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Patient Safety & Pharmacovigilance

Siponimod

BAF312

EU Safety Risk Management Plan

Active substance (INN or common name):	Siponimod
Product concerned (brand name):	Mayzent®
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Template version 6.4, Effective from 12-Dec-2023

Rationale for submitting an updated RMP: The risk management plan (RMP) was updated to version (v) 7.2 in response to a recommendation received in the Type IB variation report Request for Supplementary Information (with Procedure no.: EMA/VR/0000273065).

Summary of significant changes in this RMP:

- Reinstated the important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers' in the summary of safety concerns for siponimod, risk minimization measures, and Key Safety Messages (KSM) in Physician's checklist, and Patient/Caregiver Guide, corresponding to this important potential risk, as recommended in the Type IB variation report Request for Supplementary Information (with Procedure no.: EMA/VR/0000273065).

Part	Major changes compared to RMP v7.1
Part I	• Updated reference to proposed SmPC • Updated 'Additional monitoring of the product in the EU' from 'Yes' to 'No'
Part II	• Module SVII. Identified and Potential Risks o Section 8.2, Module SVII.2. New safety concerns and reclassification with a submission of an updated RMP: Reinstated the important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers'. o Section 8.3.1, Module SVII.3.1 Presentation of important identified risks and important potential risks: Reinstated risk table for the important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers' (8.3.1.9, Table 8-18) . • Module SVIII: Summary of the Safety Concerns o Important potential risks: Reinstated the important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers'.
Part III	No updates
Part IV	No updates
Part V	• Section 12.1, Module V.1 Routine Risk minimization measures - Table 12-1: Description of RMM by safety concern o Reinstated routine risk minimization measures for the important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers' • Section 12.2, Module V.2 Additional Risk minimization measures: o Reinstated additional risk minimization measures for the important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers' from the safety areas of interest in Educational Materials • Section 12.3, Module V.3 Summary Table of Risk Minimization Measures o Reinstated risk minimization measures for the important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers'
Part VI	• Updated according to the changes made in the main body of the RMP.
Part VII Annexes	

Part	Major changes compared to RMP v7.1
Annex number	Description of changes
Annex 1	No change
Annex 2	No change
Annex 3	No change
Annex 4	No change
Annex 5	No change
Annex 6	• Reinstated the KSM addressing the important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers'
Annex 7	No change
Annex 8	• Updated Summary of changes to RMP over time

Other RMP versions under evaluation

Version number: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP:

Version number: 6.1

Approved with procedure: EMEA/H/C/004712/II/0020

Date of approval: 06-Jul-2023

QPPV name: Dr. Justin Daniels PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization applicant´s QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AJ	Adherence Junctions
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AV	Atrioventricular
BCC	Basal Cell Carcinoma
BRB	Blood Retinal Barrier
CDP	Confirmed Disability Progression
CI	Confidence Interval
CM	Cryptococcal Meningitis
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disorder
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP2C9	Cytochrome P450 2C9
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EMA/EMEA	European Medicines Agency
EU	European Union
HCPs	Health Care Professionals
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSV	Herpes Simplex Virus
IBD	International Birth Date
IgG	Immunoglobulin G
IR	Incident Rate
IRIS	Immune Reconstitution Inflammatory Syndrome
IRR	Incidence Rate Ratios
JC/JCV	John Cunningham Virus
KSM	Key Safety Messages

LMP	Last Menstrual Period
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
OIs	Opportunistic Infections
OR	Odds Ratio
pAR	Preliminary Assessment Report
PBPK	Physiologically-Based Pharmacokinetic
PG	Pharmacogenetic
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PL	Patient Leaflet
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
PRAC	Pharmacovigilance Risk Assessment Committee
PRES	Posterior Reversible Encephalopathy Syndrome
PSUR	Periodic Safety Update Report
PSUSA	PSUR Single Assessment
PTY	Patient-Treatment-Years
PUVA	Psoralen (P) and Ultraviolet A (UVA)
PV	Pharmacovigilance
PY	Patient Year
RMM	Risk Minimization Measures
RMP	Risk Management Plan
RRMS	Relapsing-Remitting Multiple Sclerosis
S1P	Sphingosine-1-Phosphate
S-db	Safety Data Base
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SMR	Standardized Mortality Ratios
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
TdP	Torsades de Pointes
TJ	Tight Junctions
UK	United Kingdom
ULN	Upper Limit of Normal

USA	United States of America
UTI	Urinary Tract Infection
UV	Ultraviolet
VZV	Varicella-Zoster Virus
WOCBP	Women of Child-Bearing Potential

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product(s) Overview

Active substance(s) (INN or common name)	Siponimod
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, Sphingosine-1-phosphate (S1P) receptor modulators (L04AE03)
Marketing Authorization Applicant	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Mayzent®
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical name: Siponimod fumaric acid
	Summary of mode of action: Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator. Siponimod binds selectively to two out of five G-protein-coupled receptors (GPCRs) for S1P, namely S1P1 and S1P5. By acting as a functional antagonist on S1P1 receptors on lymphocytes, siponimod prevents egress from lymph nodes. This reduces the recirculation of T cells into the central nervous system (CNS) to limit central inflammation. Siponimod spares effector memory T cells in peripheral tissues and blood and does not impair lymphocyte activation. In animal studies, direct effects have been demonstrated for siponimod on neural cells via S1P1 on astrocytes and S1P5 on oligodendrocytes. In a mouse model of experimental autoimmune encephalomyelitis a direct neuroprotective effect, independent from effects on lymphocytes, was also demonstrated for siponimod applied centrally (via intracerebroventricular infusions).
	Important information about its composition: Contains lactose monohydrate
Hyperlink to the Product Information	[Current approved SmPC] [Proposed SmPC]
Indication(s) in the EEA	Current: Siponimod is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.
	Proposed: Not applicable.
Dosage in the EEA	Current: Treatment has to be started with a titration pack that lasts for 5 days. Treatment starts with 0.25 mg once daily on days 1 and

	2, followed by once daily doses of 0.5 mg on day 3, 0.75 mg on day 4, and 1.25 mg on day 5, to reach the patient's prescribed maintenance dose of siponimod starting on day 6. The recommended maintenance dose of siponimod is 2 mg taken once daily. The recommended maintenance dose of siponimod in patients with a CYP2C9 *2*3 or *1*3 genotype is 1 mg taken once daily.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: 0.25 mg film-coated tablets 1 mg film-coated tablets 2 mg film-coated tablets
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Secondary Progressive Multiple Sclerosis (SPMS)

Incidence:

A literature search was conducted to retrieve worldwide estimates for the incidence of SPMS. No specific studies reporting on the incidence of SPMS were retrieved. SPMS follows an initial relapsing-remitting course (Relapsing-remitting multiple sclerosis [RRMS]). In the absence of treatment, approximately 50% of individuals diagnosed with RRMS transition to SPMS within 10 years and up to 90% of RRMS patients transition to SPMS within 20-25 years (Gross and Watson 2017).

Globally, the estimated median annual incidence of multiple sclerosis (MS) in 2013 was 4.0 per 100,000 (interquartile range: 1.5 to 7.5) according to estimates from the (Multiple Sclerosis International Federation 2013). On a regional level, Europe had the highest estimated median annual incidence in 2013 (5.5 per 100,000), followed by Asia (3.0 per 100,000), Africa (1.0 per 100,000), and the Americas (0.6 per 100,000). Countries reporting the highest estimated median annual incidence of MS included Canada (13.4 per 100,000), Latvia (11.6 per 100,000), and Czech Republic (11.0 per 100,000) (Multiple Sclerosis International Federation 2013).

Prevalence:

A literature search was conducted to retrieve worldwide estimates for the prevalence of SPMS. The Atlas of MS reported that the number of people with overall MS worldwide increased from 2.1 million in 2008 to 2.3 million in 2013 (Browne et al 2014). According to the MS Atlas, there was a wide variation in the prevalence of MS in Europe from 22 to 227 per 100,000 population. The prevalence of MS was particularly high in western European countries varying between 100 and 227 per 100,000 population (Multiple Sclerosis International Federation 2013). According to a recent study, the 2012 overall MS prevalence in the United States was estimated to be 149.2 per 100,000 individuals (95% CI: 147.6-150.9) (Dilokthornsakul et al 2016). The study further reported that the prevalence of MS in the US has remained stable between 2008 and 2012. Approximately 85% of all MS patients are initially diagnosed with RRMS (National MS Society 2017).

The prevalence estimates per 100,000 for SPMS ranged from 1.9 in Japan to 60.6 in Norway (Itoh et al 2003, Simonsen et al 2017). The prevalence estimates for SPMS in population-based studies in Europe ranged from 2.8 (95% CI: 0.8-7.1) per 100,000 in a rural province in Spain (Modrego et al 1997) to 60.6 (95% CI 51.7-70.6) per 100,000 in a central region of Norway (Simonsen et al 2017).

Prevalence estimate worldwide for SPMS in Canada was reported to be 18 per 100,000 persons (Sloka et al 2005). The prevalence estimates for MS from South America were reported from a systematic review and meta-analysis of prevalence studies on MS in Argentina (Rojas et al 2012). In this review, the combined result of 4 studies showed that the prevalence of MS was 17 per 100,000 inhabitants and 6 studies reported that the proportion of all MS to be SPMS was 21.5% (95% CI: 19.3%-23.0%).

The prevalence estimates for SPMS in population-based studies in the Middle East ranged from 2.0 (95% CI 1.6-2.5) per 100,000 over a 1year measure in residents of the Middle Black Sea region (Akdemir et al 2017) to 6.7 (95% CI: 2.9-13.2) per 100,000 in the ethnically heterogeneous region of Edirne (Celik et al 2011).

In Asia and Oceania, prevalence estimates were available from Japan and New Zealand. Estimates from Japan were very similar and ranged from 1.9 (95% CI: 0.8-4.0) per 100,000 for residents of Asahikawa (Itoh et al 2003) to 3.3 (95% CI: 1.7-5.8) per 100,000 for residents of Tokachi province of Hokkaido (Nakamura et al 2009). The estimate for SPMS prevalence from New Zealand was 22.8 (95% CI: 21.3-24.3) per 100,000 (Taylor et al 2010).

Many factors have been put forward to explain variation for SPMS prevalence estimates including selection criteria, MS criteria used, availability of disease-modifying treatments and exposure to risk factors. All the studies (except the largest one which indicated that their participants were diagnosed by a neurologist with no further details, Manouchehrinia et al 2017) reported using the Poser criteria, which was initially defined for the purposes of epidemiologic studies and clinical trials, or the more recently defined McDonald criteria, which make it possible to diagnose MS at an earlier stage than when using the Poser criteria (Houzen et al 2017). Both criteria provided safeguards against incorrect diagnosis but according to Lorscheider et al (2016) there was no gold-standard objective definition of SPMS and diagnosis was often accompanied by delay as progression after various time periods needed to be confirmed for SPMS patients. Only 2 studies reported on the proportion of their participants which were given disease-modifying treatments but the impact of treatment on the prevalence of SPMS cannot be ignored (Confavreux and Vukusic 2014, Brassat 2017). Toncev et al (2011) reported a prevalence of 20.7 (95% CI: 15.9-26.6) per 100,000 in 2006 in a Serbian population which did not have access to these treatments. Although this estimate was on the higher end for prevalence estimates in Europe, it cannot be inferred with certainty that the higher prevalence was only because of treatment level differences. In comparison, El-Salem et al (2006) reported a relatively low 1-year prevalence estimate of 3.2 (95% CI: 1.7-5.5) per 100,000 in a Jordanian population of which around 60% of all MS patients were receiving beta-interferon treatment.

Demographics of the population in the SPMS indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

A higher prevalence of SPMS in women than in men was systematically reported in several studies (Pekmezovic et al 2001, El Salem et al 2006, Hashemilar et al 2011, Toncev et al 2011, Houzen et al 2017). For example, in the Canadian study, Sloka et al (2005) reported that approximately 29% of SPMS cases were male whereas 71% of the cases were females. Average ages of SPMS cases on prevalence day ranged from 46.9 to 59.6 years (Toncev et al 2011, Taylor et al 2010).

Risk factor for transition to SPMS

Several risk factors which promoted a transition from RRMS to SPMS have been investigated and are discussed below. Included studies were chosen carefully as the timing of the assessment of the risk was crucial in determining whether it was a risk factor for transition from RRMS status to SPMS status, or in reality a symptom, a result or an explanation (e.g. specific gene expression) of SPMS status. There is agreement across the studies that treatment, some genetic factors, some measures of RRMS severity and smoking had an effect on the transition time from RRMS to SPMS. Stand-alone studies on the reported effect of no contraceptive use, low vitamin D at MS onset and presence of active epilepsy on shortening conversion time to SPMS still needed to be confirmed. Effects of age at MS onset and sex on transition rates were still widely debated.

Age

Average time to conversion from RRMS to SPMS was reported in 6 studies (Galimberti et al 2007, Koch et al 2008, Pokryszko-Dragan et al 2008, Koch et al 2010, Al-Hamadani et al 2012, Harding et al 2013). In these population based studies, the mean duration to conversion ranged 9.9 ±4.1 year in Iraq (Al-Hamadani et al 2012) to 23.30 years (95% CI: 20.9-25.7) in The Netherlands (Koch et al 2008).

There is an ongoing debate as to whether primary and secondary MS have a similar age at onset of progression (Tremlett and Zhao 2017, Vukusic 2017). Arguments for and against mention the difficulty to determine the exact time of onset of progression in a patient who already showed clinical activity and disability potentially resulting in a differential measurement bias (Vukusic 2017). On the other hand, it has also been mentioned that RRMS patients often get erroneously excluded from studies as they have not developed SPMS yet thus introducing a selection bias (Tremlett and Zhao 2017). Amongst retrieved studies, in the United Kingdom (UK), 1,825 adult-onset MS patients had a shorter time for conversion to SPMS state compared to 111 paediatric-onset MS patients, although paediatric-onset patients still converted at a median younger age than adult onset MS patients (Harding et al 2013). In this study, paediatric-onset MS cases had a median duration to progression of 32 years, whilst adult-onset MS cases had a median duration of 18 years till progression. On the other hand, Al-Hamadani

et al (2012) reported that in their cross-sectional study in Iraq, children under the age of 10 had a shorter time for conversion to SPMS compared to adolescents (aged 10-18 years) with an MS onset. Koch et al (2010) reported that the hazard ratio of reaching SPMS increased by 27.1% (95% CI: 23.4%-30.9%) for every 5-year increase in onset age in 5,162 Canadian MS cases that were treatment free. This finding was confirmed in a Polish medical chart review study of 100 patients by Pokryszko-Dragan et al (2008) and in multi-national study (Spain, Hungary, The Netherlands, Germany and Norway) of 574 patients by Riise et al (1992). Results from the Dutch Groningen MS database were contradictory with findings of an effect of age at MS onset in one report (Koch et al 2008) and findings of no association in 2 other reports (Koch et al 2007, Koch et al 2009). No association with age of onset was reported in a 15-year follow-up if a population-based cohort in Sweden (Eriksson et al 2003) and in a cross-sectional study on 431 patients in Norway (Benjaminsen et al 2017).

Sex

Two studies reported that sex had an impact on conversion rates from RRMS to SPMS: in a single-center chart review study in Poland where being a man shortened the progression time (p=0.0338) (Pokryszko-Dragan et al 2008) and in a large multicenter study in Canada where the hazard ratio of being a man for shortening conversion time was 1.43 (95% CI: 1.30-1.58) (Koch et al 2010). Several other studies reported that sex had no impact (Riise et al 1992, Eriksson et al 2003, Koch et al 2007, Koch et al 2008, Harding et al 2013).

Treatment

The use of immunomodulatory treatment increased the time to conversion from RRMS to SPMS; however, this difference was not statistically significant (Koch et al 2008, Koch et al 2009). In the Groningen MS database, users of immunomodulatory treatment had a mean time to progression of 25.6 years (95% CI: 21.3-29.8) whilst non-users had a mean time to progression of 22.3 years (95% CI: 19.9-24.7). A multivariable Cox regression analysis showed that the use of immunomodulatory treatment was a significant predictor of conversion from RRMS to SPMS with a hazard ratio of 0.30 (95% CI: 0.15-0.61) adjusted for age and gender (Koch et al 2008).

Genetic factors

Galimberti et al (2007) reported that amongst 226 MS cases (of which 15.9% had converted to SPMS) and 235 matched controls, carriers of non-wild-type haplotypes in CXCL10 gene (GTCC or CCCC) compared to wild type (GGTT) haplotype carriers were more likely to convert quickly to SPMS (median values of 10 or 9 years to progression compared to 16 years to progression, p=0.08). They also reported that the presence of the wild-type GGTT haplotype in CXCL10 gene did not increase risk of developing MS and acted as protective factor towards the progression to SPMS in subjects affected by RRMS. A meta-analysis, which included 3,869 subjects from eight studies (MS 1,666, controls 2,203) showed a lack of association

between the CCR5-Δ32 polymorphism and SPMS risk in Europeans (Song and Lee 2014). Ratzer et al (2013) hypothesized that different MS subtypes would show differences in gene expression that could be traced to specific subsets of peripheral blood mononuclear cells but after analysis only minor differences were observed between MS subgroups.

Severity of RRMS

Pokryszko-Dragan et al (2008) reported that an increase in annual exacerbation rate and an increase in annual progression of disability in RRMS phase were both correlated with a shortened conversion time to SPMS (correlation of -0.56 and -0.51, respectively) in a single-center retrospective study with 100 participants. In the same manner, Koch et al (2007) reported that in the Groningen MS database, higher baseline values for expanded disability status scale and MS severity score also shortened conversion time (p=0.011 and p=0.009, respectively). Similar conclusions were found in the Eriksson et al (2003) study where presence of high bout frequency (compared to low bout frequency), incomplete degree of remission after the latest relapse and presence of cognitive symptoms all contributed to a shortened time for RRMS to convert to SPMS. Incomplete degree of remission after the last relapse was also confirmed as a factor associated with reduced time to SPMS conversion in a review by Rovaris et al (2006) where it was reported that an incomplete recovery from the initial exacerbation has consistently been associated with a reduced time to secondary progression. On the other hand, not all studies retrieved during the literature search confirmed the effect of onset symptoms as a predictor for early conversion from RRMS to SPMS. Koch et al (2010) mentioned that the presence of motor onset symptoms increased the conversion in a large Canadian study with a hazard ratio with a 95% CI of 1.03 to 1.31 (exact value missing from publication), adding that this was not the case for cerebellar, ataxia or brainstem symptoms. Using the Groningen MS database, none of the onset symptoms were found to be predictive (Koch et al 2007, Koch et al 2008, Koch et al 2009).

Smoking

Degelman and Herman (2017) selected 5 studies for inclusion in a meta-analysis with the aim to examine the association between smoking and MS progression from RRMS to SPMS. The analysis comprised 379 SPMS patients who developed from 1,837 RRMS patients. A statistically significant association, hazard ratio of 1.80 (95% CI: 1.04–3.10), was found between smoking and the progression to SPMS despite substantial heterogeneity, p=0.01; I^2=68%. The meta-analysis showed that smoking contributed to a moderate 80% increase in SPMS risk compared to non-smoking. This was in line with results from a previous meta-analysis (Handel et al 2011) although the relationship in the previous review was not statistically significant. In comparison to the effect of smoking on the RRMs to SPMS conversion, the Degelman and Herman (2017) review also reported that smoking led to a modest 50% increase in MS risk in comparison to non-smoking and failed to detect a

statistically significant relationship between smoking and clinically isolated syndrome to definite MS conversion.

Contraceptive use and being nulliparous

Conversion to SPMS was associated with never having used contraceptives compared to having used contraceptives both before and after or only after onset of MS ($p<0.05$) (Gava et al 2014). Studying the 277 participants of the Groningen MS database, authors reported that being nulliparous had no effect on the conversion time from RRMS to SPMS (Koch et al 2009).

Vitamin D levels

In a small case-control study with 19 SPMS participants and 38 RRMS participants matched for sex, age and year of MS diagnosis, low deseasonalized vitamin D levels at the time of MS diagnosis made it more likely that RRMS patients converted to SPMS (Muris et al 2016).

Epilepsy

Amongst 431 MS patients, 70% of the RRMS group which had active epilepsy converted to SPMS whilst only 35% of those who did not have active epilepsy, irrespective of age, beta-interferon use or history of epilepsy ($p=0.02$) (Benjaminsen et al 2017).

The main existing treatment options:

To date, the following disease modifying therapies are approved for MS:

- Interferon beta-1b (Betaseron®, Extavia®)
- Interferon beta-1a (Avonex®, Rebif®)
- Glatiramer acetate (Copaxone®)
- Natalizumab (Tysabri®)
- Fingolimod (Gilenya®)
- Mitoxantrone (Novantrone®)
- Teriflunomide (Aubagio®)
- Dimethyl fumurate (Tecfidera®)
- Alemtuzumab (Lemtrada®)
- Peginterferon beta-1a (Plegridy®)
- Ocrelizumab (Ocrevus®)
- Cladribine (Mavenclad®)

- Ofatumumab (Kesimpta®)
- Ublituximab-xiiy (Briumvi®)
- Ozanimod (Zeposia®)

Ponezimod (Ponvory®) Most are approved for RRMS or relapsing forms of MS (RMS, defined as RRMS and SPMS with relapses). Two currently approved MS therapies include SPMS in their labels in some countries. Mitoxantrone is approved in the United States of America (USA) for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting MS. The evidence for efficacy in SPMS rests mainly on a study that included a subpopulation with high inflammatory disease activity consistent with a relapsing SPMS subtype (Hartung et al 2002). Cumulative-dose dependent cardiotoxicity and an increased risk of secondary acute myeloid leukemia (Buttmann et al 2016), precludes its use in long-term treatment. Interferon beta (IFNB)-1b is approved in the EU (and in some other non-US countries) for patients with SPMS with active disease as evidenced by relapses, although several randomized controlled trials have since reported that IFNB does not show any benefit in disability outcomes (La Mantia et al 2012).

Natural history of the indicated condition in the SPMS population, including mortality and morbidity:

Multiple sclerosis (MS) is the most common autoimmune demyelinating disorder of the CNS, affecting more than 2.3 million individuals worldwide in 2013 (MSIF 2016).

Approximately 85% of patients present with a relapsing-remitting course with neurological stability between relapses (relapsing-remitting MS [RRMS]). With time, an increasing number of these patients (>50% within 15 to 20 years) experience a deceasing frequency of relapses and in parallel a steady disability worsening, called “progression”. Natural history studies have shown that once an Expanded Disability Status Scale (EDSS) score of 4 (limited walking ability but able to walk at least 500 meters without aid or rest) is reached, further progression develops independent of relapses, i.e., at a similar rate irrespective of individual relapse frequency (Confavreux et al 2000, Vukusic and Confavreux 2003). The stage of disease progression independent of relapses is called secondary progressive phase of MS (SPMS) (Lublin and Reingold 1996, Vukusic and Confavreux 2003, Kremenchutzky et al 2006, Tremlett et al 2008, Confavreux et al 2000, Tremlett et al 2009, Scalfari et al 2010, Lublin et al 2014, Novotna et al 2015). The transition from RRMS to SPMS is determined retrospectively based on evidence that disability progression is occurring independently of relapses, though relapses and focal inflammatory activity may still continue to be present.

RRMS, SPMS with relapses, and SPMS without relapses form a continuum in the phenotypic development of MS over time. Accordingly, neuroanatomic (histopathology, magnetic

resonance imaging [MRI]), immunologic and genetic features of MS are shared among these disease stages with only quantitative differences for inflammatory and neurodegenerative pathology (Frischer et al 2009, Gourraud et al 2011, Antel et al 2012, Cree 2014). These findings have led to a recent revision of the traditional categorization into RRMS, SPMS and primary progressive multiple sclerosis (PPMS) (Lublin and Reingold 1996) to a strictly descriptive one, based on the course of MS with relapsing and progressive MS being the subdivided as 'active' or 'not active' based on presence or absence of acute disease activity (relapses or lesion formation in MRI) (Lublin et al 2014). The distinction of relapsing or non-relapsing SPMS is determined retrospectively, based on presence or absence of recent relapse or MRI lesion activity (e.g., over at least the previous 1 year (Lublin et al 2014).

Secondary progressive multiple sclerosis is associated with significant, irreversible disability, interfering with day-to-day activities. Reduced ambulatory capacity with rates of wheelchair use between 44 and 58%, compared with 1 to 7% for RRMS, is the leading clinical feature. Farther into progression, cognition deficits, ataxia, upper extremity and sphincter dysfunction become very common. Cognitive dysfunction is a primary cause of declining quality of life, and deterioration in information processing speed has been found to be most predictive marker of unemployment (Strober et al 2014). Overall quality of life scores in SPMS are significantly lower than amongst RRMS patients (Orme et al 2007).

Mortality in SPMS

Three studies reported on mortality in SPMS patients. In a population-based Hungarian study with 740 participants with a total of 10,303 person-years of follow-up, the standard mortality ratio from all causes in a mixed group of RRMS/SPMS cases was 2.34 (95% CI: 1.91-2.84) (Sandi et al 2016). This increase in mortality was not due to cardiovascular disease or malignancies (which may be expected due to the fact that these diseases tend to be the leading causes of death in more elderly persons), but due to suicides (which may be explained by the fact that Hungary was one of the leading countries for rates of suicide) (Sandi et al 2016). Rousseau et al (2017) reported that SPMS patients had a mortality rate of 18.2 per 1,000 person-years in a MS Canadian cohort with 127 cases of SPMS. In comparison, in the same Canadian cohort, RRMS cases had a mortality rate of 7.2 per 1,000 person-years. The median survival for SPMS cases was 19.0 years (95% CI: 11.2-26.7) in a Yugoslavian cohort with 63 SPMS cases. This estimate was much shorter than that for RRMS cases (38.0 years, 95% CI: 21.2-54.7) (Levic et al 1999).

Important co-morbidities:

Co-morbidities in SPMS

SPMS is characterized by a multitude of related symptoms. Gross and Watson (2017) reported using data from US National Health and Wellness Survey that even after controlling for baseline characteristics, impairment in physical functioning and general disease burden was greater in

SPMS patients than in RRMS patients. Concerning mood disorders, SPMS cases had a higher prevalence of suicide ideation at 26.3% compared to the prevalence of 20.9% in RRMS and PPMS cases (Strupp et al 2016).

In terms of true co-morbidities which are conditions that cannot be described as one of the many symptoms of MS, articles retrieved focused on cardiovascular diseases, epilepsy, thyroid function, renal failure and venous edema.

Two studies, one in 265 consecutive hospital MS cases in Italy and one using a Swedish MS register, reported that cardiovascular disease burden was higher in SPMS cases when compared to RRMS cases (Roshanisefat et al 2014, Moccia et al 2015). SPMS was associated with an increased risk for a combination of overall cardiovascular conditions as well as pulmonary heart disease and deep vein thrombosis compared to non-MS population (Roshanisefat et al 2014).

Active epilepsy was already described as a risk factor for transition to SPMS from RRMS status (Benjaminsen et al 2017). Etemadifar et al (2013) also reported that the proportion of SPMS cases in a group with epilepsy was higher at 25.9% compared to the proportion of SPMS cases in a group without epilepsy at 6.3%. Nonetheless, epilepsy was not considered a co-morbid condition once SPMS was established in a study on 280 definite MS cases in Chile (Uribe-San-Martin et al 2014), although this could also be explained by the observation that current age and age at MS onset were significantly lower in the group which had epilepsy.

Thyroid dysfunction was present in 2% of SPMS cases but only 0.8% of RRMS cases (statistical significance for difference not reached) in a study with 700 consecutive MS patients treated with IFNB in France (Kreisler et al 2003). In another group that was treatment-free, thyroid disease was present in 22.8% of SPMS cases whilst autoimmune thyroiditis was observed in 8.1% of SPMS cases. These prevalences were not significantly different in other MS subtypes and thus no association between SPMS and the frequency of thyroid disease or autoimmune disease was confirmed (Niederwieser et al 2003).

Renal failure was associated with SPMS when compared to other MS subtypes in a longitudinal cohort study of MS patients as all renal failure cases were described in SPMS cases (Viart et al 2012). The proportion of SPMS cases with venous edema was 59% (Solaro et al 2006).

Important co-morbidities in the overall MS population

Cardiovascular Disease

In a large, population-based cohort study conducted between 1987 and 2009 using the Swedish National Inpatient Register, researchers reported elevated, age-and sex, country of birth and calendar period-adjusted incidence rate ratios (IRRs) in the MS- versus general-population for stroke (1.71, 95% CI: 1.46-2.00), MI (1.85, 95% CI: 1.59-2.15), and heart failure (1.97, 95%

CI: 1.52-2.56), but a reduced IRR for atrial fibrillation/flutter in MS patients versus the general-population (0.63, 95% CI: 0.46-0.87) (Jadidi et al 2013).

From a cohort study using the UK GPRD and national death certificates between 2001 and 2008, (Lalmohamed et al 2012) reported an elevated IRR of death due to cardiovascular disease in MS patients versus age- and sex- and practice matched non-MS controls: IRR 2.42 (95% CI: 1.47-3.97).

Depression

Lifetime prevalence rates of major depression between 43% and 50% and annual prevalence of 25.7% was reported in patients 18-45 years of age attending MS clinics. An elevated risk for depression among persons with MS compared to those without MS was shown (adjusted odds ratio (OR) 2.3, 95% CI: 1.6 - 3.3) (Joffe et al 1987, Patten et al 2003, Feinstein 2004).

In Norway, 31.0% of MS patients reported depression compared to 16.1% in the general population (Beiske et al 2008).

Reported levels of depression using a self-rating questionnaire were significantly higher ($p < 0.001$) for MS patients (n=325) than healthy subjects (n=183) (MS patients: mean=5.6 vs healthy subjects: mean=3.8) (da Silva et al 2011). In a Norwegian sample of 172 MS patients and 58,688 controls, depression was reported by 26.2% of the men with MS compared with 10.8% of the controls ($p < 0.001$). The corresponding figures for women were 25.2% versus 10.4% ($p < 0.001$). Overall, 25.6% of MS patients versus 10.6% of controls reported depression (Dahl et al 2009).

Two cross-sectional surveys revealed a prevalence of mild depressive symptoms between 45% and 51% in MS patients and a registry showed a depression prevalence of 46% in the US, which is higher than in the general US population (16.2%) (Bamer et al 2008, Marrie et al 2009).

In a study conducted in Iran in 2009, severe depression (per Beck depression inventory [BDI]) among MS patients was present in 24.4% of subjects with RRMS, 48.3% of those with PPMS and 45.8% of those with SPMS. Moderate depression was found in 33.3% of those with RRMS, 31% of those with PPMS, and 30.6% of those with SPMS (Kargarfard et al 2012).

Falls, accidents and suicide

The risk for death by accidents in Denmark was 37% higher in MS patients than in the general population (SMR=1.37; 95% CI: 1.08, 1.71). MS patients had a statistically non-significant elevated risk of death from falls (SMR=1.29; 95% CI: 0.075, 2.06). However, they had a particularly high risk for deaths from burns (SMR= 8.90; 95% CI: 5.18, 14.25) and suffocation (SMR=5.57; 95% CI: 2.78, 9.96) (Brønnum Hansen et al 2006). In Denmark, drivers with MS were 3.4 (95% CI: 0.73, 17.15) times more often treated in the emergency department after an accident than drivers without MS (Lings 2002). Furthermore, 52.3% to 54.0% of MS patients reported falls in the last 6 months and 2 months, respectively (Cattaneo et al 2002,

Finlayson et al 2006). In another study, 39.3% of the MS patients reported to have had recent falls that required medical attention more than 6 months ago and 11.9% that required medical attention reported falls in the last 6 months (Peterson et al 2008). A study in the GPRD in the UK revealed that MS patients had a 1.2-fold increased risk of any fracture compared to the year of birth, gender and practice-matched general population (adjusted Hazard ratio [HR]=1.23; 95% CI: 1.09, 1.38) (Bazelier et al 2011).

In Denmark, persons with MS compared to the general population had more than twice the risk to commit suicide (SMR=2.1; 95% CI: 1.8, 2.6) which is similar to data from Sweden (SMR=2.3, 95% CI=1.9, 2.8), and Finland (SMR=1.7; 95% CI: 0.9, 2.7) (Fredrikson et al 2003, Brønnum-Hansen et al 2005, Sumelahti et al 2010). The risk was particularly high the first year after diagnosis (SMR=3.2, 95% CI: 1.4, 6.0) (Brønnum-Hansen et al 2005). In Canada, the proportion of suicide among MS deaths was 7.5 times that for the age-matched general population (Sadovnick et al 1991). Suicide rates seem to increase with age and completed suicide is more common in men (Stern 2005). Crude suicide rate among MS patients in Sweden was 71 per 100,000 PY and significantly higher in males than in females ($p < 0.001$) (Fredrikson et al 2003). Nevertheless, in studies in Finland and Denmark, no elevated risk of suicide was observed in MS patients (Sumelahti et al 2002, Stenager et al 2011).

Urinary tract infection (UTI)

A publication by (de Sèze et al 2007) reported median incidence of upper UTI in MS patients to be 8% (ranging from 0% to 23%); however, the applicable time period (i.e. yearly, biennially, etc.) for this estimate is not explicitly mentioned therein.

Lower UTI was reported on average in 30% of MS patients and ranged from 13% to 80%. Prevalence of upper UTI in MS patients was reported to be between 2.2% and 22.8% (de Sèze et al 2007).

MS patients had a much higher risk of fatal UTI compared to matched controls (OR=11.3) (95% CI: 10.1, 12.6) (Redelings et al 2006).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

An extensive non-clinical safety program served as a basis for the safety assessment of Siponimod in humans. The non-clinical safety evaluation consisted of safety pharmacology, acute, subacute and chronic oral toxicity studies in rat and cynomolgus monkey as well as studies to assess genotoxicity, carcinogenicity, reproductive and developmental toxicity in rats and rabbits, local tolerability, photoreactive potential, immunotoxicity, dependence and abuse potential and an assessment to qualify impurities. The toxicological test species (mouse, rat, rabbit and cynomolgus monkey) were sufficiently exposed to siponimod and its major metabolites, supporting the validity of the toxicological models.

Adverse effects in the chronic toxicity studies were seen in animals at exposure hundreds of times higher than the clinical exposure levels or had limited human relevance. Altogether non-clinical safety data revealed no special hazard relevant for humans, except on embryo-fetal development.

Non-clinical safety findings identified have been addressed by numerous clinical assessments.

Respiratory and CNS safety pharmacology investigations in the rat demonstrated only minor transient effects on the respiratory function and no adverse neuropharmacological effects. Assessment of cardiovascular safety pharmacology in rat, guinea pig and monkey showed transient heart rate reduction.

Single and repeated dose toxicity studies by the oral route have been conducted in mice (up to 13 weeks), rats (up to 26 weeks) and monkeys (up to 52 weeks). Siponimod-related decreases in total lymphocyte counts have been evidenced at all dose levels in repeat dose toxicity studies across species. The effects were reversible or partially reversible and in line with the pharmacological mode of action of siponimod. Dose-limiting toxicities in animal species were nephrotoxicity in mice, body weight development in rats and adverse CNS effects and gastro-intestinal effects in monkeys. The main target organs of toxicity identified by histopathology in rodents included the lung, liver, thyroid, kidney and the uterus/vagina. In monkeys, effects on muscle and skin were observed in individual animals. In the chronic studies, the no-observed-adverse-effect levels (NOAELs) in rats were set at 50 and 15 mg/kg/day for males and females, respectively, and in monkeys at 10 mg/kg/day for both sexes. Cmax and AUC-based exposure multiples of 190 to 342 in rats and of 171 to 222 in monkeys for systemic effects were calculated relative to a maintenance dose of 2 mg/day.

Siponimod is non-genotoxic, has no phototoxic potential and no abuse and dependence potential. Consistent with an immunomodulatory effect, siponimod induced increased incidences of malignant lymphoma in mice in carcinogenicity study; the human relevance is unknown.

In carcinogenicity studies, increased incidences of hemangiosarcomas and hemangiomas were observed in mice at all dose levels in both sexes, but not in rats. Mechanistic studies showed activation of vascular endothelial cells, leading to induction of abnormal angiogenesis and finally hemangiosarcomas. No sustained vascular endothelial cell activation and no increased incidences of hemangiosarcomas were found in rats. Mouse, rat and human endothelial cell cultures demonstrated different responses upon siponimod treatment. Human and rat cells showed no proliferative responses as opposed to mouse cells. Therefore, the siponimod-induced hemangiosarcomas in mice are considered species-specific and there is no evidence to suggest an associated risk to humans.

In rats, siponimod-related neoplastic changes (follicular cell adenoma/carcinoma) in the thyroid gland in males only and non-neoplastic, proliferative changes in the thyroid gland (males only) and in the liver (both sexes) are considered to be due to a well-known rodent specific effect ('liver-thyroid-axis'). These changes are considered to represent adaptive effects in rodents with limited human relevance.

No relevant effects were identified in male and female reproductive organs or related endocrine systems in repeat dose toxicology studies. No impact on mating or sperm parameters were identified in a male fertility study in rats treated up to 200 mg/kg/day before and during mating with non-treated females and no effects on female fertility were observed.

Embryo-fetal development studies showed a dose-dependent increase in embryo- and fetotoxicity in rats and rabbits, and a teratogenic effect in rats at dose levels that did not produce maternal toxicity. In a pre- and post-natal development study in rats, increased numbers of dead and malformed pups were identified. The most common fetal malformations included cleft palate, malrotated limbs, edema and abnormal shape of incisors.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat-dose toxicity studies:	
Adverse clinical signs and effects on CNS Mouse, rat, monkey: Dose-dependent effects on food consumption, body weight and unspecific CNS effects, including convulsions, were reported at doses above maximum tolerated dose (MTD) and were related to general toxicity. No changes in brain; no proconvulsive effects.	Very high safety margins (≥ 410-fold in mouse, ≥ 190-fold in rat, ≥ 385-fold in monkey), therefore human relevance unlikely
Lymphoid system Mouse, rat, rabbit, monkey: Decreases in total lymphocyte counts and redistribution in thymus, spleen, lymph nodes were observed at all dose levels. Generally reversible and are consistent with the	S1P related in all species Human relevant

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat-dose toxicity studies:	
pharmacological activity of siponimod. Secondary lymphoid atrophy at high doses due to general toxicity.	
No generalized immunosuppression and increased infection rates reported in toxicology studies, however some of the lesions in gastro-intestinal tract (GIT) can be due to alteration of the local immune system and reactivation of infections.	
Lungs	
Mouse:	No safety margins
Inflammatory changes at all doses	Human relevance unknown
Vascular System	
Rat:	
Increased incidence of vascular inflammation (spontaneous polyarteritis of rats) at all doses in the 2-year carcinogenicity study in rats (Wistar) involving various organs. Alterations (mainly hemorrhage and degenerative changes) considered secondary to the vascular inflammation were observed in the brain and other organs (incl. kidney with chronic progressive nephropathy).	No safety margins S1P related in rodents Human relevance unlikely as not reported in monkeys or humans treated with S1P modulators.
Not observed in mouse or monkey.	
Mouse: See *carcinogenicity* below	
Kidney	
Mouse:	
Nephrotoxicity. Not observed in rat or monkey	Safety margins ≥ 502-fold, therefore human relevance unlikely.
Liver and Thyroid Gland	
Hepatocellular hypertrophy (mouse and rat) and thyroid follicular cell hypertrophy (rat only).	No human relevance as rodent specific adaptive findings related to metabolizing enzyme induction.
Lacrimal Glands and cornea	
Mouse, rat:	
Degenerative lesions in lacrimal gland, cornea ulceration.	Human relevance unlikely as not reported in monkeys or humans treated with S1P modulators.
Uterus and vagina	
Rat:	
Changes at doses above MTD. Likely due to general toxicity and hormonal imbalance.	Reproductive organs of female rats are very sensitive to general toxicity therefore human relevance unlikely.
No changes in reproductive organs in any species.	
Adrenal glands	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat-dose toxicity studies:	
Rat:	
Increased organ weight.	Human relevance unlikely.
Gastrointestinal tract (GIT)	
Monkey:	Safety margins ≥ 171-fold
Diarrhea, inflammation; likely via reactivation of infections	Human relevance unknown.
Skeletal Muscle	
Monkey:	Safety margins ≥ 171-fold,
Myofiber degeneration	therefore human relevance unlikely.
Skin	
Monkey:	Safety margins ≥ 171-fold,
Follicular atrophy, dermatitis	therefore human relevance unlikely.
Genotoxicity	
Siponimod was not mutagenic, clastogenic or aneugenic in any of the *in vitro* or *in vivo* studies performed	No mutagenic risk for patients based on non-clinical data
Carcinogenicity	
Mouse: Lymphoma	Human relevance unknown
Mouse: Hemangioma/hemangiosarcoma	Human relevance unlikely (mouse specific sustained angiogenesis)
Rat: Thyroid follicular adenoma/carcinoma	No human relevance (rat specific adaptive findings related to metabolizing enzyme induction).
Fertility	
Rat: No effects on male and female fertility	
Reproductive and developmental toxicity	
Rat, rabbit embryo-foetal development:	S1P related in rodents.
Embryotoxic, fetotoxic and teratogenic.	Safety margins < 1-fold
Rat prenatal and postnatal development:	Relevance for women of child-bearing potential (WOCBP).
Adverse clinical signs and malformations in F1 pups. Delayed sexual maturation and changes in immunophenotyping parameters in F1 adults.	
Local tolerance, phototoxicity, dependence and abuse potential	No risk for patients based on non-clinical data.
No adverse effects identified	
Safety Pharmacology	
Cardiovascular	
Rat, guinea pig, rabbit, monkey:	
Transient heart rate decrease. Atrioventricular conduction abnormalities.	S1P related Human relevant

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat-dose toxicity studies:	
Respiratory	
Rat:	
Transient minor effects on lung function	Human relevance unknown
CNS	
Rat:	No risk for patients based on non-clinical data
No adverse effects	
Mechanism for Drug interactions	None identified preclinical

Important identified risks from non-clinical data and confirmed by clinical data (see Section 8.3) are bradyarrhythmia and reactivation of infections. Important potential risk based on non-clinical data is reproductive toxicity (see Section 8.3). These risks are discussed in Module SVII and / or Part II of Module SVIII. There are no other important potential risks identified in non-clinical safety studies which would not have been refuted by clinical data or which would be of unknown significance.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Four pools / safety databases (S-dbs) have been created for the assessment of safety:

- S-db1 focusing on the placebo-controlled, double-blind part of studies BAF312A2304 (hereafter referred as A2304) and BAF312A2201 (hereafter referred as A2201) to assess safety compared to placebo.
- S-db2 and S-db4 intending to assess long-term safety of the doses of 2 mg or higher and including double-blind and open-label periods; these 2 pools include the same patients (all patients receiving at least one dose of siponimod 2 mg or higher) but for different exposure periods: S-db2 includes exposure only while on siponimod 2 mg or higher; S-db4 includes exposure while on any lower doses of siponimod in addition to exposure while on siponimod 2 mg or higher.
- S-db3 specifically focusing on the initiation of siponimod and up-titration period.

Details on patients and exposure periods included in each pool are described below:

S-db1: Controlled Pool (0.25 mg, 0.5 mg, 1.25 mg, 2 mg, 10 mg, placebo)

Patients included in the pool: patients in the double-blind, placebo-controlled pool (S-db1) studies A2201 and A2304 Core Part, by dose and treatment group.

Data included in the pool: data collected during the reporting double-blinded treatment period including a 30-day follow-up period. Data collected under A2304 core part open-label siponimod treatment (i.e. after permanent discontinuation of double-blind study drug) is not included.

S-db2: Long-Term Safety Pool (2-10 mg)

Patients included in the pool: all patients receiving at least one dose of siponimod 2 mg or higher (10 mg).

Data included in the pool:

a. Data collected during the treatment period when patient was treated with the target siponimod 2 mg or 10 mg in the core (controlled and open-label) and/or extension phases of studies A2201 and A2304, including A2304 core part open-label siponimod treatment, if any.

b. Data collected during the dose titration up to the target dose prior to period (a) above.

c. Data collected after a dose reduction from siponimod 2 mg to 1 mg (permitted per protocol due to low lymphocyte counts or tolerability). Similarly, for patients who received the

10 mg dose and then switched to 2 mg (and subsequently from 2 mg to 1 mg dose), data collected while receiving reduced dose.

Data collected during a 30-day follow-up period after last dose of study drug is included.

S-db3: Titration Pool (2 mg)

Patients included in the pool: patients who underwent dose titration from no-treatment or placebo to siponimod 2 mg either at dose initiation in the core and/or extension phases of studies A2201, A2201E1 and A2304 or during dose restart after an interruption of 4 days or more.

Patients from Study A2201 receiving siponimod 2 mg in core phase without titration and titrated up to siponimod 2 mg in the BAF312A2201E1 (hereafter referred as A2201E1) extension phase are included for the periods when they had dose titration only. That is, 29 patients from Studies A2201 and A2201E1 are included in the titration pool, 7 of these patients at the time of dose initiation data and 23 at the time of dose restart data.

Patients who underwent a partial titration from zero dose but were discontinued before reaching the siponimod 2 mg dose are also included in the titration pool.

Data included in the pool: data in the titration periods up to 15 days after start of dose titration. This includes first titration (dose initiation) and any dose restart after dose interruption of 4 days or more. Special focus is on dose initiation and the first dose restart.

Dose initiation and dose restart to siponimod 2 mg are defined as follows:

Dose initiation to siponimod 2 mg: the first titration for a patient receiving the siponimod 2 mg dose, regardless if the first titration to siponimod 2 mg for that patient occurred during double-blind, dose-blinded, or open-label treatment and regardless of previous treatment with (or titration to) siponimod doses other than 2 mg (or placebo). This pool does not include patients who received the first siponimod 2 mg dose without titration.

Dose restart to siponimod 2 mg: the titration periods after ≥ 4 consecutive days in patients with siponimod treatment stopped, other than the first titration, for a patient receiving the siponimod 2 mg dose, regardless of whether the titration occurred during double-blind, dose-blinded, or open-label treatment and regardless of previous treatment with (or titration to) siponimod doses other than 2 mg (or placebo); these patients would have been previously treated with (or titrated up to) siponimod 2 mg. If a patient took the first siponimod 2 mg dose without titration, any subsequent titration periods up to siponimod 2 mg are considered dose restart and are therefore included in this pool.

S-db4: Long-Term Safety Pool (2-10 mg broad)

This pool is referred to as "Long-term safety pool (2-10 mg broad)" to indicate that this pool includes the broadest exposure period for patients who received siponimod 2 mg or 10 mg.

Patients included in the pool: all patients receiving at least one dose of siponimod 2 mg or higher (10 mg).

Data included in the pool: data collected during the siponimod treatment period with any dose, provided the patient received at least one dose of siponimod 2 mg or 10 mg. This includes the period when patients from Study A2201 were receiving siponimod 0.25 mg, 0.5 mg, 1.25 mg or 10 mg prior to switching to siponimod 2 mg. Controlled double-blinded, open-label and extension data are included.

Table 4-1 Population in pooled datasets

Database	Studies	Pooled treatment groups
S-db1: Controlled pool RRMS and SPMS	A2201 A2304 CP	BAF312 0.25 mg BAF312 0.5 mg BAF312 1.25 mg BAF312 2 mg BAF312 10 mg Placebo
S-db2: Long-term safety pool (2-10 mg) RRMS and SPMS	A2201, A2201E1, A2304CP, A2304EP (up to 04-Dec-2024 cutoff date)	BAF312 ≥ 2 mg Includes all patients receiving at least one dose of BAF312 2 mg or higher: includes exposure only while on BAF312 2 mg or higher*
S-db3: Titration pool RRMS and SPMS	A2201, A2201E1, A2304CP, A2304EP (up to 04-Dec-2024 cutoff date)	BAF312 2 mg
S-db-4: Long-term safety pool (2-10 mg broad) RRMS and SPMS	A2201, A2201E1, A2304CP, A2304EP (up to 04-Dec-2024 cutoff date)	BAF312 ≥ 2 mg Includes all patients receiving at least one dose of BAF312 2 mg or higher: includes exposure while on any lower doses of BAF312 in addition to exposure while on BAF312 2 mg or higher

* includes titration period and periods after a dose decrease for tolerability
CP=core part, EP=extension part, MCT= mobile cardiac telemetry
Source: SCS Table 1-3

Duration of exposure was defined as the number of days on study drug, starting from the day of first dose of study medication until the day of last dose. For each treatment group, patient-

years of exposure was calculated as the sum of the number of days on study drug for all patients in the group divided by 365.25.

Exposure is presented for the controlled pool and the two long-term pools. For the titration pool exposure data is not summarized.

In the long-term pools, if a patient was treated in both the core and extension studies/parts, duration of exposure to a treatment is defined as the sum of exposure duration in each study/part. The off-drug periods within each study/part were not excluded. For some patients, a substantial siponimod treatment interruption (gap) was reported between the last dose treatment in the core and the first dose treatment in the extension. This gap was summarized using standard descriptive statistics.

Exposure in the controlled pool (double-blind, randomized, placebo-controlled)

A summary of the overall number of patients exposed and duration of exposure for the Controlled Pool is shown in Table 4-2. Duration of exposure in controlled group by age group and gender is presented in Table 4-3 and duration of exposure by race is presented in Table 4-4.

Table 4-2 Duration of exposure to BAF312 by treatment - Controlled Pool (Safety Set)

Duration of exposure to study drug	BAF312 0.25mg N=51	BAF312 0.5mg N=43	BAF312 1.25mg N=42	BAF312 2mg N=1148	BAF312 10mg N=50	Placebo N=607
Any exposure - n (%)	51 (100)	43 (100)	42 (100)	1148 (100)	50 (100)	607 (100)
Cumulative exposure - n (%)						
≥1 day	51 (100)	43 (100)	42 (100)	1148 (100)	50 (100)	607 (100)
≥7 days	50 (98.0)	43 (100)	42 (100)	1135 (98.9)	46 (92.0)	606 (99.8)
≥1 month	50 (98.0)	42 (97.7)	42 (100)	1117 (97.3)	42 (84.0)	601 (99.0)
≥3 months	38 (74.5)	39 (90.7)	32 (76.2)	1083 (94.3)	38 (76.0)	586 (96.5)
≥6 months	0 (0)	16 (37.2)	0 (0)	1032 (89.9)	23 (46.0)	530 (87.3)
≥9 months	0 (0)	0 (0)	0 (0)	962 (83.8)	0 (0)	482 (79.4)
≥12 months	0 (0)	0 (0)	0 (0)	865 (75.3)	0 (0)	418 (68.9)
≥18 months	0 (0)	0 (0)	0 (0)	542 (47.2)	0 (0)	252 (41.5)
≥24 months	0 (0)	0 (0)	0 (0)	277 (24.1)	0 (0)	116 (19.1)
≥30 months	0 (0)	0 (0)	0 (0)	81 (7.1)	0 (0)	30 (4.9)
≥36 months	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)
Exposure in months						
n	51	43	42	1148	50	607
Mean	3.0459	5.5210	3.0578	17.7296	4.6285	16.5130
SD	0.51033	1.38992	0.39777	8.49818	2.32910	8.20316
Min	0.033	0.394	1.216	0.033	0.033	0.197
Q1	2.9900	5.7170	3.0230	12.1230	3.0550	10.5790

Duration of exposure to study drug	BAF312 0.25mg N=51	BAF312 0.5mg N=43	BAF312 1.25mg N=42	BAF312 2mg N=1148	BAF312 10mg N=50	Placebo N=607
Median	3.1540	5.9470	3.1540	17.3635	5.9140	16.0990
Q3	3.2530	6.2090	3.2200	23.9180	6.2090	23.3590
Max	3.778	6.604	3.581	36.238	6.867	35.581
Patient-time (patient-years)	12.942	19.783	10.700	1696.107	19.285	835.278

- Patient years is the sum of the exposure in days over all patients / 365.25. A month is 365.25/12 days.

Source: Annex 7 Table 1.2-1.1

Table 4-3 Duration of exposure to BAF312 by age group and gender - Controlled Pool (safety set)

		BAF312 0.25mg N=51		BAF312 0.5mg N=43		BAF312 1.25mg N=42		BAF312 2mg N=1148		BAF312 10mg N=50		Placebo N=607	
Age	Sex	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)
Total	Total	51 (100)	12.942	43 (100)	19.783	42 (100)	10.700	1148 (100)	1696.107	50 (100)	19.285	607 (100)	835.278
	Male	9 (17.6)	2.321	13 (30.2)	6.501	11 (26.2)	2.765	450 (39.2)	687.191	20 (40.0)	8.485	239 (39.4)	332.974
	Female	42 (82.4)	10.621	30 (69.8)	13.282	31 (73.8)	7.935	698 (60.8)	1008.916	30 (60.0)	10.800	368 (60.6)	502.304
18-30 years	Total	10 (19.6)	2.672	10 (23.3)	4.047	12 (28.6)	3.127	38 (3.3)	39.333	13 (26.0)	5.215	32 (5.3)	24.352
	Male	2 (3.9)	0.537	3 (7.0)	1.492	4 (9.5)	1.029	11 (1.0)	14.681	4 (8.0)	1.531	10 (1.6)	8.055
	Female	8 (15.7)	2.135	7 (16.3)	2.555	8 (19.0)	2.098	27 (2.4)	24.652	9 (18.0)	3.684	22 (3.6)	16.297
31-45 years	Total	33 (64.7)	8.140	26 (60.5)	12.163	26 (61.9)	6.561	391 (34.1)	595.228	31 (62.0)	11.511	219 (36.1)	290.427
	Male	6 (11.8)	1.521	7 (16.3)	3.449	6 (14.3)	1.487	155 (13.5)	244.006	14 (28.0)	6.029	95 (15.7)	128.171
	Female	27 (52.9)	6.619	19 (44.2)	8.714	20 (47.6)	5.074	236 (20.6)	351.222	17 (34.0)	5.482	124 (20.4)	162.256

		BAF312 0.25mg N=51		BAF312 0.5mg N=43		BAF312 1.25mg N=42		BAF312 2mg N=1148		BAF312 10mg N=50		Placebo N=607	
Age	Sex	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)
46-55 years	Total	8 (15.7)	2.130	7 (16.3)	3.573	4 (9.5)	1.012	519 (45.2)	772.755	6 (12.0)	2.559	244 (40.2)	346.951
	Male	1 (2.0)	0.263	3 (7.0)	1.560	1 (2.4)	0.249	205 (17.9)	314.060	2 (4.0)	0.925	98 (16.1)	144.688
	Female	7 (13.7)	1.867	4 (9.3)	2.013	3 (7.1)	0.763	314 (27.4)	458.695	4 (8.0)	1.634	146 (24.1)	202.263
>55 years	Total	0 (0)	0	0 (0)	0	0 (0)	0	200 (17.4)	288.791	0 (0)	0	112 (18.5)	173.548
	Male	0 (0)	0	0 (0)	0	0 (0)	0	79 (6.9)	114.444	0 (0)	0	36 (5.9)	52.060
	Female	0 (0)	0	0 (0)	0	0 (0)	0	121 (10.5)	174.347	0 (0)	0	76 (12.5)	121.488

- Subject time is the sum each subject's treatment exposure in years based on the number of subjects in each category.
- Patient years is the sum of the exposure in days over all patients / 365.25.

Source: Annex 7 Table 1.2-2.1

Table 4-4 Duration of exposure to BAF312 by race - Controlled Pool (Safety set)

	BAF312 0.25mg N=51		BAF312 0.5mg N=43		BAF312 1.25mg N=42		BAF312 2mg N=1148		BAF312 10mg N=50		Placebo N=607	
Race	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)
White	50 (98.0)	12.685	42 (97.7)	19.241	41 (97.6)	10.432	1093 (95.2)	1632.226	48 (96.0)	18.789	572 (94.2)	791.957
Black or African American	1 (2.0)	0.257	0 (0)	0.000	1 (2.4)	0.268	8 (0.7)	8.605	0 (0)	0.000	4 (0.7)	3.772
Asian	0 (0)	0.000	0 (0)	0.000	0 (0)	0.000	30 (2.6)	32.194	0 (0)	0.000	18 (3.0)	17.433

	BAF312 0.25mg N=51		BAF312 0.5mg N=43		BAF312 1.25mg N=42		BAF312 2mg N=1148		BAF312 10mg N=50		Placebo N=607	
Race	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)
Unknown	0 (0)	0.000	0 (0)	0.000	0 (0)	0.000	5 (0.4)	7.297	0 (0)	0.000	5 (0.8)	9.210
Other	0 (0)	0.000	1 (2.3)	0.542	0 (0)	0.000	12 (1.0)	15.785	2 (4.0)	0.496	8 (1.3)	12.906

- Subject time is the sum each subject's treatment exposure in years based on the number of subjects.
- Patient years is the sum of the exposure in days over all patients / 365.25.in each category

Source: Annex 7 Table 1.2-1.1a

Exposure in the long-term safety pools

A summary of the overall number of patients exposed to siponimod and the duration of exposure for the 2 long-term safety pools [broad (1) patients with the broadest exposure period, (2) patients with exposure to 2 mg and/or 10 mg] is shown in Table 4-5. Duration of exposure in controlled group by age group and gender is presented in Table 4-6 and duration of exposure by race is presented in Table 4-7.

Table 4-5 Duration of exposure to BAF312 by treatment - Long-term Safety Pools (Safety Set)

Duration of Exposure to study drug	BAF312 2-10mg broad(1) N=1737	BAF312 2-10mg(2) N=1737
Any exposure - n (%)	1737 (100)	1737 (100)
Cumulative exposure - n (%)		
≥1 day	1737 (100)	1737 (100)
≥7 days	1716 (98.8)	1716 (98.8)
≥1 month	1692 (97.4)	1691 (97.4)
≥3 months	1648 (94.9)	1645 (94.7)
≥6 months	1588 (91.4)	1582 (91.1)
≥9 months	1515 (87.2)	1509 (86.9)
≥12 months	1455 (83.8)	1447 (83.3)
≥18 months	1361 (78.4)	1352 (77.8)
≥24 months	1291 (74.3)	1275 (73.4)
≥30 months	1217 (70.1)	1202 (69.2)
≥36 months	1166 (67.1)	1146 (66.0)
≥4 years	1064 (61.3)	970 (55.8)
≥5 years	940 (54.1)	859 (49.5)
≥6 years	751 (43.2)	745 (42.9)
Exposure in months		
n	1737	1737
Mean	59.3923	57.7774
SD	36.8617	37.27451
Min	0.033	0.033
Q1	23.4910	21.7490
Median	65.7740	59.0390
Q3	92.2220	92.2220
Max	119.458	119.458

Duration of Exposure to study drug	BAF312 2-10mg broad(1) N=1737	BAF312 2-10mg(2) N=1737
Patient-time (patient-years)	8597.027	8363.265
Exposure gap in days		
n	1031	943
Mean	48.8	45.1
SD	102.20	99.70
Min	0	0
Q1	0.0	0.0
Median	6.0	3.0
Q3	28.0	27.0
Max	769	769

(1) Safety data collected while on any dose of BAF312 in all patients who received at least one dose of 2 mg or 10 mg.

(2) Safety data of all patients receiving at least one dose of 2mg or 10mg and collected while on 2 mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- Patient years is the sum of the exposure in days over all patients / 365.25. A month is 365.25/12 days.

- For patient treated in both the core and extension phase of a study, duration of exposure is calculated as the sum of exposure duration in each phase without counting the off-drug period between phases.

- The exposure gap to BAF312 is defined as the days between the last dose treatment of BAF312 in the core phase and the first dose treatment of BAF312 in the extension phase, non-inclusive.

Source: Annex 7 Table 1.2-1.2

Table 4-6 Duration of exposure to BAF312 by age group and gender - Long Term Safety Pools (Safety set)

		BAF312 2-10mg broad(1) N=1737		BAF312 2-10mg(2) N=1737	
Age	Sex	Subjects n(%)	Subject time (years)	Subjects n(%)	Subject time (years)
18-30 years	Male	27 (1.6)	119.763	27 (1.6)	101.688
	Female	64 (3.7)	245.241	64 (3.7)	201.308
31-45 years	Male	254 (14.6)	1265.732	254 (14.6)	1226.097
	Female	380 (21.9)	1914.617	380 (21.9)	1811.800
46-55 years	Male	290 (16.7)	1487.297	290 (16.7)	1479.721
	Female	429 (24.7)	2151.794	429 (24.7)	2130.068
>55 years	Male	106 (6.1)	537.287	106 (6.1)	537.287
	Female	187 (10.8)	875.296	187 (10.8)	875.296

		BAF312 2-10mg broad(1) N=1737		BAF312 2-10mg(2) N=1737	
Age	**Sex**	**Subjects n(%)**	**Subject time (years)**	**Subjects n(%)**	**Subject time (years)**

(1) Safety data collected while on any dose of BAF312 in all patients who received at least one dose of 2 mg or 10 mg.

(2) Safety data of all patients receiving at least one dose of 2mg or 10mg and collected while on 2 mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- Patient years is the sum of the exposure in days over all patients / 365.25. A month is 365.25/12 days.

- For patient treated in both the core and extension phase of a study, duration of exposure is calculated as the sum of exposure duration in each phase without counting the off-drug period between phases.

- The exposure gap to BAF312 is defined as the days between the last dose treatment of BAF312 in the core phase and the first dose treatment of BAF312 in the extension phase, non-inclusive.

Source: Annex 7 Table 1.2-2.2

Table 4-7 Duration of exposure to BAF312 by race - Long Term Safety Pools (Safety set)

	BAF312 2-10mg broad(1) N=1737		BAF312 2-10mg(2) N=1737	
Race	**Subjects n(%)**	**Subject time (years)**	**Subjects n(%)**	**Subject time (years)**
White	1653 (95.2)	8206.569	1653 (95.2)	7972.807
Black or African American	11 (0.6)	42.471	11 (0.6)	42.471
Asian	43 (2.5)	197.753	43 (2.5)	197.753
Unknown	10 (0.6)	61.653	10 (0.6)	61.653
Other	20 (1.2)	88.581	20 (1.2)	88.581

(1) Safety data collected while on any dose of BAF312 in all patients who received at least one dose of 2 mg or 10 mg.

(2) Safety data of all patients receiving at least one dose of 2 mg or 10 mg and collected while on 2 mg or 10 mg treatment (including dose titration period and reduced dose due to tolerability).

- Patient years is the sum of the exposure in days over all patients / 365.25. A month is 365.25/12 days.

- For patient treated in both the core and extension phase of a study, duration of exposure is calculated as the sum of exposure duration in each phase without counting the off-drug period between phases.

- The exposure gap to BAF312 is defined as the days between the last dose treatment of BAF312 in the core phase and the first dose treatment of BAF312 in the extension phase, non-inclusive.

Source: Annex 7 Table 1.2-1.2a

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnant or nursing (lactating) women. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 30 days after the last dose of siponimod.	Reproductive and developmental studies in pregnant rats and rabbits have demonstrated siponimod induced embryo toxicity and fetotoxicity in both species. Siponimod is excreted into milk in the lactating rat (with a 2-fold lower exposure in milk compared to plasma). Measurements of siponimod in human breast milk have not been performed. There are no data on the effects of siponimod on the breastfed child or the effects of siponimod on milk production.	Use in pregnancy: No Use during lactation: Yes	Reproductive toxicity is an important potential risk. As per the label (SmPC Section 4.6), women receiving siponimod should not breast-feed. As per SmPC Section 4.3, siponimod is contraindicated during pregnancy and in WOCBP not using effective contraception.
CYP2C9 metabolisers defined by genotyping as *3*3 genotype. Patients using (or having used within 4 weeks before initial dosing) concomitant medications that are potent inducers of CYP2C9.	Based on a dedicated pharmacogenetic study in healthy subjects, the systemic clearance of siponimod is significantly reduced in subjects homozygous for the CYP2C9*3*3 genotype compared with the most prevalent genotype (CYP2C9*1*1, wild type). This results in an	No	Potential long-term safety implications in CYP2C9 poor metabolisers is an important potential risk.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	approximate fourfold increase in drug exposure as measured by the area under the curve for drug plasma concentration over time. For this reason, patients with homozygosity for CYP2C9*3, or refusal to test for this polymorphism were excluded from the study owing to possible safety concerns related to the associated chronic/long-term increased exposure.		
Patients with malignancies other than localized basal cell carcinoma.	Consistent with an immunomodulatory mode-of-action, siponimod induced increased incidences of malignant lymphoma in mice. S1P receptor modulators are not classical immunosuppressant, preserve in general effector memory T (TEM) lymphocyte function and act most likely through lymphocyte redistribution. Patients receiving siponimod as part of an immunosuppressive regimen could be at risk of developing lymphoma and other malignancies, particularly of the skin.	No	Malignancies is an important potential risk.
Diagnosis of macular edema during pre-randomization phase.	Continuation of Siponimod in patients with macular edema has not been evaluated.	No	Macular edema is an important identified risk.
Diabetic patients with not well-controlled disease or	Patients with diabetes mellitus are at increased	No	Macular edema is an important identified

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
organ complications (e.g. neuropathy).	risk of developing macular edema.		risk; included patients with diabetes mellitus.
Patients with active infections including bacterial, fungal, viral infections including active hepatitis infections (defined as antibody positive) and tuberculosis and HIV infections. Positive results of screening period testing for serological markers for hepatitis A, B, C, and E indicating acute or chronic infection.	A core PD effect of siponimod is a dose dependent reduction of peripheral lymphocyte count to 20 to 30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. No increase in overall number of infections was observed in A2304 study except chronic viral infections reactivation. Patients with positive results for acute/chronic viral infections like hepatitis B (A, E and C) as well as HIV positive were excluded from the study.	No	Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML) is an important potential risk. Varicella-zoster virus (VZV) infection reactivation, Cryptococcal meningitis, and Progressive multifocal leukoencephalopathy (PML) are important identified risks
Negative for varicella-zoster virus IgG antibodies at Screening	Included as an exclusion criterion based on the mechanism of action which could potentially increase susceptibility to such infections.	No	Varicella-zoster virus (VZV) Infections reactivation is an important identified risk.
Patients who have been treated with immunosuppressive medication prior to siponimod.	Siponimod can be started immediately after discontinuation of beta interferon or glatiramer acetate. While switching from other disease modifying therapies, the half-life and mode of action of the other therapy must be considered to avoid an additive immune effect whilst at the same time minimizing risk of	Yes	Not applicable.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	disease reactivation, except alemtuzumab (not allowed anytime).		
History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.	History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes is a routine exclusion criterion in development studies.	No	There were no confirmed reports of hypersensitivity cases reported in siponimod development program. SmPC section 4.3 (Contraindications) includes an advice: Hypersensitivity to the active substance or to any of the excipients.
Any of the following conditions or treatments that may affect cardiovascular function: History of or current significant cardiac disease including cardiac failure (NYHA functional class II-IV), myocarditis, cardiomyopathy, angina pectoris or myocardial infarction (within 6 months), unstable angina (within 6 months), stroke (within 6 months), TIA (within 6 months), decompensated heart failure requiring hospitalization (within 6 months) or uncontrolled arterial hypertension. Cardiac conduction or rhythm disorders including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus	Initiation of siponimod treatment may result in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving AV block. Vascular tone and blood pressure are regulated by the concerted activity of S1P1, S1P2, and S1P3 receptors expressed on vascular ECs and smooth muscle cells (Ohmori et al 2003; Waeber and Walther 2014; Yatomi 2006). Several studies with isolated cerebral, basilar and mesenteric arteries further suggest that S1P may constrict or dilate vessels depending on the vessel type, the initial tonus of the vessel, and the S1P	No	Bradyarrhythmia is an important identified risk. Hypertension is an identified risk. Thromboembolic events is an important potential risk.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
syndrome, Mobitz Type II second degree atrioventricular-block (AV-block) or higher grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker. Cardiac arrhythmias requiring treatment or a history of cardiac syncope. Patients receiving treatment with Class Ia or III antiarrhythmic drugs (e.g., quinidine, disopyramide, amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, ajmaline, procainamide). Conditions requiring treatment with medication that may cause AV block and suppress AV conduction with the exception of beta-blockers (e.g. carbamazepine, non-dihydropyridine calcium-channel blockers, or cardiac glycosides) Patients receiving at randomization (at treatment initiation) heart-rate slowing calcium channel blockers (ivabradine, verapamil or diltiazem), or other substances which may decrease heart rate such	receptor subtypes involved (Coussin et al 2002; Salomone et al 2003; Hemmings et al 2004, Waeber and Walther 2014).		

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
as digoxin, anticholinesteratic agents or pilocarpine at treatment initiation and treatment re- start. PR interval >230 msec. Long QT syndrome or QTcF prolongation >450 msec in males or >470 msec in females, on screening electrocardiogram (ECG) Severe autonomic nervous system dysfunction Cardiac condition requiring catheter ablation Other cardiovascular conditions or treatments that may significantly impact the safety of the patient as determined by the investigator			
Any of the following pulmonary conditions: History of or active severe respiratory disease, including chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction patients with severe asthma or asthma requiring regular	In repeat-dose toxicity studies in mice up to 13 weeks and rats up to 4 weeks, lung changes were characterized by fibrosis and smooth muscle hypertrophy/ hyperplasia and/or foci with fibrin/hyaline material with inflammatory reaction. The mechanism leading to the pulmonary changes is unclear but may involve pharmacological action on S1P1 receptors.	No	Bronchoconstriction is a potential risk.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
treatment with oral steroids			
Patients with any of the following hepatic conditions prior to randomization: History of alcohol abuse, chronic liver or biliary disease Total or conjugated bilirubin greater than 1.5 times ULN range, unless in the context of Gilbert's syndrome Alkaline phosphatase (AP) greater than 1.5 times the ULN range AST (SGOT), ALT (SGPT) or Gamma-glutamyl-transferase (GGT) greater than 3 times the ULN range	Siponimod's hepatic metabolism is the major elimination mechanism. Cytochrome P450 (CYP) 2C9 is the major metabolizing enzyme for siponimod. CYP3A4 metabolizes siponimod to a lesser extent. The unbound siponimod Cmax and AUCs were comparable in subjects with mild hepatic impairment, 15-17% increased for subjects with moderate hepatic impairment and 50% increased in subjects with severe hepatic impairment in comparison with matched healthy subjects.	No	Liver function tests elevated is an identified risk
Any of the following abnormal laboratory values prior to randomization: serum creatinine >1.7 mg/dL (150 µmol/L) white blood cell (WBC) count < 3500/mm^3 (<3.5 x 10^9/L) lymphocyte count <800/mm^3 (<0.8 x 10^9/L) serum potassium >ULN or other clinically significant laboratory assessment (i.e. hypomagnesemia or hypokalemia)	In renal impairment study total and unbound siponimod Cmax and AUCs were only marginally affected in subjects with severe renal impaired functions, with comparable Cmax and only slightly increased AUCs (by 23-33%) compared to healthy subject group [CBAF312A2129].	No	Lymphopenia is an identified risk

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions due to exposure limitations during a set course of the studies. Rare adverse reactions or adverse reactions with a long latency or those caused by prolonged/cumulative exposure will become evident with continuing safety monitoring in the post-marketing setting.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	In clinical studies, female patients of childbearing potential were required to have a negative pregnancy test prior to siponimod treatment and contraceptive measures were mandated per protocol during dosing and for 30 days after the last dose of siponimod. Patients who became pregnant during the study were required to discontinue study treatment. As of 31-Dec-2017, 15 pregnancies had been reported in 12 female patients participating in siponimod clinical trials in MS (SCS Table 5-5). In addition, one pregnancy with normal outcome was reported in the female partner of a male patient who was randomized to placebo in A2304 Core part. Of these 12 female patients receiving siponimod, 7 patients had post-conception exposure to siponimod for approximately 22-78 days. Of the 7 patients with post-conception exposure, 3 patients delivered normal babies, 3 patients had elective abortion and one had a spontaneous abortion. There are no or limited amount of data available from the use of siponimod in pregnant women. Animal studies have demonstrated siponimod induced embryotoxicity and foetotoxicity in rats and rabbits and teratogenicity in rats, including embryo-foetal deaths and skeletal or visceral malformations. Female patients of childbearing potential should have a negative pregnancy test prior to commencing siponimod treatment. Female patients of childbearing potential should use highly

	effective contraception during treatment and for at least 10 days following the last dose of siponimod.
Breastfeeding women	Not included in the clinical development program.
Population with relevant different ethnic origin	The evaluations of siponimod PK in the clinical study in Japanese subjects and the Phase I/Phase II and Phase III PopPK analyses (in Caucasians, Blacks, Japanese and subjects of another race, and in Japanese and Chinese subjects, respectively) suggest that race/ethnicity does not significantly affect siponimod PK. However, in A2304 CP study the numbers of patients assigned to siponimod group in the Asian and Black/African American subgroups were small (30 patients and 8 patients respectively).
Subpopulations carrying relevant genetic polymorphisms	In the pooled analysis in siponimod program there was little difference in the overall incidence of treatment emergent adverse event (TEAEs) between the genotype subgroups. In most SOCs there were small differences between the genotype subgroups. For the risk of the macular edema the incidence rate was higher in the poor metabolizer (*3/WT, *2/*3) subgroup (IR=2.8; CI: 1.1, 5.7) than for the extensive metabolizer (WT/WT, *2/WT, *2/*2) subgroup (IR=0.9; CI: 0.5, 1.5). Also, the poor metabolizer (3/WT, *2/*3) subgroup had a slightly higher IR (9.7; CI: 6.1, 14.8) for the risk of the hypertension than the extensive metabolizer (WT/WT, *2/WT, *2/*2) subgroup (IR=8.7; CI: 7.2, 10.4).
Elderly patients (≥ 65 years of age)	Not included in the clinical development program
Pediatric patients (≤ 18 years of age)	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	Siponimod must not be used in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustments are needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment in these patients. Patients with severe hepatic conditions or chronic liver/biliary disease or high level of liver function test (LFT) (AST [SGOT], ALT [SGPT] or gamma-glutamyl-transferase greater than 3 times the ULN range) were excluded in clinical studies. The unbound siponimod pharmacokinetics AUC is 15% and 50% higher in subjects with moderate and severe hepatic impairment, respectively, in comparison with healthy subjects for the 0.25 mg

	single dose studied. The mean half-life of siponimod was unchanged in hepatic impairment (CBAF312A2122). There are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated LFT values.
Patients with renal impairment	No dose adjustments are needed in patients with renal impairment. Patients with severe renal impairment (serum creatinine value >1.7 mg/dL (150 µmol/L) were excluded from clinical studies. Mean siponimod half-life and Cmax (total and unbound) were comparable between subject with severe renal impairment and healthy subjects. Total and unbound AUCs were only slightly increased (by 23 to 33%), compared to healthy subjects (CBAF312A2129).

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in milligrams (mg) of active substance sold during the reporting interval 26-Mar-2023 to 25-Mar-2024 and the Defined Daily Dose (DDD). Two DDD can be prescribed: 1 mg (4 film-coated tablets of 0.25 mg) and 2 mg (1 film-coated tablet of 2 mg) based on the CYP2C9 genotype of the patient. The exposure was computed separately for these two types of daily doses (corresponding to two different types of packaging). Moreover, the titration period (separate packaging for the 5 days with increasing dose from 0.25 to 1.25 mg) was not considered as it is negligible compared to the overall exposure. Mayzent 1 mg strength (line extension) has also been approved in the USA on 24-Aug-2021 and in the EU on 16-Feb-2022. The sales volume of siponimod during the reporting interval was approximately 0.61 kilograms (kg) (active pharmaceutical ingredient) for the 0.25 mg dosing, 0.69 kg for the 1 mg daily dosing and 11.6 kg for the 2 mg. The estimated exposure during the reporting interval is 19,470 PTY and cumulative patient exposure since the first launch of siponimod is estimated to be approximately 50,657 PTY.

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Estimated post-marketing (non-clinical trial) exposure

Film-coated tablets	Previous reporting interval (26-Mar-2022 to 25-Mar-2023)		Current reporting interval (26-Mar-2023 to 25-Mar-2024)		Cumulative (Until 25-Mar-2024)	
	Amount sold (Kg)	Estimated exposure (PTY)	Amount sold (Kg)	Estimated exposure (PTY)	Amount sold (Kg)	Estimated exposure (PTY)
0.25 mg	0.7	1,774	0.61	1,664	2.0	5,541
1 mg	0.3	909	0.69	1,875	1.0	2,795
2 mg	9.7	13,341	11.6	15,931	30.9	42,321
Total	**10.7**	**16,024**	**12.9**	**19,470**	**33.9**	**50,657**

Kg: Kilogram; PTY: Patient-Treatment-Years; mg: Milligram

Source of data: Worldwide sales volume

This table includes previous interval data obtained from Apr 2022 to Mar 2023; current interval data obtained from Apr 2023 to Mar 2024; cumulative data obtained from IBD to Mar 2024

Table 6-2 Interval and Cumulative exposure in PTY from marketing experience by region

Film-coated tablets	Current reporting interval (26-Mar-2023 to 25-Mar-2024)			Cumulative (until 25-Mar-2024)		
	EU/EEA	USA	ROW**	EU/EEA	USA	ROW**
0.25 mg	685	104	875	2,475	992	2,074
1 mg	1,545	329	1.0	2,233	560	1.5
2 mg	7,816	2,925	5,190	18,667	11,077	12,577
Total PTY*	**10,046**	**3,358**	**6,066**	**23,375**	**12,629**	**14,653**

EEA: European Economic Area; IBD: International Birth Date; PTY: Patient-Treatment-Years; ROW: Rest of the World; USA: United States of America; mg: Milligram.

This table includes current data obtained from Apr 2023 to Mar 2024; cumulative data obtained from IBD to Mar 2024.

Source of data: Worldwide sales volume.

*The values in the column are calculated by using formulas in excel. The sum up values may not match with the total as the figures are rounded off.

**Sales originating from the United Kingdom and Switzerland are presented under ROW.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

A comprehensive 8-factor abuse potential assessment was carried on the basis of relevant chemistry, nonclinical and clinical data of siponimod and including post-marketing data on fingolimod ([Abuse Potential Assessment]) was done for the FDA.

Overall, chemistry, non-clinical and clinical data with siponimod do not indicate any signals of abuse, misuse or dependence potential in animals or humans, nor do the data demonstrate any potential pharmacological similarities to existing drugs of abuse or psychoactive effects that may be of interest for drug abuse, such as reinforcing, mood-elevating, sedative, stimulant, hallucinogenic or acute cognitive effects. These data are consistent with post-market data for the pharmacologically similar drug fingolimod, which has not shown any signs of abuse, misuse, diversion or dependence in the community. Therefore, it can be concluded that siponimod has no abuse or dependence potential and is not expected to be subject to abuse, misuse or diversion in the community, or result in harm to public health as a result of abuse, misuse or dependence.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

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

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

The safety concerns for siponimod were reviewed in light of the updated Good pharmacovigilance practice (GVP) Module V (rev. 2; Mar-2017). Based on the revised definition of 'important' safety concern, the following safety concerns which were classified as identified and potential risks are not considered important for RMP from the list of safety concerns. These risks are appropriately addressed in the product label and patient leaflet.

Hypertension:

- Treatment with siponimod resulted in an increase in systolic blood pressure and small increases in diastolic blood pressure early after treatment initiation reaching maximum effect after approximately 6 months of treatment (around systolic 3 mmHg, diastolic 1.2 mmHg) and staying stable thereafter. Consistent with these blood pressure changes on chronic dosing a higher incidence of treatment-emergent hypertension AEs was reported in siponimod 2 mg patients compared to placebo patients in the Controlled pool (12.2% vs 8.7%; Odds ratio of 1.5 [95% CI: 1.0, 2.0]). No grade 3, 4 AEs and AEs leading to siponimod discontinuation were reported. The incidence rate of hypertension did not increase with longer exposure. The incidence rate in the Long-term pool S-db4 (broad) (6.0 per 100 PY [95% CI: 5.2, 6.8]) is comparable to the incidence rate in the siponimod 2 mg group in the Controlled pool (8.8 per 100 PY [95% CI: 7.4, 10.4]) (See SCS Section 4.1.2.1).
- Severe events including hypertensive crisis, malignant hypertension or accelerated hypertension have not been reported in the siponimod clinical development program.
- Hypertension is an identified risk and is included as an adverse drug reaction (ADR) in the SmPC.
- Based on data presented above and the risk minimization measures already considered in the SmPC, hypertension is not classified as important risk and can be managed by standard anti-hypertensive medication.

- No additional risk minimisation measures are planned. Novartis will monitor for changes in frequency / severity of the risk by applying routine pharmacovigilance including data mining technologies.

Liver function tests elevated:

- As noted with other S1P receptor modulators, increased hepatic enzymes (mostly ALT elevation) were reported in MS patients treated with siponimod (ALT > 3×ULN in 5.6% of patients on siponimod 2 mg, 1.3% on placebo in the Controlled pool). However these elevations were mild (few patients showed elevations of > 5×ULN) and asymptomatic. In the Controlled pool, most ALT level rises for the siponimod 2 mg group occurred within approximately 28 days of starting treatment. Following treatment discontinuation ALT returned to baseline values within 1-3 months. Fewer patients experienced elevations in AST: 1.1% patients in the siponimod 2 mg group and 0.8% patients in the placebo group had an AST elevation of 3×ULN and 1 siponimod patient (0.1%) had AST >10×ULN. Liver-related AEs were slightly more frequent on siponimod 2 mg than on placebo, but the imbalance was driven by liver-related investigation AEs (such as increased transaminases) which were mainly mild or moderate. Elevated liver function test AEs were reported in 13.2% siponimod 2 mg (IR: 9.5 per 100 PY), and 4.0% placebo patients (IR: 2.9 per 100 PY). No serious hepatotoxic events or patient meeting Hy's law criteria for hepatotoxicity were reported. In the long-term pool (2-10 mg, broad) a similar proportion of patients had raised liver enzymes [See SCS Section 3.4.1.1]).

- The risk is appropriately described and 'liver function tests elevated' are included as an ADR in the SmPC.

- The risk is not classified as important risk in the RMP based on the data presented above, label recommendations considered in the SmPC and as the clinical impact on patients is considered low in relation to the severity of the indication treated.

- No additional risk minimisation measures are planned. Novartis will monitor for changes in frequency / severity of the risk by applying routine pharmacovigilance including data mining technologies.

Seizures:

- In the Controlled pool, seizures were reported as treatment emergent adverse events (AEs) in 17 (1.5%) siponimod 2 mg patients and 3 (0.5%) placebo patients. Seven of these patients receiving siponimod had relevant prior medical conditions (epilepsy, stroke) potentially contributing to the risk for seizure. Of these nine patients (9/17) did not have alternate explanation for the reported event of seizures and a causal relationship to siponimod cannot be excluded. The majority (7/9) of these were partial seizures which occurred as a solitary event or as a few episodes which resolved with a short course of antiepileptic medication.

There was no increase in the rate of seizure AEs in the Long-term pools (IR of 0.9 per 100 PY [95% CI 0.7, 1.2]) compared to the Controlled pool (1.1 per 100 PY [95% CI: 0.7, 1.7]) (See SCS Section 2.1.5.4).

- Epileptic seizures occur more frequently in MS patients than in the general population (Eriksson et al 2002, Marrie et al 2015). Allen et al (2013) used two large record-linked statistical datasets, one for the Oxford region of England (from 1963–1998) and one for the whole of England (from 1999–2011) and found that there is an elevation of risk of epilepsy after MS which was 3- to 4-fold. Burman and Zelano (2017) compared patient data from the Swedish MS register (n=14,545) with 43,635 age- and sex-matched controls which showed a cumulative epilepsy incidence of 3.5% in patients with MS versus 1.4% in the control group.
- Seizures are an identified risk and are included as an ADR in the SmPC.
- Based on the data presented above in the elderly and advanced disease population, labelling recommendation considered in the SmPC and as it could be treated by standard anti-epileptic medication, seizures are not classified as important risk in the RMP.
- No additional risk minimisation measures are planned. Novartis will monitor for changes in frequency/ severity of the risk by applying routine pharmacovigilance including data mining technologies.

Lymphopenia:

- Lymphopenia is a key pharmacodynamic effect of this class of compounds and is a known risk (SCS Section 3.3.1). Lymphopenia is from laboratory measures for which the resulting potential clinical outcome (infections) is already an identified risk. Per GVP Module V Rev 2, the RMP should address only the risks that are undesirable clinical outcomes.
- Siponimod SmPC provides guidance on monitoring of the haematology parameters as required and prior to commencement of siponimod treatment.
- No further characterization is planned, this risk will be followed up via routine pharmacovigilance. No additional risk minimisation measures are planned.

Bronchoconstriction:

- Siponimod induces a mild increase in airway resistance upon treatment initiation with no evidence of further progression with continuous therapy. For pulmonary assessments in Study A2304, mean changes from baseline over time were generally small and similar between treatment groups. Patients with mild or moderate asthma, and patients with other mild or moderate pulmonary disease (e.g. COPD) were permitted to participate in the study. At Month 3 and Month 6 of treatment, mean changes in FEV1 from baseline in the

siponimod group were -0.1 L at each time point, with no change in the placebo group. On long term treatment, this reduction did not translate into clinically significant AEs.

- In the Controlled pool, bronchoconstriction AEs were reported in 10 (0.9%) siponimod 2 mg patients and 2 (0.3%) placebo patients (OR of 2.7, 95% CI: 0.6, 12.2). These were most commonly asthma, reported in 5 (0.4%) siponimod 2 mg patients and in 1 (0.2%) placebo patient. None of these were reported as SAEs, led to study drug discontinuation, or were assessed by investigators as grade 3 or grade 4. There is no evidence for an increase in the incidence of respiratory events with continuing siponimod treatment in the Long-term pool. In the Long-term pools, bronchoconstriction AEs were reported in 21 (1.2%) siponimod 2 mg patients (IR: 0.5 per 100 PY) and asthma is the common reported event for 8 (0.5%) siponimod 2 mg patients (IR: 0.2 per 100 PY) (SCS Section 2.1.5.6).

- The risk is fully described in the SmPC and decreased pulmonary function tests are included as an ADR in siponimod SmPC.

- Based on the data presented above and the risk minimization measures already considered in the SmPC, bronchoconstriction is not classified as important risk as the clinical impact on patients is considered low in relation to the severity of the indication treated.

- No additional risk minimisation measures are planned. Novartis will monitor for changes in frequency / severity of the risk by applying routine pharmacovigilance including data mining technologies.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

The identified and potential risks described in Table 8-1 and Table 8-2 were classified as important risks as the clinical impact of these risks on patients is considered significant in relation to the severity of the indication treated.

Table 8-1 Important identified risks

Risk	Risk/benefit impact (Rationale for classification as important identified risk)
Varicella-zoster virus (VZV) infections reactivation	A core pharmacodynamic effect of siponimod is a dose dependent reduction of peripheral lymphocyte count to 20 to 30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. At therapeutic doses siponimod has no generalized immunosuppressive properties. The immune system effects of siponimod may increase the risk of infections. Reactivation of VZV infection was reported in 2.9% of siponimod 2 mg patients and 0.7% of placebo patients in

Risk	Risk/benefit impact (Rationale for classification as important identified risk)
	the Controlled pool. Herpes zoster was the most common PT in the siponimod 2 mg group (2.2%) and was reported for 0.7% of placebo patients. Cases of meningitis or meningoencephalitis (caused by varicella zoster virus) have been reported on siponimod treatment. VZV infection reactivation may cause serious debilitation, require hospitalization and more aggressive treatment, and could potentially lead to death.
Cryptococcal meningitis	The immune system effects of siponimod may increase the risk of infections. Cases of cryptococcal meningitis (CM) have been reported on siponimod treatment.
Bradyarrhythmia (including conduction defects) during treatment initiation	This risk is based on the transient pharmacodynamic effect, which is expected to occur in most patients at treatment initiation. Siponimod effects on cardiac rhythm and conduction observed in the clinical trials are consistent with known biology of S1P receptor modulation and are similar to the responses to vagal stimulation. The heart rate effect of S1P receptor modulation is mediated by the same ion channel (G protein coupled inwardly rectified potassium channel [GIRK]) associated with parasympathetic nervous system. These manifest as 1) negative chronotropic effect resulting in the transient decrease of heart rate and 2) transient dromotropic effect with delays in atrio-ventricular conduction, observed in the 12 lead ECG as PR interval prolongation and AV blocks of first and second degree (predominantly as Mobitz type I). If the risk is not appropriately managed or prevented could result in serious cardiac effects.
Macular edema	Macular edema is a known risk of S1P receptor modulator drugs. The pathophysiological mechanism is based upon the interaction between siponimod and the S1P1 receptor present on endothelial cells. S1PR1 signaling is responsible for maintaining cell-to-cell and cell-to-matrix adhesion complexes. The use of siponimod is thought to downregulate this receptor, thus leading to downregulation of adhesion complexes and subsequent increased vascular permeability resulting in edema. Macular edema was reported as an AE in 20 (1.7%) siponimod 2 mg patients and 1 (0.2%) placebo patients in the Core phase of the Pivotal study (OR 10.7, 95% CI: 1.4, 80.3). Considered ‘important’ as drug induced macular edema could result in long-term visual impairment in patients receiving siponimod.

Table 8-2 Important potential risks

Risk	Risk-benefit impact (Rationale for classification as important potential risk)
Potential long-term safety implications in CYP2C9 poor metabolisers	**Effect on siponimod exposure:** Siponimod is primarily metabolized by cytochrome P450CYP2C9 (79.3%) and to a lesser extent by CYP3A4 (18.5%). CYP2C9 is a polymorphic enzyme and the 2C9 genotype influences siponimod metabolism. Siponimod exposure is 61%, 91% and 284% higher in intermediate metabolizers *1*3 and in poor metabolizers *2*3 and *3*3, respectively compared to extensive metabolizers *1*1. Risk is considered 'Important' as clinical data related to chronic higher exposure in subjects with reduced metabolic clearance are limited. **Effect of CYP2C9/3A4 inhibitors and inducers:** Drug-drug interaction (DDI) effect in presence of CYP3A or CYP2C9 perpetrator drugs is also predicted to be dependent on the CYP2C9 genotype. Risk is considered 'Important' as interactions with co-administered drugs have the potential to affect the effectiveness or safety of siponimod (Co-administration of siponimod with CY2C9/CYP3A4 inhibitors and CYP2C9/CYP3A4 inducers).
Reactivation of chronic viral infections (other than VZV), and progressive multifocal leukoencephalopathy (PML) and opportunistic infections, other than cryptococcal meningitis.	The immune system effects of siponimod may increase the risk of infections. No cases of PML have been reported for siponimod in the development program; however, they have been reported for another sphingosine 1-phosphate (S1P) receptor modulator in the post-marketing setting. Long-term experience with siponimod treatment is currently limited.
Thromboembolic events	It is a potential risk with other S1P modulator (fingolimod). In the Controlled pool, AEs meeting the definition of thromboembolic events were reported in similar proportions of patients in the siponimod 2 mg (33 patients, 2.9%) and placebo (15 patients, 2.5%) groups (Odds Ratio=1.2, 95% CI: 0.6, 2.2), with no events in the other siponimod dose groups. Hypertension a risk factor for Ischemic cerebrovascular event is an identified risk for siponimod. Risk is considered 'Important" and cannot be fully delineated based on current short-term data. Long-term observation of patients treated with siponimod post-approval should help to better delineate the risk.
Malignancies (excluding BCC and SCC)	Apart from lymphoma in female mice at high doses, pre-clinical data do not suggest an increased risk of malignancies with siponimod. No increase in lymphoma

Risk	Risk-benefit impact (Rationale for classification as important potential risk)
	incidence was observed in the rat carcinogenicity study, nor was lymphoma observed in the 52-week monkey study. Malignancies were not increased on siponimod treatment in clinical studies compared to placebo. In the Controlled pool, AEs meeting this term were reported for 21 (1.8%) patients receiving siponimod 2 mg [Odds ratio 0.8 vs Placebo (95% CI 0.4, 1.6)], and 14 (2.3%) placebo patients. Majority of these were skin malignancies (1.3%, 15 siponimod patients and 1.3%, 8 placebo patients in the Controlled pool). Nevertheless, the risk is considered 'Important'; the long-term observation of patients treated with siponimod post-approval should help to better delineate the risk.
Reproductive toxicity	Reproductive and developmental studies in pregnant rats and rabbits have demonstrated siponimod induced embryotoxicity and fetotoxicity in both species and teratogenicity in rats. Increased incidences were observed following prenatal exposure to siponimod starting at a dose 2 times the higher than that reached in humans taking 2 mg/day. Furthermore, the (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis in rodents [NCO Section 4.5.5]. Pregnant women should be advised of a potential risk to the foetus.
Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses).	Cases of posterior reversible encephalopathy syndrome (PRES) have been reported for another sphingosine 1-phosphate (S1P) receptor modulator (fingolimod). PRES has been associated with the use of several immunosuppressive and immunomodulating agents which can cause endothelial dysfunction, e.g. cyclosporine, tacrolimus (Wong et al 2003).

Table 8-3 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Safety in patients over 60 years old (including elderly)	To date clinical experience in patients aged above 61 years is limited.
Use during lactation	In lactating rats dosed with a single oral dose of 10 mg/kg, siponimod and its metabolites passed into the milk. It is not known if siponimod is present in human milk. There are no data on the effects of siponimod on the breast-fed child or on milk production.

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Long-term safety risks	The clinical trial program had a limited follow-up time of patients (1024 [59%] patients treated for 2 years and 127 [7.3%] patients treated for more than 5 years). New data from the ongoing long-term extension study and post marketing data will provide further evidence on the incidence of cardiovascular risk, malignancies, and opportunistic infections in patients receiving siponimod and will help to further characterize the risks.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

- The important potential risk 'Potential long-term safety implications in CYP2C9 poor metabolisers' which was proposed for removal in RMP v7.1 has been reinstated in the RMP v7.2 as recommended by EMA in the Type IB variation report Request for Supplementary Information (with Procedure no.: EMA/VR/0000273065).

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important identified risk: Varicella-zoster virus (VZV) infection reactivation

Table 8-4 Clinical trial data: Infection, includes Varicella-zoster virus (VZV) infection reactivation (Safety-set)

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	Placebo N=607 n (%) (95% CI)	n (IR*) (95% CI) 31-Dec-2017 (2)	n (IR*) (95% CI) 29-Oct-2021 (3)	n (IR*) (95% CI) 31-Oct-2022 (4)	n (IR*) (95% CI) Final data (5)
All AEs	34 (2.0) (1.4, 2.8)	4 (0.5) (0.1, 1.2)	78 (1.8) (1.4, 2.2)	119 (1.6) (1.3, 1.9)	124 (1.6) (1.3, 1.9)	124 (1.5) (1.3, 1.8)
Resolved/resolved with sequalae	33 (1.9) (1.3, 2.7)	4 (0.5) (0.1, 1.2)	67 (1.5) (1.2, 1.9)	105 (1.4) (1.2, 1.7)	110 (1.4) (1.1, 1.7)	110 (1.4) (1.1, 1.6)
AEs related to study drug	22 (1.3) (0.8, 1.9)	1 (0.1) (< 0.1, 0.6)	50 (1.1) (0.8, 1.5)	78 (1.0) (0.8, 1.3)	80 (1.0) (0.8, 1.2)	80 (1.0) (0.8, 1.2)

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
AEs leading to study drug interruption	6 (0.3) (0.1, 0.8)	0 (0) (0, 0.4)	11 (0.2) (0.1, 0.4)	13 (0.2) (< 0.1, 0.3)	14 (0.2) (< 0.1, 0.3)	14 (0.2) (< 0.1, 0.3)
AE requiring concomitant medication or non-drug therapy	33 (1.9) (1.3, 2.7)	3 (0.3) (< 0.1, 1.0)	73 (1.7) (1.3, 2.1)	111 (1.5) (1.2, 1.8)	116 (1.5) (1.2, 1.8)	116 (1.4) (1.2, 1.7)
AE leading to discontinuation	0 (0) (0, 0.2)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	3 (< 0.1) (< 0.1, 0.1)	3 (< 0.1) (< 0.1, 0.1)	3 (< 0.1) (< 0.1, 0.1)
AE by CTCAE grade (3/4)	3 (0.2) (< 0.1, 0.5)	0 (0) (0, 0.4)	6 (0.1) (< 0.1, 0.3)	7 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)
SAEs	2 (0.1) (< 0.1, 0.4)	0 (0) (0, 0.4)	5 (0.1) (< 0.1, 0.3)	8 (0.1) (< 0.1, 0.2)	8 (< 0.1) (< 0.1, 0.2)	8 (< 0.1) (< 0.1, 0.2)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.
- A patient with multiple occurrences is counted only once within each category.
- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.
- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.
- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.

Source: Annex 7 Table 5-1

Table 8-5 Other details: Varicella-zoster virus (VZV) infection reactivation

Varicella-zoster virus (VZV) infection reactivation	**Details**
Potential mechanisms	The key pharmacodynamic effect of siponimod is a dose dependent reduction of the peripheral lymphocyte count by up to approximately 70-80% due to

Varicella-zoster virus (VZV) infection reactivation	Details
	redistribution of lymphocytes to secondary lymphoid organs. This is because Siponimod down-modulates S1P1 receptors on lymphocytes to prevent egress from secondary lymphoid organs. The resultant sequestration of T and B lymphocytes in lymphoid tissues results in marked reduction of lymphocytes, but not myeloid leukocytes, in the blood. This process is reversible; lymphocytes reappear in the blood after the cessation of treatment, indicating that siponimod does not have cytolytic effects on lymphocytes. The absence of a significant increase in overall infection rates (including serious infections) with siponimod therapy, despite the reduction in peripheral blood lymphocyte count, may be related to the fact that the memory effector subset of T-cells are relatively unaffected by siponimod in the peripheral circulation. The relatively short T1/2 of siponimod (about 30 hours) results in a fast recovery of ALC to normal values and re-establishment of normal immune competence. Lymphocyte counts typically return to the normal range in the vast majority (90%) of SPMS patients within 10 days of stopping therapy. After stopping siponimod treatment residual lowering effects on peripheral lymphocyte count may persist for up to 3 to 4 weeks after the last dose.
Evidence source(s) and strength of evidence	Given the biologic plausibility and the well-characterized risk of infections with the other S1P modulator, infections are not unexpected. In the controlled pool, reactivation of VZV infection was reported for a higher percentage of siponimod 2 mg patients vs placebo, but incidences were low (2.9% of siponimod 2 mg patients and 0.7% of placebo patients). The exposure adjusted rate of VZV reactivation did not increase with long-term exposure (IR: 1.7, 95% CI: 1.4, 2.2, for Long-term pool [broad] vs IR: 1.9 95% CI 1.3, 2.7 for the Controlled pool). In the Phase III study, decrease in lymphocyte count observed in patients in the siponimod 2 mg group is seen early after commencing treatment and is maintained as long as the patient continues siponimod therapy. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase III PopPKPD]. There was no increase in the number of infections following siponimod treatment compared to placebo, or with increasing average siponimod steady-state concentration and decreasing average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use. Cases of herpes viral infection, including cases of meningitis or meningoencephalitis caused by varicella zoster virus, and opportunistic infections (includes cryptococcal infections and JCV causing PML) have been reported for S1P receptor modulators, including siponimod, and other therapies for MS.
Characterization of the risk:	See table above and EU SCS Section 2.1.5.2.

Varicella-zoster virus (VZV) infection reactivation	**Details**
	Herpes zoster was the most common preferred term in the siponimod 2 mg group (2.2%) and was reported for 0.7% of placebo patients. Majority of these are non-serious infections required supportive treatment, and few serious cases required anti-viral agents and antibiotics. Cases of meningitis or meningoencephalitis (caused by varicella zoster virus) have been reported on siponimod treatment.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) are at an increased risk of VZV infections. The patients with negative VZ virus-IgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in case of an MS relapse.
Preventability	Section 4.3 of SmPC: Siponimod is contraindicated in patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis. Refer to Section 4.4 of SmPC. Vigilance for signs or symptoms of infections overall including opportunistic infections, is recommended. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Initiation of treatment with siponimod should be delayed in patients with severe active infection until resolution. Suspension of treatment with siponimod, should be considered if a patient develops a serious infection. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after discontinuation of siponimod, vigilance for infection should be continued throughout this period. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with siponimod (see SmPC Section 4.4). Initiation of treatment with siponimod should be postponed for 1 month to allow the full effect of vaccination to occur. When switching patients from another disease modifying therapy to siponimod, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation. As part of additional risk minimization activity, education materials to HCPs to assist in managing and counseling the patients as well as for educating patients/care givers about the risk while using siponimod is proposed.

Varicella-zoster virus (VZV) infection reactivation	Details
Impact on the benefit-risk balance of the product	Majority of the events reported under the risk term were non-serious, required supportive treatment, and few serious cases required anti-viral agents and antibiotics. Treatment with siponimod was continued in the majority of cases and most cases resolved. Therefore, for the individual patient, the overall impact of the risk is anticipated to be low. The benefit-risk profile of siponimod in the indication of SPMS remains positive, as siponimod demonstrated efficacy in the advanced disease population to placebo and a standard of care continue to outweigh the manageable risk of VZV infection reactivation.
Public health impact	The potential public health impact in patients receiving siponimod 2 mg is considered to be low although care is needed in patients who have other risk factors which may pre-dispose to severe infection e.g. concomitant immunosuppressive therapy.

8.3.1.2 Important identified risk: Cryptococcal meningitis

Clinical trial data

During the extension phase of the Study A2304, a 62-year-old female patient had a confirmed cryptococcal meningitis (positive gram staining of CSF, positive Cryptococcal antigen test and CSF fungal culture revealed *Cryptococcus neoformans*) after approximately 2.5 years of Siponimod (BAF312) treatment at the dose of 2 mg/day. The patient had no history of HIV/AIDS, recent high dose steroid/immunosuppressant use or exposure to birds. The patient completely recovered from the event after receiving appropriate treatment including anti-fungal medications.

Table 8-6 Other details: Cryptococcal meningitis

Cryptococcal meningitis	Details
Potential mechanisms	Although the interactions between host and fungal pathogens like Cryptococcus neoformans (C. neoformans) remain to be fully deciphered, evidence indicate that most clinical cases of infection result from the reactivation of subclinical granuloma containing cryptococcal cells, mainly in immune-compromised patients due to untreated HIV infection (Park et al 2009). Clinical observations have also revealed few cases of cryptococcal meningitis, as well as cutaneous and pulmonary cryptococcal infections, in patients taking fingolimod (Grebenciucova et al 2016, Ward et al 2016), justifying safety warnings and precautions in its prescribing information (Gilenya [fingolimod] EU Summary of Product Characteristics 2017), (Gilenya [fingolimod] US Prescribing Information 2016).

Cryptococcal meningitis	**Details**
	The potential links between increased risks of C. neoformans infection and fingolimod treatments are currently not clearly understood and preclinical data suggest a key role for S1P signaling pathway in the control of C. neoformans reactivation in rodents (McQuiston et al 2010; McQuiston et al 2011; Farnoud et al 2015). Interestingly, S1P3 signaling was recently shown to be essential for the ability of mouse macrophages to kill bacteria and protect mice from bacterial sepsis (Hou et al 2017). Hence, if similar S1P3-mediated events also exist in human (which needs to be demonstrated), functional antagonism at the level of S1P3 receptors on macrophages could be considered as a potential underlying mode of action for fingolimod to increase the risks of *C. neoformans* infection.
Evidence source(s) and strength of evidence	A confirmed (positive CSF Gram stain and CSF fungal culture) case of cryptococcal (*C. neoformans*) meningitis was reported in a 62-year old female patient participating in the extension part of Phase III clinical trial, BAF312A2304 after approximately 2.5 years of siponimod treatment at the dose of 2 mg/day. The patient had no history of HIV/AIDS, recent high dose steroid/immunosuppressant use or exposure to birds. The patient completely recovered from the event after receiving appropriate treatment including anti-fungal medications. Cases of herpes viral infection, including cases of meningitis or meningoencephalitis caused by varicella zoster virus, and opportunistic infections (includes cryptococcal infections and JCV causing PML) have been reported for S1P receptor modulators, including siponimod, and other therapies for MS.
Characterization of the risk:	Cases of cryptococcal meningitis (CM) have been reported on siponimod treatment.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) are at an increased risk of cryptococcal infections.
Preventability	Section 4.3 of SmPC: Siponimod is contraindicated in patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis. Refer to Sections 4.4 of SmPC. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms and signs of CM. The treatment with siponimod should be suspended until the diagnosis of CM has been excluded. If CM is diagnosed, appropriate treatment should be initiated Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after discontinuation of siponimod, vigilance for infection should be continued throughout this period.

Cryptococcal meningitis	Details
	When switching patients from another disease modifying therapy to siponimod, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation. As part of additional risk minimization activity, education materials to HCPs to assist in managing and counseling the patients as well as for educating patients/care givers about the risk while using siponimod is proposed.
Impact on the benefit-risk balance of the product	The benefit-risk profile of siponimod in the indication of SPMS remains positive, as siponimod demonstrated efficacy in the advanced disease population to placebo and a standard of care continue to outweigh the risk of cryptococcal meningitis.
Public health impact	The potential public health impact in patients receiving siponimod 2 mg is considered to be low although care is needed in patients who have other risk factors which may pre-dispose to cryptococcal meningitis e.g. concomitant immunosuppressive therapy.

8.3.1.3 Important identified risk: Bradyarrhythmia (including conduction defects) during treatment initiation

Table 8-7 Clinical trial data: Bradyarrhythmia (including conduction defects and bradycardia) during treatment initiation

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	Placebo N=607 n (%) (95% CI)	n (IR*) (95% CI) 31-Dec-2017 (2)	n (IR*) (95% CI) 29-Oct-2021 (3)	n (IR*) (95% CI) 31-Oct-2022 (4)	n (IR*) (95% CI) Final data (5)
All AEs	125 (8.0) (6.7, 9.5)	32 (3.9) (2.7, 5.5)	166 (4.1) (3.5, 4.7)	166 (2.8) (2.4, 3.2)	166 (2.6) (2.2, 3.0)	167 (2.1) (1.8, 2.5)
Resolved/resolved with sequalae	110 (7.0) (5.8, 8.4)	27 (3.3) (2.2, 4.8)	125 (3.0) (2.5, 3.6)	125 (1.7) (1.4, 2.1)	125 (1.6) (1.3, 1.9)	125 (1.6) (1.3, 1.9)
AEs related to study drug	113 (7.2) (5.9, 8.6)	28 (3.4) (2.3, 4.9)	150 (3.6) (3.1, 4.3)	150 (2.1) (1.8, 2.5)	150 (1.9) (1.6, 2.3)	150 (1.9) (1.6, 2.2)
AEs leading to study drug interruption	0 (0) (0, 0.2)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)
AE requiring concomitant medication or non-drug therapy	3 (0.2) (< 0.1, 0.5)	0 (0) (0, 0.4)	5 (0.1) (< 0.1, 0.3)	5 (< 0.1) (< 0.1, 0.2)	5 (< 0.1) (< 0.1, 0.1)	5 (< 0.1) (< 0.1, 0.1)

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
AE leading to discontinuation	13 (0.7) (0.4, 1.3)	0 (0) (0, 0.4)	18 (0.4) (0.2, 0.6)	18 (0.3) (0.2, 0.4)	18 (0.3) (0.2, 0.4)	18 (0.2) (0.1, 0.4)
AE by CTCAE grade (3/4)	5 (0.3) (< 0.1, 0.7)	0 (0) (0, 0.4)	9 (0.2) (< 0.1, 0.4)	9 (0.1) (< 0.1, 0.3)	9 (0.1) (< 0.1, 0.2)	9 (0.1) (< 0.1, 0.2)
SAEs	9 (0.5) (0.2, 1.0)	0 (0) (0, 0.4)	11 (0.2) (0.1, 0.4)	11 (0.2) (< 0.1, 0.3)	11 (0.2) (< 0.1, 0.3)	11 (0.1) (< 0.1, 0.3)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	Placebo N=607 n (%) (95% CI)	n (IR*) (95% CI) 31-Dec-2017 (2)	n (IR*) (95% CI) 29-Oct-2021 (3)	n (IR*) (95% CI) 31-Oct-2022 (4)	n (IR*) (95% CI) Final data (5)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.

- A patient with multiple occurrences is counted only once within each category.

- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.

- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.

- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.

- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.

- Only Adverse Events occurring during Dose Initiation (i.e. up to 7 days after the first dose of study drug) are listed in this table.

Source: Annex 7 Table 5-2

Table 8-8 Other details: Bradyarrhythmia (including conduction defects) during treatment initiation

Bradyarrhythmia (including conduction defects) during treatment initiation	Details
Potential mechanisms	Siponimod is a potent selective S1P modulator and dose initiation may result in transient AV conduction delays and heart rate reduction. It is due to the chronotropic and dromotropic effects associated with the human atrial inward-rectifying G protein coupled potassium channel (GIRK/IKACh) which is thought to be causing transient heart rate reduction as observed with by S1P receptor agonists. Data suggest that in humans, S1P1 (rather than S1P3) may play a dominant role in the regulation of atrial myocyte function, AV conduction and heart rate (Brinkmann 2007).
Evidence source(s) and strength of evidence	In the Clinical Pharmacology studies, (single doses up to 75 mg, multiple doses up to 20 mg qd) and studies in PM/DM patients (highest dose 10 mg qd), a dose-dependent decrease in mean heart rate was observed over the first 24 h post-dose, plateauing at doses of 5 mg and above. Decreases in heart rate were transient and peaked approximately 2 h post-dose for all doses. In Study A2201, when siponimod was started without dose titration in the maintained dose of 2 mg or 10 mg five transient symptomatic bradyarrhythmic events were observed on Day 1. The events resolved without sequelae after drug discontinuation. Other findings included dose dependent, transient decrease in heart rate on Day 1 with the maximum decreases observed 2 hours post first dose (mean change of app. 10 bpm for 10 mg dose) in Period 1 of the study. Based upon these observations, dose titration was implemented in Study A2201 in Period 2. Following the introduction of the initial-dose titration scheme, there were no symptomatic bradyarrhythmic events or AV-blocks of concern. In Study A2304, the targeted maintenance dose of 2 mg of siponimod was reached through 6 days of titration. In this study, the most prominent decreases in heart rate were observed on Day 1, 4 hours post dose (mean decreases of 5.30 bpm in siponimod and 0.76 bpm in placebo group); in general 5.9% of siponimod patients were observed with HR <50 bpm compared with 1.2% of placebo patients. During the titration period for the combined terms of bradyarrhythmia and bradycardia, 7.4% of patients in the siponimod group and 2.9% of placebo group had events, transient and mostly asymptomatic. Discontinuation due to first or second degree AV block was reported in 0.2% siponimod (2 first degree AV block and 2 second degree AV Mobitz type I; one patient experienced both) and none in placebo patients (A2304, Listing 14.3.1-1.2).
Characterization of the risk:	See table above and SCS Section 4.3 In general, in the pooled safety analysis, the observed bradycardias and conduction disorders, mostly 1st degree AV blocks (siponimod 2 mg 8.8%,

Bradyarrhythmia (including conduction defects) during treatment initiation	**Details**
	placebo 4.3%), were asymptomatic and transient and therefore considered benign with limited safety risk. No second degree AV blocks of Mobitz type II or higher degree were observed. Most AV blocks and sinus pauses occurred above the therapeutic dose of 2 mg with notably higher incidence under non titrated conditions compared to dose titration conditions (HV studies). In addition, during dose restarts, siponimod appeared to induce fewer events of interest and findings in comparison to treatment initiation. No additional effects on heart rate or AV conduction were observed with chronic siponimod dosing. In a sub-group analysis, the risk of symptomatic or significant bradycardia (<40 bpm or <50 bpm) was low in patients with cardiac risk and without history of cardiac disease, including conduction disorders. In both patient groups the observed safety events and findings were mild, transient and did not require clinical intervention.
Risk factors and risk groups	Patients with underlying medical history and/or receiving co-medications that might increase the risk of bradycardia or in whom bradycardia may be poorly tolerated include: • second degree Mobitz type II or higher AV block, • sick-sinus syndrome • sino-atrial heart block, • history of symptomatic bradycardia or recurrent syncope, • cerebrovascular disease, • history of myocardial infarction, • congestive heart failure, • history of cardiac arrest, • uncontrolled hypertension • severe sleep apnoea • patients with significant QT prolongation (QTc >500 msec) • Other potential risk factors include concomitant administration with: Class Ia (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products, beta blockers, and heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
Preventability	SmPC section 4.3 contraindicates use of siponimod in patients: • who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure.

Bradyarrhythmia (including conduction defects) during treatment initiation	**Details**
	• with a history of second-degree Mobitz type II atrioventricular (AV) block, third degree AV block, sinoatrial heart block or sick sinus syndrome, if they do not wear a pacemaker. SmPC Section 4.4 provides guidance and recommendations during siponimod treatment initiation, treatment interruption during treatment initiation (first 6 days of siponimod treatment) and after dose restart (after missing 4 or more consecutive daily doses) to minimize the decreased heart rate and conduction effects in patients with and without cardiovascular risk. Treatment initiation with a 6 day dose titration phase is usually well tolerated. As a precautionary measure, patients with sinus bradycardia (heart rate <55 bpm), history of first or second degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure should be observed for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia. Obtaining an ECG prior to dosing and at the end of the observation period is recommended. As part of additional risk minimization activity, education materials to HCPs to assist in managing and counseling the patients as well as for educating patients/care givers about the risks while using siponimod is proposed. For further details See Table 12-2.
Impact on the benefit-risk balance of the product	Dose titration during dose initiation and dose restart mitigates the effects of siponimod on heart rate and AV conduction. The observed bradycardias and conduction disorders, mostly AVB first degree, were asymptomatic and transient limited to treatment initiation and therefore considered of benign cardiac nature with limited safety hazards and no risk observed on further chronic continuous treatment. The decrease in heart rate induced by siponimod can be reversed by atropine or isoprenaline. The benefit-risk profile of siponimod in the indication of SPMS remains positive, as siponimod demonstrated efficacy in the advanced disease population as compared to placebo and a standard of care continue to outweigh the manageable risk of bradyarrhythmia.
Public health impact	Apart from the transient effects observed during treatment initiation, siponimod does not appear to be associated with any significant changes in heart rate or atrioventricular conduction based on available long-term data. The potential for significant impact on public health is anticipated to be low.

8.3.1.4 Important identified risk: Macular edema

Table 8-9 Clinical trial data: Macular edema

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
All AEs	21 (1.2) (0.7, 1.8)	1 (0.1) (< 0.1, 0.6)	28 (0.6) (0.4, 0.9)	42 (0.5) (0.4, 0.7)	44 (0.5) (0.4, 0.7)	50 (0.6) (0.4, 0.8)
Resolved/resolved with sequalae	15 (0.9) (0.5, 1.4)	0 (0) (0, 0.4)	19 (0.4) (0.3, 0.7)	28 (0.4) (0.2, 0.5)	29 (0.4) (0.2, 0.5)	30 (0.4) (0.2, 0.5)
AEs related to study drug	16 (0.9) (0.5, 1.5)	0 (0) (0, 0.4)	20 (0.4) (0.3, 0.7)	30 (0.4) (0.3, 0.6)	32 (0.4) (0.3, 0.5)	35 (0.4) (0.3, 0.6)
AEs leading to study drug interruption	10 (0.6) (0.3, 1.1)	0 (0) (0, 0.4)	12 (0.3) (0.1, 0.5)	15 (0.2) (0.1, 0.3)	17 (0.2) (0.1, 0.3)	17 (0.2) (0.1, 0.3)
AE requiring concomitant medication or non-drug therapy	7 (0.4) (0.2, 0.8)	0 (0) (0, 0.4)	9 (0.2) (< 0.1, 0.4)	14 (0.2) (< 0.1, 0.3)	15 (0.2) (0.1, 0.3)	15 (0.2) (< 0.1, 0.3)
AE leading to discontinuation	12 (0.7) (0.4, 1.2)	1 (0.1) (< 0.1, 0.6)	16 (0.4) (0.2, 0.6)	23 (0.3) (0.2, 0.4)	23 (0.3) (0.2, 0.4)	23 (0.3) (0.2, 0.4)
AE by CTCAE grade (3/4)	5 (0.3) (< 0.1, 0.7)	1 (0.1) (< 0.1, 0.6)	6 (0.1) (< 0.1, 0.3)	9 (0.1) (< 0.1, 0.2)	9 (0.1) (< 0.1, 0.2)	10 (0.1) (< 0.1, 0.2)
SAEs	3 (0.2) (< 0.1, 0.5)	0 (0) (0, 0.4)	3 (< 0.1)(< 0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).
- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.
- A patient with multiple occurrences is counted only once within each category.
- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.
- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.
- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the

population.
- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.
Source: Annex 7 Table 5-3

Table 8-10 Other details: Macular edema

Macular edema	Details
Potential mechanisms	S1P and its receptors S1P1 and S1P3 play a key role in the regulation of endothelial and epithelial barriers (Brinkmann 2007). The cellular components of the blood retinal barrier (BRB-endothelial cells, epithelial cells, astrocytes) express S1P receptors and these receptors tightly control endothelial and epithelial barriers. The BRB contains both tight junctions (TJ) and adherence junctions (AJ) between its cellular compartments. This suggests that pharmacological activation of S1P receptors on the BRB may at the same time increase/protect AJ between cells (via S1P1 receptor agonism), thereby strengthening the barrier, but may also reduce TJ between the cellular components (via S1P3 receptor agonism), thereby reducing barrier function. A reduction of TJ via S1P receptors may be of particular concern in cases of pre-damage, e.g. in diabetic retinopathy. In vivo data suggest that siponimod bares the potential to signal or down-modulate S1P1 in the endothelium, depending on the local conditions. The final outcome may depend on the inflammatory state of the tissue, the steady-state levels of S1P1 versus S1P2 and S1P3 in endothelial cells and the association of the S1P receptors with other molecules in lipid rafts (Singleton 2006).
Evidence source(s) and strength of evidence	Drug induced Macular edema has been reported with other S1P modulators. S1P modulators pharmacological action on the endothelial barrier function has been associated with incidence of macular edema. In the Controlled pool, macular edema (including cystoid macular edema) was reported as an AE in 18 (1.0%) siponimod 2 mg patients (OR of 10.7 vs Placebo 95% CI: 1.4, 80.3) and 1 (0.2%) placebo patient. There is no evidence of an increase in the incidence rate of macular edema over time [IR 0.6 per 100 PY, (95% CI 0.4, 0.8) vs IR 1.2 (95% CI 0.7, 1.8)] with siponimod treatment and the reported cases in the Long-term pool were consistent with the observations in the Controlled pool.
Characterization of the risk:	See table above and refer to SCS Section 2.1.5.5. Macular edema was reported most frequently in the first 3 months of treatment, for 9 (0.8%) siponimod 2 mg subjects and none in placebo subjects. The incidence was less after 3 months of siponimod treatment (0.1%-0.4%). Most of the subjects are asymptomatic. Most macular edema AEs were non-serious, with SAEs reported for 3 (0.3%) subjects in the siponimod 2 mg group and none in the other treatment groups. In most cases, macular edema improved after the drug was withdrawn.
Risk factors and risk groups	Patients with a history of diabetes mellitus, uveitis and underlying/co-existing retinal disorders are considered at increased risk of developing macular

Macular edema	Details
	edema. Such patients should undergo an ophthalmic evaluation prior to initiating siponimod therapy and have follow-up evaluations while receiving siponimod therapy.
Preventability	The SmPC Section 4.4 recommends that all patients have ophthalmological examination 3-4 months after treatment initiation. Patients with diabetes mellitus, history of uveitis or a history of retinal disorders should undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy in case of any visual disturbances. It is recommended that siponimod be discontinued if a patient develops macular edema. Siponimod therapy should not be initiated in patients with macular oedema until resolution. A decision on whether or not siponimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient. As part of additional risk minimization activity, education materials for HCPs to assist in managing and counseling the patients as well as for educating patients/care givers about the risks while using siponimod is proposed.
Impact on the benefit-risk balance of the product	Macular edema was generally detected with symptoms of visual disturbances during routine visits or with the ophthalmological assessment as scheduled in the study protocol. Macular edema improved on discontinuing siponimod treatment. The benefit-risk profile of siponimod in the indication of SPMS remains positive, as siponimod demonstrated efficacy in the advanced disease population as compared to placebo and a standard of care continue to outweigh the well characterized and manageable risk of macular edema.
Public health impact	Macular edema is a well-known risk with other S1P modulator and the expected public health impact is anticipated to be low.

8.3.1.5 Important identified risk: Basal cell carcinoma

Table 8-11 Clinical trial data: Basal cell carcinoma (Safety Set)

	Controlled pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	Placebo N=607 n (%) (95% CI)	n (IR*) (95% CI) 31-Dec-2017 (2)	n (IR*) (95% CI) 29-Oct-2021 (3)	n (IR*) (95% CI) 31-Oct-2022 (4)	n (IR*) (95% CI) Final data (5)
All AEs	12 (0.7) (0.4, 1.2)	7 (0.8) (0.3, 1.7)	28 (0.6) (0.4, 0.9)	62 (0.8) (0.6, 1.1)	68 (0.8) (0.7,1.1)	71 (0.9) (0.7,1.1)
Basal cell carcinoma	12 (0.7)	7 (0.8)	28 (0.6)	62 (0.8)	68 (0.8)	71 (0.9)
Resolved/resolved with sequalae	12 (0.7) (0.4, 1.2)	7 (0.8) (0.3, 1.7)	24 (0.5) (0.3, 0.8)	58 (0.8) (0.6, 1.0)	64 (0.8) (0.6, 1.0)	65 (0.8) (0.6, 1.0)

	Controlled pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
AEs related to study drug	6 (0.3) (0.1, 0.7)	5 (0.6) (0.2, 1.4)	12 (0.3) (0.1, 0.5)	39 (0.5) (0.4, 0.7)	45 (0.5) (0.4, 0.7)	46 (0.5) (0.4, 0.7)
AEs leading to study drug interruption	0 (0) (0,0.2)	0 (0) (0,0.4)	1 (< 0.1) (< 0.1, 0.1)	5 (< 0.1) (< 0.1,0.2)	5 (< 0.1) (< 0.1, 0.1)	5 (< 0.1) (< 0.1, 0.1)
AE requiring concomitant medication or non-drug therapy	11 (0.6) (0.3, 1.1)	4 (0.5) (0.1, 1.2)	25 (0.6) (0.4, 0.8)	57 (0.8) (0.6, 1.0)	63 (0.8) (0.6, 1.0)	65 (0.8) (0.6, 1.0)
AE leading to discontinuation	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	3 (< 0.1) (< 0.1, 0.1)	3 (< 0.1) (< 0.1, 0.1)	3 (< 0.1) (< 0.1, 0.1)
AE by CTCAE grade (3/4)	4 (0.2) (< 0.1, 0.6)	1 (0.1) (< 0.1, 0.6)	7 (0.2) (< 0.1, 0.3)	16 (0.2) (0.1, 0.3)	18 (0.2) (0.1, 0.3)	19 (0.2) (0.1, 0.4)
SAEs	12 (0.7) (0.4,1.2)	6 (0.7) (0.3,1.5)	26 (0.6) (0.4,0.9)	60 (0.8) (0.6,1.0)	66 (0.8) (0.6, 1.0)	68 (0.8) (0.6, 1.0)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, <0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.
- A patient with multiple occurrences is counted only once within each category.
- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.
- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.
- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.

Source: Annex 7 Table 5-6

Table 8-12 Other details: Basal cell carcinoma

Basal cell carcinoma	**Details**
Potential mechanisms	Unknown. A hypothetical mechanism is based on the systemic immunosuppression and reduced immunosurveillance.

Basal cell carcinoma	**Details**

Evidence source(s) and strength of evidence	Non-clinical data:
	• At therapeutic doses, siponimod has no generalized immunosuppressive properties as it neither impairs in vitro T- or B-cell activation or proliferation, cytokine or antibody production nor does it alter the capacity to mount an immune response to neo-antigens or pathogens in vivo.
	• Siponimod is non-genotoxic
	• The 2 years carcinogenicity studies in rodents identified:
	  • hemangiosarcoma in mice, with unlikely human relevance
	  • Thyroid tumours in rats, with no human relevance
	  • Lymphosarcoma in mice, with unknown human relevance

Characterization of the risk:	Basal cell carcinoma is a superficial, slowly growing papule or nodule that derives from certain epidermal cells. Metastasis is rare, but local growth can be highly destructive. Treatment may involve curettage and electrodesiccation, surgical excision, cryosurgery, topical chemotherapy, or, occasionally, radiation therapy or drug therapy.
Risk factors and risk groups	Patients with advanced age, prior prolonged immunosuppressive medication, and exposure to UV radiation.
Preventability	Vigilance for skin lesions is warranted and caution should be exercised against exposure to sunlight without protection. SmPC Section 4.4 includes the following recommendations: Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UVB radiation or PUVA photochemotherapy.
Impact on the benefit-risk balance of the product	The benefit-risk of siponimod remains positive, as the benefits of stronger and sustained efficacy as compared to placebo with standard of care continue to outweigh the well characterized and manageable risk of Basal cell carcinoma.
Public health impact	The potential public health impact in patients receiving siponimod is considered to be low although care is needed in patients who have other risk factors which may pre-dispose to skin malignancies e.g. elderly age, other immunosuppressive therapy, or exposure to UV radiation.

8.3.1.6 Important identified risk: Squamous cell carcinoma (SCC)

Table 8-13 Clinical trial data: Squamous cell carcinoma

	Controlled pool		Long Term Safety Pool (2-10mg) (1)			
	BAF312 2mg N=1148	Placebo N=607	N=1737			
	n (IR*) (95% CI)	n (IR*) (95% CI)	n (IR*) (95% CI) 31-Dec-2017 (2)	n (IR*) (95% CI) 29-Oct-2021 (3)	n (IR*) (95% CI) 31-Oct-2022 (4)	n (IR*) (95% CI) Final data (5)
All AEs	2 (0.1) (< 0.1, 0.4)	1 (0.1) (< 0.1, 0.6)	7 (0.2) (< 0.1, 0.3)	26 (0.3) (0.2, 0.5)	32 (0.4) (0.3, 0.5)	34 (0.4) (0.3, 0.6)
Bowen's disease	1 (< 0.1)	1 (0.1)	5 (0.1)	15 (0.2)	18 (0.2)	18 (0.2)
Squamous cell carcinoma	1 (< 0.1)	0 (0)	3 (< 0.1)	7 (< 0.1)	8 (< 0.1)	8 (< 0.1)
Squamous cell carcinoma of skin	0 (0)	0 (0)	0 (0)	6 (< 0.1)	8 (< 0.1)	10 (0.1)
Resolved/resolved with sequale	1 (< 0.1) (< 0.1, 0.3)	1 (0.1) (< 0.1, 0.6)	6 (0.1) (< 0.1, 0.3)	22 (0.3) (0.2, 0.4)	26 (0.3) (0.2, 0.5)	27 (0.3) (0.2, 0.5)
AEs related to study drug	0 (0) (0, 0.2)	1 (0.1) (< 0.1, 0.6)	2 (< 0.1) (< 0.1, 0.2)	18 (0.2) (0.1, 0.4)	22 (0.3) (0.2, 0.4)	24 (0.3) (0.2, 0.4)
AEs leading to study drug interruption	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0,< 0.1)	1 (<0.1) (< 0.1,< 0.1)	1 (<0.1) (< 0.1,< 0.1)	1 (< 0.1) (< 0.1,< 0.1)
AE requiring concomitant medication or non-drug therapy	2 (0.1) (< 0.1, 0.4)	0 (0) (0, 0.4)	4 (< 0.1) (< 0.1, 0.2)	22 (0.3) (0.2, 0.4)	26 (0.3) (0.2, 0.5)	26 (0.3) (0.2, 0.4)
AE leading to discontinuation	2 (0.1) (< 0.1, 0.4)	0 (0) (0, 0.4)	5 (0.1) (< 0.1, 0.3)	17 (0.2) (0.1, 0.4)	22 (0.3) (0.2, 0.4)	22 (0.3) (0.2, 0.4)
AE by CTCAE grade (3/4)	0 (0) (0, 0.2)	0 (0) (0, 0.4)	2 (< 0.1) (< 0.1, 0.2)	5 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)
SAEs	2 (0.1) (< 0.1, 0.4)	1 (0.1) (< 0.1, 0.6)	7 (0.2) (< 0.1, 0.3)	26 (0.3) (0.2, 0.5)	32 (0.4) (0.3, 0.5)	34 (0.4) (0.3, 0.6)

	Controlled pool		Long Term Safety Pool (2-10mg) (1)			
	BAF312 2mg N=1148	Placebo N=607	N=1737			
	n (IR*) (95% CI)	n (IR*) (95% CI)	n (IR*) (95% CI) 31-Dec-2017 (2)	n (IR*) (95% CI) 29-Oct-2021 (3)	n (IR*) (95% CI) 31-Oct-2022 (4)	n (IR*) (95% CI) Final data (5)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.
- A patient with multiple occurrences is counted only once within each category.
- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.
- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.
- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically. .

Source: Annex 7 Table 5-11

Table 8-14 Other details: Squamous cell carcinoma (SCC)

Squamous cell carcinoma	Details
Potential mechanisms	Unknown. A hypothetical mechanism is based on the systemic immunosuppression and reduced immunosurveillance.
Evidence source(s) and strength of evidence	Non-clinical data: • At therapeutic doses, siponimod has no generalized immunosuppressive properties as it neither impairs in vitro T- or B-cell activation or proliferation, cytokine or antibody production nor does it alter the capacity to mount an immune response to neo-antigens or pathogens in vivo. • Siponimod is non-genotoxic • The 2 years carcinogenicity studies in rodents identified: • hemangiosarcoma in mice, with unlikely human relevance

Squamous cell carcinoma	**Details**
	• Thyroid tumours in rats, with no human relevance • Lymphosarcoma in mice, with unknown human relevance
Characterization of the risk:	Squamous cell carcinoma is a common form of keratinocytic skin cancer, which forms in the middle and outer layer of the skin. It causes red nodules, scaly, red patches on lips or inside the mouth, open sores, or wartlike sore on or in the anus or on genitals. Metastasis risk is low, although is higher than with BCC. Treatment may involve curettage and electrodesiccation, surgical excision, cryosurgery, topical chemotherapy, or, occasionally, radiation therapy, photodynamic therapy, laser surgery, or drug therapy.
Risk factors and risk groups	Patients with advanced age, prior prolonged immunosuppressive medication, and exposure to UV radiation.
Preventability	Vigilance for skin lesions is warranted and caution should be exercised against exposure to sunlight without protection. SmPC Section 4.4 includes the following recommendations: Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UVB radiation or PUVA photochemotherapy.
Impact on the benefit-risk balance of the product	The benefit-risk of siponimod remains positive, as the benefits of stronger and sustained efficacy as compared to placebo with standard of care continue to outweigh the well characterized and manageable risk of Squamous cell carcinoma.
Public health impact	The potential public health impact in patients receiving siponimod is considered to be low although care is needed in patients who have other risk factors which may pre-dispose to skin malignancies e.g. elderly age, other immunosuppressive therapy, or exposure to UV radiation.

8.3.1.7 Important identified risk: Progressive multifocal leukoencephalopathy (PML)

Clinical trial data

One case of PML has been reported in the siponimod clinical development (Annex 7 Table 5-10).

Table 8-15 Other details: Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML)	Details
Potential mechanisms	The pharmacodynamic immune system effects of siponimod may increase the risks of infections. PML is a reactivation of latent JC virus in a host with immune suppression (i.e., immunocompromised conditions - including the use of immunosuppressors, immunosenescence, etc.). The issue of reactivation is important because the cells responsible for surveillance for such infections, the effector memory T-cells, are not affected by siponimod (Wu et al 2020) and as seen with other S1P receptor modulator fingolimod (Mehling et al 2008, Brinkmann et al 2009, Johnson et al 2010). The reason for development of PML with natalizumab is not totally understood, but indiscriminate blockade of lymphocyte migration into the CNS (i.e. an effect on all lymphocyte subsets, including effector memory cells) may play a differentiating role for natalizumab vs. fingolimod. Additionally, natalizumab leads to extrusion of CD38+ cells from bone marrow, cells that are purported to harbor latent John Cunningham virus (JCV) infection. No such effect is seen with siponimod.
Evidence source(s) and strength of evidence	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product. Cases of PML were observed while on treatment with other S1P receptor modulators (fingolimod, ozanimod). Cases of PML have also been reported while on treatment with siponimod in the post-marketing setting and in long-term safety clinical trial.
Characterization of the risk:	See SCS Section 2.1.5.1. This serious infection carries a mortality rate in excess of 20% based on the experience with natalizumab cases (D'Amico et al 2016).At present there is no treatment or cure for PML (Aksamit 2006, O'Connor 2007). Early diagnosis is important to clinical outcome and to prevent disability (Brew et al 2010).
Risk factors and risk groups	PML primarily affects individuals with suppressed immune systems. In recent years, the most common underlying immunosuppressive illness has been AIDS. However, a variety of non-AIDS immunosuppressive illnesses has been associated with the occurrence of PML. These include lymphoreticular malignancy, most commonly chronic lymphocytic leukaemia or non-Hodgkin lymphoma. JC virus is a double-stranded DNA human polyomavirus acquired in childhood. After infection, it remains latent in the body. 50-70% of the adult population is seropositive. It is believed that all seropositive individuals harbor latent virus in kidney, lymphoreticular tissue, or brain. PML is considered a reactivation infection. Whether the reactivation occurs systemically, with immunosuppression causing dissemination to the brain at that time, or the reactivation occurs from latent virus in the brain remains unclear (Aksamit 2006). In people who are immunosuppressed, JC virus can reactivate and cause PML which is usually fatal. Cases of PML have

	been reported with another MS drug, natalizumab, a monoclonal antibody that blocks lymphocyte migration into the CNS (i.e. an effect on all lymphocyte subsets, including effector memory cells). Additionally, natalizumab has effects, such as mobilization of JC virus carrying bone marrow precursor cells and splenic marginal zone B cells, which are not seen with fingolimod. The natalizumab label describes 3 risk factors that are known to increase the risk of PML in patients under therapy with natalizumab: treatment duration longer than 2 years, prior treatment with an immunosuppressant and presence of anti-JCV antibodies. Patients with all 3 known risk factors have an estimated risk of PML of 11/1,000. When evaluating the risk with fingolimod, the specific risk factors should be considered: The presence of anti-JCV antibodies Switching to fingolimod after treatment with natalizumab for >2 years and duration of washout of natalizumab. Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide). Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) are at an increased risk of PML.
Preventability	Section 4.3 of SmPC: Siponimod is contraindicated in patients with history of progressive multifocal leukoencephalopathy. Refer to Section 4.4 of SmPC: The immune system effects of siponimod may increase the risk of infections. Physicians should be vigilant for clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. If PML is suspected, siponimod treatment should be suspended until PML has been excluded. If PML is confirmed, treatment with siponimod should be discontinued. After stopping MAYZENT in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS). Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors modulators, including MAYZENT, who developed PML, and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken. Initiation of treatment with siponimod should be delayed in patients with severe active infection until resolution. Suspension of treatment with siponimod, should be considered if a patient develops a serious infection. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after

	discontinuation of siponimod, vigilance for infection should be continued throughout this period. When switching patients from another disease modifying therapy to siponimod, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation. As part of additional risk minimization activity, education materials to HCP to assist in managing and counseling the patients as well as for educating patients/care givers about the risk while using siponimod is proposed.
Impact on the benefit-risk balance of the product	Progressive Multifocal Leukoencephalopathy (PML) is a serious infection that carries a mortality rate in excess of 20% based on the experience with natalizumab cases (D'Amico et al 2016). At present there is no treatment or cure for PML (Aksamit 2006, O'Connnor 2011). Early diagnosis is important to clinical outcome and to prevent disability (Brew et al 2010). Treatment for PML should focus on strengthening the immune system. In addition, other commonly used anti-virals for PML included mefloquine, mirtazapine, checkpoint inhibitors, T-cells, corticosteroids, and filgrastim. Limited evidence does not suggest a significant increase in risk of infection (other than reactivation of VZV infection) with continued treatment with the siponimod 2 mg dose. This is in line with findings in animal studies which show that cellular and humoral immunological constituents are maintained with no impairment of immuno-surveillance through relatively unaffected effector memory T cells [Nonclinical Overview (NCO)]. The benefits of sustained efficacy (compared to placebo) outweigh the manageable risk of Infections.
Public health impact	PML is rare serious CNS infection with debilitating effects. If not managed properly as per treatment recommendations in the label could be potentially life-threatening and fatal.

8.3.1.8 Important identified risk: Malignant melanoma

Table 8-16 Clinical trial data: Malignant melanoma

	Controlled pool N=1755		**Long Term Safety Pool (2-10mg) (1) N=1737**			
	BAF312 2mg N'=1148	**Placebo N'=607**				
	n (IR*) (95% CI)	**n (IR*) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
All AEs	2 (0.1) (< 0.1, 0.4)	0 (0) (0,4)	2 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)	8 (< 0.1) (< 0.1, 0.2)	8 (< 0.1) (< 0.1, 0.2)

	Controlled pool N=1755		Long Term Safety Pool (2-10mg) (1) N=1737			
	BAF312 2mg N'=1148	Placebo N'=607				
	n (IR*) (95% CI)	n (IR*) (95% CI)	n (IR*) (95% CI) 31-Dec-2017 (2)	n (IR*) (95% CI) 29-Oct-2021 (3)	n (IR*) (95% CI) 31-Oct-2022 (4)	n (IR*) (95% CI) Final data (5)
Malignant melanoma in situ	2 (0.1)	0 (0)	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)
Malignant melanoma	0 (0)	0 (0)	0 (0)	4 (< 0.1)	5 (< 0.1)	5 (< 0.1)
Superficial spreading melanoma stage unspecified	0 (0)	0 (0)	0 (0)	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)
Resolved/resolved with sequale	2 (0.1) (< 0.1, 0.4)	0 (0) (0, 0.4)	2 (< 0.1) (< 0.1, 0.2)	5 (< 0.1) (< 0.1, 0.2)	6 (< 0.1) (<0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)
AEs related to study drug	1 (< 0.1) (< 0.1, 0.3)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	6 (<0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)
AEs leading to study drug interruption	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)
AE requiring concomitant medication or non-drug therapy	1 (< 0.1) (< 0.1, 0.3)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	6 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)
AE leading to discontinuation	2 (0.1) (< 0.1, 0.4)	0 (0) (0, 0.4)	2 (< 0.1) (< 0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)
AE by CTCAE grade (3/4)	1 (< 0.1) (< 0.1, 0.3)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	3 (< 0.1) (< 0.1, 0.1)	4 (< 0.1) (< 0.1, 0.1)	4 (< 0.1) (< 0.1, 0.1)
SAEs	2 (0.1) (< 0.1, 0.4)	0 (0) (0, 0.4)	2 (< 0.1) (< 0.1, 0.2)	7 (< 0.1) (< 0.1, 0.2)	8 (< 0.1) (< 0.1, 0.2)	8 (< 0.1) (< 0.1, 0.2)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

	Controlled pool N=1755		Long Term Safety Pool (2-10mg) (1) N=1737			
	BAF312 2mg N'=1148	Placebo N'=607				
	n (IR*) (95% CI)	n (IR*) (95% CI)	n (IR*) (95% CI) 31-Dec-2017 (2)	n (IR*) (95% CI) 29-Oct-2021 (3)	n (IR*) (95% CI) 31-Oct-2022 (4)	n (IR*) (95% CI) Final data (5)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.

- A patient with multiple occurrences is counted only once within each category.

- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.

- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.

- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.

- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.

Source: Annex 7 Table 5-9

Table 8-17 Other details: Malignant melanoma

Malignant melanoma	Details
Potential mechanisms	Unknown. A hypothetical mechanism is based on the systemic immunosuppression and reduced immunosurveillance.
Evidence source(s) and strength of evidence	Cases reported in clinical trials and the post marketing setting. There were 27 cumulative cases (10 CT and 17 post marketing cases) through 25-Mar-2024. This consisted of 12 cases with limited information, 8 cases assessed as unlikely due to therapy with siponimod due to a lack of temporal association, and 4 cases that were confounded. In the remaining 3 cases (all CT cases) a causal association between melamona and therapy with siponimod could not be excluded.
Characterization of the risk:	Malignant melanoma is a type of skin cancer that develops from the pigment-producing cells called melanocytes. It is characterized by the rapid growth of abnormal and malignant melanocytes, which can invade surrounding tissues and spread to other parts of the body. Malignant melanoma is considered the most dangerous form of skin cancer due to its high potential for metastasis. Early detection and treatment are crucial for improving the prognosis and survival rates of individuals with this condition.

Risk factors and risk groups	Patients with advanced age, prior prolonged immunosuppressive medication, and exposure to UV radiation
Preventability	Vigilance for skin lesions is warranted and caution should be exercised against exposure to sunlight without protection. SmPC Section 4.4 includes the following recommendations: Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UVB radiation or PUVA photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed.
Impact on the benefit-risk balance of the product	There are relatively few cases of malignant melanoma in subjects on therapy with siponimod. The benefit risk remains positive.
Public health impact	The incidence is expected to be low on the basis on data currently available.

8.3.1.9 Important potential risk: Potential long-term safety implications in CYP2C9 poor metabolisers

Table 8-18 Other details: Potential long-term safety implications in CYP2C9 poor metabolisers

Potential long-term safety implications in CYP2C9 poor metabolizers	**Details**
Potential mechanisms	**Effect on siponimod exposure:** Siponimod is mainly metabolized by the polymorphic enzyme CYP2C9 (79.3%), followed by a lower contribution of CYP3A4 (18.5%). In the Caucasian population, the prevalence of the 6 most prominent CYP2C9 genotypes ranges from 62% to 65% for CYP2C9*1*1, 20% to 24% for CYP2C9*1*2, 1% to 2% for CYP2C9*2*2, 9% to 12% for CYP2C9*1*3, 1.4% to 1.7 % for CYP2C9*2*3 and 0.3% to 0.4% for CYP2C9*3*3. The PK of siponimod varied between CYP2C9*1*1 (wild type) extensive metabolizers and subjects with other CYP2C9 genotypes. Overall, regarding siponimod elimination, CYP2C9*1*1 and *1*2 subjects behave as extensive metabolizers, *2*2 and *1*3 subjects as intermediate metabolizers and *2*3 and *3*3 subjects as poor metabolizers. The siponimod exposure is therefore approximatively 25%, 61%, 91% and 284% higher in CYP2C9*2*2, *1*3, *2*3 and *3*3 subjects, respectively, as compared to *1*1 subjects. **Effects of CYP2C9/3A4 inhibitors and inducers:** The CYP2C9 genotype influences the fractional contributions of the 2 oxidative metabolism pathways

	(CYP2C9 and CYP3A4) for overall elimination of siponimod: the hepatic CYP2C9 contribution to metabolism is anticipated to be 80.4% and 7.4% in CYP2C9*1*1 and *3*3 genotypes, respectively, according to PBPK (physiologically based pharmacokinetics) modelling. CYP3A4 plays a minor role in siponimod metabolism for the CYP2C9*1*1 genotype, with a contribution of 17.5% to the overall elimination of siponimod; its contribution to the overall systemic clearance is expected to be greater in subjects with lower CYP2C9 activity associated with a reduced total clearance (82.2% contribution in the *3*3 genotype). Considering the variable CYP3A4 and CYP2C9 contributions to the overall clearance of siponimod in the different CYP2C9 genotypes, it is expected that the CYP2C9 genotype influences the effects of CYP3A4 and CYP2C9 inhibitors and inducers.
Evidence source(s) and strength of evidence	An exploratory PK/pharmacogenetic (PG) analysis in the first-in-human study indicated that heterozygous CYP2C9*3 carriers tend to have a higher AUC of siponimod compared to subjects not carrying the *3 allele. Consequently, the PK of siponimod was assessed in CYP2C9 extensive and poor metabolizers (CYP2C9*1*1 genotype and CYP2C9*2*3 or *3*3 genotypes, respectively) in [Study A2128]. In addition, two PopPK analyses on Phase I/II and Phase III data identified CYP2C9 as a significant predictor of siponimod systemic clearance. In clinical DDI studies, a 2-fold higher and a 2-fold lower siponimod exposure was observed when co-administered with fluconazole (a moderate CYP2C9/CYP3A4 inhibitor) and with rifampin (a moderate CYP2C9/strong CYP3A4 inducer), respectively. Complementary modeling indicated that with decreased CYP2C9 metabolic activity in the respective genotypes, a stronger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated, especially for inhibitors. Under the proposed genotype-based dosing recommendations, Siponimod exposure is predicted to increase by 1.05-1.71-fold across genotypes in presence of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole), moderate CYP3A4 inhibitors (e.g. erythromycin), or weak CYP3A4/2C9 inhibitors (e.g. fluvoxamine) when compared to CYP2C9*1*1 subjects receiving a 2 mg qd maintenance dose without co-administration of any CYP2C9/CYP3A4 perpetrator drug. In presence of moderate CYP2C9 /CYP3A4 inhibitors (e.g. fluconazole), siponimod exposure is expected to be 1.78-2.15-fold higher in all genotypes except CYP2C9*2*2. A larger increase of 2.73-fold is predicted for the CYP2C9*2*2 patients. Strong CYP3A4/moderate CYP2C9 inducers (e.g., rifampin, carbamazepine) are predicted to reduce siponimod exposure by approximately 61% to 76%. Moderate CYP3A4 inducers (e.g. modafinil) are predicted to reduce Siponimod exposure by approximately 19% to 51%.
Characterization of the risk:	See SCS Sections 5.1.1.2 and 5.3. In the development program, patients randomized to siponimod received doses of 2 mg daily irrespective of genotype. The majority of patients in the siponimod 2 mg (84.3%) and (86.2%) placebo groups were extensive metabolizers. The mean exposure to siponimod 2 mg was 17.98 months for extensive metabolizers (WT/WT;*2/WT;*2/*2) and 16.66 months for poor siponimod metabolizers (*3/WT;*2/*3). The mean exposure to placebo was 16.70 months and 15.35 months for extensive and poor metabolizers, respectively.

	In the Controlled pool, events of fatigue, peripheral edema and depression were observed at a slightly higher incidence rate in the poor metabolizer (*3/WT, *2/*3) subgroup than in the extensive metabolizer (WT/WT, *2/WT, and *2/*2 [*2*2 being pooled in this analysis with the extensive metabolizers considering the only slightly reduced metabolic clearance]) subgroup. For macular edema the incidence rate was higher in the poor metabolizer (*3/WT, *2/*3) subgroup (IR = 2.8; CI: 1.1, 5.7) than for the extensive metabolizer (WT/WT, *2/WT, *2/*2) subgroup (IR = 0.9; CI: 0.5, 1.5) of the siponimod 2 mg group. A slightly higher incidence rate was also observed for hypertension in the poor metabolizer subgroup (IR=9.7; CI: 6.1, 14.8) compared to the extensive metabolizer subgroup (IR=8.7; CI: 7.2, 10.4). The incidence of SAEs does not appear to be influenced by CYP2C9 genotype. In the siponimod 2-10 mg (broad) pool, the proportions of patients with at least one SAE were 20.3% and 22.6% in the extensive metabolizer and poor metabolizer subgroups, respectively. In the pooled data, imbalances in few events in the poor metabolizer than in the extensive metabolizer subgroup are inconclusive for an assessment on the CYP2C9 genomic polymorphism effect on the safety of siponimod. No subgroup analyses were performed in RRMS/SPMS patients to assess any impact of CYP2C9/CYP3A4 inducers and inhibitors on siponimod safety or efficacy.
Risk factors and risk groups	Patients with CYP2C9*3*3 genotype
Preventability	See SmPC Sections 4.2, 4.3, 4.4, 4.5 and 5.2. Before initiation of treatment with siponimod, patients should be genotyped for CYP2C9 to determine their CYP2C9 metabolizer status. In patients homozygous for CYP2C9*3 (CYP2C9*3*3 genotype) genotype (poor metabolizer) (approximately 0.3 to 0. 4% of the population) use of siponimod is contraindicated. Use of siponimod in these patients results in substantially elevated siponimod plasma levels. The recommended maintenance dose is 1 mg daily in patients with a CYP2C9*2*3 genotype and in patients with a *1*3 genotype to avoid increased exposure to siponimod. Siponimod is primarily metabolised by cytochrome P450CYP2C9 (79.3%), and to a lesser extent by CYP3A4 (18.5%). CYP2C9 is a polymorphic enzyme and DDI effect in presence of CYP3A4 or CYP2C9 perpetrator drugs is predicted to be dependent on the CYP2C9 genotype. As there is potential to affect the siponimod PK by use of other medicinal products, SmPC section 4.5, provides recommendations on the use of combination treatment in the CYP2C9 patient groups. • Education materials for the HCPs and patients/care givers include a Physician's Checklist to consider prior to prescribing Mayzent and a Patient/Caregiver Guide. • The guide for the prescriber includes a checklist of actions to be taken before starting treatment with siponimod, including genotyping, checking and warning for medicines that may alter the effect of siponimod or that may be affected by siponimod.
Impact on the benefit-risk balance of the product	Exploratory PK/PG analysis and invitro studies demonstrated that siponimod is mainly metabolized by the polymorphic enzyme CYP2C9 (79.3%), followed by a lower contribution of CYP3A4 (18.5%). Genetic polymorphism of CYP enzymes played a significant role in the clinical effects of drug treatment as well as in the

	development of DDIs. In the development program, all patients irrespective of genotype received siponimod 2 mg. in the pooled data, no marked imbalances were observed in the poor metabolizer subgroups compared to extensive metabolizers for a conclusive assessment of the CYP2C9 genomic polymorphism effect on safety of siponimod. The benefit-risk profile of siponimod in the indication of SPMS remains positive, with the current available data, as siponimod demonstrated efficacy in the advanced disease population as compared to placebo and a standard of care continue to outweigh the manageable risk of potential long-term safety in CYP2C9 poor metabolizers.
Public health impact	Not expected to be clinically significant based on the data available and potential public health impact is anticipated to be low.

8.3.1.10 Important potential risk: Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)

Table 8-19 Clinical trial data: Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)

	Controlled Pool			Long Term Safety Pools (2-10mg) (1)		
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
All AEs	0 (0) (0, 0.2)	0 (0) (0, 0.4)	2 (< 0.1) (< 0.1,0.2)	5 (< 0.1) (< 0.1, 0.2)	5 (< 0.1) (< 0.1, 0.1)	5 (< 0.1) (< 0.1, 0.1)
Resolved/resolved with sequalae	0 (0) (0, 0.2)	0 (0) (0, 0.4)	2 (< 0.1) (< 0.1, 0.2)	4 (< 0.1) (< 0.1, 0.1)	4 (< 0.1) (< 0.1, 0.1)	4 (< 0.1) (< 0.1, 0.1)
AEs related to study drug	0 (0) (0, 0.2)	0 (0) (0, 0.44)	1 (< 0.1) (< 0.1, 0.1)	2 (< 0.1) (< 0.1, <0.1)	2 (< 0.1) (< 0.1, <0.1)	2 (< 0.1) (< 0.1, <0.1)
AEs leading to study drug interruption	0 (0) (0, 0.2)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)
AE requiring concomitant medication or non-drug therapy	0 (0) (0, 0.2)	0 (0) (0, 0.4)	2 (< 0.1) (< 0.1, 0.2)	5 (< 0.1) (< 0.1, 0.2)	5 (< 0.1) (< 0.1, 0.1)	5 (< 0.1) (< 0.1, 0.1)
AE leading to discontinuation	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
AE by CTCAE grade (3/4)	0 (0) (0, 0.2)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	2 (< 0.1) (< 0.1, <0.1)	2 (< 0.1) (< 0.1, < 0.1)	2 (< 0.1) (< 0.1, < 0.1)
SAEs	0 (0) (0, 0.2)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	2 (< 0.1) (< 0.1, < 0.1)	2 (< 0.1) (< 0.1, < 0.1)	2 (< 0.1) (< 0.1, < 0.1)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, <0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.
- A patient with multiple occurrences is counted only once within each category.
- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.
- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.
- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.

Source: Annex 7 Table 5-17

Table 8-20 Other details: Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)

Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)	**Details**
Potential mechanisms	The key pharmacodynamic effect of siponimod is a dose dependent reduction of the peripheral lymphocyte count by up to approximately 70-80% due to redistribution of lymphocytes to secondary lymphoid organs. This is because Siponimod down-modulates S1P1 receptors on lymphocytes to prevent egress from secondary lymphoid organs. The resultant sequestration of T and B lymphocytes in lymphoid tissues results in marked reduction of lymphocytes, but not myeloid leukocytes, in the blood. This process is reversible; lymphocytes reappear in the blood after the cessation of treatment, indicating that siponimod does not kill lymphocytes. The absence of a significant increase in overall infection rates (including serious infections) with siponimod therapy, despite the reduction in peripheral blood lymphocyte count, may be related to the fact that the memory effector subset of T-cells do not appear to be affected by siponimod, remaining in the peripheral circulation.
Evidence source(s) and strength of evidence	In the Phase III study, decrease in lymphocyte count observed in patients in the siponimod 2 mg group is seen early after commencing treatment and is maintained as long as the patient continues siponimod therapy. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase III PopPKPD]. There was no increase in the number of infections following siponimod treatment compared to placebo, or with increasing average siponimod steady-state concentration and decreasing average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use. Herpes viral infections (other than VZV re-activation) based on the risk term were reported similarly for patients in the siponimod 2 mg group [26 (2.3%)] and the placebo group [14 (2.3%)]. Cases of herpes viral infections and opportunistic infections (cryptococcal infections and PML) were observed while on treatment with other S1P modulator (Fingolimod). In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, Herpes

Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)	**Details**
	Simplex Virus (HSV)), fungal (e.g. Cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal.
Characterization of the risk:	See table above and SCS Section 2.1.5.1. Oral herpes (1.7% vs 2.1%) was the most commonly reported event followed by herpes simplex event (0.3% vs 0.3%) in the siponimod and placebo groups respectively. No cases of serious systemic herpes viral infections (other than VZV) have been reported for siponimod in the development program.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) are at an increased risk of VZV infections. The patients with negative VZ virus-IgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in *case* of an MS relapse.
Preventability	Section 4.3 of SmPC: Siponimod is contraindicated in patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis. Refer to Section 4.4 of SmPC: The immune system effects of siponimod may increase the risk of infections, including opportunistic infections. Vigilance for signs or symptoms of infections overall including opportunistic infections, is recommended. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Initiation of treatment with siponimod should be delayed in patients with severe active infection until resolution. Suspension of treatment with siponimod, should be considered if a patient develops a serious infection. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after discontinuation of siponimod, vigilance for infection should be continued throughout this period.

Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)	**Details**
	A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with siponimod (see SmPC Section 4.4). Initiation of treatment with siponimod should be postponed for 1 month to allow the full effect of vaccination to occur. When switching patients from another disease modifying therapy to siponimod, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation. As part of additional risk minimization activity, education materials to HCP to assist in managing and counseling the patients as well as for educating patients/care givers about the risk while using siponimod is proposed.
Impact on the benefit-risk balance of the product	Herpes viral infections other than VZV may cause serious debilitation, require hospitalization and more aggressive treatment, and delay in diagnosis could potentially lead to death. Thus, although long-term experience with siponimod treatment is currently limited, evidence does not suggest a significant increase in risk of herpes viral infections (other than VZV infection) with continued treatment with the siponimod 2mg dose. This is in line with findings in animal studies which show that cellular and humoral immunological constituents are maintained with no impairment of immuno-surveillance through relatively unaffected effector memory T cells [Nonclinical Overview (NCO)]. The benefits of sustained efficacy (compared to placebo) outweigh the manageable risk of Infections.
Public health impact	Although the majority of the reported infections were not severe, in rare cases they could have an impact on public health if not managed as per the label, given that some infections could be potentially fatal.

8.3.1.11 Important potential risk: Thromboembolic events

Table 8-21 Thromboembolic events overview

	Controlled Pool				Long Term Safety Pool (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
All AEs	35 (2.0) (1.4, 2.8)	16 (1.9) (1.1, 3.1)	69 (1.6) (1.2, 2.0)	97 (1.3) (1.1, 1.6)	104 (1.3) (1.1, 1.6)	108 (1.3) (1.1, 1.6)
Resolved/resolved with sequalae	25 (1.4) (0.9, 2.1)	9 (1.1) (0.5, 2.0)	50 (1.1) (0.8, 1.5)	69 (0.9) (0.7, 1.2)	73 (0.9) (0.7,1.1)	74 (0.9) (0.7,1.1)
AEs related to study drug	4 (0.2) (< 0.1, 0.6)	1 (0.1) (< 0.1, 0.6)	9 (0.2) (< 0.1, 0.4)	13 (0.2) (< 0.1, 0.3)	13 (0.2) (< 0.1, 0.3)	13 (0.2) (< 0.1, 0.3)
AEs leading to study drug interruption	4 (0.2) (< 0.1, 0.6)	2 (0.2) (< 0.1, 0.8)	6 (0.1) (< 0.1, 0.3)	8 (0.1) (< 0.1, 0.2)	8 (< 0.1) (< 0.1, 0.2)	8 (< 0.1) (< 0.1, 0.2)
AE requiring concomitant medication or non-drug therapy	18 (1.0) (0.6, 1.6)	10 (1.2) (0.6, 2.1)	36 (0.8) (0.6, 1.1)	51 (0.7) (0.5, 0.9)	55 (0.7) (0.5, 0.9)	56 (0.7) (0.5, 0.9)
AE leading to discontinuation	3 (0.2) (< 0.1, 0.5)	2 (0.2) (< 0.1, 0.8)	7 (0.2) (< 0.1, 0.3)	10 (0.1) (< 0.1, 0.2)	11 (0.1) (< 0.1, 0.2)	11 (0.1) (< 0.1, 0.2)
AE by CTCAE grade (3/4)	9 (0.5) (0.2, 1.0)	5 (0.6) (0.2, 1.4)	21 (0.5) (0.3, 0.7)	31 (0.4) (0.3, 0.6)	35 (0.4) (0.3, 0.6)	35 (0.4) (0.3, 0.6)
SAEs	16 (0.9) (0.5, 1.5)	7 (0.8) (0.3, 1.7)	34 (0.8) (0.5, 1.1)	50 (0.7) (0.5, 0.9)	54 (0.7) (0.5, 0.9)	55 (0.7) (0.5, 0.9)
On-treatment deaths	0 (0) (0, 0.2)	1 (0.1) (< 0.1, 0.6)	0 (0) (0, < 0.1)	1 (< 0.1) (< 0.1, <0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.
- A patient with multiple occurrences is counted only once within each category.
- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.
- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.
- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.

Source: Annex 7 Table 5-5

Table 8-22 Other details: Thromboembolic events

Thromboembolic events	Details
Potential mechanisms	Mechanism currently unknown. There is no data in the clinical or preclinical database which suggests that siponimod alters platelet function. There are no known reports of S1P receptor expression on platelets. Vascular tone and blood pressure are regulated by the concerted activity of S1P1, S1P2, and S1P3 receptors expressed on vascular ECs and smooth muscle cells (Ohmori et al 2003; Waeber and Walther 2014; Yatomi 2006). Several studies with isolated cerebral, basilar and mesenteric arteries further suggest that S1P and, e.g. fingolimod, may constrict or dilate vessels depending on the vessel type, the initial tonus of the vessel, and the S1P receptor subtypes involved (Coussin et al 2002; Salomone et al 2003; Hemmings et al 2004, Waeber and Walther 2014).
Evidence source(s) and strength of evidence	Current evidence is based on the clinical and post-marketing data from other S1P modulator (Fingolimod) where a causal relationship is not established.
Characterization of the risk:	See table above and SCS Section 2.1.5.3. Treatment emergent AEs that were subcategorized as ischemic cerebrovascular conditions in the Controlled pool and were observed in 7 siponimod 2 mg patients ((0.6%) [95% CI: (0.2, 1.3]) and none in Placebo group (0 (0) [95% CI: 0, 0.6]). These included 2 patients with transient ischemic attack who continued on study drug and the symptoms resolved with treatment. Majority of the remaining cases had risk factors that could explain the reported event of stroke. Events that were subcategorized as hemorrhagic cerebrovascular conditions in the Controlled pool were observed in 3 siponimod 2 mg patients (0.3%) and 2 patients (0.3%) receiving placebo. Events that were subcategorized as related to ischemic heart disease in the Controlled pool were observed in 8 siponimod 2 mg patients (0.7%) and 5 patients (0.8%) receiving placebo [Odds Ratio = 0.8, 95% CI: 0.3, 2.6]. Thromboembolic events in the Long-term pool were consistent with those observed in the Controlled pool. In the Long-term pool, thromboembolic events were reported in 68 (3.9%) siponimod 2 mg and 10 mg patients (IR: 1.5 per 100 PY [95% CI: 1.1, 1.9] with 35 additional cases to those included in the Control pool [IR: 1.9 per 100 PY (95% CI: 1.3, 2.7)]. Numbers of cases are few and inconclusive following review of the multi-system thrombotic events. Long-term observation of patients treated with siponimod should help to better delineate the risk.
Risk factors and risk groups	Elderly age and advanced disease with disability (immobility), preexisting cardiovascular disease including hypertension are risk factors for thromboembolic events.

Thromboembolic events	Details
	Since this is a potential risk, no attributable increase due to siponimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	No specific risk factors have been identified to predict the occurrence of thromboembolic events in individual patients receiving siponimod. • SmPC Section 4.3 contraindicates use of siponimod in patients who in the previous 6 months had a myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure. - Hypertension is a known risk factor for ischemic stroke and is included as an ADR in the Siponimod SmPC. The SmPC recommends regular monitoring of vital signs in patient receiving siponimod. The SmPC does not recommend the use of siponimod in patients with cerebrovascular disease and uncontrolled hypertension.
Impact on the benefit-risk balance of the product	The number of thromboembolic events reported in the siponimod clinical studies was low, with no overall imbalance between treatment groups. Magnitude of risk (if any) cannot be fully delineated based on current data. Long-term observation of patients treated with siponimod post approval should help to better delineate the risk.
Public health impact	Potential public health impact is considered to be low considering the advance disease condition and elderly age.

8.3.1.12 Important potential risk: Malignancies (excluding BCC, SCC and malignant melanoma)

Table 8-23 Clinical trial data: Malignancies (excluding BCC, SCC and malignant melanoma)

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
All AEs	9 (0.5) (0.2, 1.0)	6 (0.7) (0.3, 1.5)	26 (0.6) (0.4, 0.8)	43 (0.6) (0.4, 0.8)	43 (0.5) (0.4, 0.7)	46 (0.5) (0.4, 0.7)
Resolved/resolved with sequalae	5 (0.3) (< 0.1, 0.7)	1 (0.1) (< 0.1, 0.6)	9 (0.2) (< 0.1, 0.4)	15 (0.2) (0.1, 0.3)	16 (0.2) (0.1, 0.3)	16 (0.2) (0.1, 0.3)

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
AEs related to study drug	5 (0.3) (< 0.1, 0.7)	3 (0.3) (< 0.1, 1.0)	18 (0.4) (0.2, 0.6)	28 (0.4) (0.2, 0.5)	28 (0.3) (0.2, 0.5)	29 (0.3) (0.2, 0.5)
AEs leading to study drug interruption	0 (0) (0, 0.2)	1 (0.1) (< 0.1, 0.6)	0 (0) (0, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)
AE requiring concomitant medication or non-drug therapy	8 (0.5) (0.2, 0.9)	3 (0.3) (< 0.1, 1.0)	18 (0.4) (0.2, 0.6)	30 (0.4) (0.3, 0.6)	31 (0.4) (0.3, 0.5)	32 (0.4) (0.3, 0.5)
AE leading to discontinuation	7 (0.4) (0.2, 0.8)	5 (0.6) (0.2, 1.4)	24 (0.5) (0.3, 0.8)	39 (0.5) (0.4, 0.7)	41 (0.5) (0.4, 0.7)	42 (0.5) (0.4, 0.7)
AE by CTCAE grade (3/4)	6 (0.3) (0.1, 0.7)	6 (0.7) (0.3, 1.5)	21 (0.5) (0.3, 0.7)	32 (0.4) (0.3, 0.6)	33 (0.4) (0.3, 0.6)	34 (0.4) (0.3, 0.6)
SAEs	8 (0.5) (0.2, 0.9)	6 (0.7) (0.3, 1.5)	25 (0.6) (0.4, 0.8)	41 (0.5) (0.4, 0.7)	43 (0.5) (0.4, 0.7)	44 (0.5) (0.4, 0.7)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	1 (0.1) (< 0.1, < 0.1)

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(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.
- A patient with multiple occurrences is counted only once within each category.
- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.
- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.
- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.

Source: Annex 7 Table 5-8

Table 8-24 Other details: Malignancies (excluding BCC, SCC and malignant melanoma)

Malignancies (excluding BCC, SCC and malignant melanoma)	Details
Potential mechanisms	Potential mechanism unknown. A hypothetical mechanism would be related to systemic immunomodulation and reduced immunosurveillance.

Evidence source(s) and strength of evidence	Non-clinical data:
	• At therapeutic doses, siponimod has no generalized immunosuppressive properties as it neither impairs in vitro T- or B-cell activation or proliferation, cytokine or antibody production nor does it alter the capacity to mount an immune response to neo-antigens or pathogens in vivo.
	• Siponimod is non-genotoxic
	• The 2 years carcinogenicity studies in rodents identified:
	  • hemangiosarcoma in mice, with unlikely human relevance
	  • Thyroid tumors in rats, with no human relevance
	  • Lymphosarcoma in mice, with unknown human relevance

Characterization of the risk:	See table above and SCS Section 2.1.5.7. In the Controlled pool malignancies did not show an increased rate for siponimod treatment compared to placebo. Squamous cell carcinoma (SCC) of the skin, melanoma, and seminoma were reported in siponimod-treated patients. Of the reported events (other than skin related malignancies) of clinical interest related to malignancies: a case of CNS lymphoma (non-Hodgkin lymphoma of the B cell type) was reported in a 57-year-old male approximately 16 months after switching from placebo to siponimod 2 mg, from the double-blind study drug to open label siponimod. No increase in the IR (per 100 PY) of malignancy-related events was observed in the long-term safety pools (IR of 1.2 per 100 PY [95% CI: 0.9, 1.6]) as compared to the controlled pool (1.2 per 100 PY [95% CI: 0.8, 1.9]). On long-term exposure as of 4-Dec-2024, malignancies (excluding BCC, SCC, and malignant melanoma) in the long-term pool included breast cancers as the most frequently reported event [IR of 0.2 per 100 PTY (95% CI 0.1, 0.3)], followed by colorectal cancers, and testicular neoplasms [IR of <0.1 (<0.1, 0.2)].
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) are at increased risk for malignancies.

Malignancies (excluding BCC, SCC and malignant melanoma)	Details
	Since this is a potential risk, no attributable increase due to siponimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	SmPC Section 4.3 states that siponimod treatment is contraindicated in patients with active malignancies. No apparent pattern for patient's features to prevent/predict the event. SmPC Section 4.4 includes the following recommendations: Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UVB radiation or PUVA photochemotherapy.
Impact on the benefit-risk balance of the product	Although siponimod has an effect on the immune system and immunosuppression can be associated with skin malignancies (mainly squamous cell carcinoma and melanoma), the available data for siponimod do not suggest an increase of such malignancies. If patients develop symptoms of malignancy including any skin lesions, they should immediately seek medical care. No impact on the benefit risk identified.
Public health impact	The number of events of any type of malignancy to date, and the duration of follow-up, is relatively limited and does not permit conclusions at this time on any potential long-term risk.

8.3.1.13 Important potential risk: Reproductive toxicity

Table 8-25 Clinical trial data: Reproductive toxicity

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
All AEs	8 (0.5) (0.2,0.9)	0 (0) (0,0.4)	21 (0.5) (0.3, 0.7)	37 (0.5) (0.3, 0.7)	38 (0.5) (0.3, 0.6)	39 (0.5) (0.3, 0.6)
Resolved/resolved with sequalae	3 (0.2) (< 0.1, 0.5)	0 (0) (0, 0.4)	10 (0.2) (0.1, 0.4)	19 (0.2) (0.1, 0.4)	20 (0.2) (0.1, 0.4)	20 (0.2) (0.1, 0.4)

	Controlled Pool				Long Term Safety Pools (2-10mg) (1)	
	BAF312 2mg N=1148 n (%) (95% CI)	**Placebo N=607 n (%) (95% CI)**	**n (IR*) (95% CI) 31-Dec-2017 (2)**	**n (IR*) (95% CI) 29-Oct-2021 (3)**	**n (IR*) (95% CI) 31-Oct-2022 (4)**	**n (IR*) (95% CI) Final data (5)**
AEs related to study drug	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	2 (< 0.1) (< 0.1, < 0.1)	2 (< 0.1) (< 0.1, < 0.1)	2 (< 0.1) (< 0.1, < 0.1)
AEs leading to study drug interruption	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)
AE requiring concomitant medication or non-drug therapy	2 (0.1) (< 0.1, 0.4)	0 (0) (0, 0.4)	9 (0.2) (< 0.1, 0.4)	17 (0.2) (0.1, 0.4)	18 (0.2) (0.1, 0.3)	18 (0.2) (0.1, 0.3)
AE leading to discontinuation	0 (0) (0, 0.2)	0 (0) (0, 0.4)	1 (< 0.1) (< 0.1, 0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)	1 (< 0.1) (< 0.1, < 0.1)
AE by CTCAE grade (3/4)	0 (0) (0, 0.2)	0 (0) (0, 0.4)	3 (< 0.1) (< 0.1, 0.2)	3 (< 0.1) (< 0.1, 0.1)	3 (< 0.1) (< 0.1, 0.1)	3 (< 0.1) (< 0.1, 0.1)
SAEs	0 (0) (0, 0.2)	0 (0) (0, 0.4)	5 (0.1) (< 0.1, 0.3)	6 (< 0.1) (< 0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)	6 (< 0.1) (< 0.1, 0.2)
On-treatment deaths	0 (0) (0, 0.2)	0 (0) (0, 0.4)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)	0 (0) (0, < 0.1)

(1) Safety data of all subjects (from CBAF312A2201, CBAF312A2304 and their extensions) receiving at least one dose of 2mg or 10mg and collected while on 2mg or 10mg treatment (including dose titration period and reduced dose due to tolerability).

- N=Number of subjects in the Analysis Set; N'=Number of subjects in each treatment group of the controlled pool.
- A patient with multiple occurrences is counted only once within each category.
- MedDRA version 26.1 and (CompoundCaseRetrievalStrategy_Project_MedDRA V27.0_20241128) have been used for the reporting of adverse events.
- On-treatment death: Number of subjects who died up to 30 days after the last dose of study drug with principal cause of death belonging to the risk grouping.
- *Exposure adjusted incidence rate IR is calculated by n/T, i.e. the number of subjects who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
- Preferred Terms are presented in descending frequency of AEs based on BAF312 2mg of Controlled Pool, then on Placebo of Controlled Pool, then on Long Term Safety Pool cutoffs (newer to older) and then alphabetically.

Source: Annex 7 Table 5-.4

Table 8-26 Other details: Reproductive toxicity

Reproductive toxicity	Details
Potential mechanisms	S1P receptors are expressed on endothelial vascular cells (Brinkmann et al 2007) and are involved in angiogenesis during embryonic development (Xiong et al 2014). Siponimod-related effects on vascular tissues were observed during embryo-fetal development in pregnant rats and rabbits.
Evidence source(s) and strength of evidence	Reproductive and developmental studies in pregnant rats and rabbits have demonstrated siponimod-induced embryotoxicity and fetotoxicity in both species and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat/F1 generation pups and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2.2 times the exposure in humans at the highest recommended dose of 2 mg/day (2.4, Non-Clinical Overview). The safety margin is < 1-fold.
Characterization of the risk:	See table above and SCS Sections 2.1.5.8, 5.4. As of 31-Dec-2017, a total of 15 pregnancies had been reported in 12 female patients participating in siponimod clinical trials in MS. In addition, one pregnancy (with normal outcome) was reported in the female partner of a male patient who was randomized to placebo. Of these 12 female patients receiving siponimod, 7 patients had post-conception exposure to siponimod for approximately 22-78 days. Of the 7 patients with post-conception exposure, 3 patients delivered normal babies, 3 patients had elective abortion and one had a spontaneous abortion. Of the reported 15 pregnancies, eight resulted in successful delivery to full term with no maternal complications or neonatal abnormalities.
Risk factors and risk groups	Females of childbearing potential not using an effective form of contraception.
Preventability	SmPC Section 4.3 Contraindication, During pregnancy and in women of childbearing potential not using effective contraception. SmPC Section 4.6 states that women should have a negative pregnancy test before initiating treatment with siponimod and be advised of a potential risk to the foetus if siponimod is used during pregnancy or if the patient becomes pregnant while taking this medicinal product. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using siponimod and for at least ten days after stopping treatment with siponimod. When stopping siponimod therapy for planning a pregnancy the possible return of disease activity should be considered.
Impact on the benefit-risk balance of the product	No maternal complications or neonatal abnormalities were reported of the reported pregnancies at full term.

Reproductive toxicity	Details
Public health impact	No significant effect is expected if effective contraceptive measures are used in females of childbearing potential.

8.3.1.14 Important potential risk: Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)

Table 8-27 Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS relapses)

Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS relapses)	Details
Potential mechanisms	Unexpected neurological or psychiatric symptoms/signs includes cases in the judgement of the investigator the disability progression is unusually severe or medically unexpected and warrants specific notification (e.g, PRES, ADEM, Atypical MS relapses). PRES has been associated with the use of several immunosuppressive and immunomodulating agents which can cause endothelial dysfunction, e.g. cyclosporine, tacrolimus (Wong et al 2003).
Evidence source(s) and strength of evidence	Cases of PRES have been reported in the clinical trials and in the post-marketing setting of fingolimod (included as ADR in fingolimod SmPC). In the clinical studies ADEM like rare events occurred in patients treated with fingolimod at higher dose (1.25 mg or 5 mg).
Characterization of the risk:	No cases of PRES or events with unusual presentation reported in the siponimod development program. Cases of PRES should require immediate treatment and the causative factors corrected without delay. Life-supporting treatments may be required and appropriate treatment is expected to ensure a full recovery.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to siponimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	Currently unknown.
Impact on the benefit-risk balance of the product	No current impact to the benefit-risk is identified.
Public health impact	Not expected to be clinically significant based on the data available and potential public health impact is considered to be low.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

None.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	• Varicella-zoster virus (VZV) infection reactivation • Cryptococcal meningitis • Bradyarrhythmia (including conduction defects) during treatment initiation • Macular edema • Basal cell carcinoma (BCC) • Squamous cell carcinoma (SCC) • Progressive multifocal leukoencephalopathy (PML) • Malignant melanoma
Important potential risks	• Potential long-term safety implications in CYP2C9 poor metabolisers • Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML) • Thromboembolic events • Malignancies (excluding BCC, SCC and malignant melanoma) • Reproductive toxicity • Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)
Missing information	None

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the safety concerns specified below:

- Important potential risk: Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML).
    - Siponimod Opportunistic infections checklist
    - Suspected PML checklist
- Important potential Risk: Unexpected neurological signs/symptoms (includes, PRES, ADEM, Atypical/Severe MS relapse)
    - Siponimod unexpected neurological signs and symptoms checklist

Other forms of routine pharmacovigilance activities

Adjudication of risk

Opportunistic infections (including PML): Independent review of cases of suspected PML by External Adjudication Committee.

Objectives: To further characterize the risk of opportunistic infections (including PML), an independent adjudication committee will be formed to review potential PML cases from clinical trial, spontaneous case reports identified by Novartis. The cases report will be reviewed in singly or as aggregate by members of the expert Panel on an ad-hoc basis and when required.

Milestones: Adjudication panel review report along with the cases reported during a review period will be presented in each PSUR.

10.2 Part III.2. Additional pharmacovigilance activities

CBAF312A2411: PRegnancy outcomes Intensive Monitoring (PRIM)

Program short name and title:

Siponimod PRegnancy outcomes Intensive Monitoring (enhanced Pharmacovigilance program)

Rationale and program objectives:

The overall objective of the siponimod PRegnancy Outcome Intensive Monitoring program is to prospectively collect and evaluate safety data on pregnancy outcomes and congenital malformations related to siponimod exposure immediately before (up to 10 days before last menstrual period [LMP]) and during pregnancy.

The findings from this program will be used to evaluate the potential risk of reproductive toxicity, according to the RMP.

Primary objective:

- To estimate the proportion of major congenital malformations associated with exposure to siponimod immediately before and during pregnancy among live births and live births, still births and termination of pregnancy for fetal anomaly (TOPFA).

Secondary objectives:

- To estimate the proportion of minor congenital malformations associated with exposure to siponimod immediately before and during pregnancy among live births and live births, still births and termination of pregnancy for fetal anomaly (TOPFA).
- To estimate the proportion of pregnancy outcomes (live births, still births, spontaneous abortions, elective terminations) associated with exposure to siponimod immediately before and during pregnancy.
- To estimate the proportion of overall congenital malformations associated with exposure to siponimod immediately before and during pregnancy.
- To estimate the proportion of major congenital malformations by system organ class (SOC).
- To estimate the proportion of physical and cognitive development delays at 12 months of age among infants with maternal exposure to siponimod during pregnancy.
- To estimate the proportion of serious infections at 12 months of age among infants with maternal exposure to siponimod during pregnancy.

Program design:

Prospectively reported pregnancy cases undergoing enhanced pharmacovigilance follow-up.

Program population:

Prospective cases of maternal exposure during pregnancy.

Variables and data sources:

Cases from spontaneous post-marketing report sources, post-marketing observational studies and patient-oriented programs, and reports from the Novartis clinical trials program, if prospectively reported to Novartis to receive enhanced data collection questionnaires. Data is entered into the Novartis global safety database (ARGUS) per Novartis standard operating procedures (SOPs) governing pharmacovigilance safety procedures.

The primary pregnancy outcome of interest is the proportion of infants/fetuses with major and minor congenital malformations as adjudicated by expert reviewers utilizing European surveillance of congenital anomalies (EUROCAT 2015) of live births or live births, stillbirths, and termination of pregnancy due to fetal anomaly (TOPFA). Minor congenital malformations and information on spontaneous abortion, stillbirth, and elective termination are collected, as is information on infant AEs.

Milestones:

Start of data collection: Q4 2019

Interim report: Each PSUR

End of data collection: Q4 2029

Final program report: PSUR 2030

CBAF312A2006 Healthcare Professionals and Patient/Caregivers Survey

Program short name and title:

Survey among healthcare professionals (neurologists treating patients with MS along with MS specialist nurses) and patients in selected European countries to evaluate the knowledge and behaviors required for the safe use of siponimod.

Rationale and program objectives:

In order to increase understanding of the effective and safe use of siponimod HCPs and patients/caregivers will be provided educational information on the specific areas of interest as proposed in the siponimod RMP.

The overall objective of this survey, amongst HCPs and patients/caregivers in selected European countries, is to evaluate whether HCPs and patients/caregivers receive the educational materials and to capture their knowledge and behavior around specific siponimod safety measures.

Study design:

Survey to be completed independently by HCPs (neurologists treating patients with MS and MS specialist nurses) and patients/caregivers.

The web-based survey will be conducted in EU countries where Mayzent (siponimod) is available on the market and reimbursed for at least 6 months, to capture their early experiences and behaviors.

Study population:

The study will be conducted across two populations:

- HCPs who prescribe, monitor and oversee the management / or provide in person medical supervision of patients on siponimod. These will include treating physicians as well as MS specialist nurses across identified EU markets that represent distribution and prevalence of MS and countries that will be included in the launch program over time (including Germany, France, Italy, Netherlands, Nordics and Poland)
- Patients/Caregivers of patients who are taking siponimod for their SPMS, across EU markets that will be included in the launch program (including Germany, France, Italy, Netherlands, Nordics and Poland)

Milestones

Final report of study results: 31-Dec-2025

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: 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				
None proposed				
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				
None proposed				
Category 3 - Required additional pharmacovigilance activities				
CBAF312A2411 PRegnancy outcomes Intensive Monitoring (PRIM)	The overall objective of the siponimod PRIM program is to prospectively collect and evaluate safety data on pregnancy outcomes and congenital malformations related to siponimod exposure immediately before (up to 10 days before last menstrual period [LMP]) and during pregnancy.	Reproductive toxicity	Periodic update	Each PSUR
			Final report	PSUR 2030
CBAF312A2006 Healthcare professionals and patient/caregivers survey	The objective of this survey is to measure whether healthcare professionals (HCPs) and patients/caregiv	To measure the effectiveness of HCP educational material	Final report	31-Dec-2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	ers in selected European countries, receive the educational materials and to capture their knowledge and behavior around specific Mayzent (siponimod) safety measures.			

11 Part IV: Plans for post-authorization efficacy studies

No plans for any post-authorization studies at this stage.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities

Varicella-zoster virus (VZV) infection reactivation	**Routine risk communication:**
	SmPC Section 4.8 (Undesirable effects),
	PL Section 4 (possible side effects).
	Routine risk minimization activities recommending specific clinical measures to address the risk:
	SmPC Section 4.3 contraindicates the use of siponimod in patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis
	SmPC Section 4.4 and PL Section 2 include following recommendations:
	• Prior to Siponimod treatment initiation,
	  • Test for varicella zoster virus (VZV) antibody in patients without physician confirmed or undocumented full course vaccination against VZV.
	  • Provide varicella vaccination for antibody-negative patients
	  • Obtain a recent complete blood count (within last 6 months or after discontinuation of prior therapy)
	• Delay the Siponimod treatment in patients with severe active infection until resolution.
	• Vigilance for infection during Siponimod treatment and up to 3 to 4 weeks after treatment discontinuation.
	• Stop Siponimod treatment if patient develop serious infection.
	• Use effective diagnostic and therapeutic strategies for patients with symptoms of infection while on Siponimod therapy.
	• Exercise caution when Siponimod is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies.
	• Avoid attenuated live vaccines while on Siponimod treatment and for 4 weeks after stopping the Siponimod treatment.
	Other routine risk minimization measures beyond the Product Information:
	Legal status: Restricted medical prescription

Safety concern	Routine risk minimization activities
Cryptococcal meningitis	**Routine risk communication:** SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 contraindicates use of siponimod in patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC Section 4.4 and PL Section 2 include following recommendations: • Patient with symptoms and signs of CM should undergo prompt diagnostic evaluation • Stop Siponimod treatment until the exclusion of the diagnosis of CM. • Appropriate treatment should be initiated, if CM is diagnosed **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription
Bradyarrhythmia (including conduction defects) during treatment initiation	**Routine risk communication:** SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 and PL Section 3. • Siponimod needs to be re-initiated with a new titration pack when a dose is missed on one day during the first 6 days of treatment or maintenance treatment is interrupted for 4 or more consecutive daily doses SmPC Section 4.3 contraindicates use of siponimod in patients: • who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure. • with a history of second degree Mobitz type II atrioventricular (AV) block, third degree AV block, sinoatrial heart block or sick sinus syndrome, if they do not wear a pacemaker. SmPC Section 4.4 includes following recommendations: • An up-titration scheme to gradually increase the dose to reach the maintenance dose on Day 6. • Observe patients with sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (patients with NYHA class I and II) for a period of 6 hours after the first dose of siponimod

Safety concern	Routine risk minimization activities

for signs and symptoms of bradycardia, obtain an ECG prior to dosing and at the end of the observation period.

- Use of Siponimod is not recommended in patients with the following cardiac conditions and in patients taking certain antiarrhythmic, heart-rate lowering medications during treatment initiation. If treatment with siponimod is considered in these patients, it is recommended to seek advice from a cardiologist for determining an appropriate strategy for siponimod treatment initiation monitoring or switching the treatment to a non-heart-rate lowering treatment.
- In patients with a history of uncontrolled hypertension or severe untreated sleep apnoea as significant bradycardia may be poorly tolerated in these patients.
- In patients with a history of recurrent syncope or symptomatic bradycardia.
- In patients with pre-existing significant QT prolongation or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties.
- In patients with Class Ia and class III antiarrhythmic medicinal products or with heart-rate-lowering calcium channel blockers, or other substances that may decrease heart rate.
- In patients with a resting heart rate ≤ 50 bpm under chronic beta-blocker treatment, beta-blocker treatment should be interrupted before treatment initiation with Siponimod. If resting heart rate is >50 bpm siponimod treatment can be initiated and treatment with beta blocker can be re-initiated after siponimod has been up-titrated to the target maintenance dose.

SmPC Section 4.7 includes following recommendations for patients during treatment initiation

- As dizziness may occasionally occur when initiating therapy with siponimod, patients should not drive or use machines during the first day of treatment initiation with siponimod.

Other routine risk minimization measures beyond the Product Information:

Pack size: Titration pack consists of 12 film-coated tablets of 0.25 mg dose in a wallet. The titration pack allows gradual increase of the dose over a period of 5 days. Titration ends on day 6 when the maintenance dose is reached. Titration minimizes the risk to experience symptomatic bradycardia or bradyarrhythmia

Titration pack:

Titration	Titration dose	Titration regimen
Day 1	0.25 mg	1 tablet of 0.25 mg
Day 2	0.25 mg	1 tablet of 0.25 mg
Day 3	0.5 mg	2 tablets of 0.25 mg
Day 4	0.75 mg	3 tablets of 0.25 mg

Safety concern	Routine risk minimization activities
	Day 5 1.25 mg 5 tablets of 0.25 mg Legal status: Restricted medical prescription.
Macular edema	**Routine risk communication:** SmPC Section 4.8 (Undesirable effects). PL Section 4 (possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** PL Section 2 includes recommendation to monitor the symptoms of macular edema and to consult the physician for an ophthalmic examination. The SmPC Section 4.4 includes following recommendations: • An ophthalmic evaluation after 3 - 4 months of treatment initiation with Siponimod. • Siponimod should be used with caution in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in the risk of macular oedema. It is recommended that these patients undergo ophthalmic evaluation prior to the initiation and during the treatment with siponimod treatment. • As cases of macular edema have occurred on longer-term treatment, patients should report visual disturbances at any time while on Siponimod treatment and an evaluation of the fundus, including the macula, is recommended. • It is recommended that siponimod be discontinued if a patient develops macular edema • Siponimod therapy should not be initiated in patients with macular edema until resolution. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Basal Cell Carcinoma (BCC)	**Routine risk communication:** SmPC Section 4.8 (Undesirable effects). PL Section 4 (possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies. SmPC Section 4.4 includes the following recommendations: • Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These

Safety concern	Routine risk minimization activities
	patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Squamous cell carcinoma (SCC)	**Routine risk communication:** SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies. SmPC Section 4.4 includes the following recommendations: • Skin examination is recommended for all patients at treatment initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Progressive multifocal leukoencephalopathy (PML)	**Routine risk communication:** <u>None</u> **Routine risk minimization activities recommending specific clinical measures to address the risk:** PL Section 2 includes advice on monitoring symptoms of PML and immediate reporting to physician during or after stopping the treatment with siponimod. SmPC Section 4.3 includes following recommendations: • Siponimod is contraindicated in patients with history of progressive multifocal leukoencephalopathy. SmPC Section 4.4 includes following recommendations: • Before initiating treatment, a recent complete blood count should be available. • Initiation of treatment should be delayed in patients with active infection until resolution.

Safety concern	Routine risk minimization activities
	• Vigilance for infection should be continued during siponimod treatment and up to 3 to 4 weeks after treatment discontinuation. • Suspension of treatment with siponimod should be considered if patient develop serious infection. • Be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. • Exercise caution when siponimod is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. • Avoid attenuated live vaccines while on siponimod treatment and for 4 weeks after stopping the siponimod treatment. • Cases of PML have been reported with sphingosine 1-phosphate receptor modulators, including siponimod, and other therapies for MS. If a patient is suspected with PML, siponimod treatment should be suspended until PML have been excluded. If PML is confirmed, treatment with siponimod should be discontinued. • After stopping MAYZENT in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS). • Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors modulators, including MAYZENT, who developed PML, and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was generally within a few months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Malignant melanoma	**Routine risk communication:** SmPC Section 4.8 (Undesirable effects). PL Section 4 (possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies. SmPC Section 4.4 includes the following recommendations: • Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These

Safety concern	Routine risk minimization activities
	patients should not receive concomitant phototherapy with UV-radiation or PUVA-photochemotherapy. • PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Potential long-term safety implications in CYP2C9 poor metabolisers	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 includes following recommendations: • Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their metaboliser status. • Siponimod should not be used in patients with a CYP2C9*3*3 genotype. • A maintenance dose of 1 mg daily is recommended in patients with a CYP2C9*2*3 or *1*3 genotypes. SmPC Section 4.3 includes the following recommendation: • Use of siponimod is contraindicated in patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metabolizer) SmPC Section 4.4 includes following recommendations: • Before initiation of treatment with siponimod, patients must be genotyped for CYP2C9 to determine their metaboliser status. • Patients homozygous for CYP2C9*3 (CYP2C9*3*3) should not be treated with siponimod, use in these patients results in substantially elevated siponimod plasma levels. • A maintenance dose of 1 mg daily is recommended in patients with a CYP2C9*2*3 or *1*3 genotypes to avoid increased exposure to siponimod. SmPC Section 4.5 includes following recommendations: • Because of a significant increase in exposure to siponimod, concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor. • Due to an expected reduction in siponimod exposure, caution should be applied when siponimod is combined o with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients regardless of genotype. o with moderate CYP3A4 inducers (e.g. modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: • Pack size: o Pack of 120 film-coated tablets of 0.25 mg dose: This pack is for the use in patients with a CYP2C9*1*3 or *2*3 genotypes, the recommended maintenance dose for these populations is 1 mg siponimod daily (4 tablets of 0.25 mg). o Pack of 28 (or 98 in some countries) film-coated tablets of 1 mg dose: This pack is for the use in patients with a CYP2C9*1*3 or *2*3 genotypes, the recommended maintenance dose for these populations is 1 mg siponimod daily (1 tablet of 1 mg). • Legal status: Restricted medical prescription.
Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** PL Section 2 includes advice on monitoring symptoms of CM and immediate reporting to physician during or after stopping the treatment with siponimod. SmPC Section 4.3 includes following recommendations: • Siponimod is contraindicated in patients with history of, immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis. SmPC Section 4.4 includes following recommendations: • Before initiating treatment, a recent complete blood count should be available. • Delay the Siponimod treatment in patients with active infection until resolution. • Vigilance for infection during siponimod treatment and up to 3 to 4 weeks after treatment discontinuation. • Stop Siponimod treatment if patient develop serious infection. • Use effective diagnostic and therapeutic strategies for patients with symptoms of infection while on siponimod therapy. • Exercise caution when siponimod is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. • Avoid attenuated live vaccines while on siponimod treatment and for 4 weeks after stopping the siponimod treatment. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Thromboembolic events	**Routine risk communication:** None.

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.3 includes following recommendations: • Use of siponimod is contraindicated in patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure. SmPC Section 4.4 - Due to the risk of serious cardiac rhythm disturbances or significant bradycardia, siponimod should not be used in patients with uncontrolled hypertension during treatment initiation. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Malignancies (excluding BCC, SCC, and malignant melanoma)	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies. SmPC Section 4.4 includes the following recommendations: Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed, and also recommends to limit the exposure to sun and UV rays. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Reproductive toxicity	**Routine risk communication:** SmPC Section 4.6 (Fertility, pregnancy and lactation) **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 contraindicates the use of siponimod during pregnancy and in women of childbearing potential not using effective contraception. SmPC Section 4.4 includes following recommendation: • Due to risk for the foetus, siponimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing

Safety concern	Routine risk minimization activities
	potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for at least 10 days after discontinuation SmPC Section 4.6 and PL Section 2 includes effective contraception recommendations and negative pregnancy test prior to initiating treatment with siponimod. When stopping siponimod therapy for planning a pregnancy the possible return of disease activity should be considered. SmPC Section 4.6 and PL Section 2 includes recommendation not to breast-feed while on siponimod treatment. **Other routine risk minimization measures beyond the Product Information** Legal status: Restricted medical prescription.
Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 includes recommendation that physician should promptly schedule complete physical and neurological examination and should consider magnetic resonance imaging when patient on siponimod develops any unexpected neurological symptoms/signs or accelerated neurological deterioration. PL Section 2 included recommendation for monitoring of symptoms and report immediately to physician. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.

12.2 Part V.2. Additional Risk minimization measures

Educational material

- Physician's Checklist to consider prior to prescribing Mayzent
- Patient/Caregiver Guide
- Pregnancy reminder card for women of childbearing potential (WOCBP)

Objectives:

To provide health care professionals (HCPs) (includes physicians and nurses) and patients/care givers with educational information on the following safety areas of interest:

- Bradyarrhythmia (including conduction defects) during treatment initiation

- Infections, including varicella zoster reactivation, reactivation of the other viral infections, PML and other rare opportunistic infections including cryptococcal meningitis
- Reproductive toxicity
- Macular edema
- Basal cell carcinoma (BCC)
- Squamous cell carcinoma (SCC)
- Malignancies (excluding BCC, SCC and malignant melanoma)
- Malignant melanoma
- Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)
- Potential long-term safety implications in CYP2C9 poor metabolisers (on siponimod exposure and effects of CYP2C9/3A4 inhibitors and inducers)

The goal is for this information to assist the HCPs in managing and counselling patients who are either currently being treated with siponimod, or in whom therapy with siponimod is proposed as well as for educating patients/caregivers about the risks while using siponimod, as well as on receipt and usage of the titration initiation pack, treatment adherence (treatment initiation (during the first 6 days), maintenance dosing, and re-initiation in patients with missed dose/treatment interruption for a day during treatment initiation or for 4 or more consecutive days during maintenance therapy).

Rationale for the additional risk minimization activity:

- To increase understanding of the safe and effective use of siponimod.

Target audience and planned distribution path:

Target audience: HCPs managing MS patients (physicians and nurses) and patients who are either currently being treated with siponimod, or to whom therapy with siponimod is proposed.

Distribution path: Dissemination of the educational materials to HCPs involved in treatment with siponimod.

Plans to evaluate the effectiveness of the risk minimization measures and criteria for success

The effectiveness of the materials will be evaluated and monitored based on process and outcome indicators.

Outcome indicators are assessed by monitoring of the AEs related to the safety areas of interest recorded in the Novartis safety database.

Specific benchmarks will be defined to evaluate the success of the risk minimization measures. The results of the monitoring of the risk minimization measures will be included in each PSUR.

In addition, Novartis will conduct post-approval, a survey among healthcare professionals (neurologists treating patients with MS and MS specialist nurses) and SPMS patients/caregivers in selected European countries to confirm that HCPs and patients/caregivers receive the educational materials and to assess their knowledge of the actions required for the safe use of siponimod. The survey (process indicator) will also evaluate reported behaviors relative to the risks covered by the educational materials.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities

Varicella-zoster virus (VZV) infection reactivation	**Routine risk minimizations measures:**
	SmPC Section 4.8 (Undesirable effects).
	PL Section 4 (possible side effects).
	SmPC Section 4.3 contraindicates use of siponimod in patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis.
	SmPC Section 4.4 and PL Section 2 include following recommendations:
	• Prior to Siponimod treatment initiation,
	  • Test for varicella zoster virus (VZV) antibody in patients without physician confirmed or undocumented full course vaccination against VZV.
	  • Provide varicella vaccination for antibody-negative patients.
	  • Obtain a recent complete blood count (within last 6 months or after discontinuation of prior therapy).
	• Delay the Siponimod treatment in patients with severe active infection until resolution.
	• Vigilance for infection during Siponimod treatment and up to 3 to 4 weeks after treatment discontinuation.
		Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
		None
		Additional pharmacovigilance activities:
		None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Stop Siponimod treatment if patient develop serious infection. • Use effective diagnostic and therapeutic strategies for patients with symptoms of infection while on Siponimod therapy. • Exercise caution when Siponimod is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. • Avoid attenuated live vaccines while on Siponimod treatment and for 4 weeks after stopping the Siponimod treatment. **Additional risk minimization measures:** Educational materials for HCPs and patients/care givers - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	
Cryptococcal meningitis	**Routine risk minimization measures** SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). SmPC Section 4.3 contraindicates use of siponimod in patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC Section 4.4 and PL Section 2 include following recommendations • Patients with symptoms and signs of CM should undergo prompt diagnostic evaluation • Stop siponimod treatment until the exclusion of the diagnosis of CM. • Appropriate treatment should be initiated, if CM is diagnosed **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: AE follow-up checklist for adverse reaction Adjudication of Opportunistic Infections (OIs) (including CM) cases. **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	- Patient/Caregiver Guide	
Bradyarrhythmia (including conduction defects) during treatment initiation	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). SmPC Section 4.2 and PL Section 3 included recommendation on initiating the treatment with titration pack and on reinitiation of treatment if a dose is missed during the first 6 days of treatment or when maintenance treatment is interrupted for 4 or more consecutive daily doses. SmPC Section 4.3 contraindicates use of siponimod in patients • who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure • with a history of second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker. SmPC Section 4.4 includes following recommendations: • Apply an up-titration scheme to reach the maintenance dose on day 6 at treatment start. • Observe patients with sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (patients with NYHA class I and II) for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia, obtain an ECG prior to dosing and at the end of the observation period. • Use of Siponimod is not recommended in patients with the following cardiac conditions and in patients taking certain antiarrhythmic, heart-rate lowering medications during treatment initiation. If	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None. **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	treatment with Siponimod is considered in these patients, it is recommended to seek advice from a cardiologist for determining an appropriate strategy for siponimod treatment initiation monitoring or switching the treatment to a non-heart-rate lowering treatment. - In patients with a history of uncontrolled hypertension or severe untreated sleep apnoea as significant bradycardia may be poorly tolerated in these patients. - In patients with a history of recurrent syncope or symptomatic bradycardia. - In patients with pre-existing significant QT prolongation or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties. - In patients with Class Ia and class III antiarrhythmic medicinal products or with heart-rate-lowering calcium channel blockers, or other substances that may decrease heart rate. - In patients with a resting heart rate ≤ 50 bpm under chronic beta-blocker treatment, beta-blocker treatment should be interrupted before treatment initiation with Siponimod. If resting heart rate is > 50 bpm siponimod treatment can be initiated and treatment with beta blocker can be re-initiated after siponimod has been up-titrated to the target maintenance dose. SmPC Section 4.7 includes following recommendations for patients during treatment initiation • As dizziness may occasionally occur when initiation therapy with siponimod, patients should not drive or use machines during the first day of treatment initiation with siponimod. **Pack size**: Titration pack consists of 12 film-coated tablets of 0.25 mg dose in a	

<table>
<tr><th>Safety concern</th><th>Risk minimization measures</th><th>Pharmacovigilance activities</th></tr>
<tr><td></td><td>wallet. The titration pack allows gradual increase of the dose over a period of 5 days. Titration ends on day 6 when the maintenance dose is reached. Titration minimizes the risk to experience symptomatic bradycardia or bradyarrhythmia.

Titration pack:
<table>
<tr><th>Titration</th><th>Titration dose</th><th>Titration regimen</th></tr>
<tr><td>Day 1</td><td>0.25 mg</td><td>1 tablet of 0.25 mg</td></tr>
<tr><td>Day 2</td><td>0.25 mg</td><td>1 tablet of 0.25 mg</td></tr>
<tr><td>Day 3</td><td>0.5 mg</td><td>2 tablets of 0.25 mg</td></tr>
<tr><td>Day 4</td><td>0.75 mg</td><td>3 tablets of 0.25 mg</td></tr>
<tr><td>Day 5</td><td>1.25 mg</td><td>5 tablets of 0.25 mg</td></tr>
</table>
Additional risk minimization measures:
Educational material for HCPs and patients/care givers.
- Physician’s Checklist to consider prior to prescribing Mayzent
- Patient/Caregiver Guide</td><td></td></tr>
<tr><td>Macular edema</td><td>Routine risk minimization measures:
SmPC Section 4.8 (Undesirable effects).
PL Section 4 (possible side effects).
PL Section 2 includes recommendation to monitor the symptoms of macular edema and to consult the physician for an ophthalmic examination.
The SmPC Section 4.4 included following recommendations:
An ophthalmic evaluation after 3 - 4 months of treatment initiation with Siponimod.
Siponimod should be used with caution in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in the risk of macular edema. It is recommended that these patients undergo ophthalmic evaluation prior to the initiation and during the treatment with siponimod treatment.</td><td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
None

Additional pharmacovigilance activities:
None</td></tr>
</table>

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• As cases of macular edema have occurred on longer-term treatment, patients should report visual disturbances at any time while on Siponimod treatment and an evaluation of the fundus, including the macula is recommended. • Siponimod should be discontinued if a patient develops macular edema • Siponimod therapy should not be initiated in patients with macular edema until resolution. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	
Basal cell carcinoma	**Routine risk minimization measures** SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies SmPC Section 4.4 includes the following recommendations -Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	
Squamous cell carcinoma (SCC)	**Routine risk minimization measures** SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies SmPC Section 4.4 includes the following recommendations -Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Progressive multifocal leukoencephalopathy (PML)	**Routine risk minimization measures:** PL Section 2 includes advice on monitoring symptoms of PML instruction for immediate reporting to physician during or after stopping the treatment with siponimod.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC Section 4.3 includes following recommendations: Siponimod is contraindicated in patients with history of progressive multifocal leukoencephalopathy SmPC Section 4.4 includes following recommendations: Before initiating treatment, a recent complete blood count should be available. Initiation of treatment should be delayed in patients with active infection until resolution. Vigilance for infection should be continued during siponimod treatment and up to 3 to 4 weeks after treatment discontinuation. Suspension of treatment with siponimod should be considered if patient develop serious infection. Be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. Exercise caution when siponimod is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. Avoid attenuated live vaccines while on siponimod treatment and for 4 weeks after stopping the siponimod treatment. Cases of PML have been reported with sphingosine 1-phosphate receptor modulators, including siponimod, and other therapies for MS. If a patient is suspected with PML, siponimod treatment should be suspended until PML have been excluded. If PML is confirmed, treatment with siponimod should be discontinued. After stopping MAYZENT in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS). Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors modulators, including MAYZENT, who developed PML, and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's	AE follow-up checklist for PML Adjudication of Opportunistic infections (OIs) (including PML) cases **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was generally within a few months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.	
Malignant melanoma	**Routine risk minimization measures:** SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies. SmPC Section 4.4 includes the following recommendations: • Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-radiation or PUVA-photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Potential long-term safety implications in CYP2C9 poor metabolisers	**Routine risk minimization measures:** SmPC Section 4.2 included following recommendations: • Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their metaboliser status. • Siponimod should not be used in patients with a CYP2C9*3*3 genotype. • A maintenance dose of 1 mg daily is recommended in patients with a CYP2C9*2*3 or *1*3 genotypes. SmPC Section 4.3 includes the following recommendation: • Use of siponimod is contraindicated in patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metabolizer). SmPC Section 4.4 included following recommendations: • Before initiation of treatment with siponimod, patients must be genotyped for CYP2C9 to determine their metaboliser status. • Patients homozygous for CYP2C9*3 (CYP2C9*3*3) should not be treated with siponimod, use in these patients results in substantially elevated siponimod level. • A maintenance dose of 1 mg daily is recommended in patients with a CYP2C9*2*3 or *1*3 genotypes to avoid increased exposure to siponimod. SmPC Section 4.5 included following recommendations: • Because of a significant increase in exposure to siponimod, concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor. • Due to an expected reduction in Siponimod exposure, caution should be applied when siponimod is combined o with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients regardless of genotype. o with moderate CYP3A4 inducers (e.g. modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype. Pack size: • Pack of 120 film-coated tablets of 0.25 mg dose: This pack is for the use in patients with a CYP2C9*1*3 or *2*3 genotypes, the recommended maintenance dose for these populations is 1 mg siponimod daily (4 tablets of 0.25 mg). • Pack of 28 (or 98 in some countries) filmcoated tablets of 1 mg dose: This pack is for the use in patients with a CYP2C9*1*3 or *2*3 genotypes, the recommended maintenance dose for these populations is 1 mg siponimod daily (1 tablet of 1 mg). Legal status: Restricted medical prescription. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers - Physician's Checklist to consider prior to prescribing Mayzent. - Patient/Caregiver Guide.	
Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other	**Routine risk minimization measures:** PL Section 2 includes advice on monitoring symptoms of CM instruction for immediate reporting to physician during or after stopping the treatment with siponimod.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)	SmPC Section 4.3 includes following recommendations: - Siponimod is contraindicated in patients with history of immunodeficiency syndrome progressive multifocal leukoencephalopathy or cryptococcal meningitis. SmPC Section 4.4 included following recommendations: Before initiating treatment, a recent complete blood count should be available. Delay the Siponimod treatment in patients with active infection until resolution. Vigilance for infection during Siponimod treatment and up to 3 to 4 weeks after treatment discontinuation. Stop Siponimod treatment if patient develop serious infection. Use effective diagnostic and therapeutic strategies for patients with symptoms of infection while on Siponimod therapy. Exercise caution when Siponimod is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. Avoid attenuated live vaccines while on Siponimod treatment and for 4 weeks after stopping the Siponimod treatment. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.	AE follow-up checklist for adverse reaction Adjudication of opportunistic infections (including PML) cases. **Additional pharmacovigilance activities:** None
Thromboembolic events	**Routine risk minimization measures:** SmPC Section 4.3 includes following recommendations: - Use of siponimod is contraindicated in patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities**:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	- SmPC Section 4.4- Due to the risk of serious cardiac rhythm disturbances or significant bradycardia, siponimod should not be used in patients with uncontrolled hypertension during treatment initiation **Additional risk minimization measures:** None.	None
Malignancies (excluding BCC, SCC and malignant melanoma)	**Routine risk minimization measures:** SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies. SmPC Section 4.4 includes the following recommendations: Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed, and also recommends to limit the exposure to sun and UV rays. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Reproductive toxicity	**Routine risk minimization measures:** SmPC Section 4.3 contraindicates the use of siponimod during pregnancy and in women of childbearing potential not using effective contraception. SmPC Section 4.4 includes following recommendation:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	- Due to risk for the foetus, siponimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for at least 10 days after discontinuation SmPC Section 4.6 and PL Section 2 included effective contraception recommendations and recommendation to have a negative pregnancy test before initiating treatment with siponimod. When stopping siponimod therapy for planning a pregnancy the possible return of disease activity should be considered. SmPC Section 4.6 and PL Section 2 included recommendation not to breast-feed while on siponimod treatment. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide - Pregnancy reminder card for WOCBP	**Additional pharmacovigilance activities**: CBAF312A2411 PRegnancy outcomes Intensive Monitoring (PRIM)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)	**Routine risk minimization measures:** SmPC Section 4.4 includes recommendation that physician should promptly schedule complete physical and neurological examination, and should consider magnetic resonance imaging when patient on siponimod develops any unexpected neurological symptoms/signs or accelerated neurological deterioration. PL Section 2 included recommendation on monitoring of symptoms and report immediately to physician. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up checklist for adverse reaction. **Additional pharmacovigilance activities**: None

13 Part VI: Summary of the risk management plan for Mayzent® (Siponimod)

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

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

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

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

13.1 Part VI: I. The medicine and what it is used for

Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity. It contains siponimod as the active substance and it is given as 0.25 mg, 1 mg and 2 mg film-coated tablets.

Further information about the evaluation of Mayzent's benefits can be found in Mayzent's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use including treatment adherence, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Mayzent, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

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

If important information that may affect the safe use of Mayzent is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI: II.A: List of important risks and missing information

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

Table 13-1 List of important risks and missing information

Important identified risks	• Varicella-zoster virus (VZV) infection reactivation • Cryptococcal meningitis • Bradyarrhythmia (including conduction defects) during treatment initiation • Macular edema • Basal cell carcinoma (BCC) • Squamous cell carcinoma (SCC) • Progressive multifocal leukoencephalopathy (PML) • Malignant melanoma
Important potential risks	• Potential long-term safety implications in CYP2C9 poor metabolisers • Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML) • Thromboembolic events • Malignancies (excluding BCC, SCC and malignant melanoma) • Reproductive toxicity • Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)
Missing information	• None

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk: Varicella-zoster virus (VZV) infection reactivation

Evidence for linking the risk to the medicine	Given the biologic plausibility and the well-characterized risk of infections with the other S1P modulator, infections are not unexpected. In the controlled pool, reactivation of VZV infection was reported for a higher percentage of Mayzent 2 mg patients vs placebo, but incidences were low (2.9% of Mayzent 2 mg patients and 0.7% of placebo patients). The exposure adjusted rate of VZV reactivation did not increase with long-term exposure (IR: 1.7, 95% CI: 1.4, 2.2, for Long-term pool (broad) vs IR: 1.9 95% CI 1.3, 2.7 for the Controlled pool). In the Phase III study, decrease in lymphocyte count observed in patients in the Mayzent 2 mg group is seen early after commencing treatment and is maintained as long as the patient continues Mayzent therapy. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase III PopPKPD]. There was no increase in the number of infections following Mayzent treatment compared to placebo, or with increasing average Mayzent steady-state concentration and decreasing average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use. Cases of herpes viral infections, opportunistic infections (includes cryptococcal infections) and PML were observed while on treatment with another S1P modulator (Fingolimod). In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. Cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported with the use of fingolimod, some of which have been fatal.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) are at an increased risk of VZV infections. The patients with negative VZ virus-IgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in case of an MS relapse.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects). PL Section 4 (possible side effects). SmPC Section 4.3 includes following contraindications:

	Patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC Section 4.4 and PL Section 2 include following recommendations: • Prior to Mayzent treatment initiation, • Test for varicella zoster virus (VZV) antibody in patients without physician confirmed or undocumented full course vaccination against VZV. • Provide varicella vaccination for antibody-negative patients. • Obtain a recent complete blood count (within last 6 months or after discontinuation of prior therapy). • Delay the Mayzent treatment in patients with severe active infection until resolution. • Vigilance for infection during Mayzent treatment and up to 3 to 4 weeks after treatment discontinuation. • Stop Mayzent treatment if patient develop serious infection. • Use effective diagnostic and therapeutic strategies for patients with symptoms of infection while on Mayzent therapy. • Exercise caution when Mayzent is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. • Avoid attenuated live vaccines while on Mayzent treatment and for 4 weeks after stopping the Mayzent treatment. **Additional risk minimization measures**: Educational materials for HCPs and patients/care givers - Physician's Checklist to consider prior to prescribing Mayzent -Patient/Caregiver Guide
Additional pharmacovigilance activities	None

Table 13-3 Important identified risk: Cryptococcal meningitis

Evidence for linking the risk to the medicine	Given the biologic plausibility and the well-characterized risk of infections with another S1P modulator, infections are not unexpected. Cases of cryptococcal meningitis (CM) have been reported on siponimod treatment. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase III PopPKPD]. There was no increase in the number of infections following Mayzent treatment compared to placebo, or with increasing average Mayzent steady-state concentration and decreasing

	average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use. Cases of herpes viral infections, opportunistic infections (includes cryptococcal infections) and PML were observed while on treatment with another S1P modulator (Fingolimod). In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. Cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported with the use of fingolimod, some of which have been fatal.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) are at an increased risk of cryptococcal infections.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects). PL Section 4 (possible side effects). SmPC Section 4.3 includes following contraindications: Patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC Section 4.4 and PL Section 2 include following recommendations: • Patient with such symptoms and signs should undergo prompt diagnostic evaluation • The treatment with Mayzent should be stopped until the diagnosis of CM has been excluded. • Appropriate treatment should be initiated, if CM is diagnosed **Additional risk minimization measures**: Educational materials for HCPs and patients/care givers - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide
Additional pharmacovigilance activities	None

Table 13-4 Important identified risk: Bradyarrhythmia (including conduction defects) during treatment initiation

Evidence for linking the risk to the medicine	In the Clinical Pharmacology studies, (single doses up to 75 mg, multiple doses up to 20 mg qd) and studies in PM/DM patients (highest dose 10 mg qd), a dose-dependent decrease in mean heart rate was observed over the first 24 h post-dose, plateauing at doses of 5 mg and above. Decreases in heart rate were transient and peaked approximately 2 h post-dose for all doses. In Study A2201, when Mayzent was started without dose titration in the maintained dose of 2 mg or 10 mg five transient symptomatic

	bradyarrhythmic events were observed on Day 1. The events resolved without sequelae after drug discontinuation. Other findings included dose dependent, transient decrease in heart rate on Day 1 with the maximum decreases observed 2 hours post first dose (mean change of app. 10 bpm for 10 mg dose) in Period 1 of the study. Based upon these observations, dose titration was implemented in Study A2201 in Period 2. Following the introduction of the initial-dose titration scheme, there were no symptomatic bradyarrhythmic events or AV-blocks of concern. In Study A2304, the targeted maintenance dose of 2 mg of Mayzent was reached through 6 days of titration. In this study, the most prominent decreases in heart rate were observed on Day 1, 4 hours post dose (mean decreases of 5.30 bpm in Mayzent and 0.76 bpm in placebo group); in general 5.9% of Mayzent patients were observed with HR <50 bpm compared with 1.2% of placebo patients. During the titration period for the combined terms of bradyarrhythmia and bradycardia, 51 patients in the Mayzent group and 15 in the placebo group had events, transient and mostly asymptomatic. Discontinuation due to first or second degree AV block was reported in 0.2% Mayzent (2 first degree AV block and 2 second degree AV Mobitz type I; one patient experienced both) and none in placebo patients (A2304).
Risk factors and risk groups	Patients with underlying medical history and/or receiving co-medications that might increase the risk of bradycardia or in whom bradycardia may be poorly tolerated include: • second degree Mobitz type II or higher AV block, • sick-sinus syndrome • sino-atrial heart block, • history of symptomatic bradycardia or recurrent syncope, • cerebrovascular disease, • history of myocardial infarction, • congestive heart failure, • history of cardiac arrest, • uncontrolled hypertension • severe sleep apnea patients with significant QT prolongation (QTc >500 msec) • Other potential risk factors include concomitant administration with: Class Ia (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products, beta blockers, and heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). SmPC Section 4.2 and PL Section 3 included recommendation on initiating the treatment with titration pack and reinitiating treatment when

a dose is missed during the first 6 days of treatment or missed doses for 4 or more consecutive daily doses during maintenance treatment.

- Mayzent needs to be re-initiated with a new titration pack when a dose is missed on one day during the first 6 days of treatment or maintenance treatment is interrupted for 4 or more consecutive daily doses.

SmPC Section 4.3 includes following contraindications:

- Patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure
- Patients with a history of second degree Mobitz type II atrioventricular (AV) block, third degree AV block, sinoatrial heart block or sick sinus syndrome, if they do not wear a pacemaker.

SmPC Section 4.4 includes following recommendations:

Apply an up-titration scheme to reach the maintenance dose on day 6 at treatment start.

Observe patients with sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (patients with NYHA class I and II) for a period of 6 hours after the first dose of Mayzent for signs and symptoms of bradycardia, obtain an electrocardiogram (ECG) prior to dosing and at the end of the observation period.

Use of Mayzent is not recommended in patients with the following cardiac conditions and in patients taking certain antiarrhythmic, heart-rate lowering medications during treatment initiation. If treatment with Mayzent is considered in these patients, it is recommended to seek advice from a cardiologist for determining an appropriate strategy for Mayzent treatment initiation monitoring or switching the treatment to a non-heart-rate lowering treatment.

- In patients with a history of uncontrolled hypertension or severe untreated sleep apnoea as significant bradycardia may be poorly tolerated in these patients.
- In patients with a history of recurrent syncope or symptomatic bradycardia.
- In patients with pre-existing significant QT prolongation or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties.
- In patients with Class Ia and class III antiarrhythmic medicinal products or with heart-rate-lowering calcium channel blockers, or other substances that may decrease heart rate.
- In patients with a resting heart rate ≤ 50 bpm under chronic beta-blocker treatment, beta-blocker treatment should be interrupted before treatment initiation with Mayzent. If resting heart rate is > 50 bpm Mayzent treatment can be initiated and treatment with beta blocker can be re-initiated after Mayzent has been up-titrated to the target maintenance dose.

SmPC Section 4.7 includes following recommendations for patients during treatment initiation

- As dizziness may occasionally occur when initiating therapy with Mayzent, patients should not drive or use machines during the first day of treatment initiation with Mayzent.

Pack size: Titration pack consists of 12 film-coated tablets of 0.25 mg dose in a wallet. The titration pack allows gradual increase of the dose over a period of 5 days. Titration ends on day 6 when the maintenance dose is reached. Titration minimizes the risk to experience symptomatic bradycardia or bradyarrhythmia.

Titration pack:

Titration	Titration dose	Titration regimen
Day 1	0.25 mg	1 tablet of 0.25 mg
Day 2	0.25 mg	1 tablet of 0.25 mg
Day 3	0.5 mg	2 tablets of 0.25 mg
Day 4	0.75 mg	3 tablets of 0.25 mg
Day 5	1.25 mg	5 tablets of 0.25 mg

Additional risk minimization measures:

Educational materials for HCPs and patients/care givers

- Physician's Checklist to consider prior to prescribing Mayzent
- Patient/Caregiver Guide

Additional pharmacovigilance activities	None

Table 13-5 Important identified risk: Macular edema

Evidence for linking the risk to the medicine	Drug induced Macular edema has been reported with other S1P modulators. S1P modulators pharmacological action on the endothelial barrier function has been associated with incidence of macular edema. In the Controlled pool, macular edema (including cystoid macular edema) was reported as an AE in 20 (1.7%) Mayzent 2 mg patients (Odds ratio of 10.7 vs Placebo 95% CI: 1.4, 80.3) and 1 (0.2%) placebo patient. There is no evidence of an increase in the incidence rate of macular edema over time [IR 0.6, per 100 PY (95% CI 0.4, 0.8) vs IR 1.2 (95% CI: 0.7, 1.8)] with Mayzent treatment and the reported cases in the Long-term pool were consistent with the observations in the Controlled pool.
Risk factors and risk groups	Patients with a history of diabetes mellitus, uveitis and underlying/co-existing retinal disorders are considered at increased risk of developing macular edema. Such patients should undergo an ophthalmic evaluation prior to initiating Mayzent therapy and have follow-up evaluations while receiving Mayzent therapy.

Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects). PL Section 4 (possible side effects). PL Section 2 includes recommendation to monitor the symptoms of macular edema and to consult the physician for an ophthalmic examination. The SmPC Section 4.4 included following recommendations: • An ophthalmic evaluation after 3 - 4 months of treatment initiation with Mayzent. • Mayzent should be used with caution in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease due to a potential increase in the risk of macular edema. It is recommended that these patients undergo ophthalmic evaluation prior to the initiation and during the treatment with Mayzent treatment. • As cases of macular edema have occurred on longer-term treatment, patients should report visual disturbances at any time while on Mayzent treatment and an evaluation of the fundus, including the macula is recommended. • It is recommended that Mayzent be discontinued if a patient develops macular edema. A decision on whether or not Mayzent should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient. • Mayzent therapy should not be initiated in patients with macular edema until resolution. **Additional risk minimization measures**: Educational materials for HCPs and patients/care givers: - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide
Additional pharmacovigilance activities	None

Table 13-6 Important identified risk: Basal Cell Carcinoma

Evidence for linking the risk to the medicine	Basal cell carcinoma has been reported for other S1P modulators. In study A2304, basal cell carcinoma was the most common neoplasm and was reported with a similar incidence in the Mayzent 2 mg (1.1%, 12 patients) and placebo (1.3%, 7 patients) groups. However, additional cases in patients treated with Mayzent have been reported with longer exposure.
Risk factors and risk groups	Patients with advanced age, prior prolonged immunosuppressive medication, and exposure to UV radiation.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects),

	PL Section 4 (possible side effects). SmPC Section 4.3 contraindicates use of Mayzent in patients with active malignancies SmPC Section 4.4 includes the following recommendations Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. These patients should be cautioned against exposure to sunlight without protection. These patients and they should not receive concomitant phototherapy with UV-B radiation or PUVA photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. **Additional risk minimization measures**: Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide
Additional pharmacovigilance activities	None

Table 13-7 Important identified risk: Squamous cell carcinoma (SCC)

Evidence for linking the risk to the medicine	Squamous cell carcinoma has been reported for other S1P modulators. In study A2304, squamous cell carcinoma was reported with a similar incidence in the Mayzent 2 mg (0.2%, 2 patients) and placebo (0.2%, 1 patient) groups. However, additional cases in patients treated with Mayzent have been reported with longer exposure.
Risk factors and risk groups	Patients with advanced age, prior prolonged immunosuppressive medication, and exposure to UV radiation.
Risk minimization measures	SmPC Section 4.8 (Undesirable effects), PL Section 4 (possible side effects). SmPC Section 4.3 contraindicates use of Mayzent in patients with active malignancies SmPC Section 4.4 includes the following recommendations Skin examination is recommended for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. These patients should be cautioned against exposure to sunlight without protection. These patients and they should not receive concomitant phototherapy with UV-B radiation or PUVA photochemotherapy.

	PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist to consider prior to prescribing Mayzent -Patient/Caregiver guide
Additional pharmacovigilance activities	None

Table 13-8 Important identified risk: Progressive multifocal leukoencephalopathy (PML)

Evidence for linking the risk to the medicine	In the Phase III study, decrease in lymphocyte count observed in patients in the Mayzent 2 mg group is seen early after commencing treatment and is maintained as long as the patient continues Mayzent therapy. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase III PopPKPD]. There was no increase in the number of infections following Mayzent treatment compared to placebo, or with increasing average Mayzent steady-state concentration and decreasing average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use. Cases of PML were observed while on treatment with other S1P receptor modulators (fingolimod, ozanimod). In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. Cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) are at an increased risk of PML.
Risk minimization measures	**Routine risk minimization measures:** PL Section 2 includes advice on monitoring symptoms of PML and instruction for immediate reporting to physician during or after stopping the treatment with Mayzent. SmPC Section 4.3 includes following contraindications: Patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC Section 4.4 included following recommendations:

	• Before initiating treatment, a recent complete blood count should be available. • Initiation of treatment should be delayed in patients with active infection until resolution. • Vigilance for infection should be continued during Mayzent treatment and up to 3 to 4 weeks after treatment discontinuation. • Suspension of treatment with siponimod should be considered if patient develop serious infection. • Be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. • Exercise caution when Mayzent is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. • Avoid attenuated live vaccines while on Mayzent treatment and for 4 weeks after stopping the Mayzent treatment. • Cases of progressive multifocal leukoencephalopathy (PML) have been reported with another sphingosine 1-phosphate receptor modulators. If a patient is suspected with PML, Mayzent treatment should be suspended until PML have been excluded. If PML is confirmed, treatment with siponimod should be discontinued. • After stopping MAYZENT in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS). • Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors modulators, including MAYZENT, who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was generally within a few months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken. **Additional risk minimization measures:** Educational materials for HCPs and patients/care givers: - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide
Additional pharmacovigilance activities	None See Section II.C of this summary for an overview of post-authorisation development plan.

Table 13-9 Important identified risk: Malignant melanoma

Evidence for linking the risk to the medicine	Routine risk communication:

	SmPC Section 4.8 (Undesirable effects). PL Section 4 (possible side effects).
Risk factors and risk groups	Patients with advanced age, prior prolonged immunosuppressive medication, and exposure to UV radiation.
Risk minimization measures	**Routine risk minimization measures recommending specific clinical measures to address the risk:** SmPC Section 4.3 contraindicates use of Siponimod in patients with active malignancies. SmPC Section 4.4 includes the following recommendations: • Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with siponimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. • PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription.
Additional pharmacovigilance activities	None

Table 13-10 Important potential risk: Potential long-term safety implications in CYP2C9 poor metabolisers

Evidence for linking the risk to the medicine	An exploratory PK/PG analysis in the first-in-human study indicated that heterozygous CYP2C9*3 carriers tend to have a higher AUC of Mayzent compared to subjects not carrying the *3 allele. Consequently, the PK of Mayzent was assessed in CYP2C9 extensive and poor metabolizers (CYP2C9*1*1 genotype and CYP2C9*2*3 or *3*3 genotypes, respectively) in [Study A2128]. In addition, two PopPK analyses on Phase I/II and Phase III data identified CYP2C9 as a significant predictor of Mayzent systemic clearance. In clinical DDI studies, a 2-fold higher and a 2-fold lower Mayzent exposure was observed when co-administered with fluconazole (a moderate CYP2C9/CYP3A4 inhibitor) and with rifampin (a moderate CYP2C9/strong CYP3A4 inducer), respectively. Complementary PBPK modeling indicated that with decreased CYP2C9 metabolic activity in

	the respective genotypes, a stronger effect of the CYP3A4 perpetrators on Mayzent exposure is anticipated, especially for inhibitors. Under the proposed genotype-based dosing recommendations, Mayzent exposure is predicted to increase by 1.05-1.71-fold across genotypes in presence of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole), moderate CYP3A4 inhibitors (e.g. erythromycin), or weak CYP3A4/2C9 inhibitors (e.g. fluvoxamine) when compared to CYP2C9*1*1 subjects receiving a 2 mg qd maintenance dose without co-administration of any CYP2C9/CYP3A4 perpetrator drug. In presence of moderate CYP2C9 /CYP3A4 inhibitors (e.g. fluconazole), Mayzent exposure is expected to be 1.78-2.15-fold higher in all genotypes except CYP2C9*2*2. A larger increase of 2.73-fold is predicted for the CYP2C9*2*2 patients. Strong CYP3A4/moderate CYP2C9 inducers (e.g., rifampin, carbamazepine) are predicted to reduce Mayzent exposure by approximately 61% to 76%. Moderate CYP3A4 inducers (e.g. modafinil) are predicted to reduce Mayzent exposure by approximately 19% to 51%.
Risk factors and risk groups	Patients with CYP2C9*3*3 genotype.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 included following recommendations: • Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their metaboliser status. • Siponimod should not be used in patients with a CYP2C9*3*3 genotype. • A maintenance dose of 1 mg daily is recommended in patients with a CYP2C9*2*3 or *1*3 genotypes. SmPC Section 4.3 included the following recommendation: • Use of siponimod is contraindicated in patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metabolizer) SmPC Section 4.4 included following recommendations: • Before initiation of treatment with siponimod, patients must be genotyped for CYP2C9 to determine their metaboliser status. • Patients homozygous for CYP2C9*3 (CYP2C9*3*3) should not be treated with siponimod, use in these patients results in substantially elevated siponimod plasma levels. • A maintenance dose of 1 mg daily is recommended in patients with a CYP2C9*2*3 or *1*3 genotypes to avoid increased exposure to siponimod. SmPC Section 4.5 included following recommendations: • Because of a significant increase in exposure to siponimod, concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a

	moderate CYP2C9/CYP3A4 dual inhibitor (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor. • Due to an expected reduction in siponimod exposure, caution should be applied when siponimod is combined o with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients regardless of genotype. o with moderate CYP3A4 inducers (e.g. modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype. **Pack size:** • Pack of 120 film-coated tablets of 0.25 mg dose: This pack is for the use in patients with a CYP2C9*1*3 or *2*3 genotypes, the recommended maintenance dose for these populations is 1 mg siponimod daily (4 tablets of 0.25 mg). • Pack of 28 (or 98 in some countries) film-coated tablets of 1 mg dose: This pack is for the use in patients with a CYP2C9*1*3 or *2*3 genotypes, the recommended maintenance dose for these populations is 1 mg siponimod daily (1 tablet of 1 mg). **Legal status:** Restricted medical prescription. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers - Physician's Checklist to consider prior to prescribing Mayzent. - Patient/Caregiver Guide.
Additional pharmacovigilance activities	None.

Table 13-11 Important potential risk: Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)

Evidence for linking the risk to the medicine	In the Phase III study, decrease in lymphocyte count observed in patients in the Mayzent 2 mg group is seen early after commencing treatment and is maintained as long as the patient continues Mayzent therapy. The relationships between infections and drug concentration/lymphocyte count in SPMS population, including covariates of infection rate and/or its relationship with treatment were explored in a population pharmacokinetic/pharmacodynamic analysis [CBAF312A Phase III PopPKPD]. There was no increase in the number of infections following Mayzent treatment compared to placebo, or with increasing average Mayzent steady-state concentration and decreasing average steady-state lymphocyte count. There did not appear to be a change in infection rate with corticosteroid use.

	Herpes viral infections (other than VZV re-activation) based on the risk term were reported similarly for patients in the Mayzent 2 mg group [26 (2.3%)] and the placebo group [14 (2.3%)]. Cases of herpes viral infections and opportunistic infections (includes cryptococcal infections and PML) were observed while on treatment with other S1P modulator (Fingolimod). In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. Cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) are at an increased risk of VZV infections. The patients with negative VZ virus-IgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in *case* of an MS relapse.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3 includes following contraindications: Patients with history of Immunodeficiency syndrome, progressive multifocal leukoencephalopathy or cryptococcal meningitis SmPC Section 4.4 included following recommendations: • Before initiating treatment, a recent complete blood count should be available. • Delay the Mayzent treatment in patients with active infection until resolution. • Vigilance for infection during Mayzent treatment and up to 3 to 4 weeks after treatment discontinuation. • Stop Mayzent treatment if patient develop serious infection. • Use effective diagnostic and therapeutic strategies for patients with symptoms of infection while on Mayzent therapy. • Exercise caution when Mayzent is concomitantly used with antineoplastic, immuno-modulatory or immunosuppressive therapies. • Avoid attenuated live vaccines while on Mayzent treatment and for 4 weeks after stopping the Mayzent treatment. • **Additional risk minimization measures:** Educational materials for HCPs and patients/care givers: - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide

Additional pharmacovigilance activities	None

Table 13-12 Important potential risk: Thromboembolic events

Evidence for linking the risk to the medicine	Current evidence is based on the clinical and post-marketing data from other S1P modulator (Fingolimod) where a causal relationship is not yet established.
Risk factors and risk groups	Elderly age and advanced disease with disability (immobility), preexisting cardiovascular disease including hypertension are risk factors for thromboembolic events. Since this is a potential risk, no attributable increase due to Mayzent has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3 includes following recommendations: - Use of Mayzent is contraindicated in patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure. SmPC Section 4.4- Due to the risk of serious cardiac rhythm disturbances or significant bradycardia, Mayzent should not be used in patients with uncontrolled hypertension during treatment initiation. SmPC Section 4.8- Hypertension as an ADR **Additional risk minimization measures**: None
Additional pharmacovigilance activities	None

Table 13-13 Important potential risk: Malignancies (excluding BCC, SCC and malignant melanoma)

Evidence for linking the risk to the medicine	Non-clinical data:
	• At therapeutic doses, Mayzent has no generalized immunosuppressive properties as it neither impairs in vitro T- or B-cell activation or proliferation, cytokine or antibody production nor does it alter the capacity to mount an immune response to neo-antigens or pathogens in vivo.
	• Mayzent is non-genotoxic
	• The 2 years carcinogenicity studies in rodents identified:
	  • hemangiosarcoma in mice, with unlikely human relevance
	  • Thyroid tumors in rats, with no human relevance
	  • Lymphosarcoma in mice, with unknown human relevance

Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) are at increased risk for malignancies. Since this is a potential risk, no attributable increase due to Mayzent has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3 contraindicates use of Mayzent in patients with active malignancies. SmPC Section 4.4 includes the following recommendations: Skin examination is recommended for all patients at initiation, and then every 6 to12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be advised to promptly report any suspicious skin lesions to their physician. Patients treated with Mayzent should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. PL Section 2 includes recommendation to monitor the symptoms of skin malignancies and to consult the physician in case changes are observed, and also recommends to limit the exposure to sun and UV rays. **Additional risk minimization measures:** Educational materials for HCPs and patients/care givers: - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide
Additional pharmacovigilance activities	None

Table 13-14 Important potential risk: Reproductive toxicity

Evidence for linking the risk to the medicine	Reproductive and developmental studies in pregnant rats and rabbits have demonstrated Mayzent-induced embryotoxicity and fetotoxicity in both species and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat/F1 generation pups and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to Mayzent starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day. The safety margin is < 1-fold.
Risk factors and risk groups	Females of childbearing potential not using an effective form of contraception.
Risk minimization measures	**Routine risk minimization measures**

	SmPC Section 4.3 contraindicates the use of Mayzent during pregnancy and in women of childbearing potential not using effective contraception. SmPC Section 4.4 includes following recommendation: • Due to risk for the foetus, Mayzent is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for at least 10 days after discontinuation. SmPC Section 4.6 and PL Section 2 includes effective contraception recommendations. Need for negative pregnancy test prior to Mayzent treatment initiation. When stopping Mayzent therapy for planning a pregnancy the possible return of disease activity should be considered. SmPC Section 4.6 and PL Section 2 includes recommendation not to breast-feed while on Mayzent treatment. **Additional risk minimization measures:** Educational materials for HCPs and patients/care givers - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide card - Pregnancy Reminder Card for women of childbearing potential
Additional pharmacovigilance activities	CBAF312A2411 PRegnancy outcomes Intensive Monitoring (PRIM).

Table 13-15 Important potential risk: Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses)

Evidence for linking the risk to the medicine	Cases of PRES have been reported in the clinical trials and in the post-marketing setting of fingolimod (included as ADR in fingolimod SmPC). In the clinical studies ADEM like rare events occurred in patients treated with fingolimod at higher dose (1.25 mg or 5mg).
Risk factors and risk groups	Since this is a potential risk, no attributable increase to Mayzent has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.4 includes recommendation that physician should promptly schedule complete physical and neurological examination and should consider magnetic resonance imaging when patient on Mayzent develops any unexpected neurological symptoms/signs or accelerated neurological deterioration. PL Section 2 includes recommendation on monitoring of symptoms and report immediately to physician.

	Additional risk minimization measures: Educational material for HCPs and patients/care givers. - Physician's Checklist to consider prior to prescribing Mayzent - Patient/Caregiver Guide.
Additional pharmacovigilance activities	None

13.2.3 Part VI: II.C: Post-authorization development plan

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

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

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

Table 13-16 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CBAF312A2411 Pregnancy outcomes Intensive Monitoring (PRIM)	The overall objective of the Mayzent Pregnancy Outcome Intensive Monitoring program is to prospectively collect and evaluate safety data on pregnancy outcomes and congenital malformations related to Mayzent exposure immediately before (up to 10 days before last menstrual period [LMP]) and during pregnancy
CBAF312A2006 HCP and patient/caregivers survey	The objective of this survey, amongst HCPs and patients/caregivers in selected European countries, is to evaluate whether HCPs and patients/caregivers receive the educational materials and to capture their knowledge and behavior around specific Mayzent safety measures

14 Part VII: Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study program

Table 14-1 Planned and ongoing studies

Study	Summary of objectives	Safety concerns addressed	Milestones
CBAF312A2411 PRegnancy outcomes Intensive Monitoring (PRIM) Category 3 PASS	The overall objective of the siponimod PRIM program is to prospectively collect and evaluate safety data on pregnancy outcomes and congenital malformations related to siponimod exposure immediately before (up to 10 days before last menstrual period [LMP]) and during pregnancy.	Reproductive toxicity	Periodic update: Each PSUR Final report: PSUR 2030
CBAF312A2006 Healthcare professionals and patient/caregivers survey. Category 3 PASS	The objective of this survey is to measure whether healthcare professionals (HCPs) and patients/caregivers in selected European countries, is to evaluate whether HCPs and patients/caregivers receive the educational materials and to capture their knowledge and behavior around specific Mayzent	To measure the effectiveness of HCP educational material	Final report: 31Dec2025

Study	Summary of objectives	Safety concerns addressed	Milestones
	(siponimod) safety measures.		

Table 14-2 Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
CBAF312A2304 EXPAND A multi-center, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312 Category 3 PASS	To evaluate the long-term safety and tolerability of siponimod	• Varicella-zoster virus (VZV) infection reactivation • Cryptococcal meningitis • Bradyarrhythmia (including conduction defects) during treatment initiation • Macular edema • Basal cell carcinoma (BCC) • Squamous cell carcinoma (SCC) • Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML) • Cryptococcal meningitis • Potential long-term safety implications in CYP2C9 poor metabolizers • Malignancies (excluding BCC, SCC and malignant melanoma) • Thromboembolic events • Unexpected neurological or psychiatric symptoms/signs (e.g;	Periodic update: Each PSUR Final report: 30-Jan-2024

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
		PRES, ADEM, Atypical MS Relapses) Long-term safety risks	

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

Table 14-3 Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority

Study number, Study name (version number)	Procedure number in which protocol was approved
Category 1 and 2 studies in PV plan that were approved	
None	
Category 3 studies in PV plan that were not requested to be reviewed	
None	
Category 3 studies in PV plan that were requested to be reviewed	
[CBAF312A2411] PRegnancy outcomes Intensive Monitoring (PRIM)	Approved (MEA 002)
[CBAF312A2006] HCP and patient/caregivers survey	Approved (MEA 004)

Annex 4 - Specific adverse drug reaction follow-up forms

This annex contains the specific adverse event targeted follow-up checklists used to collect additional data for the following siponimod RMP risks:

Targeted follow-up checklists:

Important identified risk: Cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML), AND Important potential risk: Reactivation of chronic viral infections (other than VZV) and opportunistic infections, other than cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML)

Siponimod Opportunistic Infections Checklist

(Version 1.0, Dated: Aug-2018)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.	
Part I	
Event Description: Summary of clinical course Approximate onset date of symptoms that led to the diagnosis: _____ What were the initial presenting symptoms/signs? _____	
Diagnosis *(Please include corresponding event onset dates)*	
Is the event a newly identified/ new onset infection	☐ Yes ☐ No ☐ Unknown
Is the infection recurrent	☐ Yes ☐ No ☐ Unknown
Is the infection an exacerbation of previous infection	☐ Yes ☐ No ☐ Unknown
Is the infection chronic	☐ Yes ☐ No ☐ Unknown
Is the infection considered to be “opportunistic’	☐ Yes ☐ No ☐ Unknown
Agent/ microorganism	
Is the infection caused by a Gram-positive bacterium	☐ Yes ☐ No ☐ Unknown

Is the infection caused by a Gram-negative bacterium	☐ Yes ☐ No ☐ Unknown
Is the infection :	
☐ a Mycobacterial infection	☐ Yes ☐ No ☐ Unknown
☐ a Pseudomonas aeruginosa	☐ Yes ☐ No ☐ Unknown
☐ a Polyomavirus infection	☐ Yes ☐ No ☐ Unknown
☐ a Cytomegalovirus infection	☐ Yes ☐ No ☐ Unknown
☐ a Toxoplasma infection	☐ Yes ☐ No ☐ Unknown
☐ a systemic fungal infection (e.g. Aspergillus or Pneumocystis infection) *(If Yes Please Complete Part II of the checklist)*	☐ Yes ☐ No ☐ Unknown
☐ None of the above *(Please specify):*_____	

Treatment *(Please specify the treatment received)*_____

Did the patient receive intravenous treatment for infection Yes ☐ No ☐ Unknown ☐

Did the clinical course of infection require change of treatment Yes ☐ No ☐ Unknown ☐

Did the treatment require strength and/or frequency change Yes ☐ No ☐ Unknown ☐

Event Outcome

☐Complete recovery ☐Recovered with sequelae ☐Condition improving

☐Condition unchanged ☐Condition deteriorating ☐Fatal ☐Unknown

Action taken with Siponimod: ☐Discontinued ☐Continued ☐Unknown

Diagnostic tests ***(****Please check all that apply and specify reference range if applicable)*

Test	Baseline levels (at Siponimod start)				Current levels (at onset of infection)			
	Date	Result (Reference range)	Unit		Date	Result (Reference range)	Unit	
Absolute neutrophil count				☐ Unknown				☐ Unknown

Absolute lymphocyte count				☐ Unknown				☐ Unknown
Absolute white blood cell count				☐ Unknown				☐ Unknown

Were any of the following diagnostic tests performed? (*Please check all that apply and describe)*

☐ Culture of blood, urine, cerebrospinal, peritoneal or pleural fluids

☐ Imaging studies (e.g. MRI, CAT or CT)

☐ Bone marrow examination

☐ Specialized serologic tests

☐ None of the above

Results: _____

Relevant medical history (concurrent and pre-existing conditions) *(Please specify medical condition and date of onset)*

☐ Recurrent infections or chronic infections	☐ Chronic disease (e.g. diabetes, cancer Kaposi's sarcoma)
☐ Poor nutritional status (e.g. BMI < 21)	☐ Corticosteroid use
☐ Poor social status	☐ Long-term use of antibiotics
☐ Traveling or contact with contagious agent	☐ Any biologics used
☐ Invasive device (e.g. dialysis, catheter, feeding tube)	☐ Malignancies (Leukemia/Lymphoma/Myeloproliferative disorders)
☐ Surgical procedure	☐ Any chemotherapy or radiation therapy
☐ Trauma with open wound or burns	☐ Other relevant history (please specify)
☐ Weakened immune system (e.g. HIV/AIDS)	☐ Sarcoidosis
☐ Close contact with birds	☐ Recent travel to endemic disease areas or contact with contagious agent
☐ Other disturbances of the immune system (e.g. history of low CD4/CD8 ratio)	☐ Contact with eucalyptus trees

☐ None of the above	

How long has the patient had Multiple Sclerosis (years/months or specific date of diagnosis) _____

List all MS treatments and duration:

Drug	**Dose**	**Start and stop dates of therapy**

List all concomitant or prior immunosuppressive therapies (e.g., monoclonal antibodies, cancer chemotherapy or cytoreductive treatments, corticosteroids, radiation therapy):

Drug/Intervention	**Dose**	**Start and Stop dates of therapy**

<u>Part II: Please provide the following information if the reported event is Cryptococcal Meningitis</u>

Approximate onset date of symptoms that led to the diagnosis_____

What were the initial presenting symptom(s)?

☐ Subacute Headache ☐ Nausea/Vomiting ☐ None of the above

☐ Confusion ☐ Seizure(s) ☐ Others (*please specify*)____

☐ Lethargy ☐ Cranial nerve palsies

☐ Coma ☐ Papilledema

☐ Fever ☐ Neck stiffness

CBC (specifically absolute lymphocyte counts):

Test	Date	Result (please provide units)

Please indicate Cryptococcus diagnostic testing:

CSF Cryptococcus antigen test ☐ Positive (titer) ☐ Negative ☐ Not done

Serum Cryptococcus antigen test ☐ Positive (titer) ☐ Negative ☐ Not done

India ink microscopy ☐ Positive ☐ Negative ☐ Not done

Fungal culture results:_____

Anti-Cryptococcal Treatment:

Drug	Dose	Start and stop dates of therapy

Suspected Progressive Multifocal Leukoencephalopathy (PML)

(Version 5.1, Dated: Nov-2024)

Please provide the following information in addition to routine information request forms.

Did the patient present with any of the following signs or symptoms? Check all that apply.

☐ Hemiparesis ☐ Cognitive impairment ☐ Weakness ☐ Headaches
☐ Hemianopia ☐ Personality changes ☐ Aphasia ☐ None of the above
☐ Brainstem deficits ☐ Dysarthria ☐ Visual impairment ☐ Others (*please specify*)
☐ Clumsiness/ Cerebellar deficits ☐ Sensory deficits ☐ Fever_____

Was brain MRI/MRA performed? ☐ **Yes** *(provide recent and prior reports and/or summarize below)*

☐ **No** ☐ **Unknown**

Date/Results:_____

_____

_____

CSF JCV analysis ☐ **Yes** *(provide results below)* ☐ **No** ☐ **Unknown**

Type of test (PCR, JCV antibody)	Test date	Result

Please include results of other relevant tests

Type of test	Test date	Result
JCV (serum or urine)		
Anti JCV antibody index		
WBC		
Brain biopsy		
Other		

Absolute lymphocyte counts (please provide up to 12 months prior to PML onset)

Date	Absolute lymphocyte count	Date	Absolute lymphocyte count

PML-IRIS

Did this patient receive a diagnosis of IRIS (Immune Reconstitution Inflammatory Syndrome)?

☐ Yes - onset date (DD/MMM/YYYY) ☐ No ☐ Unknown

What is the outcome of the patient's PML-IRIS?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Fatal ☐ Unknown

Provide the date of the assessed outcome of PML-IRIS (DD/MMM/YYYY):

Patient History:

Does the patient have a history of any immunosuppressive disorders prior to the start of the suspect drug (eg, HIV infection; malignancy, e.g., leukemia, lymphoma, myeloproliferative diseases; sarcoidosis; other disturbances of the immune system, e.g., history of low CD4/CD8 ratio; other)?

☐ Yes *(summarize below)* ☐ No ☐ Unknown

Immune disorder	Date of onset	Status (active, inactive)	Other details

List prior MS therapies:

Drug	Dose	Start date	Stop date

Has the patient taken any of the following medications in the past or currently? Check all that apply and include dates of starting and completing and indication the medication in the space below.

☐ Chemotherapy/ Cytoreductive therapy *please specify*

☐ Corticosteroids *specify dose and duration*

☐ Other immunosuppressant drugs *please specify*

☐ Radiation therapy

☐ None of the above

Additional details:

_____

_____

_____

Important potential Risk: MS Product and Unexpected neurological signs/symptoms (includes, PRES, ADEM, Atypical/Severe MS relapse)

MS Product & Unexpected Neurological Signs/Symptoms (includes, PRES, ADEM, Atypical/Severe MS relapse) Checklist

(Version 2.0, Dated: Feb-2021)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Final diagnosis (*provide date of diagnosis*):_____

Event Description: _____

Adverse event reported *(please also provide onset date):*

Sign(s) and symptom(s) of the adverse event:

Motor system	☐ spasticity ☐ paresis/plegia ☐ others:___	Sensory system	☐ Numbness ☐ Headache ☐ others:___	Visual system:	☐ vision loss/blindness ☐ reduced color vision ☐ Vision blurred ☐ Homonymous hemianopsia
Cognitive system	☐ confusion ☐ language impaired ☐ memory loss ☐ Coma ☐ others:___	Brainstem system	☐ slurred speech ☐ nystagmus ☐ trouble swallowing ☐ others:___	Cerebellar system	☐ ataxia ☐ poor coordination ☐ slurred speech ☐ others:___
Bowel/bladder	☐ incontinence ☐ retention ☐ impotence ☐ others:_____				

☐ Seizure, please specify type of seizure _____

☐ Meningismus

☐ Fever

Treatment details: _____

Workup for the event

Imaging investigations (*please provide summary of results and copy of the results, including date)**:**

MRI(s):	☐ Yes	☐ No	☐ Unknown
CT scan:	☐ Yes	☐ No	☐ Unknown

Others (please specify): _____

Findings:

Laboratory investigations *(please provide summary of results and copy of the results, including date and reference ranges)***:**

Blood analysis: ☐ Yes ☐ No ☐ Unknown

CSF analysis: ☐ Yes ☐ No ☐ Unknown

Others (please specify):_____

Findings:

EEG(s) *(please provide summary of results and copy of the results, including date)*:

☐ Yes ☐ No ☐ Unknown

Findings: _____

Brain biopsy *(please provide summary of results and copy of the results, including date)*:

☐ Yes ☐ No ☐ Unknown

Findings: _____

Expanded Disability status scale (EDSS) score during event onset: _____

Additional investigations if available (please provide reports and dates):

_____

Do any of the following apply?

☐ Treatment discontinued *(provide date)*

☐ Treatment interrupted *(provide date(s))*

☐ No change

Please specify the treatment given for the reported events:

_____

What was the outcome of the event *(provide date)***:**

☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Fatal
☐ Unknown

Relevant medical history (concurrent and pre-existing conditions):

(Please specify medical condition and date of onset)

First MS symptoms (describe symptoms and dates): _____

Previous disease modifying treatment(s) before starting treatment *(please provide start and stop dates: circle last drug taken)*:

Interferon beta-1a: ☐ Glatiramer acetate: ☐

Interferon beta-1b: ☐ Mitoxantrone: ☐

Natalizumab: ☐ Others (please specify): ☐

Treatment details: _____

Prior to start of first disease modifying treatment for MS

Expanded Disease disability scale (EDSS) score:_____

MRI results:_____

Prior to start of treatment (Gilenya/Mayzent/Kesimpta)

Expanded Disability status scale (EDSS) score:_____

MRI results:_____

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimization activities

Key safety messages of additional risk minimization measures

Physician education pack:

- The Summary of Product Characteristics
- Physician's Checklist to consider prior to prescribing Mayzent
- Patient/Caregiver Guide
- Pregnancy Reminder Card for women of childbearing potential

Physician's Checklist:

Potential long-term safety implications in CYP2C9 poor metaboliser:

- Perform genotyping for CYP2C9 before treatment initiation to determine the Siponimod maintenance dose. Test requires a DNA sample obtained via blood or saliva (buccal swab). The test identifies two variant alleles for CYP2C9: CYP2C9*2 (rs1799853, c.430C>T) and CYP2C9*3 (rs1057910, c.1075A>C). Both are single nucleotide polymorphisms. This genotyping can be done using a Sanger sequencing method or PCR based assay methods. For further clarifications please refer to your local laboratory.
- Do not prescribe siponimod in patients homozygous for CYP2C9*3*3.
- Adjust the maintenance dose to 1 mg in patients with CYP2C9*2*3 or *1*3 genotypes.

Bradyarrhythmia (including conduction defects) during treatment initiation:

- Initiate treatment with a titration pack that lasts for 5 days. Start treatment with 0.25 mg on day 1, up titrated to the maintenance dose of 2 mg or 1 mg on day 6 based on the CYP2C9 metaboliser status.
- If a titration dose is missed on one day during the first 6 days of treatment, treatment must be re-initiated with a new titration pack.
- If the maintenance dose is interrupted for 4 or more consecutive daily doses, treatment must be re-initiated with a new titration pack.
- Monitoring requirements at treatment initiation:
    - Prior to initiating treatment:
        - Perform vitals and baseline ECG prior to the first dose of siponimod in patients with sinus bradycardia (heart rate [HR] <55 bpm), history of first- or second-

degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure (patients with NYHA class I and II).

- Until 6 hours after first dose:
  - Observe patients with sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (patients with NYHA class I and II) for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia and obtain an ECG at the end of the 6-hour monitoring period.
  - If necessary, the decrease in heart rate induced by siponimod can be reversed by parenteral doses of atropine or isoprenaline
- Extended observation (>6 hours after first dose):
  - If, at the 6-hour time point, the heart rate is at the lowest value following the first dose, extend heart rate monitoring for at least 2 more hours and until the heart rate increases again.
  - Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients requiring pharmacological intervention during monitoring at treatment initiation/re-initiation. Repeat the first dose monitoring after the second dose of siponimod.
  - Appropriate management should be initiated and observation continued until the symptoms/findings have resolved, if the following events are observed:
    - New onset third degree AV block occurring at any time
    - Where at the 6-hour time point the ECG shows: New onset second degree or higher AV block, or QTc interval ≥ 500 msec

  If pharmacological treatment is required, monitoring should be continued overnight and 6-hour monitoring should be repeated after the second dose.
- Mayzent is contraindicated in:
  - Patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring in-patient treatment), or New York Heart Association (NYHA) class III/IV heart failure.
  - Patients with a history of second degree Mobitz type II atrioventricular (AV) block, third degree AV block, sino-atrial heart block or sick sinus syndrome, if they do not wear a pacemaker.

- Mayzent is not recommended in:
  - Patients with the below conditions. Siponimod treatment should be considered in these patients only if the anticipated benefits outweigh the potential risks and a cardiologist must be consulted to determine appropriate monitoring. At least overnight extended monitoring is recommended.
    - QTc prolongation >500 msec
    - Severe untreated sleep apnoea
    - History of symptomatic bradycardia
    - History of recurrent syncope
    - Uncontrolled hypertension
    - Concomitant treatment with class Ia (e.g. quinidine, procainamide) or class III anti-arrhythmic medications, calcium channel blockers (such as verapamil, diltiazem) and other medications (e.g. ivabradine or digoxin) which are known to decrease the heart rate

Infections, including varicella zoster reactivation, reactivation of the other viral infections, PML and other rare opportunistic infections:

- There is an increased risk of infections including serious infections, in patients treated with siponimod.
- Before initiating treatment, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended 3 to 4 months after treatment initiation and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte counts $<0.2 \times 10^9$/l, if confirmed, should lead to dose reduction to 1 mg, because in clinical studies siponimod dose was reduced in patients with absolute lymphocyte counts $<0.2 \times 10^9$/l. Confirmed absolute lymphocyte counts $<0.2 \times 10^9$/l in a patient already receiving siponimod 1 mg should lead to interruption of siponimod therapy until the level reaches 0.6×10^9/l when re-initiation of siponimod can be considered.
- Before starting siponimod, test for antibodies to varicella zoster virus (VZV) in patients without a physician-confirmed history of varicella or without documentation of a full course of vaccination against VZV. If tested negative, vaccination is recommended and treatment with siponimod should be postponed for 1 month to allow the full effect of vaccination to occur.
- Siponimod is contraindicated in patients with immunodeficiency syndrome.

- Siponimod is contraindicated in patients with history of progressive multifocal leukoencephalopathy or cryptococcal meningitis.
- Do not initiate siponimod treatment in patients with severe active infection until infection is resolved.
- Exercise caution when administering concomitant treatment with anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) due to the risk of additive immune system effects.
- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to one month after treatment with siponimod.
- Monitor patients carefully for signs and symptoms of infections during and after treatment with siponimod:
    - Prompt diagnostic evaluation should be performed in patients with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis; siponimod treatment should be suspended until exclusion; appropriate treatment of infection, if diagnosed, should be initiated.
    - Cases of herpes viral infection (including cases of meningitis or meningoencephalitis caused by varicella zoster viruses) have occurred with siponimod at any time during treatment.
    - Cases of cryptococcal meningitis (CM) have been reported for siponimod.
    - Cases of progressive multifocal leukoencephalopathy (PML) have been reported for S1P receptor modulators, including siponimod, and other therapies for MS. Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment should be suspended until PML has been excluded. If PML is confirmed, treatment with siponimod should be discontinued.
    - Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors modulators, including siponimod, who developed PML and subsequently discontinued treatment. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

Macular oedema:

- Arrange an ophthalmological evaluation prior to initiating therapy and follow-up evaluations while receiving therapy in patients with a history of diabetes mellitus, uveitis or underlying/co-existing retinal disease.
- An ophthalmological evaluation 3-4 months after treatment initiation with siponimod is recommended.
- Instruct the patient to report visual disturbances at any time while on siponimod therapy.
- Do not initiate siponimod treatment in patients with macular oedema until resolution.

Reproductive toxicity:

- Siponimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Advise women of potential serious risks to the foetus if siponimod is used during pregnancy or if the patient becomes pregnant while taking it.
- A negative pregnancy test result is required prior to initiation of treatment in women of childbearing potential and must be repeated at suitable intervals.
- Women of childbearing potential should be counselled before treatment initiation and regularly thereafter about the serious risks of siponimod to the foetus, facilitated by the pregnancy-specific patient reminder card.
- Women of childbearing potential must use effective contraception during treatment and for at least 10 days following discontinuation of treatment with siponimod.
- Siponimod should be stopped at least 10 days before a pregnancy is planned. When stopping siponimod for planning a pregnancy the possible return of disease activity should be considered.
- Counsel the patient in case of inadvertent pregnancy.
- If a woman becomes pregnant while on treatment with siponimod, treatment must be discontinued. Pregnant women should be advised of potential serious risks to the foetus, and ultrasonography examinations should be performed.
- Should a pregnancy occur during treatment or within 10 days following discontinuation of treatment with siponimod, please report it to Novartis by calling [insert local number] or visiting [insert URL], irrespective of adverse outcomes observed.
- Novartis has put in place a PRegnancy outcomes Intensive Monitoring (PRIM) programme, which is a registry based on enhanced follow-up mechanisms to collect information about

pregnancy in patients exposed to siponimod immediately before or during pregnancy and on infant outcomes 12 months post-delivery.

Other reminders:

- Perform liver function tests prior to initiating siponimod treatment. If patients develop symptoms suggestive of hepatic dysfunction during treatment with siponimod, request a liver enzymes check. Discontinue treatment if significant liver injury is confirmed. Siponimod is contraindicated in patients with severe liver impairment (Child-Pugh class C).
- Be vigilant for skin malignancies while on treatment with siponimod. Perform skin examination prior to treatment initiation and then every 6 to 12 months taking into consideration clinical judgement. Careful skin examinations should be maintained with longer treatment duration. Patients should be referred to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UVB radiation or PUVA photochemotherapy. Siponimod is contraindicated in patients with active malignancies.
- Should a patient develop any unexpected neurological or psychiatric symptoms/signs or accelerated neurological deterioration, a complete physical and neurological examination should promptly be scheduled and MRI should be considered.
- Caution should be exercised in elderly patients with multiple co-morbidities, or advanced disease/disability (due to possible increased risks of, for example, infections, bradyarrhythmic events during treatment initiation).
- If siponimod is discontinued, the possibility of recurrence of high disease activity should be considered.
- Provide patients with the Patient/Caregiver Guide and Pregnancy Reminder Card for women of childbearing potential.
- Be familiar with the Mayzent Prescribing Information.

Patient/Caregiver Guide:

- What Mayzent is and how it works.
- What multiple sclerosis is.
- Patients should read the package leaflet thoroughly before starting treatment and should keep the package leaflet in case they need to refer to it again during treatment
- The importance of reporting adverse reactions.

- Before starting treatment, a DNA sample via blood or saliva (buccal swab) is taken to determine the CYP2C9 genotype to help determine appropriate dosing of siponimod. In certain cases, the patient may not receive treatment with siponimod due to specific CYP2C9 genotype status.
- Patients need to have chickenpox vaccination 1 month before starting siponimod treatment, if the patient is not protected against the virus.
- Siponimod is not recommended in patients with cardiac disease or taking concomitant medicines known to decrease heart rate. Patients should tell any doctor they see that they are being treated with siponimod.
- For patients with certain heart problems, an ECG before initiating treatment with siponimod will be needed. The need for observation (including an ECG monitoring) for 6 hours in a clinic after the first dose of siponimod on day 1, if the patient has heart problems. Information that the monitoring may need to extend overnight, if the patient experiences symptoms during the first 6 hours.
- Patients should report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations) after the first dose of siponimod and during the titration period.
- Before starting treatment patients should provide a recent complete blood count (CBC). Assessments of CBC are also recommended 3 to 4 months after treatment initiation and at least yearly thereafter, and in case of signs of infection.
- The signs and symptoms of infection during, and up to one month after treatment with siponimod need to be reported immediately to the prescriber, including the following:
    - Headache accompanied by stiff neck, sensitivity to light, fever, flu-like symptoms, nausea, rash, shingles and/or confusion or seizures (fits) (may be symptoms of meningitis and/or encephalitis, caused by either a fungal or viral infection).
    - If you believe your MS is getting worse or if you notice any new symptoms during and after treatment with Mayzent, for example changes in mood or behaviour, new or worsening weakness on one side of the body, changes in vision, confusion, memory lapses or speech and communication difficulties. These may be symptoms of PML or of an inflammatory reaction (known as immune reconstitution inflammatory syndrome or IRIS) that can occur in patients with PML as Mayzent is removed from their body after they stop taking it.
- Patients should report any symptoms of visual impairment immediately to the prescriber during and for up to one month after the end of treatment with siponimod.

- Patients should call the doctor if a dose is missed during the first 6 days of treatment or for 4 or more consecutive days after initiating treatment with siponimod. Treatment needs to be reinitiated with a new titration pack.
- Liver function tests should be performed before starting treatment and repeated if there are symptoms suggestive of hepatic dysfunction.
- Patients should report any unexpected neurological or psychiatric symptoms/signs (such as sudden onset of severe headache, confusion, seizures and vision changes) or accelerated neurological deterioration to their doctors.
- Due to the potential teratogenic risk of siponimod women of childbearing potential should:
    - Be informed before treatment initiation and regularly thereafter by their physician about siponimod serious risks to the foetus, and about the contraindication in pregnant women and in women of childbearing potential not using effective contraception, facilitated by the Pregnancy Reminder Card.
    - Have a negative pregnancy test before starting siponimod, which should be repeated at suitable intervals.
    - Be using effective contraception during treatment and for at least 10 days after stopping treatment to avoid pregnancy due to the potential risk of harm to the unborn baby.
    - Report immediately to the prescribing physician any (intended or unintended) pregnancy, during treatment and up to 10 days following discontinuation of siponimod, treatment.
- Patients should be informed about the risk of skin malignancies and the need for skin examinations at the start of the treatment and thereafter while on treatment with siponimod. Patients should be cautioned against exposure to sunlight without protection. Also, patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy. Patients should inform their doctor immediately if they notice any skin nodules (e.g., shiny, pearly nodules), patches or open sores that do not heal within weeks. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in colour, shape or size over time.
- After stopping treatment with Mayzent, patients should inform their doctor immediately if their disease symptoms are getting worse (e.g. weakness or visual changes) or if they notice any new symptoms.
- Contact details of the siponimod prescriber.

Pregnancy Reminder Card for women of childbearing potential

- Siponimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
- Doctors will provide counselling before treatment initiation and regularly thereafter regarding the potential teratogenic risk of siponimod and required actions to minimize this risk.
- Patients will be informed by their doctor of the need for effective contraception while on treatment and for 10 days after discontinuation.
- A pregnancy test must be carried out and negative results verified by the doctor before starting treatment. It must be repeated at suitable intervals.
- Patients must use effective contraception during the treatment with siponimod.
- While on treatment, women must not become pregnant. If a woman becomes pregnant or wants to become pregnant, siponimod should be discontinued. Effective contraception should be maintained for at least 10 days following discontinuation of treatment with siponimod.
- Patients should Inform their doctor immediately if they think they are pregnant. Doctors will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy.
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with siponimod.
- Women exposed to siponimod during pregnancy are encouraged to join the pregnancy exposure programme (PRegnancy outcomes Intensive Monitoring, PRIM) that monitors outcomes of pregnancy.
- Should a pregnancy occur during treatment or within 10 days following discontinuation of treatment with siponimod, it should be immediately reported to the doctor or to Novartis by calling [insert local number] or visiting [insert URL], irrespective of adverse outcomes observed.

Annex 7 - Other supporting data (including referenced material)

Brief Statistical Description and Supportive Outputs

The [Brief Statistical Description portion and Supportive Outputs of Annex 7] is presented separately.

MedDRA Search terms for spontaneous post-marketing data

Not applicable.

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Only key references are provided. All other references are available upon request.

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BAF312 SCS

CBAF312A Phase III PopPKPD

Non-clinical overview

PSUR (dated (26-Mar-2023 - 25-Mar-2024)

Annex 8 – Summary of changes to the risk management plan over time

Table 14-4 Summary of changes to the risk management plan over time

Version	Approval date/ Procedure	Change
1.5	First approved RMP 13-Jan-2020 EMEA/H/C/004712/0000	**Safety concerns** Important identified risks • Varicella-zoster virus (VZV) infection reactivation • Cryptococcal meningitis • Bradyarrhythmia (including conduction defects) during treatment initiation • Macular edema Important potential risks • Potential long-term safety implications in CYP2C9 poor metabolisers • Reactivation of chronic viral infections (other than VZV), progressive multifocal leukoencephalopathy (PML) and opportunistic infections, other than cryptococcal meningitis • Thromboembolic events • Malignancies • Reproductive toxicity • Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses) Missing information • Safety in patients over 60 years old (including elderly) • Use during lactation • Long-term safety risks **Pharmacovigilance Plan** CBAF312A2304 (EXPAND) Phase III study extension part PRegnancy outcomes Intensive Monitoring (PRIM) HCPs survey (for assessment of effectiveness of risk minimization measures) **Post-authorization efficacy plan** None **Risk minimization measures** Physician education pack:

Version	Approval date/ Procedure	Change
		• The Summary of product characteristics • Physician's Checklist to consider prior to prescribing Mayzent • Patient/Caregiver Guide • Pregnancy reminder card for WOCBP (Women of childbearing potential) **Annex 4** • Siponimod Opportunistic infections checklist • Suspected PML checklist • Siponimod unexpected neurological signs and symptoms checklist
2.1	07-Jan-2021 EMEA/H/C/PSUSA/00010818/202003	**Safety concerns** Important identified risks • Basal cell carcinoma (BCC) Important potential risks • Malignancies (excluding BCC) **Pharmacovigilance Plan** Submission date of the final CSR of study CBAF312A2304 was updated **Risk minimization measures** Updated in alignment with SmPC changes. **Other changes:** PRIM study code added (CBAF312A2411)
3.1	16-Feb-2021 EMEA/H/C/004712/X/0007	The RMP has been updated to include 1 mg film-coated tablet strength and consequential minor updates along the document. The name "HCP Checklist" is revised to "Physician's Checklist to consider prior to prescribing Mayzent" in alignment with RMP Annex 6 and SmPC Annex IID, wherever applicable. **Safety concerns** None **Phamacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** None **Annex 4** None

Version	Approval date/ Procedure	Change
4.0	EMEA/H/C/PSUSA/00010818/202109	**Safety concerns** Important identified risks • Squamous cell carcinoma (SCC) Important potential risks • Malignancies (excluding BCC and SCC) **Phamacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** None
4.1	EMEA/H/C/PSUSA/00010818/202109	**Safety concerns** The RMP has been updated to include new cases of the important identified risks “Varicella zoster virus infection reactivation” and “Cryptococcal meningitis” and consequential updates along the document **Phamacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** Updated information for two safety concerns - “Varicella zoster virus infection reactivation” and “Cryptococcal meningitis” in alignment with the Product Information updates.
4.2	04-May-2022 EMEA/H/C/PSUSA/00010818/202109	**Safety concerns** Preventability information updated for safety concerns including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignancies excluding BCC and SCC. **Pharmacovigilance Plan** None **Post-authorization efficacy plan** None **Risk minimization measures** Updated for important identified risks (BCC and SCC) and important potential risk (malignancies excluding BCC and SSC), to align with SmPC and ensure consistency in terms of the amount of details provided.

Version	Approval date/ Procedure	Change
5.0	Withdrawn	**Safety concerns** Reproductive toxicity language revised **Pharmacovigilance Plan** Additional pharmacovigilance activities updated for the inclusion of Pregnancy Registry study. **Post-authorization efficacy plan** None **Risk minimization measures** Summary of pharmacovigilance activities updated.
6.1	06-Jul-2023 EMEA/H/C/004712/II/0020	**Safety concerns** Reclassified important potential risk of Progressive multifocal leukoencephalopathy (PML) to important identified risk. Renamed “Reactivation of chronic viral (other than VZV), progressive multifocal leukoencephalopathy (PML) and opportunistic infections, other than cryptococcal meningitis” risk to “Reactivation of chronic viral infections (other than VZV) and Opportunistic infections, other than Cryptococcal meningitis and Progressive multifocal leukoencephalopathy (PML)”. **Pharmacovigilance Plan** Routine pharmacovigilance activities updated to include PML checklist, and to reflect the renamed risk in the checklist **Post-authorization efficacy plan** None **Risk minimization measures** Routine risk minimization measures added for upgraded important identified risk PML. Updated education materials to HCP. PML guidance revised for confirmed cases.

Version	Approval date/ Procedure	Change
7.0	Not applicable/ EMEA/H/C/PSUSA/00010818/202403	**Safety concerns** None **Pharmacovigilance Plan** CBAF312A2411 Pregnancy outcomes Intensive Monitoring secondary objectives updated to be aligned with secondary objectives from the study protocol. **Post-authorization efficacy plan** None **Risk minimization measures** Routine risk minimization measures updated to include IRIS in the important identified risk PML. Updated HCP checklist and Patient/caregiver guide.
7.1	Not applicable (EMA/VR/0000273065)	**Safety concerns** Important identified risks • Addition of Malignant melanoma Important potential risks • Remove potential long-term safety implications in CYP2C9 poor metabolisers • Rename Malignancies (excluding BCC and SCC) to Malignancies (excluding BCC, SCC and malignant melanoma) **Missing Information** • Removal of “Safety in patients over 60 years old (including elderly),” “Use during lactation,” and “Long term safety” **Pharmacovigilance Plan** CBAF312A2304 EXPAND study removed from additional pharmacovigilance activities throughout the RMP and updated milestones related to completed Extension Part. **Post-authorization efficacy plan** None **Risk minimization measures** Physician's Checklist, Patient/caregiver Guide and Pregnancy reminder card updated

Version	Approval date/ Procedure	Change
7.2	To be updated (EMA/VR/0000273065)	**Safety concerns** Important potential risks: Reinstated the important potential risk ‘Potential long-term safety implications in CYP2C9 poor metabolisers’ **Pharmacovigilance Plan** None. **Post-authorization efficacy plan** None **Risk minimization measures** Reinstated the routine and additional risk minimization measures for the important potential risk ‘Potential long-term safety implications in CYP2C9 poor metabolisers’ **Annexes:** In Annex 6, the KSM addressing the important potential risk ‘Potential long-term safety implications in CYP2C9 poor metabolisers’ were reinstated

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