidal ideation, 2 suicide attempts, 1 event of self-injurious ideation, 1 case of depression with suicidal features, and 1 medically assisted suicide. A risk analysis performed by the applicant included data from C-SSRS, TEAEs, case narratives, depression outcomes, and epidemiological comparisons. The applicant reported that most suicidal ideation and behaviour events were captured by C-SSRS, that discrepancies with TEAE reporting were due to variability in investigator reporting, data entry errors, or external triggers, and that overall incidences were consistent with background rates in MS populations. In the ongoing Study LTS17043, 17 participants experienced suicidality events (two suicide attempts and 15 cases of suicidal ideation). Thirteen ideation events were identified via C-SSRS only, and two were captured both as TEAEs and via C-SSRS. One suicide attempt led to hospitalisation with permanent discontinuation, and one intentional overdose to temporary interruption. One ideation case required hospitalisation, and three led to temporary interruptions. All events were assessed by the investigators as not related to tolebrutinib. Suicidal behaviour has been included in section 4.4 of the SmPC.

A total of 48 **pregnancies** were reported in the clinical development program of tolebrutinib, including 26 with tolebrutinib exposure, 22 with teriflunomide exposure, and none with placebo. Outcomes included 16 live births, 11 elective terminations, 6 spontaneous abortions, and 4 unspecified abortions. Eleven pregnancies remain ongoing. No congenital malformations were observed among the live births following tolebrutinib exposure.

9.4.1. Uncertainties and limitations about unfavourable effects

The toxicities observed in non-clinical studies only partially overlap with clinical events but generally developed with sufficient safety margins towards the human AUC at the MRHD, which can likely be attributed to the different metabolic rates and profiles between humans and animal species.

The primary clinical safety concern associated with tolebrutinib relates to liver injury, which could not be mechanistically elucidated in non-clinical investigations and is an important identified risk in the tolebrutinib RMP. While the introduction of weekly LFT monitoring has facilitated earlier identification of hepatic events and treatment interruption, the updated data show that weekly LFTs do not fully prevent the occurrence of hepatic events, including marked ALT elevations. Uncertainty remains regarding the contribution of concomitant hepatotoxic medicinal products or herbal preparations to the occurrence and magnitude of ALT elevations, and a contributory role cannot be excluded. Measures addressing these uncertainties are reflected in the SmPC, including the boxed text in section 4.4, strict weekly LFT monitoring during the first 12 weeks, and specific precautions on concomitant hepatotoxic medicinal products and avoidance of hepatotoxic herbal or dietary supplements, supported by additional pharmacovigilance and risk minimisation activities, including a PASS and educational materials. DILI is included as an important identified risk in the RMP.

Uncertainty is raised with regard to the higher number of suicidal behaviour events in the tolebrutinib group compared to placebo and teriflunomide. Despite the risk analysis provided by the applicant, the underlying reason for the imbalance has not been fully clarified, and the exclusion of patients with psychiatric comorbidities further adds uncertainty. A treatment-related risk cannot be excluded, and a corresponding warning has been included in section 4.4 of the SmPC. Further, "Suicidal behaviour and

attempts" will be followed up in PSURs.

No congenital abnormalities were observed in live births following tolebrutinib exposure; however, the available data are limited, including reports of ongoing pregnancies and spontaneous abortions, and are therefore insufficient to establish the safety of tolebrutinib during pregnancy. Embryo-foetal development studies with tolebrutinib in rats and rabbits did not indicate any risk for foetal malformations or impact on pregnancy rate, numbers of *corpora lutea* and implantation sites at more than 160-fold and 300-fold higher exposures than the human AUC at the MRHD, respectively. Further, "reproductive toxicity" will be followed up in PSURs.

Haemorrhage is an identified risk for approved BTK inhibitors due to the reporting of (major) bleeding events (≥Grade 3) in 2 to 4% of treated patients with B-cell malignancies (von Hundelshausen, 2021). Patients with risk factors that predispose to excessive bleeding (i.e. bleeding disorder/ platelet dysfunction, platelet count <150 x 10^9/L, etc.) have been excluded from clinical studies with tolebrutinib. Likewise, patients were not allowed to receive concomitant anticoagulant/ antiplatelet treatment during the studies. These risk factors are stated in section 4.8 of the SmPC, and a warning on haemorrhage has been added to sections 4.4 and 4.5. Further, "Haemorrhages" has been included as an important potential risk in the RMP.

Available data do not fully exclude a possible contribution of tolebrutinib to the development of neoplasms. Uncertainty remains regarding a potential contribution of tolebrutinib to the occurrence of malignancies. Although no strong evidence for a causal relation has been established, a contribution cannot be excluded given the mechanism of action of BTK inhibitors and the observed incidence rates relative to background rates in MS populations. As a consequence, the product information informs on a potential class effect for malignancies in line with other approved BTKi, and malignancies is included as important potential risk in the RMP.

9.5. Effects Table

Table 51 Effects Table for CENRIFKI {treatment of non-relapsing secondary progressive multiple sclerosis (nrSPMS) in adults} (data cut-off: 11 September 2024*).*

Effect (short description)	***Treatment***	***Control***	***Uncertainties/ Strength of evidence***	***Ref***
Favourable Effects				
Time to onset of 6-month CDP (PE)	Toleb. 60 mg 171/754 22.6	Placebo 116/377 30.7	**SOE:** Superiority of toleb. against placebo Hazard Ratio (95% CI): 0.693 (0.546, 0.880) P = 0.0026	(1)
Time to onset of 3-month CDP (first SE)	Toleb. 60 mg 208/754 27.6	Placebo 129/377 34.2	**SOE:** Superiority of toleb. against placebo Hazard Ratio (95% CI): 0.757 (0.607,0.944) P = 0.0134	(1)
Total number of new and/or enlarging T2-hyperintense lesions (second SE) Adjusted mean number	Toleb. 60 mg 280/754 1.835	Placebo 176/377 2.948	**SoE:** Superiority of toleb. against placebo Relative risk (95% CI): 0.622 (0.432, 0.897) P = 0.0110	(1)
Unfavourable Effects				

Effect (short description)	*Treatment*		*Control*	*Uncertainties/ Strength of evidence*	*Ref*
	Tolebrutinib 60 mg (1) **Tolebrutinib 60 mg (2)**	**Placebo**	**Teriflunomide 14 mg**		
AESI increase of ALT >3 × ULN	27/752 (3.6) 51/933 (5.5)	5/375 (1.3)	49/939 (5.2)	**SoE:** weekly LFTs from Week 1 to Week 12, boxed text in section 4.4, additional warning on hepatotoxic co-medication **Unc:** use of hepatotoxic co-medications	(1), (2)
AESI atrial fibrillation/ atrial flutter no.	3 1	0	0	**SoE:** important potential risk in line with other BTKi, warning included in the PI	(1), (2)
AESI severe infections – no./ total no. (%)	39/752 (5.2) 21/933 (2.3)	11/375 (2.9)	18/939 (1.9)	**SoE**: PTs mainly related to COVID-19; no TEAEs of infections with fatal outcome; no imbalance of opportunistic infections across treatment groups	(1), (2)
AESI Moderate or severe haemorrhagic events – no./ total no. (%)	6/752 (0.8) 20/933 (2.1)	5/375 (1.3)	16/939 (1.7)	**SoE:** No imbalance between treatment groups. Warning and information on handling of patients with risk factors for bleeding and interaction between tolebrutinib and concomitantly administered antiplatelet/ anticoagulant medication included in the SmPC; haemorrhage (as a class effect) has been included in the RMP.	(1), (2)
- Mild haemorrhagic events – no./ total no. (%)	96/752 (12.8) 157/933 (16.8)	20/375 (5.3)	77/939 (8.2)		
AESI – Thrombocytopenia, platelet count < 75 x 10^9/L	1 0	0	0	SoE: mean platelet counts decreased not more than 10% from baseline values.	
Suicidal behaviour (SMQ)	9/752 (1.2) 7/933 (0.8)	0	1/939 (0.1)	**SoE:** Shift tables in C-SSRS do not indicate an imbalance between treatment groups during treatment, warning in SmPC and report of Suicidal behaviour and attempts in future PSURs **Unc:**	(1), (2)

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
SOC Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	31/752 (4.1) 54/933 (5.8)	9/375 (2.4)	25/939 (2.7)	**SoE:** 18 of 31 (46 of 54) TEAEs with tolebrutinib in study EFC16645 (Pool A) benign in nature (8 of 9 TEAEs with placebo; 18 of 25 with teriflunomide). Imbalance of uterine leiomyoma between tolebrutinib and teriflunomide in Pool A (21 vs. 3 cases), primarily attributed to increased detection related to bleeding tendencies **Unc:**	(1), (2)
- Malignancies (OAEI)	12/752 (1.6) 8/933 (0.9)	1/375 (0.1)	7/939 (0.7)	**SoE:** class label in the SmPC; RMM in the RMP. **Unc:** 7 cases of breast cancer in study EFC16645 and Pool A combined with tolebrutinib vs. 2 cases with teriflunomide and none with placebo.	

Abbreviations: CDP: confirmed disability progression; CDI: confirmed disability improvement; toleb.: Tolebrutinib; KM: Kaplan-Meier; Ref: reference; Unc: uncertainties; SoE: strength of evidence;.

Notes: (1) placebo-controlled study EFC16645; (2) Pool A

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The efficacy and safety of Tolebrutinib primarily originate from one pivotal, randomised, double-blind, placebo-controlled study (EFC16645).

The inclusion criteria defined a population with SPMS that was relapse-free for at least 24 months with no restrictions to MRI based acute focal inflammatory activity. In full alignment with the MS biology, at baseline 12.7% (n=142) of these subjects were identified to have Gd+ lesions, although relapses were absent. The pivotal study was designed in line with the recommendations of the EMA Multiple Sclerosis guideline (EMA/CHMP/771815/2011 Rev. 2), including the use of time to 6-month CDP based on EDSS as primary endpoint and a number of relevant functional and MRI-based secondary endpoints.

Benefits:

The most important favourable effect in SPMS is preventing or delaying disability progression, which represents the key determinant of long-term outcomes in MS. Tolebrutinib showed a 31% risk reduction compared to placebo for the time to 6-month CDP based on statistically significant results for the primary endpoint (HR 0.693 (95% CI: 0.546 to 0.880), p=0.0026). The magnitude of the treatment effect is considered clinically relevant based on sample size calculations. The Kaplan-Meier curves of cumulative incidence rate for the onset of 6-month CDP showed a sustained effect with an early separation with a lower proportion of patients in the tolebrutinib group with 6-month CDP events throughout the treatment period. Based on Kaplan-Maier estimates the absolute treatment difference for subjects free of 6-month CDP was 5.1% at month 12 and reached 10.3% at month 48 in favour of tolebrutinib. Pre-specified sensitivity analyses confirmed the results received in the primary analysis. The absolute risk reduction of 5.1% at month 12 compared to placebo corresponded to a number needed to treat of 20 subjects to prevent one CDP event. At month 48, the absolute reduction of 10.3% compared to placebo corresponded to a number needed to treat of 10 subjects.

Given the irreversible nature of disability accumulation and the lack of approved therapies specifically targeting progression independent of relapse activity, this effect is of high clinical relevance, especially as the studied patients represent a population with advanced disease (mean EDSS 5.53), where even

modest delays in disability accumulation translate into preservation of ambulation and functional independence. This is further supported by consistent effects on lower limb function as assessed by secondary endpoints.

Importantly, the clinical relevance of the observed effect also needs to be interpreted in the context of the unmet medical need in SPMS that differs across SPMS subpopulations. Patients with non-active SPMS represent the subgroup with the highest unmet medical need, as no approved therapies are currently available that specifically target disability progression in the absence of relapse activity. In contrast, patients with evidence of acute focal inflammatory activity may still derive benefit from existing anti-inflammatory DMT. However, no product is specifically licensed for SPMS patients being relapse free, e.g., SPMS without relapses for two years.

At the same time, the absence of effects on upper limb function, cognition, brain volume loss and quality of life limit the breadth of the overall patient benefit. These domains are also of high importance in progressive MS.

Although subgroup analyses should not be overestimated, they further inform the interpretation of efficacy. Based on pre-specified, non-powered subgroup analyses, a more pronounced treatment effect was observed in patients with evidence of focal acute inflammatory activity at baseline by means of Gd+ lesions (n=142), whereas the effect in patients without Gd+ lesions (n=989) was smaller. The risk reduction was 65% (HR 0.35 [95% CI 0.183, 0.656]) as compared to subjects without Gd+ lesions (87.3% of the overall study population) (risk reduction 22%, HR 0.78 [95% CI 0.601, 1.006]). A *post hoc* analysis in those patients being non-active (no relapse in the 2 prior years and no Gd+ lesions at baseline) provided similar results (HR 0.767 [[95% CI] 0.593, 0.992]; unadjusted p = 0.0433). New *post hoc* Kaplan-Meier analyses more specifically illustrate the obtained differences in effect magnitude between the subgroups with and without Gd+ lesions at baseline. These differences were suggested to reflect seemingly different behaviour in the placebo groups more than the disability event rates in the tolebrutinib groups, with the placebo group with Gd+ lesions -whether by chance or not - exhibiting the highest rate of disability (the small subgroup who demonstrated two biological drivers of disability progression, i.e. a neuroinflammation plus a focal acute inflammatory component compared to the larger subgroup with only one biological driver of disability progression, i.e., a neuroinflammation component), while the incidence of 6-month sustained disability progression was considered lowest in those patients treated with tolebrutinib and who showed Gd+ lesions at baseline.

Overall, although results based on subgroups for active and non-active SPMS subjects remained directionally consistent and even statistically significant, the difference in magnitude of effect introduces some uncertainty to the extent to which the observed benefit reflects an effect on progression independent of acute focal inflammatory activity. It cannot be excluded that the overall effect appears to be mainly influenced by the presence of acute and focal inflammatory disease activity -which is still in line with the mechanism of action of the BTK inhibitor tolebrutinib - against acute and focal inflammatory activity as well as neuroinflammation.

In the pivotal study the confirmation of disability progression relied on the PIRA concept, i.e., confirmation of disability accumulation independently of relapse activity. The PIRMA concept, i.e. progression independent of relapses and brain and spinal cord MRI focal acute inflammatory activity, would have been more useful to gain insight disability progression independent of acute and focal inflammatory activity. Basic MRI assessments in parallel to the EDSS scores evaluated for the assessment of sustained disability progression have not been pre-defined. Therefore, correlation of disability progression independent of acute focal inflammatory MRI activity was not possible. Accordingly, it remains uncertain whether the effect on disability progression is due to an effect of tolebrutinib on the chronic neuroinflammation.

However, *post hoc* subgroup analyses correlating the treatment effect of the primary endpoint to the proportion of baseline chronic active lesions, i.e., the PRL load - a potential marker of chronic and active inflammation - suggested that the effect of tolebrutinib appears to be greater in the subgroup of patients with 4 or more, compared to 0 PRL and 1-3 PRL.

Results from the GEMINI studies in RMS provide additional, indirect support for an effect on disability progression independent of relapse activity, whereas the negative findings in the PERSEUS study in PPMS introduced uncertainty regarding the extent to which the effect is independent of focal and acute inflammatory activity. However, these findings are not considered to invalidate the efficacy observed in the studied SPMS population**.**

Overall, the pathogenic mechanisms of SPMS are *per se* of high complexity. When interpreting the efficacy results, the 2024 revisions of the McDonald criteria with conceptualisation of MS as a disease continuum rather than a set of strictly discrete phenotypes need to be taken into account. In this framework, acute focal inflammatory activity and progression-related mechanisms may coexist to varying degrees across RRMS, SPMS and PPMS. Consequently, the magnitude of treatment effect may depend more on the biological drivers present in the studied population than on the nominal phenotype. This conceptual framework supports the relevance of the efficacy results in the studied SPMS population, including patients with and without baseline MRI activity, while also explaining that treatment effects may differ according to the status of focal and acute inflammatory activity.

Overall, an indication of "non-relapsing SPMS" as initially proposed could, from a pathophysiological perspective, be misinterpreted as if benefit was observed for those subjects being "non-active". Given the totality of data and the current scientific knowledge, the final agreed indication refers to adult patients with SPMS without relapses in the previous 2 years to align the indication with the patient population studied. This constitutes a population of significant unmet medical need. Further characterisation of the study population and treatment effects, including efficacy outcomes in subgroups defined by disease activity (e.g. active versus non-active disease, with a more pronounced effect observed in patients with active disease), is considered acceptable to be described in section 5.1 of the SmPC in order to appropriately inform prescribers.

Risks:

Overall, the safety findings with tolebrutinib 60 mg in the clinical studies do not point towards a clearly unacceptable risk in the studied patient population. The incidences of the most frequently reported TEAEs (in ≥ 10% of participants) were comparable across treatment groups in study EFC16645 and Pool A. Based on the completed phase 3 studies and ongoing studies up to the data cut-off, a majority of TEAEs were mild and moderate in severity, and serious TEAEs did not increase with longer treatment duration. Moreover, TEAEs rarely led to discontinuation of tolebrutinib treatment.

The most relevant safety concern for tolebrutinib is hepatotoxicity, which manifested in ALT increases >3 × ULN, including five confirmed cases of Hy's law occurring during a period when LFTS were scheduled less frequently, i.e. when LFTs were performed every two weeks. One of these cases resulted in a fatal outcome. In this case, liver injury evolved rapidly between scheduled assessments, and the two-week monitoring interval likely delayed detection. In response, weekly liver function monitoring during the first 12 weeks has been implemented as part of the proposed risk-minimisation measures. Cross-programme analyses (data cut-off 20 January 2026) of 920 participants monitored weekly during treatment initiation across studies GEMINI, PERSEUS, EFC16645 and LTS17043 showed ALT elevations >3×ULN in 4% of participants, with one case fulfilling Hy's law criteria reported under the weekly monitoring schedule. However, this case was confounded by the ingestion of a traditional herbal preparation known to contain hepatotoxic ingredients.

Implementation of weekly monitoring was associated with earlier detection of ALT elevations and shorter recovery following treatment interruption compared with less frequent monitoring. Late-onset ALT elevations were uncommon and did not show a consistent pattern suggestive of a distinct late-onset hepatotoxicity profile. In the pooled Phase 3 dataset, no increased frequency of ALT >3×ULN events, including late-onset cases, was observed with concomitant hepatotoxic medication. However, interpretation is limited by the low number of events, and a contributory effect of individual co-medications cannot be excluded.

These findings indicate that hepatotoxicity is predominantly an early-onset risk and support the rationale for weekly monitoring during the initial treatment period, highlighting the importance of strict adherence to the established risk-minimisation measures. Given the characteristics and vulnerability of the target population, more frequent testing during the first 12 weeks is unlikely to be operationally feasible, and weekly LFTs represent a reasonable monitoring approach while there is still a clinically relevant residual risk of hepatic events. The boxed text in section 4.4 of the SmPC, outlining mandatory liver tests, and defining thresholds for treatment interruption or discontinuation, aims to reduce the risk. Monitoring is not limited to the initial 12 weeks but continues thereafter with reduced frequency, supporting ongoing detection of hepatic events beyond the early treatment phase. Additional warnings on the concomitant use of hepatotoxic medicines and on avoiding hepatotoxic herbal preparations have been added to the SmPC to address potential factors that may contribute to liver injury. As patients with elevated baseline liver parameters were excluded from the pivotal Phase 3 study, corresponding contraindications have been implemented in the SmPC. Moreover, a PASS study (ToleAdhere) is proposed to evaluate the adherence to liver function monitoring in the post-marketing setting. In addition, further risk minimisation measures, including a prescriber guide, patient guide and patient card, are implemented to support adherence to liver function monitoring and risk awareness, together with voluntary prescriber education and continued HAC review in the post-marketing period.

Overall, these measures are considered a necessary approach to monitor and mitigate the hepatic risk. Strict adherence to the proposed monitoring strategy is essential, however, a residual risk cannot be fully excluded.

Serious infection is an important identified risk with tolebrutinib exposure, consistent with observations reported for other BTKi (Pilmis et al., 2023). While overall infection rates were comparable between tolebrutinib and teriflunomide, two fatal cases involving opportunistic pathogens underline the clinical relevance in highly immunocompromised patients or those with predisposing factors. These risks are addressed in the SmPC through warnings and a contraindication in patients with severe immunodeficiency or uncontrolled infections, as well as information on concomitant immunosuppressive therapy. Opportunistic infections are addressed in section 4.4 of the SmPC.

Atrial fibrillation and atrial flutter are known class effects of BTKi (Gambril et al., 2024). Events were infrequent in the Phase 3 studies and are considered manageable with appropriate labelling. A corresponding warning is included in section 4.4 of the SmPC and atrial fibrillation/atrial flutter are classified as an important potential risk in the RMP.

Haemorrhagic events are a recognised risk of the BTKi class, likely related to off-target effects on platelet function (Chen et al., 2018; Lipsky and Lamanna, 2020; von Hundelshausen and Siess, 2021; Duan et al., 2021). With tolebrutinib, moderate to severe haemorrhagic events (> Grade 2) were infrequent, and the overall incidence was comparable to placebo. Despite the absence of a clear risk for severe bleeding, mild bleeding events (Grade 1) occurred more frequently with tolebrutinib than with placebo and teriflunomide, largely driven by contusion and petechiae and heavy menstrual bleeding, and epistaxis, and culminating into TEAEs of anaemia. Risk factors for bleeding have been included in section 4.8 of the SmPC, and a warning on haemorrhage and concomitant

anticoagulant/antiplatelet use has been added to sections 4.4 and 4.5. In addition, haemorrhage has been classified as an important potential risk in the RMP.

An imbalance in malignancies was observed in the tolebrutinib groups, including a higher number of breast cancer cases in Study EFC16645 and Pool A. While the time to onset appears incompatible with the expected latency for solid tumours (≥5 years) (Little et al., 2024), the observed pattern, including cases in the younger patient population and a malignant germ cell tumour assessed as related, raises concern. While no strong causal relation has been established, a potential contribution cannot be excluded given the mechanism of action of BTK inhibitors and the observed incidence rates relative to background rates in MS populations. A warning on malignancies has been included in section 4.4 of the SmPC, and malignancies are classified as an important potential risk in the RMP.

An increased number of events related to suicidal behaviour was observed with tolebrutinib compared with placebo and teriflunomide. While patients with MS have an increased baseline risk of suicidality (Kalb et al., 2019, as referenced by the applicant), this does not sufficiently explain the observed imbalance. Although no clear causal relationship or consistent temporal pattern has been established, a contributory effect of a CNS-active compound cannot be excluded, particularly given the exclusion of patients with psychiatric comorbidities from the clinical programme. A warning on suicidal behaviour has been included in section 4.4 of the SmPC, with continued monitoring in the post-marketing setting.

Overall, the main safety concern is hepatotoxicity due to its potential severity, as observed in the clinical programme. Other identified and potential risks, including infections, haemorrhagic events, atrial arrhythmias, malignancies, and suicidal behaviour, are largely consistent with the pharmacological class, with some risks reflecting observed imbalances or remaining uncertainties, and are considered manageable under the proposed risk minimisation measures.

9.6.2. Balance of benefits and risks

Efficacy of Tolebrutinib was adequately demonstrated in the pivotal study EFC16645 across the overall study population, which comprised patients with SPMS who had been relapse-free for at least 24 months prior to screening, irrespective of the presence or absence of focal acute inflammatory disease activity, as evidenced by Gd+ lesions on baseline MRI. According to pre-specified but not powered subgroups, the effect was more pronounced in those subjects with baseline disease activity as represented by Gd+ lesions. This has clearly been described in the SmPC section 5.1.

During the procedure, the claimed indication was revised from "*treatment of nrSPMS in adults"* to "*treatment of adult patients with SPMS"*, and finally to "*treatment of adult patients with SPMS without relapses and with signs of disability progression (see section 5.1*)". However, while also taking considerations from ECTRIMS as external input into account, the CHMP considered that the wording of the indication should more specifically describe the studied patient population and therefore needed further amendments to "*treatment of adult patients with SPMS without relapses in the last 2 years",* thereby aligning the target population as close as possible with the population studied in the SPMS trial EFC16645, also in light of the identified risks.

Currently available DMT for MS are primarily focused on relapsing disease and no products are explicitly licensed for patients with non-active SPMS in general, or more specifically for SPMS patients without relapses. An indication for "*SPMS without relapses in the last two years*" represents a population with more advanced disease, including SPMS patients without relapses (at least for the last two years) and with or without MRI based disease activity. This indisputably is a population with an unmet medical need.

Based on the available safety data of tolebrutinib in the SPMS population studied, supported by data from the RMS population, hepatotoxicity appears to be the most relevant safety concern. Weekly liver function monitoring during the first 12 weeks allows earlier detection and management of hepatic events and comprehensive risk-minimisation measures are in place to further mitigate the risk of hepatotoxicity; however, occurrence of liver toxicity cannot be fully prevented. Overall, the clearly demonstrated benefits in an advanced SPMS population without specific treatment options are considered to outweigh the identified risks and support a favourable benefit-risk balance.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Questions to be posed to additional experts

None

9.6.3.2. Input from additional experts

Not applicable.

9.7. Benefit-risk conclusions

The overall benefit/risk balance of tolebrutinib is positive for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (see section 5.1).

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APPENDIX

DIVERGENT POSITION DATED 23 April 2026

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Cenrifki EMEA/H/C/006386/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Cenrifki indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years.

The reason for divergent opinion was the following:

Serious liver toxicity has been observed in patients treated with tolebrutinib and drug-induced liver injury (DILI) is an important identified risk. Despite a comprehensive risk management program to handle the liver toxicity, the risk to patients cannot be fully mitigated.

The observed effect of tolebrutinib in the non-relapsing SPMS population is mostly driven by those patients with focal and acute inflammation at baseline and the lack of effect of tolebrutinib in the PPMS population questions the robustness of the efficacy shown in the proposed population of patients including inactive SPMS.

Therefore, the efficacy is not considered to outweigh the identified liver toxicity for tolebrutinib in SPMS without relapses in the last 2 years and the benefit-risk is considered negative.

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