14 November 2019
EMA/CHMP/652767/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mayzent

International non-proprietary name: siponimod

Procedure No. EMEA/H/C/004712/0000

Note

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

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List of abbreviations

ACAT	Advanced compartment and transit
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ARR	annualized relapse rate
AST	Aspartate aminotransferase
AUC	Area under curve
AUCEC	Area under the effect curve
AV	Atrioventricular
AVB	Atrioventricular block
BAF312	Siponimod
BCS	Biopharmaceutics classification system
BP	Blood pressure
bpm	Beats per minute
CDP	confirmed disability progression
3m-CDP	3-months CDP
6m-CDP	6- months CDP
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hanster Ovary
CI	Confidence interval
CL/F	Apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPS	cognitive processing speed
CSF	Clinical service formulation
CTC	Common Terminology Criteria
CUAL	combined unique active lesion
CYP2C9	Cytochrome P450 enzyme 2C9 genotype
CYP3A4	Cytochrome P450 enzyme 3A4 genotype
DB	Double-blind (treatment period)
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DM	Dermatomyositis
DMT	Disease modifying therapy
DoE	Design of experiments
DSC	Differential scanning calorimetry
DRF	Dose range finding
ECG	Electrocardiogram
EFD	embryo-fetal development
EAE	Experimental autoimmune encephalomyelitis
EC	European Commission
EDSS	Expanded Disability Status Scale
ECG	Electrocardiogram

EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
T2-FLAIR	T2-weighted-Fluid-Attenuated Inversion Recovery
FMI	Final market image
FUS	Follow-up Set
GC	Gas chromatography
Gd	Gadolinium
GGT	Gamma-glutamyltransferase
GIRK	G protein coupled inwardly rectified potassium channel
GCP	Good Clinical practice
GLP	Good Laboratory practice
GMP	Good manufacturing practice
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HR	Heart rate
IA	Interim analysis
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IFNB	Interferon beta
IND	Investigational new drug
IPC	In-process control
IR	Incidence rate
IR	Infrared
iv	Intravenous
KF	Karl Fischer titration
KM	Kaplan-Meier
LC-MS/MS	liquid chromatography coupled with tandem mass spectrometry
LLOQ	lower limit of quantification
MAD	multiple ascending dose
MCT	Mobile cardiac telemetry
MF	Market formulation
MFAS	Modified Full Analysis Set
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MS-DMT	Multiple sclerosis disease modifying therapy
MSIF	MS International Federation
MSWS-12	Multiple Sclerosis Walking Scale
MTD	Maximum tolerated dose
NCO	Non-clinical overview
NDA	New drug application
NMR	Nuclear magnetic resonance
OPA	Oriented polyamide
PA	Polyamide
NOAEL	no-observed-adverse-effect levels
PASAT	Paced Auditory Serial Addition Test
PBPK	Physiologically based PK
PBVC	Percent brain volume change

PD	Pharmacodynamics
PDev	Protocol deviation
PE	Polyethylene
PEM	Peripheral effector memory
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalitis
PM	Polymyositis
PopPK	Population PK
PPMS	Primary progressive multiple sclerosis
PPS	Per-protocol Set
PT	Preferred term
PVC	Polyvinyl chloride
PY	Patient years
QTPP	Quality target product profile
RH	Relative Humidity
RMS	Relapsing multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
S1P	Sphingosine-1-phosphate
SAD	single ascending dose
SAE	Serious adverse event
SAF	Safety set
SAG	Scientifivc Advisory Group
SBP	Systolic blood pressure
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SmPC	Summary of product characteristics
SO	Statistical overview
SOC	System organ class
SOP	Standard operating procedure
SPMS	secondary progressive multiple sclerosis
ss	Steady state
T25W	Timed 25-Foot Walk Test
TDAR	T cell-dependent antibody response
TEM	T effector memory
Tmax	The time to reach the maximum concentration after drug administration
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of Toxicological Concern
TTO	Time to onset
T4	Thyroxine
UDP-GT	uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
VZV	Varicella zoster virus
WT	Wild type
XRF	X-ray fluorescence
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 13 September 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Mayzent, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2016.

The applicant applied for the following indication: Treatment of adult patients with secondary progressive multiple sclerosis.

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0098/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0098/2017 was not completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's requests for consideration

New active Substance status

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

Scientific advice

The applicant received Scientific advice from the CHMP on the development for the indication from the CHMP on 21 October 2010 (EMEA/H/SA/1667/1/2010/III), 15 December 2011 (EMEA/H/SA/1667/1/FU/1/2011/II), 15 November 2012 (EMEA/H/SA/1667/1/FU/2/2012/II), 26 June 2014 (EMEA/H/SA/1667/1/FU/3/2014/II), 25 January 2018 (EMEA/H/SA/1667/2/2017/I) and 22 March 2018 (MEA/H/SA/1667/3/2018/HTA/II). The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

Quality aspects:

- Designation of starting materials.

Nonclinical aspects:

- completeness of the overall programme, including immunosuppressive and cardiac effects.

Clinical aspects:

- Adequacy of the pharmacology and pharmacokinetics program;
- Dose selection approach;
- Study population selection criteria and powering the planned studies for either disability or relapses, to support an indication on relapses and disability;
- Comparator's choice and impact of new MS treatments gaining approval;
- Geographical location of study and representativeness with respect to the EU population;
- Design of the follow-up and of post-marketing data collection to support longer term outcomes evidence;
- Statistical plans, including pooling of disability data and interim analysis.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Mark Ainsworth Co-Rapporteur: Martina Weise

The application was received by the EMA on	13 September 2018
The procedure started on	4 October 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	10 January 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 January 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 March 2019
The following Good Clinical Practice (GCP) inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two investigator sites (Portugal and Australia) and the sponsor site (Switzerland) between 4/2/2019 and	21 August 2019

28/3/2019. The outcome of the inspection carried out was issued on:	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	7 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	29 May 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	5 September 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	18 September 2019
The CHMP agreed on a second list of outstanding issues in writing to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	30 October 2019
SAG experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	7 November 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Mayzent on	14 November 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple Sclerosis (MS) is a chronic, immune-mediated inflammatory condition that causes neuro-axonal injury in the Central Nervous System (CNS) leading to permanent and severe neurological impairment and disability. The most common onset MS form (relapsing-remitting MS, RRMS) is characterised by acute episodes of neurological dysfunction named relapses followed by variable recovery and periods of clinical stability. There are different authorised disease modifying therapies (DMT) for patients with RRMS.

More than 50% of patients who suffer from a RRMS will within a median time of 15 to 20 years from onset, develop a secondary progressive multiple sclerosis (SPMS) characterized by sustained disability with or without superimposed relapses.

With the present application, the applicant initially intended to seek approval of siponimod for the following indication:

"Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS)."

During the evaluation of the data and after Scientific Advisory Group (SAG) Neurology, the applicant has revised the proposed indication to:

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

2.1.2. Epidemiology

MS is the most common cause of serious neurological disability in young adults. It is estimated that more than 2.3 million people are affected by MS worldwide. The prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 respectively) and lowest in sub-Saharan Africa and East Asia at 2.1 and 2.2 per 100,000, respectively. MS typically starts between 20 to 40 years of age. Overall, women are affected approximately twice as often as men, except in individuals with the primary-progressive MS (PPMS), where there is no gender prevalence difference.

2.1.3. Aetiology and pathogenesis

While the exact cause of MS is unknown, it is assumed that MS is mediated by an autoimmune process triggered by an infection or other environmental factors, superimposed on a genetic predisposition.

The major contributors to this process are macrophages and microglia from the innate immune system, and T and B lymphocytes from the adaptive immune system. From the peripheral immune system, autoreactive T-helper cells are primed and stimulated to infiltrate the CNS where they target myelin antigens. Inflammation of the white and grey matter tissues in the CNS due to focal immune cell infiltration and release of cytokines are the incipient cause of tissue damage in MS not only to the myelin sheath but also to the underlying axons. This process happens over time and results in repeated attacks (clinically eloquent or not). During the acute phase, demyelination and inflammation impair or interrupts nerve transmission, giving rise to clinical signs and symptoms. Relapses are considered the clinical expression of acute inflammatory focal lesions. Afterwards, remaining permanent symptoms (sequelae) are due to permanent neuro-axonal loss or permanent injured and demyelinated neurons.

Elements from both adaptive (B and T cells) and innate (monocytes, natural killer cells and dendritic cells) immune systems all are involved in any stage of MS. During the RRMS phase, the accumulation of disability (disability worsening or progression) is mostly due to lack of complete recovery of focal inflammatory lesions. In the SPMP phase, accumulation of disability is explained by the conjunction of pathological mechanisms including focal inflammatory activity (particularly relevant in SPMS with relapses and acute lesions) and failure of biological compensation of the CNS damage (impaired remyelination and lack of biological redundancy).

2.1.4. Clinical presentation, diagnosis

The most commonly onset MS phenotype (85% of patients) is RRMS clinically characterized by relapses. Nearly half of the RRMS patients will develop within 20 years a SPMS clinically characterized by disability

worsening. There are no clear criteria that mark the transition from RRMS to SPMS. The transition is determined retrospectively based on evidence that disability progression had occurred independently of relapses, though relapses and focal inflammatory activity may continue to be present. In fact, the SPMS is a heterogeneous population including patients with relapses (usually with a prominent development of T2-weighted-Fluid-Attenuated Inversion Recovery (T2-FLAIR) lesions) and other patients without relapses. The term "relapsing MS" (RMS) applies to those affected patients either with a RRMS or SPMS with superimposed relapses. The pathological mechanism underlying relapses and typical radiological T2-FLAIR lesions is acute focal inflammatory activity. Regardless of other potential pathological mechanisms, lack of complete recovery from focal inflammatory lesion causes accumulation of disability. Therefore, patients with relapsing MS, despite suffering from different MS forms, constitute a common target for current treatment options.

Clinical manifestations in RRMS may depend on affected CNS regions. In SPMS, accumulated CNS damage is usually presented as reduced ambulation and cognitive impairment, bulbar dysfunction, visual impairment, impaired arm function, fatigue, pain and depression and sphincter control issues.

2.1.5. Management

The standard of care for acute relapses is methylprednisolone i.v. Methylprednisolone shortens the duration of a relapse but has no influence on its sequelae. Plasmapheresis may improve recovery from relapse in steroid-resistant cases, but this is rarely used.

Disease-modifying therapies (DMT) aim to modify the course of the disease by suppressing or modulating the immune responses involved in MS pathogenesis. Biologicals (therapeutic proteins, monoclonal antibodies) and small molecules have been approved for use in this therapeutic context. DMTs aim to prevent relapses and ultimately intend to decrease the rate of accumulation of disability. Due to the risks (identified or potential) of opportunistic infections, malignancies, and other systemic adverse drug reactions, several of these treatment options are considered as second-line options i.e. treatment is restricted to patients with rapidly evolving multiple sclerosis or those who had a suboptimal response to prior therapies.

Currently 12 DMTs are available (country/regional differences exist) for the treatment of MS (interferon beta-1a and interferon beta-1b, peginterferon beta-1a, glatiramer acetate, fingolimod, natalizumab, teriflunomide, dimethyl fumarate, alemtuzumab, ocrelizumab, cladribine, and mitoxantrone). Most are approved for RRMS or relapsing forms of MS (RMS, defined as RRMS and SPMS with relapses). Products for both RRMS and RMS were approved based on treatment effect on relapses, MRI lesion activity, and, some for the delay in disability worsening.

Interferon beta (IFNB)-1b is approved in the EU for patients with SPMS with active disease as evidenced by relapses. The two trials in SPMS presented as efficacy data for marketing authorization showed a consistent 30% reduction in frequency of relapses and inconsistent results for the primary endpoint “time to confirmed progression”(31% reduction in time to disability progression in one trial and no significant delay in the other trial including patients with overall less active disease than in the other study).

About the product

Siponimod is a selective modulator of G-protein coupled sphingosine-1-phosphate (S1P1) and S1P5 receptors, leading to internalization and degradation of S1P1 receptors on T and B-lymphocytes, which prevents their egress and recirculation from secondary lymphatic tissue to target organs including the CNS. Siponimod is designed not to target the S1P3 and S1P4 receptors at pharmacological doses, in contrast to fingolimod (which targets S1P1, S1P3, S1P4, and S1P5 receptors).

Siponimod acts in the periphery to impede egress of peripheral lymphocytes from secondary lymphoid organs and prevent pathogenic effector lymphocyte recirculation from lymphatic tissue to the CNS.

The initially claimed indication was *"treatment of secondary progressive multiple sclerosis in adults"*. After receiving scientific assessment of efficacy data by CHMP and considering the report from The SAG Neurology, the applicant has revised the proposed indication to:

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

Based on pharmacodynamic data of Absolute lymphocyte count (ALC) recovery dynamics and the half-life of approximately 30 h, a once-daily dosing regimen was proposed to be adequate to maintain an effective absolute lymphocyte count reduction.

Type of Application and aspects on development

This application was submitted in accordance with Article 8.3 of Directive 2001/83/EC.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 0.25 and 2 mg of siponimod (as fumaric acid co-crystal) as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, crospovidone, glyceryl dibehenate and colloidal anhydrous silica;

Tablet coating: polyvinyl alcohol, titanium dioxide (E171), red iron oxide (E172), black iron oxide (E172 – 0.25 mg tablet only)), yellow iron oxide (E172 – 2 mg tablet only), talc, soya lecithin and xanthan gum.

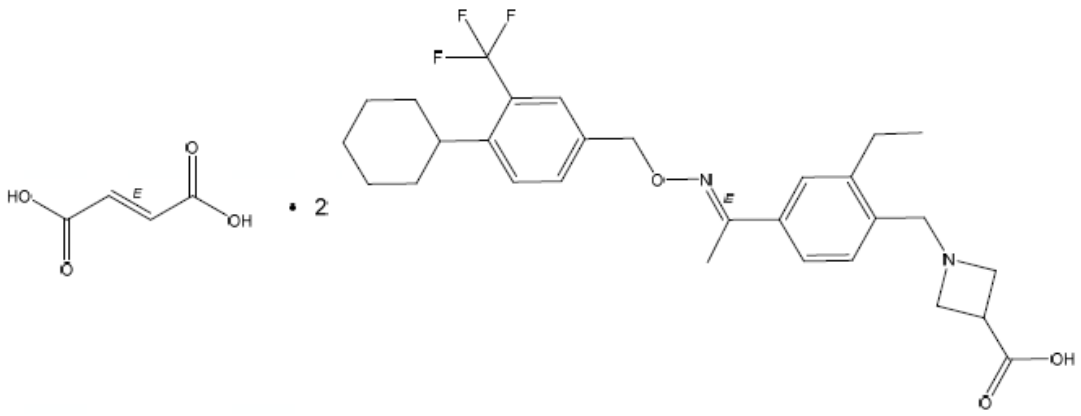
The product is available in PA/alu/PVC/alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of siponimod fumaric acid is (2*E*)-but-2-enedioic acid 1-({4-[(1*E*)-*N*-{[4-cyclohexyl-3-(trifluoro)phenyl]methoxy}ethanimidoyl]-2-ethylphenyl}methyl)azetidine-3-carboxylic acid (1:2) corresponding to the molecular formula $C_{62}H_{74}F_6N_4O_{10}$ (i.e. 2 molecules of siponimod for every 1 molecule of fumaric acid). It has a relative molecular mass of 1149.29 g/mol and the following structure:

Figure 1: Active substance structure



The chemical structure of siponimod fumaric acid was elucidated by a combination of spectroscopic and other analytical methods and the active substance is considered appropriately characterized. This data indicates that the active substance is not a fumarate salt but rather, siponimod exists as a co-crystal with fumaric acid as the co-former.

The active substance is a white to almost white non-hygroscopic crystalline powder, which is insoluble in aqueous solutions below pH 7 and very slightly soluble above pH 7.5 and in simulated intestinal fluid. It is not very soluble in many organic solvents either.

Siponimod is achiral but contains an oxime double bond with *E*-configuration, which is the desired and thermodynamically favoured isomer.

Polymorphism has been observed for siponimod fumaric acid. Only one form, the most thermodynamically stable, is selected for commerical manufacturing. A test for polymorphic form by XRPD is included in the active substance specification.

Manufacture, characterisation and process controls

Siponimod fumaric acid is chemically synthesized in convergent fashion from three well-defined starting materials with acceptable specifications. The choice of starting materials is in line with previously provided scientific advice. There are multiple chemical transformation and isolation steps between each starting material and the active substance.

Critical steps of the process have been defined, and the applied controls are considered satisfactory. Adequate in-process controls (IPCs) are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

All potential impurities were assessed for potential mutagenicity in silico according to ICH M7.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Several changes have been implemented along the way to improve process safety, increase yields, improve the quality of the active substance, and allow for scale-up. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in polyethylene (PE) bags, which comply with the EC regulation 10/2011 as amended. The bags are further stored within PE/OPA/alu/PET bags stored inside drums.

Specification

The active substance specification includes tests for appearance (visual), particle size (laser diffraction), clarity and colour of solution (Ph. Eur.), identity (IR, XRPD), related substances (HPLC and IC), residual solvents (GC), specific impurities (XRF and polarography), water content (KF), heavy metals (ICP-MS), sulfated ash (Ph. Eur.), , assay of siponimod (HPLC), assay of fumaric acid (titration) and microbiology (Ph. Eur.).

Impurities present were qualified by toxicological and clinical studies and appropriate specifications have been set. Particle size limits have been set in line with the batches used in phase III clinical studies.

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

Batch analysis data from 18 pilot to production scale batches of the active substance are provided. The results are within the specifications applicable at the time and consistent from batch to batch.

Stability

Stability data from three production scale batches of active substance from a different manufacturing site in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH), up to 24 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Further data on three batches of active substance manufactured at the proposed commercial site were also provided (up to 9 months under intermediate conditions, up to 6 months under accelerated conditions). The following parameters were tested: appearance, particle size, clarity and colour of solution, identity, related substances, water content, assay and microbiology. No trends to any of the measured parameters were observed and all remained within specification.

Photostability testing following the ICH guideline Q1B was performed on one batch. No degradation or untoward trends were observed, indicating that siponimod fumaric acid is not photosensitive.

Results under stressed conditions (water, aqueous acid, aqueous base, aqueous peroxide, all 80 ºC) indicate that siponimod fumaric acid is susceptible to hydrolysis, especially in alkaline media, so it is recommended to protect the active substance from water.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 30 months in the proposed airtight container in order to protect the active substance from water.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the product and Pharmaceutical development

The finished product is presented as film-coated tablets containing either 0.25 mg or 2 mg of siponimod. The tablets are distinguished by colour (0.25 mg: pale red; 2 mg, pale yellow) and debossing.

Siponimod fumaric acid is a BCS class II compound with good absorption characteristics but practically insoluble in aqueous media, although solubility increases slightly at low pH or above pH 6.8. The particle size distribution has been set in line with phase III clinical batches and affords sufficiently stable active substance.

Development started with a hard gelatin capsule containing the active substance and standard pharmacopoeial excipients, formulated by wet granulation. However, the results of dose range finding studies indicated the need for much lower doses of active substance. As a result, a tablet formulation was developed using common pharmaceutical processing. The excipients chosen for the tablet formulation are also well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards where appropriate. Suitable specifications have been provided for the non-pharmacopoeial film-coating pre-mixes. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility with the excipients was investigated using binary mixtures stored at elevated temperature and humidity. No incompatibilities were observed with those excipients in the proposed commercial formulation.

Development of the dissolution method has been described. The method has been shown to be discriminatory and suitable limits have been included in the specification.

The manufacturing process consists of combining the active substance and excipients, tableting and film-coating steps. The commercial process was established by optimizing the different unit operations at pilot and commercial scaleThe primary packaging is PA/alu/PVC/alu blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists blending and screening of the active substance and excipients; tableting; film-coating; packaging. The process is considered to be a non-standard manufacturing process given the low active substance content.

Major steps of the manufacturing process have been validated on three consecutive commercial scale batches of each strength according to the process description. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process pharmaceutical form. The critical steps have been defined.

A bulk holding study was carried out on two batches of each strength of film-coated tablet and a bulk hold time of up to 12 months under refrigerated conditions has been justified.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), mean mass, identity (HPLC, UV), loss on drying (halogen drying), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), degradation products (HPLC), assay (HPLC) and microbial enumeration (Ph. Eur.).

The testing monographs contain statements about changing analytical equipment and sample preparation within validated ranges. These were introduced in response to questions from regulators in other regions. However, these are considered to fall under GMP and the CHMP has recommended removing the statements from the dossier by variation, post-approval.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk from different potential sources was considered and deemed to be negligible. Testing of finished product batches indicated that all elemental impurities were well below the relevant thresholds and thus, no additional controls are required.

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

Batch analysis results were provided for nine commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from three production scale batches of each strength were generated according to the ICH guidelines. Samples were stored under a series of conditions and for variable durations: at either -20 ºC or 40 ºC/75% RH for up to 6 months; at 5 ºC, 25 ºC/60% RH, 30 ºC/65% RH and 30 ºC/75% RH for up to 24 months. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, dissolution, assay, degradation products, loss on drying and microbial enumeration. Tablet hardness was also monitored. The analytical procedures used are stability indicating.

Under refrigerated conditions, no significant changes were observed for any of the measured parameters. At 25 ºC, a small increase in degradation products and drop in assay was observed. The amount of degradation was greater at higher temperatures and humidities It was deemed that a small increase in degradation and reduction in assay was acceptable to allow patients to store tablets in a more conventional fashion, i.e. at ambient temperature rather than in the refrigerator.

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

Based on available stability data, the proposed shelf-life of 24 months stored not above 25 ºC as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the

use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Identified remarks should be removed from the finished product testing monographs as it is part of GMP.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development program was conducted in accordance with International Conference for Harmonisation (ICH) guidance in an Organization for Economic Co-operation and Development (OECD) mutual acceptance of data (MAD) compliant member state.

The nonclinical toxicology program was conducted under Good Laboratory Practices (GLP), with all pivotal toxicity (including safety pharmacology) studies being GLP compliant.

2.3.2. Pharmacology

Siponimod has been developed as a S1P modulator for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS). As an immunomodulatory agent it functions to sequester T and B lymphocytes within the secondary lymphoid organs and aims to ameliorate MS sequelae by reducing peripheral blood lymphocyte (PBL) counts. The basis for its use for the treatment of multiple sclerosis is built on the prototype S1P-modulator, fingolimod.

Primary pharmacodynamic studies

Siponimod selectively targets S1P1 and S1P5 receptors

Initial *in vitro* experiments were performed to characterise the specificity of siponimod for the various S1P receptors. In [^{35}S]GTPγS-binding assays using chinese hamster ovary (CHO) cell lines expressing

individually S1P1 to S1P5, siponimod was a much more selective agonist at S1P1 and S1P5 receptors with EC_{50} values more than 750-fold below concentrations at S1P2, S1P3 and S1P4 subtypes.

In addition to the parent compound siponimod, the binding activity of several metabolites was also investigated. Concerning the major human metabolites, M3 was pharmacologically inactive in S1P1 expressing cells, whereas M17 was ~80- and 70-fold less potent than its parent compound siponimod at S1P1 and S1P5 receptors suggesting that M17 is unlikely to be contributing to the pharmacological activity.

Siponimod exerts "functional antagonism" at S1P1 receptors, but acts as agonist at the S1P5 subtype

The binding of siponimod concentration-dependently promoted long-lasting internalization and degradation of S1P1 receptors ("functional antagonism") as demonstrated by flow cytometry analysis in CHO cells expressing a Myc-tagged S1P1 receptor. Comparison was made with the approved S1P modulator, fingolimod, which was shown to be marginally more efficient at inducing receptor internalisation. In contrast, siponimod is thought to function as an agonist for S1P5 as it failed to induce internalisation of S1P5 receptors up to the highest concentration of 1 µM, which is in line with the S1P modulator fingolimod.

Siponimod slows lymphocyte egress from lymph nodes (LN) and their recirculation to the CNS

In vivo siponimod transiently decreased PBL counts in a dose-dependent manner following single administration in healthy rats and cynomolgus monkeys. In various severe protracted and chronic progressive experimental autoimmune encephalitis (EAE) models of human MS in rats and mice, siponimod similarly decreased PBLs at doses ≥0.3 mg/kg in rats and 3 mg/kg in mice, which correlated with effective reversal of neurological deficits, and decreased inflammation (reduced macrophage infiltration, activated microglia) as well as demyelination. At the effective doses the brain to plasma ratio of siponimod exposure was approximately 5-fold. Siponimod doses of 0.3 mg/kg/day or below were less efficacious when administered during early EAE in rats compared to higher dose levels. In another EAE model in mice, continuous intracerebroventricular infusions of ≥0.45 µg/day siponimod diminished activation of astrocytes and microglia, reduced infiltration of CD3+ lymphocytes and restored GABAergic neurotransmission in the striatum.

Secondary pharmacodynamic studies

Siponimod and its metabolites M3, M16 and M17 did not show any clinically relevant *"off-target"* affinity in receptor interaction screens *in vitro*. However, oral siponimod doses of 0.03-30 mg/kg promoted significant dose-dependent permeation of Evans blue dye into the lungs of mice, which is in line with the role of the S1P1 receptor in the maintenance of endothelial vascular integrity.

Safety pharmacology programme

Safety pharmacological effects of siponimod on cardiovascular, respiratory and CNS function were tested in four GLP compliant safety pharmacology studies in accordance with ICH S7A and 7B guidelines (CPMP/ICH/539/00, CPMP/ICH/423/02). These investigations were complemented by an extensive non-GLP cardiovascular safety pharmacology package, primarily driven by the findings seen with fingolimod where treatment of some patients was associated with transient effects on heart rate, atrioventricular conduction and in some instances decreased blood pressure. Siponimod did neither significantly affect hERG currents *in vitro*, nor the QT interval in conscious telemetered guinea pigs, rabbits and monkeys *in vivo*. However, siponimod decreased the heart rate in the rabbit Langendorff heart model *ex vivo* and also induced bradycardia in association with atrioventricular (AV) dissociation and second-degree AV block in rats, rabbits, guinea pigs and monkeys *in vivo*. This inhibition of AV conduction and heart rate is also known from non-clinical and clinical experience with fingolimod and is mechanistically related to

the activation of G protein-coupled inwardly rectifying potassium (GIRK) channels, which were found to be comparably stimulated by siponimod and fingolimod in guinea pig atrial cardiomyocytes (EC_{50} values of 15.8 nM and 10.6 nM, respectively). Remarkably, siponimod re-challenge did not alter AV conduction and heart rate in guinea pigs or monkeys *in vivo*, which was confirmed during re-incubations of atrial cardiomyocytes with either siponimod or fingolimod after an interim washout period *in vitro*. This desensitisation of GIRK channels is apparently related to the downregulation of S1P receptors during prolonged exposure of siponimod or fingolimod, since GIRK channels could still be activated by the acetylcholine analogue carbachol via muscarinic M2 receptors. Thus, siponimod and fingolimod initially act as agonists at S1P1 receptors to inhibit AV conduction via stimulation of GIRK currents and subsequently as functional antagonists by down-regulation of S1P1 receptors, which interferes with continuous GIRK channel activation and resolves AV conduction abnormalities.

No effects on the CNS were seen using the Irwin test in rats at doses up to 200 mg/kg.

In respiratory studies siponimod was associated with slight increases in the tidal volume from baseline. Because in parallel this was associated with slight decreases in the respiratory rate of up to 22%, overall the minute volume was unaffected.

Overall the provided pharmacology package is sufficient to support the MAA of Mayzent.

Pharmacodynamic drug interactions

Pharmacodynamic (PD) studies addressing drug interactions were not performed. This approach is endorsed.

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) of siponimod were investigated after single oral or i.v. doses in mouse, rat and Cynomolgus monkey and following multiple administrations in repeated-dose toxicity studies of the three species, with PK values derived utilising total radioactivity following administration of C^{14}-labelled siponimod and via direct siponimod concentration analysis in plasma, blood and relevant tissue matrices. In addition, toxicokinetic determinations were performed in pregnant rabbits upon oral or i.v. administrations, respectively.

Analytical methods were appropriately validated in line with the pertinent European guideline (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr. 2**) and were therefore accepted, although validations did not achieve full GLP compliance.

Following oral administration siponimod absorption was slow to medium with tmax values of between 2-8 hours for all species. Oral bioavailability was 49-52% in rat and up to 83% in monkey. The plasma $t_{1/2}$ of siponimod was relatively long and followed two-compartmental kinetics in monkeys and humans with $t_{1/2\alpha}$ of 16-19 h and 27 h, respectively. A shorter $t_{1/2\beta}$ of 5-6 h was observed in male rats, whereas one-compartmental kinetics were noted in female rats and in mice. Significant sex-related differences in exposure were only evident in the rat after single and repeat doses due to substantially lower plasma clearance in females (0.074 l/(h·kg)) compared to males (0.4-0.5 l/(h·kg)). Exposure increased in a slightly sub-dose proportional manner following oral administration in non-clinical species. There was no notable accumulation following multiple dosing evident in rat or mouse studies with mild accumulation in monkey studies (≈1.4-3.0 based on Area Under the Curve (AUC)).

Siponimod was highly plasma protein bound (>99%) in all species tested. Quantitative whole-body autoradiography tissue distribution studies in mice and rats revealed extensive distribution of siponimod related radioactivity (i.e. siponimod and/or metabolites) following a single oral dose with the lacrimal gland the highest exposed tissue in mouse followed by liver, kidney (cortex and corticomedullar junction)

and lymph nodes. In rat, highest and longest lasting radioactivity levels were found in the adrenal cortex, myelin (represented by the nerves, cerebellar white matter and white spinal cord) and testis.

Radioactively labelled siponimod was additionally detectable in the ciliary body, choroid, lens and vitreous body of the eye of albino mice and could be traced in the lens until 271 h post dosing. In pigmented rats, radioactive components were also confirmed in the choroid at ~2.5-fold higher levels than in albino rats and were eliminated at 168 h after oral administration. Therefore, the photo-reactive potential of siponimod was evaluated in a 3T3 NRU assay *in vitro*.

Brain concentrations of siponimod were assessed in all repeat-dose toxicity studies confirming extensive distribution to the CNS with brain concentrations of 5-16 times those in plasma reported. The unbound AUC of siponimod in the brain at the respective no-observed-adverse-effect levels (NOAELs) and at the human equivalent oral dose of 2 mg was 1.31 nM·h in female rats, 0.64 nM·h and 0.49 nM·h in female and male monkeys and 0.22 nM·h in male rats and humans. The unbound Cmax was 0.066 nM in female rats, 0.34 nM and 0.028 nM in female and male monkeys, 0.15 nM in male rats and 0.012 nM in humans. All tissues analysed in non-clinical species exhibited several fold higher concentrations of siponimod than plasma.

Siponimod crossed the placenta in rabbits and was present in foetal plasma in the rabbit embryo-foetal development study at concentrations between 1.6-2.6 times the maternal plasma concentration. Siponimod-related radioactivity was also secreted into the milk of lactating rats at concentrations approximately half of those determined in maternal plasma.

Siponimod undergoes extensive metabolism *in vivo*. Hydroxylation is the primary elimination pathway followed by sulfation and glucuronidation. No studies examining affinity, induction or inhibition of cytochrome (CYP) P450 enzymes have been presented in the non-clinical section of the dossier but are included in clinical section of the dossier. *In vitro* studies suggest CYP2C9 is the predominant cytochrome P450 isoenzyme in the hepatic biotransformation of siponimod (79.3%) with a minor contribution of CYP3A4 (18.5%). The two major human metabolites were identified as metabolite M3 (produced via hydroxylation followed by glucuronidation) and M17 (cholesterol ester metabolite). The applicant states that adequate levels of M3 and M17 for toxicological evaluation were observed in monkey and mouse studies, respectively. It should be noted that these metabolites were not measured directly in TK samples acquired in the pivotal toxicity studies but instead levels have been calculated based on siponimod exposure and the ratio of the relevant metabolites to parent observed in non-pivotal (non-GLP) PK and exploratory studies. This approach was adopted as M3 and M17 were identified after the completion of pivotal repeat-dose toxicity studies at which time retention samples from those studies were no longer available. It should be noted that full method validation for the assay used in the quantification of each of these metabolites was not conducted. However, adequate justification was provided that this does not significantly affect the interpretation of these data and, given the relatively large margins of exposure between calculated metabolite concentration in non-clinical species and those observed clinically, it is accepted that their safety has been adequately qualified in pivotal non-clinical studies.

Like siponimod, M17 is highly plasma protein bound and exhibits wide tissue distribution. M17 shows significant accumulation in plasma and tissues following multiple dosing with kidney and liver exhibiting the highest concentrations following 39-week administration to mice. M3 was detected in the monkey absorption, distribution, metabolism, and excretion (ADME) study, based on this study, exposure margins at the NOAEL in the monkey repeat-dose toxicity study to human exposures are adequate.

Elimination of siponimod in non-clinical species is primarily via biliary/faecal excretion of the sulfate conjugate M4 and the hydroxylation metabolites M5, M6 and M7 in all species. Unchanged siponimod represented only ~8-9 % of the administered dose in the bile or faeces of bile duct-cannulated rats, monkeys and humans. Excretion of unchanged siponimod into urine was not detected or only in traces across all species tested. Higher levels up to 21.5 % of unchanged siponimod were solely determined

in faeces of mice. Compared to rats and monkeys, mice showed extended elimination of siponimod from tissues.

PK drug-drug interactions

There is limited non-clinical PK data presented related to the potential for PK interactions. An extensive set of *in vitro* studies investigating the potential for siponimod and metabolites M3 and M17 mediated DDI at efflux and uptake transporters do not suggest a significant risk at exposures anticipated with the proposed clinical posology (see clinical section).

2.3.4. Toxicology

The toxicity studies have been performed in line with ICH M3 (R1) requirements with rats and Cynomolgus monkeys used as the species of investigation for the repeat dose toxicity studies. In addition, studies were performed in mice and rabbits. These species are pharmacologically relevant for the assessment of the safety of siponimod.

Single dose toxicity

Single dose GLP compliant studies were performed in mice and rats as well as a non-GLP compliant study in monkeys. In mice, no siponimod related findings were evident following i.v. administration of doses of up to 200 mg/kg. Rats were dosed orally up to 2000 mg/kg with some females in the 2000 mg/kg group exhibiting mild adverse effects including piloerection, decreased body tone and abnormal gait. In monkeys, oral doses up to 60 mg/kg were generally well tolerated. Lymphopenia was seen in line with the pharmacological action of siponimod as well as mild prolongation of activated partial thromboplastin time.

Repeat dose toxicity

Siponimod induced marked to severe lymphopenia in all animal species, which was related to its primary pharmacodynamic activity at S1P receptors and consequently not considered for the determination of NOAELs. As a compensatory mechanism, myeloid hyperplasia in the bone marrow and extramedullary haematopoiesis were noted. The lymphocyte reductions manifested in dose-dependent atrophy in the white pulp of the spleen, lymphoid hyperplasia in the thymus medulla and lymphocyte depletion in lymph nodes at all doses. In addition, sinus histiocytosis was observed at ≥10 mg/kg/day p.o. or ≥4 mg/kg/day i.v. in rats and the gut-associated lymphoid tissue was reduced upon long-term dosing of ≥10 mg/kg/day p.o. for 52 weeks in monkeys. In both long-term toxicity studies in monkeys, T helper cells (≤99 %), cytotoxic T cells (≤92 %) and B cells (≤94 %) were markedly depleted, whereas natural killer cells were less affected (≤11 %). Accordingly, the T cell-dependent antibody response (TDAR) against keyhole limpet hemocyanin (KLH) was clearly reduced but still present in monkeys administered ≥10 mg/kg/day siponimod. These pronounced reductions in lymphocytes and TDAR only partially reversed in the respective 8- and 12-weeks recovery periods.

Severe nephrotoxicity developed after high siponimod doses ≥150 mg/kg/day in the 2-week oral dose range finding (DRF) study and at ≥2 mg/kg/day in the carcinogenicity study in mice. These adverse kidney events contributed to the early mortality of two animals in the DRF study and comprised renal tubular necrosis, mineralization, dilatation, hyaline casts and/or tubular basophilia with karyomegaly and elevated urea and creatinine levels. Similarly, increased hyaline droplets were observed in proximal convoluted renal tubules at oral doses ≥10 mg/kg/day in the 4-week subchronic study in rats. In the 52 weeks chronic toxicity study in monkeys, renal tubular epithelial degeneration and vacuolation associated with minimal/mild interstitial and tubular amphophilic kidney deposits were only

determined in three premature decedents of the 100 mg/kg/day high dose group, but not during regular necropsy.

Siponimod dose-dependently increased liver weights following multiple oral doses ≥5 mg/kg/day for 13 weeks in mice, long-term oral administration of ≥15 mg/kg/day in rats and ≥50 mg/kg/day in monkeys, which correlated at elevated dosages with minimal to moderate reversible centrilobular hypertrophy of hepatocytes as well as slight ALT increases in mice and rats. At high oral siponimod doses ≥150 mg/kg/day in mice and 100 mg/kg/day in monkeys, focal liver inflammations with single cell necrosis were additionally detected.

In the thyroid gland of rats, reversible follicular cell hypertrophy was identified at ≥15 mg/kg/day in males and at 50 mg/kg/day in females of the 26-week chronic toxicity study. In the rat carcinogenicity study, proliferation in the thyroid gland were detected at ≥10 mg/kg/day in male rats, which culminated in increased follicular cell adenoma/carcinoma in the thyroid gland at this dose levels in both genders and has been further assessed as rat-specific metabolic adaption related to the liver findings (see below).

Gastrointestinal intolerabilities in association with inflammation of the whole intestinal tract was prominent in all toxicity studies in monkeys at oral siponimod doses ≥50 mg/kg/day leading to morbidity and premature euthanasia of individual animals. The poor clinical condition was caused by dose-dependent protracted diarrhoea and emesis at high oral dosages ≥100 mg/kg/day.

Slight chronic vasculopathy of small to medium sized arteries in kidneys, skin, subcutis and gastrointestinal tract was detected at all oral siponimod doses ≥10 mg/kg/day in the 26 weeks oral toxicity study in monkeys. The chronic vasculopathy was accompanied by pericardial effusion and eosinophilic infiltration in two early decedents that had received ≥50 mg/kg/day siponimod. In the 2 year carcinogenicity study in rats, vascular inflammation (polyarteritis) and uterine abnormalities (dilatation, haemorrhage, inflammation, ulceration, hyperplasia of endometrial epithelium and vascular hypertrophy/hyperplasia) were induced upon long-term oral administration in all siponimod dose groups (≥10 mg/kg/day in males, ≥3 mg/kg/day in females) and primarily accounted for pre-terminal deaths. Secondary exacerbations of the vascular inflammation also consisted of haemorrhagic foci and necrosis in the brain, chronic progressive nephropathy in the kidneys, pleural fibrosis in the lungs and degeneration of seminiferous testis tubules. Degenerations of testis tubuli was similarly observed at the 300 mg/kg/day high dose level in the 2 weeks repeated-dose toxicity study in mice.

Fibrosis and smooth muscle hypertrophy/hyperplasia with marked inflammatory foci were detected in the lungs at all oral dose levels (≥5 mg/kg/day) in the 13 weeks repeated-dose toxicity study in mice and ≥10 mg/kg/day in the 2 weeks and 4 weeks multiple dose toxicity studies in rats, but were not observed in the 26 weeks chronic toxicity study in rats. Chronic pulmonary inflammation and pleural fibrosis secondary to vascular inflammation were also determined in carcinogenicity studies at ≥2 mg/kg/day in mice and at ≥3 mg/kg/day in rats, respectively. Moreover, one case of bronchio-alveolar adenoma was detected in the 150 mg/kg/day group of the 2 weeks DRF study in mice.

In the lacrimal glands of mice of the 13 week subchronic toxicity study, dose-dependent minimal to moderate vacuolar degenerations were identified after oral siponimod doses ≥15 mg/kg/day, which aggravated to marked acinar cell degeneration and atrophy at higher dosages or upon long-term dosing of ≥2 mg/kg/day in the carcinogenicity study in mice. In addition, corneal ulcerations were detected in the carcinogenicity study in rats.

Other findings like the increased adrenal gland weights with concomitant reductions of the pituitary weight and the reversible vaginal epithelium mucification and uterine atrophy were restricted to rats only or limited to exaggerated doses exceeding the maximum tolerated dose (MTD) in rats (≥100 mg/kg/day) and were therefore related to stress of the animals or attributable to the moribund

condition of the animals. Similarly, the moderate myofibre degenerations of skeletal muscle and the minimal to moderate follicular atrophy and interface dermatitis in monkeys were either limited to a few individuals in the chronic toxicity study or to the 100 mg/kg/day high dose level. Considering the absence of comparable findings in the clinical program of siponimod or fingolimod and the substantial safety margins, these adverse events are obviously without human relevance. With respect to the clinical dose of 2 mg/day, the dosages utilised in the repeat dose toxicity studies have far exceeded this on a human equivalent dose level. This is reflected in adequate exposure multiples achieved across the nonclinical species. In rats the NOAEL in the 26-week study at 50 mg/kg in males and 15 mg/kg in females is higher than that from the 4-week study, where it was defined at 10 mg/kg based on reduced body weight and food consumption. In the 26-week study these changes were transient in nature and therefore not considered adverse. From the 26-week study in rats the margin of exposure for males is high at 190-fold and 342-fold for females. In monkeys the NOAEL established in all studies was 10 mg/kg with a margin of exposure of 171-fold for males and 222 fold for females based on the 52-week study. In addition, it should be taken into consideration that some of the effects that were considered adverse, i.e. changes in lymphoid organs, could be considered secondary to the pharmacology of the compound. Overall, there would appear to be an acceptable margin of exposure from the adverse effects noted in the repeat dose toxicity studies in rats and monkeys.

Genotoxicity

The genotoxicity of siponimod was assessed in a standard battery of investigations in line with the ICH S2(R1) guideline and was found to be non-genotoxic in a bacterial reverse mutation assay test, non-clastogenic in an *in vitro* chromosomal aberration assay in human lymphocytes, and non-clastogenic/aneugenic in *in vivo* studies assessing its potential to induce micronuclei in polychromatic erythrocytes in mice and rats.

Carcinogenicity

104-week carcinogenicity studies following repeat-dose oral administration of siponimod were completed in mice and rats.

In the mouse study siponimod administration was associated with a reduction in survival in all dosage groups resulting in the premature termination of dosing at week 91 and 92 in mid and high dose male and female groups respectively with all study animals terminally sacrifices by week 101. This approach is considered acceptable and is not thought to have impacted on study results. The main causes of pre-terminal death in the mouse study were neoplastic lesions and non-neoplastic lung lesions associated with an increase in alveolar macrophages and eosinophilic material likely related to the primary pharmacological action of siponimod. A non-dose dependent statistically significant increase in lymphomas was observed in all female treatment groups with a statistically significant increase in hemangiosarcomas evident in multiple tissues in all treated groups of both sexes. Mouse lymphomas appear to be a class related effect of S1P modulators. Although no increased risk of lymphoma associated with siponimod administration has been identified in the clinical development program to date, it should be noted that individual cases of lymphoma associated with fingolimod administration have been reported. Hence, the relevance of these findings to human risk cannot be excluded at present. These findings are therefore included in section 5.3 of the Summary of Product Characteristics (SmPC). A non-dose dependent increased incidence of hemangiomas and hemangiosarcomas were evident in all siponimod treated groups. The potential mechanisms underlying this finding were investigated in dedicated *in vitro* and *in vivo* non-GLP mechanistic studies.

In the rat study, oral siponimod administration was not associated with any significant reduction in survival. Increased incidence of thyroid follicular cell adenoma was evident in all male treatment

groups with an increase in the incidence of thyroid follicular cell carcinoma evident in mid and high dose male groups. This mechanism of action was investigated in an *in vivo* mechanistic study in male rats.

Mechanistic studies

Additional *in vivo* and *in vitro* studies examining the potential molecular mechanisms underlying the observed positive results in the pivotal carcinogenicity studies were performed in rats and mice. The *in vivo* studies of 39 and 13-week duration in mice and rats respectively examined the time-course of molecular changes and species-related differences which may be related to the development of hemangiosarcomas observed in mice. Siponimod administration in mice was associated with a non-dose dependent sustained increase in plasma concentration of PLGF-2, a pro-angiogenic placental growth factor, and a sustained increase in mRNA expression of endothelial cell activation and mitotic related genes in skeletal muscle. In contrast, in rats the siponimod induced increase in PLGF-2 was more variable and transient, peaking between day 3 and 7 with no significant difference evident after that up to 13 weeks dosing. Similarly, the siponimod induced increase in mitotic related genes in rat is less robust than in the mouse study and was only evident at day 3 post treatment. The applicant's suggestion that these species related differences in angiogenic and mitotic markers may underlie the observed differences in susceptibility to hemangiosarcomas is reasonable. A further *in vitro* study examining the effects of siponimod on cultured vascular endothelial cells reports that siponimod treatment is associated with proliferation of mouse vascular endothelial cells, but not human or rat. When considering the totality of the data presented and considering that similar results were reported in pivotal carcinogenicity studies with fingolimod it is accepted that this is likely a mouse-specific effect.

The applicant also presented data demonstrating that siponimod administration is associated with an increase in liver T4-UDP-GT activity and increased circulating thyroid stimulating hormone concentration in rats. Thyroxine concentrations were not assessed. This was associated with increased liver and thyroid gland weight. This is a known rat specific effect and it is accepted that the increased incidence of thyroid follicular cell carcinomas observed in the pivotal rat carcinogenicity study is unlikely to be relevant for the assessment of human risk.

Reproductive and developmental toxicity

Male fertility was assessed in a stand-alone study at doses up to 200 mg/kg. At this dose level the animals displayed weight loss and reduced food consumption. Although epididymal weights were reduced there was no functional consequence on male fertility parameters.

The doses selected for the female fertility and early embryonic development study were based on the findings from the embryo-foetal studies and therefore the top dose was limited to 1 mg/kg. No effects on female fertility or early embryo foetal development were noted. Food intake was reduced in the premating period at doses ≥0.3 mg/kg which defined the maternal NOAEL at 0.1 mg/kg. The NOAEL for early embryo-foetal development was considered to be 1 mg/kg. Based on the toxicokinetics measured this represents a 16-fold margin of exposure at the clinical dose of 2 mg daily.

In the rat embryo-foetal development study clear teratogenic effects and embryo lethality were seen in the absence of maternal toxicity with 100% resorptions seen at doses ≥1 mg/kg/day. For this reason, the examination of foetuses for malformations and variations was only possible in the lowest dose group of 1 mg/kg. The observed malformations included cleft palate, malrotated limbs, cardiomegaly and oedema. Of note, fingolimod was also shown to be teratogenic in rats at very low doses ≥0.1 mg/kg suggesting a class effect of S1P modulators. No NOAEL could be defined in the study and the exposure margin at the LOAEL of 1 mg/kg was 19-fold. Embryolethality without maternal toxicity was also observed in the embryo-fetal development (EFD) study of siponimod in rabbits. Generalized oedema in

several foetuses of the low dose and one foetus of the 1 mg/kg/day mid dose group in the rat EFD study were related to siponimod treatment due to the effect of siponimod on vascular permeability by modulating intercellular junctions. Visceral examinations additionally revealed a higher incidence for small gallbladders in the relatively small number of foetuses that could be evaluated in the 5 mg/kg/day high dose siponimod group. Thus, the NOAEL for embryo-foetal development was set at the lowest siponimod dose of 0.1 mg/kg/day. Siponimod was below the LoQ at this dose level at some of the time points or was only marginally above the lower limit of quantification (LLOQ) (5 ng/ml) resulting in calculated $AUC_{0\text{-}24\ h}$ extrapolated from the 1 mg/kg mid dose group. Hence, no safety margin could be determined at the NOAEL for embryo-foetal development with respect to clinical exposure at the 2 mg daily dose (0.2 fold the exposure level), whereas the NOAEL for maternal toxicity of 1 mg/kg/day corresponds to a margin of exposure of 1.7 fold. In view of the observed embryonic malformations and the lack of any safety margins, the use of siponimod during pregnancy and by women of childbearing potential not using effective contraception has been contraindicated in line with fingolimod.

A pre- and post-natal development study was performed in rats. In the F0 generation dams showed increased gestation length and increased numbers of dead/malformed pups together with clinical signs and decreased body weights. Survival of the F1 generation pups was reduced postnatally. Those pups which were born had increased external, urogenital and skeletal anomalies. As adults there were no effects on reproductive function or behavioural defects. Of importance, although some changes in immunophenotyping were seen in the F1 generation, there were no differences in the TDAR responses to KLH challenge suggesting that the antibody response to antigens was not overtly affected in the F1 generation. The NOAEL for the F0 and F1 generations was the same at 0.05 mg/kg. Toxicokinetics were not performed as part of the study, however, based on extrapolation from the 1 mg/kg dose in the rat EFD study it is expected that the maternal exposure levels were approximately 0.9-fold the expected clinical exposure at 2 mg siponimod per day. Therefore, no safety margin concerning prenatal and postnatal development could be established.

Local Tolerance

The contact sensitising potential of siponimod was assessed in a murine local lymph node assay. Skin and eye irritation were assessed in rabbits. All studies were conducted according to GLP. Siponimod was a weak skin irritant in mice, which was attributed to test article remnants, without any significant findings in rabbits. There was no siponimod-related local irritation evident following a single administration to rabbits via intravenous, peri-venous or intra-arterial routes of administration. The data suggest that siponimod is unlikely to produce local irritation following dermal contact or when administered parenterally.

Other toxicity studies

Immunotoxicity

A stand-alone immunotoxicity study consisting of immunophenotyping and a TDAR was performed in rats following a period of 4 weeks dosing at levels up to 50 mg/kg. In all dose groups marked decreases in peripheral blood and splenic T cell subset counts were noted in line with the expected pharmacology. Marked decreases in T helper and cytotoxic T cell populations were also seen with mild to marked decreases in peripheral blood and splenic B cells. The primary and secondary response to the TDAR was decreased at all dose levels. Of note, these effects on immunophenotyping and the TDAR were reversible following 6 weeks of recovery. Similar effects on immunophenotyping and the TDAR were also seen in monkeys when assessed as part of the repeat dose toxicity studies, although the recovery was not complete at the end of the recovery period. In rats as part of the PPND the TDAR in the F1 generation

did not indicate an effect of siponimod treatment. Taken together the data suggest that the immunomodulatory effects siponimod are reversible upon treatment withdrawal.

Dependence

The dependence potential of siponimod was assessed in GLP compliant studies in rats. Rats displayed no test-article related withdrawal effects as assessed via body weight gain, food consumption and observations (grooming, rearing, activity in a novel environment) and no reinforcing effects were evident in at the highest dose tested. These data and the lack of off-target binding activity at proposed clinical exposures do not indicate a risk for abuse or dependence associated with siponimod.

Metabolites

No dedicated studies assessing the toxicity of major human metabolites M3 and M17 have been carried out. Metabolite concentrations were not measured directly in repeat-dose toxicity studies but were instead inferred based on the ratio of metabolite to parent present in non-GLP PK studies. Given the primary human metabolites were identified after the completion of pivotal repeat-dose toxicity studies, this approach was accepted. Of note, no pharmacological activity on S1P modulation was evident for M3 and the activity of M17 was significantly lower than that of siponimod.

Impurities

The applicant has assessed impurities for mutagenicity in-silico via an expert based (DEREK) and statistical based (MCASE) system as per ICH M7 guidance. Impurities with a structural alert were tested in bacterial reverse mutation assays. Several potential impurities were found to be genotoxic; they are controlled at the Threshold of Toxicological Concern (TTC), or are considered purged below the TTC. Several other impurities tested in AMES tests due to potential structural alerts were shown not to be genotoxic. Although the study reports for these AMES tests have been submitted, the studies were only performed in accordance with the principles of GLP but not in full GLP compliance. Nevertheless, this was accepted, and the identified impurities are regarded as non-genotoxic

Phototoxicity

Siponimod maximally absorbs at ~260 nm, but its MEC of 3309 $l \cdot mol^{-1} \cdot cm^{-1}$ at 290 nm was still above the 1000 $l \cdot mol^{-1} \cdot cm^{-1}$ trigger value. Consequently, the phototoxic potential of siponimod was investigated in line with ICH S10 requirements (EMA/CHMP/ICH/752211/2012). Nevertheless, siponimod was not phototoxic or cytotoxic up to 100 µg/ml in a 3T3 NRU assay performed with UVA irradiation *in vitro*. Higher concentrations of 316 and 1000 µg/ml could not be tested due to test item precipitations. Although the more appropriate UVB range (280-315 nm) was not studied, assay repetition was not deemed necessary, because the absorbance curve of siponimod declines at wavelengths <320 nm.

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) of siponimod is in accordance with the pertinent guideline (EMEA/CHMP/SWP/4447/00 corr. 2) and does not indicate risks for organisms in surface water, groundwater and for microorganisms.

A risk assessment for the terrestrial compartment is not required due to the low binding affinity of siponimod to sewage sludge. Due to a log Dow >3, a study on bioconcentration in fish has been submitted. As the derived BCF values were clearly below the trigger value of 2000, siponimod is not considered bioaccumulative according to the B criterion of the PBT assessment. The risk ratio for secondary poisoning for siponimod is below 1 and therefore indicates no concern for secondary poisoning via the aquatic food chain.

Siponimod is not a PBT substance but has to be classified as very persistent (vP) in sediments based on a DT50 of >180 days in sediment at 20°C determined in a transformation study in water/sediment systems. The applicant was requested to recalculate the half-lives should by using the k2 values and to normalise these values to 12°C. These updates are included in the updated ERA Table 1: Transformation products >10 % were not detected. The T criterion (NOEC <0.01 mg/l) is also fulfilled due to a NOEC of 0.0054 mg/l for fish.

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

Table 1: Summary of main ERA study results

Substance (INN/Invented Name): Siponimod			
CAS-number (if available): 1234627-85-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	log Pow at pH 4 = 5.65 log Pow at pH 7 = 5.28 log Pow at pH 10 = 4.81	Potential PBT (YES)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	429/336 L/kg	not B
Persistence	DT50	OECD TG 308 $DT_{50,\ total\ system,\ 12°C}$ = 182.5/127.4 days	vP
Toxicity	NOEC or CMR	0.0054 mg/L	T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.01	µg/L	>0.01 threshold (YES)
Other concerns (e.g. chemical class)			(NO)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc = 691 (sludge) Koc = 602 (sludge) Koc = 161 611 (loamy sand) Koc = 315 108 sandy loam) Koc = 217 060 (loam)	terrestrial studies not triggered
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water,\ 12°C}$ = 1.5/2 day $DT_{50,\ sediment,\ 12°C}$ = 397/405.6 days $DT_{50,\ whole\ system,\ 12°C}$ = 127.4/182.5 days $DT_{90,\ water,\ 12°C}$ = 11.6/14.2 day $DT_{90,\ sediment,\ 12°C}$ = 2625.4/4226.3 days $DT_{90,\ whole\ system,\ 12°C}$ = 2924.3/4226.3 days % shifting to sediment = 75.7 %/ 75.6 % at 14 days (parent + NER) $NER_{test\ end}$ = 21.4 %/24.0 % No relevant Transformation Products	River (Corg: 1.4 %)/ pond (Corg 4.9 %)

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	370	µg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	220	µg/L	
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	5.4	µg/L	*Danio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	10^{-6}	µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF_{klg} (kinetic, growth + lipid corr.)	429/ 336 L/kg	L/kg	5 % lipids, BCF based on TR, CT50: 4.3/ 5.2 d
Sediment dwelling organism	OECD 218	NOEC	2380	mg/kg	*Chironimus riparius*; normalised to 10 % Corg

2.3.6. Discussion on non-clinical aspects

Pharmacology

Sufficient *in vitro* evidence has been presented to suggest that siponimod is relatively selective for binding to S1P1 and S1P5. Binding of siponimod to S1P1 results in functional antagonism as a result of internalisation of the receptor. In contrast, binding to S1P5 results in agonist effects which may help to mediate the remyelination effects that have been seen in some animal models with the use of siponimod. Efficacy has been demonstrated in both rat and mouse models of experimental autoimmune encephalomyelitis which mostly correlated with the expected pharmacodynamic effect of reducing peripheral lymphocyte counts. Taken with the known clinical efficacy of the first-in-class S1P modulator, fingolimod, sufficient proof of concept has been shown.

The secondary pharmacology screen did not reveal any results of concern. The safety pharmacology package, and in particular the cardiovascular studies, are comprehensive and provide plausible explanations for the noted effects on heart rate and atrioventricular conduction. The proposed clinical titration regimen of siponimod until maintenance therapy is reached on day 6, is supported by the improved safety of escalating siponimod doses in telemetered monkeys.

Pharmacokinetics

Pharmacokinetic and ADME studies were performed in mouse, rat, monkey and human. Overall the ADME properties of siponimod were characterized by slow to moderate absorption rate (tmax was between 2 to 8 h in mouse, rat and monkey after po dosing), a moderate bioavailability, a medium volume of distribution including distribution in the brain and a low clearance. Data are in line with human data showing a tmax between 3-8 hours with a median of 4 hours. The terminal plasma elimination half-life was moderate in male rat and longer in mouse, female rat, monkey, and human. Siponimod was eliminated mainly by metabolism, and subsequent biliary/fecal excretion with no or negligible contribution by elimination into urine in all species. Plasma protein binding was very high in all species.

Methods of analysis

In general methods for analysis for the assessment of siponimod concentrations in relevant matrices were appropriately validated in line with the European guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr. 2**) with some minor deviations unlikely to affect the validity of results.

Metabolite exposure

Concentrations of metabolites M3 and M17 were not directly assessed in pivotal repeat-dose toxicity studies. Instead, levels in these studies were inferred based on the ratio of metabolite to parent observed in non-GLP PK and exploratory studies in relevant species, and no method validation has been submitted for the methods of analysis used to determine metabolite concentrations in these studies. M3 and M17 were identified after pivotal repeat-dose toxicity studies were completed at which time no TK retention samples from those studies were available. Although the approach was not in line with ICH S3A guidance, the CHMP agreed with the provided justification for this approach and that the safety of metabolites M3 and M17 were adequately qualified in pivotal non-clinical repeat-dose toxicity studies.

Toxicology

A significant margin of exposure exists from the identified NOAELs in the repeat dose toxicity studies and the clinical exposure levels at the clinical dose of 2 mg daily. In relation to the reproductive and developmental toxicology, significant findings of embryo-foetal toxicity and teratogenicity were seen at dose levels less than the clinical exposure levels and were attributed to the pharmaceutical class of S1P modulators because similar findings were seen with fingolimod. Due to the role of S1P modulators like siponimod during embryonic vascular development, it can be assumed that siponimod might cause foetal harm when used in pregnant women. Therefore, a contraindication on the use of siponimod during pregnancy and in women of childbearing potential not using effective contraception was included in section 4.3 of the SmPC with additional information on this risk provided in sections 4.4, 4.6 and 5.3. This is in line with the PI for pharmacologically related compound fingolimod.

Tumor findings were reported in 104-week carcinogenicity studies in both mice and rats. *In vitro* and *in vivo* mechanistic studies that examined the time course of molecular changes prior to the development of neoplastic thyroid follicular cell lesions and hemangiosarcomas in rats and mice suggest that these findings are likely species-specific effects, which were labelled as such in section 5.3 of the SmPC in line with fingolimod. Skin carcinoma was detected in the scrotum of a single male monkey in the 52-week carcinogenicity study. Although this finding was not replicated in carcinogenicity studies in rats or mice, given the established involvement of the S1P1 receptor in tumorigenesis, a warning regarding cutaneous neoplasms has been included in the product information of siponimod in line with the currently approved version of fingolimod.

A risk for the environment due to use of siponimod by patients is not expected.

2.3.7. Conclusion on the non-clinical aspects

Siponimod was evaluated in safety pharmacology and repeated dose toxicity studies in mice, rats and Cynomolgus monkeys as well as in studies to assess genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerability, photoreactive potential, immunotoxicity and dependence and abuse potential.

Overall, the primary pharmacodynamic studies provided adequate evidence that siponimod's immunomodulatory effects are due to its S1P1-mediated ability to induce sequestration of lymphocytes within secondary lymphoid organs, hence, reducing the permeation of lymphocytes into the CNS. The potential binding to S1P1 receptors on astrocytes and/or S1P5 receptors on oligodendrocytes, may additionally impact on neuronal inflammation as well as demyelination and remyelination processes. In safety pharmacology studies, findings related to the modulation of S1P1 were identified. These included transient and slight effects on the cardiovascular system and on the respiratory system. No relevant effects were identified in the CNS safety pharmacology study in rat.

Pharmacokinetic and ADME studies were performed in mouse, rat, and monkey. Oral bioavailability of siponimod was high in all species. Absorption of siponimod in animals after oral administration was slow to moderate, with tmax of 2-8 hours. Siponimod distributed to most tissues in rodents and was detected in the brain, with exposures 5-16-fold those in plasma, respectively; highest exposure was observed in white matter.

In repeat-dose toxicity studies in mice, rats and monkeys, siponimod markedly affected the lymphoid system (lymphopenia, lymphoid atrophy and reduced antibody response), which is consistent with its primary pharmacological activity at S1P1 receptors.

Dose-limiting toxicities in animal species were nephrotoxicity in mice, body weight development in rats and adverse CNS and gastrointestinal effects in monkeys. The main target organs of toxicity in the three species included the lung, liver, thyroid, kidney and uterus/vagina. In monkeys, vasculopathies and effects on muscle and skin were additionally observed. These toxicities developed at more than 30-fold higher systemic siponimod levels than the AUC-based human exposure at the maintenance dose of 2 mg/day.

Siponimod did not exert any phototoxic, and dependence potential and was not genotoxic *in vitro* and *in vivo*.

Taking into account the established role of S1P1 receptors in vascular formation during embryogenesis, the absence of any safety margins with regard to therapeutic siponimod exposure and the consistent non-clinical and clinical experience gained meanwhile with fingolimod, the use of siponimod during pregnancy and by women of childbearing potential not using effective contraception has been contraindicated.

In carcinogenicity investigations, siponimod induced lymphoma, haemangioma and haemangiosarcoma in mice, whereas follicular adenoma and carcinoma of the thyroid gland were identified in male rats. These tumour findings were either regarded as mouse-specific or attributable to metabolic liver adaptations in the particularly sensitive rat species and are of questionable human relevance, which has been clarified in the SmPC accordingly.

Based on the available non-clinical data regarding pharmacodynamics, pharmacokinetic and toxicology of siponimod, the application was considered approvable.

2.4. Clinical aspects

2.4.1. Introduction

Siponimod was characterised in a clinical pharmacology program including 20 studies in healthy subjects and special populations. Once daily dosing was determined based on pharmacokinetic and primary pharmacodynamic results.

The clinical development program in MS consists of two randomized, controlled studies; a Phase 2 study CBAF312A2201 and its long-term extension study CBAF312A2201E1 in patients with RRMS and a Phase 3 study CBAF312A2304 in SPMS with a core part and extension part.

GCP

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

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

Table 2: Tabular overview of clinical studies

Study No	Study objective	Study design
Pharmacokinetic studies		
A2101	SAD study to explore safety, tolerability, PK and PD	Two-part, single center, randomized, double-blind, placebo-controlled, SAD Phase 1 study
A2102	MAD study to evaluate safety, tolerability, PK and PD	Randomized, parallel, double-blind, placebo-controlled, time-lagged, MAD Phase 1 study
A2105	MAD study to evaluate safety, tolerability, PK and PD (repeat of Study A2102)	Randomized, parallel, double-blind, placebo-controlled, time-lagged, MAD Phase 1 study
A2104	Single dose ADME study in healthy subjects with the CYP2C9*1*1 genotype	Open-label, single oral dose Phase 1 study
A2111	Single dose study in healthy subjects with the CYP2C9*1*1 genotype to assess both the bioequivalence of the siponimod FMI tablet formulation as compared to the siponimod MF and the effect of food on the PK of the FMI	Randomized, open-label, 3-period, 3-treatment, 6-sequence, single dose, crossover Phase 1 study
A2119	Single dose study to assess the tolerability, PD and PK of 2 MR siponimod tablets (F16, F10) compared to the IR tablet (MF) and placebo	Randomized, double-blind, placebo-controlled, parallel group, single dose Phase 1 study
A2125	Multiple dose, 2-period, single-sequence study in healthy subjects with the CYP2C9*1*1 genotype to evaluate the effect of the CYP2C9/3A4 inducer rifampin on siponimod PK	Open-label, 2-period, drug interaction Phase 1 study
A2108	Single dose study in healthy subjects with the CYP2C9*1*1 genotype to evaluate the safety, tolerability and PK of siponimod when given alone and in combination with the CYP2C9/3A4 inhibitor fluconazole	Open-label, single dose, 2- period, drug interaction Phase 2 study
A2124	Single dose study in healthy subjects with CYP2C9*1*2 and *1*3 genotypes to evaluate the effect of the CYP3A4 inhibitor itraconazole on siponimod PK, safety, and tolerability	Open-label, 3-period, single sequence, crossover, drug interaction Phase 1 study
A2121	Multiple dose study in female healthy subjects with the CYP2C9*1*1 genotype to evaluate the effect of oral siponimod on the PK and PD of monophasic oral contraceptive	Open-label, multiple dose, 2-period Phase 1 study
A2126	Single dose, 2-part study in healthy subjects with the CYP2C9*1*1 genotype to measure the absolute bioavailability, safety, tolerability, and PD of oral and iv siponimod	Open-label, single dose, 2-part Phase 1 study
A2122	Single dose study in subjects with the CYP2C9*1*1 to compare the PK, safety and tolerability of siponimod in subjects with mild, moderate and severe hepatic impairment and healthy control subjects	Single dose, open-label, parallel-group Phase 1 study
A2129	Single dose study in CYP2C9*1*1 subjects (wild type genotype) to compare the PK, safety and tolerability of siponimod in subjects with renal impairment and normal renal function	Single dose, open-label, parallel-group Phase 1 study
A1101	SAD study to evaluate safety, tolerability, PK and PD in Japanese subjects	Randomized, double-blind, placebo-controlled, ascending single dose Phase 1 study
A2128	Study to assess the safety, tolerability, and PK of siponimod in subjects with CYP2C9 extensive metabolizers (CYP2C9*1*1 genotype) and poor metabolizers (CYP2C9*2*3 or *3*3 genotype)	Open-label, 2-part, single and multiple dose Phase 1 study
Pharmacodynamic studies		
A2107	DT and fixed multiple dose study to investigate the negative chronotropic effect of siponimod	Double-blind, placebo-controlled, parallel-group Phase 1 study
A2110	Multiple dose study to investigate the effect of siponimod treatment re-initiation on the initial negative chronotropic effect	Randomized, partially double-blind, placebo-controlled Phase 1 study with 3 periods (10 days of single dose drug treatment, drug discontinuation, 1 day of single dose drug re-initiation)

A2130	Multiple dose study to evaluate the modulation of immune response to T-cell dependent and T-cell independent antigen stimuli by preceding, concomitant and interrupted administration of multiple therapeutic doses of siponimod	Randomized, double-blind, placebo-controlled, parallel-group, multiple dose Phase 1 study
A2116	Multiple dose study to evaluate PD and/or PK interaction of siponimod and propranolol co-administration	Randomized, double-blind, placebo-controlled, multiple dose Phase 1 study
A2118	Multiple dose thorough QT study to assess the effects on QT interval (cardiac repolarization) at oral therapeutic and supratherapeutic doses of siponimod	Randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled Phase 1 study

Controlled efficacy studies – Phase 2 and 3

Study	Study objective/ Population	Patients randomized	Dosage	Treatment duration	Primary and secondary endpoints
Phase 3 A2304 Core Part	Randomized, double-blind, multi-center, placebo-controlled in patients with SPMS	1651	Placebo, 2 mg	Variable, <1 month to 37 months	3mCDP, 6mCDP, time to 3m confirmed 20% worsening on T25W, change in T2 lesion volume, change in brain volume, Gd-enhancing and new/enlarging T2 lesion counts, ARR, MSWS-12
Phase 2 A2201	Randomized, double-blind, multi-center, placebo-controlled, adaptive dose ranging in patients with RRMS	297	**Period 1:** Placebo 0.5 mg, 2 mg, 10 mg **Period 2:** Placebo, 0.25 mg 1.25 mg	**Period 1:** 6 months **Period 2:** 3 months	Number of CUAL, Gd-enhancing and new/enlarging T2 lesions counts, annualized relapse rate

Uncontrolled long-term efficacy studies – Phase 2 and 3

Study	Study objective/ Population	Patients randomized	Dosage	Treatment duration	Primary and secondary endpoints
A2201E1 Dose-blinded phase and open-label phase	Randomized, multi-center, dose-blinded study (no placebo) followed by open-label in patients with RRMS from A2201	184	0.25 mg, 0.5 mg, 1.25 mg, 2 mg, 10 mg (dose-blinded); 2 mg (open-label)	5 years (median 63.6 months) median exposure 24 months (dose blinded) and 41 months (open-label)	Number of CUAL, Gd-enhancing and new/enlarging T2 lesion counts, disability progression, ARR, change in brain volume

A2304 Extension Part (ongoing)	Open-label in patients with SPMS from Core Part of A2304	1220	2 mg	Up to 23 months (at data cut-off of 31-Dec-2017)	Same as Core Part

2.4.2. Pharmacokinetics

PK/PD data were derived from 15 clinical pharmacokinetics studies, pooled PK, pooled categorical analyses of primary and secondary PD effects of siponimod in Clinical Pharmacology, polymyositis (PM)/dermatomyositis (DM) patient studies and 2 Population PK analyses and an exposure-lymphocyte relationship analysis, which include data from MS patients in Studies A2201 and A2304.

In the 20 Clinical Pharmacology studies, a total of approximately 1281 subjects have been enrolled, of which approximately 880 healthy subjects, 24 hepatic impaired subjects and 8 renal impaired subjects have received siponimod and approximately 434 healthy subjects have received placebo. This includes subjects who sequentially received placebo and siponimod. In addition, approximately 363 healthy subjects were exposed to other study drugs either alone or in combination with siponimod.

Methods

Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods were used for quantification of siponimod (BAF312) and its metabolites in plasma and urine. The methods were mainly validated at a CRO and subject to audit by the site QA. Non-compartmental analysis, Pop PK and PD analyses were conducted using conventional software and methods.

Three population PK models were developed to investigate the influence of different covariates e.g. genotype, weight, co-medication on siponimod exposure along with smoking status and for PK/PD analyses of the effect of siponimod on lymphocyte counts, EDSS and infections in MS patients. A PBPK model using SimCYP was developed for prediction of siponimod Drug-Drug Interactions (DDI) with typical CYP perpetrators.

The population PK model for healthy volunteers (HV) and RRMS patients was a two-compartment disposition model with first-order elimination and mixed zero- and first-order absorption. No major PK difference was observed between the two populations. Body weight affected Cl and Vd. CYP2C9 genotype had significant impact on siponimod PK by affecting Cl. Food effect had impact on Tmax only.

A Pop PK model, including data from 1045 SPMS, patients was developed based on the previous PK model in HV and RRMS patients. Weight on CL/F and Vc/F as well as age, gender and CYP2C9 genotypes WT/*3 and *2/*3 on CL/F were significant covariates.

A PK/PD model was developed linking siponimod plasma concentrations to lymphocyte counts in HV, RRMS and SPMS patients. Lymphocyte count was lower in siponimod treated subjects compared to placebo.

A PBPK model was build using SimCYP. The model was verified by data from various studies: single ascending dose (SAD), multiple ascending dose (MAD), an absolute bioavailability study, a CYP2C9 genotype study, Pop PK and two DDI studies with fluconazole and rifampicin. All were in good agreement with predicted.

Absorption, Distribution, Metabolism, Elimination/Excretion

Table 3: Main PK parameters after siponimod single dose administration (0.1 to 75mg) to healthy subjects

Siponimod Treatment	0.1 mg[a] (N = 11)	0.3 mg[a] (N = 8)	1.0 mg[a] (N = 8)	2.5 mg[a] (N = 6)	2.5 mg[b] (N = 7)	5.0 mg[b] (N = 8)	10.0 mg[b] (N = 8)	17.5 mg[b] (N = 8)	25.0 mg[b] (N = 8)	75.0 mg[b] (N = 8)
Tlag (h)[c]	0.25 (0.00-0.27)	0.00 (0.00-0.25)	0.00 (0.00-0.25)	0.13 (0.00-0.25)	0.75 (0.50-0.77)	0.25 (0.00-0.50)	0.25 (0.00-0.50)	0.25 (0.00-0.52)	0.25 (0.00-0.50)	0.25 (0.25-0.50)
Tmax (h)[c]	4.00 (3.00-8.00)	5.00 (4.00-8.00)	5.00 (4.00-15.67)	4.00 (3.00-8.00)	6.00 (4.00-8.02)	3.00 (2.00-8.02)	5.00 (3.85-16.00)	4.00 (2.00-8.00)	3.50 (1.50-12.00)	6.00 (2.00-24.00)
T1/2 (h)[d]	33.06 [26]	33.21 [28]	45.68 [26]	27.02 [22]	29.31 [17]	31.27 [19]	32.03 [17]	42.32 [38]	47.68 [20]	56.69 [12]
Cmax (ng/mL)[d]	0.618 [39]	2.26 [6]	7.43 [42]	21.9 [35]	19.3 [19]	38.5 [21]	77.3 [25]	111 [32]	217 [29]	491 [51]
AUCinf (h*ng/mL)[d]	24.6 [39]	89.3 [20]	349 [28]	766 [36]	745 [25]	1260 [20]	2710 [14]	4230 [25]	8140 [24]	18600 [51]
AUC0-t (h*ng/mL)[d]	22.9 [41]	87.2 [20]	345 [27]	743 [36]	721 [26]	1240 [21]	2680 [13]	4200 [25]	8110 [24]	18500 [51]
CL/F (L/h)[d]	4.07 [39]	3.36 [20]	2.86 [28]	3.26 [36]	3.36 [25]	3.95 [20]	3.69 [14]	4.14 [25]	3.07 [24]	4.03 [51]
Vz/F (L)[d]	194 [31]	161 [19]	189 [32]	127 [34]	142 [23]	178 [21]	170 [22]	253 [36]	211 [29]	330 [58]

a CSF liquid formulation
b CSF capsule formulation
c Median (min-max)
d Geometric mean [% geometric mean coefficient of variation]

Absorption

In vitro, siponimod was classified as a highly permeable compound. Intestinal uptake data of siponimod suggest that luminal membrane permeability occurs most likely by a passive permeation process without an involvement of drug efflux transporters.

- **Bioavailability**

Bioavailability was studies in 5 studies: A2101, A2102, A2105, A2104, and A2126. Dose proportionality between dose and Cmax or AUC, respectively, was observed until a dose of 75 mg. No plateau appeared. The proposed posology of 2 mg falls within the range where dose proportionality was demonstrated. Tmax was approximately 3-6 hours with no apparent dose dependency. The decay in siponimod plasma concentration over time is bi-exponential. The effective half-life relevantly contributing to BAF312 accumulation is comprised between 22 h and 36 h and corresponds to the T1/2,α which could be observed after single and multiple dose administrations. The absolute bioavailability was estimated to 84%.

- **Bioequivalence**

Bioequivalence was studied in 2 studies: A2111 and A2119. Bioequivalence was established between the Final Market Image (FMI) and the Market Formulation (MF) in the fasting state.

Compared with the immediate release formulation, Tmax of the modified release formulations was increased (around 2-fold), and the Cmax and AUC were decreased. As such, the Tmax of formulation F16 and F10 were 7 and 8 hours, respectively, whereas Tmax for IR was 4 hours. Cmax and AUC of F16 were around 50 % lower the corresponding values of IR, and Cmax and AUC of F10 were 16% lower the corresponding values of IR. Due to the differences in formulations, the discrepancies in Tmax, Cmax and AUC are considered in line with expectations.

- **Influence of food**

Two clinical studies contributed with data to evaluate the influence on food: A2101 and A2111.

A delayed Tmax of 8 hours was observed in the fed state compared to 3 hours in the fasting state when administering siponimod 5 mg. Cmax was slightly lower in the fed state compared with the fasting state (0.91 [90% CI: 0.79;1.05]), whereas AUC did not differ. For siponimod 0.25 mg and 4 mg FMI, no differences were observed for siponimod 0.25 mg regarding Cmax and AUC, whereas Cmax was lower in the fed state compared with fasting for siponimod 4 mg (0.91 [90% CI: 0.86;0.97]). Despite a delay in Tmax to 8 hours after single dose, food intake had no effect on the systemic exposure of siponimod (Cmax and AUC), therefore siponimod may be taken without regard to meals, as reflected in section 4.2 of the SmPC. The influence of food on the PK after a single dose is referenced in the SmPC Section 5.2.

Distribution

Overall, siponimod was moderately distributed within the human body following oral administration. Siponimod and its metabolites were mainly confined within the plasma compartment and very highly bound to human plasma proteins (>99.9%). The volume of distribution was estimated to 291 L in the ^{14}C ADME study (A2104) and 124 L in the absolute bioavailability study (A2126), which is supported by the pop PK model finding a typical volume of distribution of 126 L.

Elimination

An apparent systemic clearance (CL/F) of 3.11 l/h was estimated in MS patients. The apparent elimination half-life of siponimod is approximately 30 hours.

The ^{14}C ADME study demonstrated that the primary route of elimination was metabolism through hydroxylation and subsequent glucuronidation or sulphation with faecal/biliary excretion. The major metabolite identified in the ^{14}C ADME study (A2104) was M3, whereas another metabolite (M17) was identified as the major metabolite in the absolute bioavailability study (A2126). M17 was not identified after 10 mg siponimod in the ^{14}C ADME study, which is due to short duration of the ADME study. M3 was not identified as an active metabolite, however M17 was estimated to account for 3% of the siponimod activity.

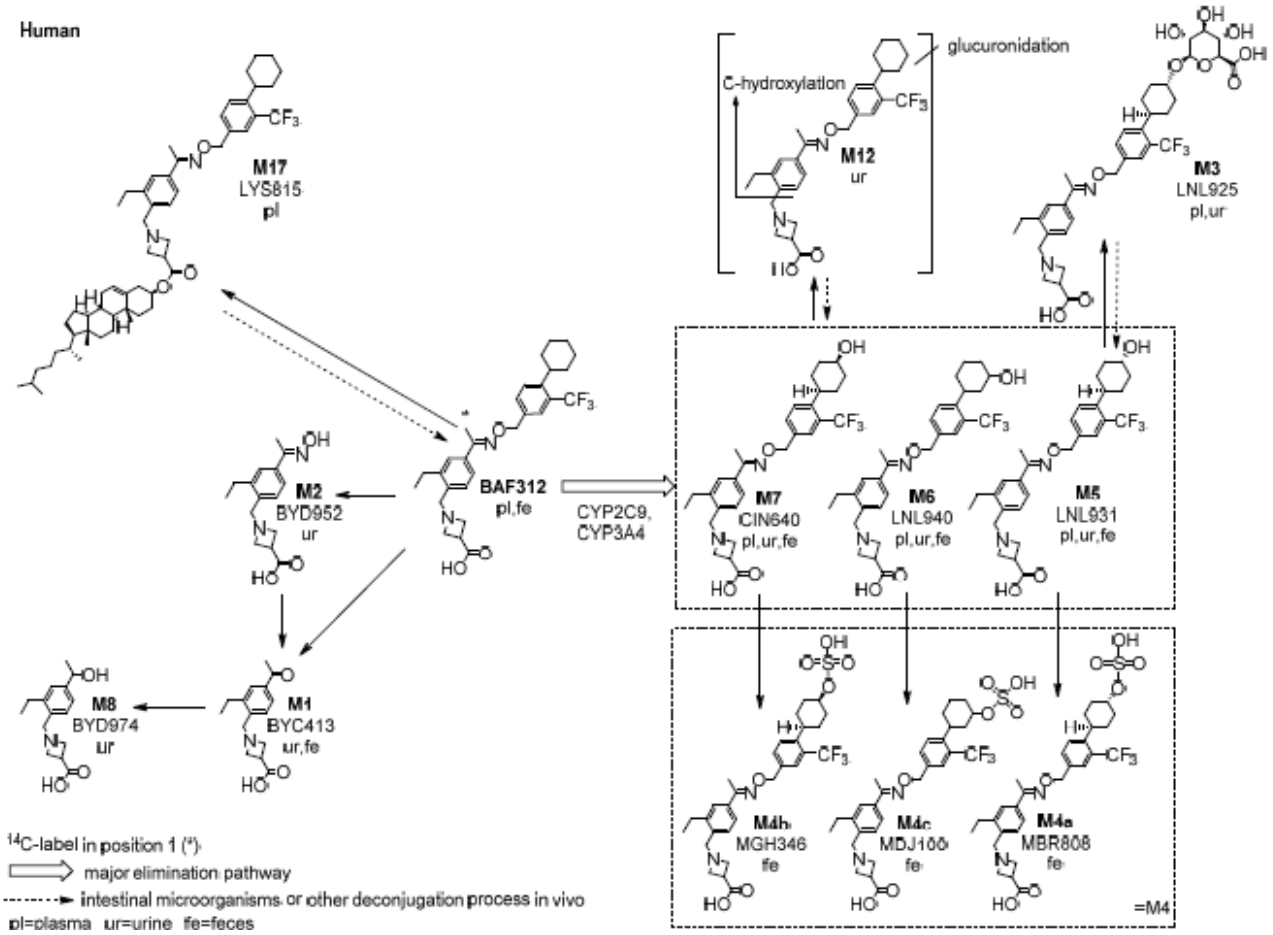
Metabolism

Based on *in vitro* studies, it was estimated that CYP2C9 and CYP3A4 contribute 79.3% and 18.5%, respectively, to the metabolism of siponimod.

The ^{14}C ADME study (Study A2104) demonstrated that siponimod was metabolised to several metabolites, of which M3 was the most prominent, accounting for 18% of the radioactivity. Five other metabolites were identified of which each accounted for 1.5 to 3.7% of the reactivity. Accumulation factors of metabolites P29.6 and P30.5 were estimated to 54.3 and 28.9, respectively, but the metabolite to parent AUCtau,ss ratios are low (0.19 and 0.11 for P29.6 and P30.5, respectively) and the metabolites do not contribute marginally to the total exposure.

The absolute bioavailability study identified M17 as the most prominent metabolite accounting for 81-97% of the parent exposure. M17 was not detected in the ^{14}C ADME study. Considering the long half-life of M17, M17 may form over time and thus the design of the ^{14}C ADME study did not permit M17 detection. The siponimod:M17 ratio after a single dose of 0.25 mg is 1:1, but after one year of 2 mg qd continuous dosing to SPMS patients in the phase 3 study the ratio remains 1:1.

Figure 2: General scheme of Siponimod (BAF312) biotransformation pathways in human

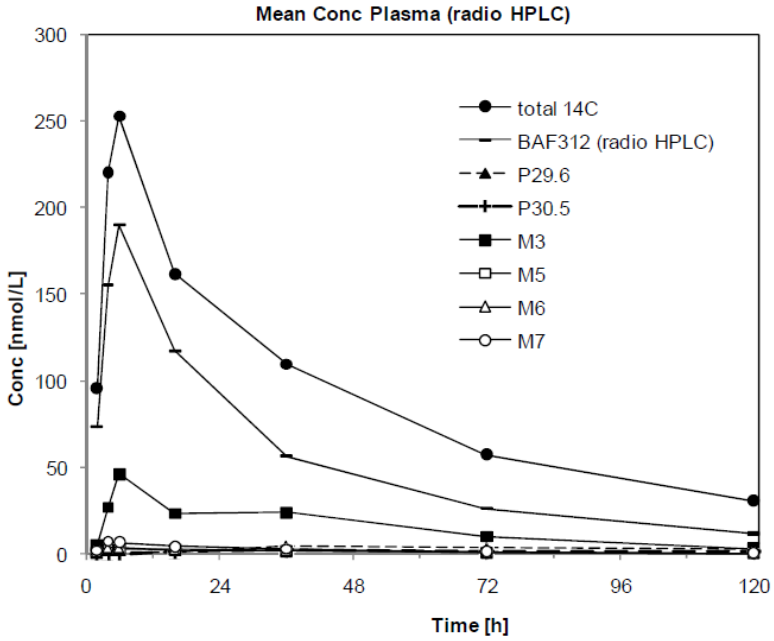


- **Pharmacokinetics of metabolites**

The PK of the main metabolites (M3 and M17) were examined in studies A2104 and A2118 (M3), and in studies A2126 and A2304 (M17). Apart from metabolites M3 and M17, all other metabolites occurred in concentrations below 10% and will, according to guideline, not be assessed further.

In the ^{14}C ADME study (A2104), Tmax of M3 was 6 hours and T½ was approximately 30 hours, which is similar to T½ of siponimod. In the QT study (A2118), M3 represented 33-39 % of AUClast and Cmax,ss of siponimod, which is indicative of a substantial presence of the M3 metabolite. In the absolute bioavailability study (study A2126), Tmax of M17 was estimated to 96 hours and T½ was approximately 155 hours. M17 was measured at end of study in the phase 3 study.

Figure 3: PK of radioactivity, BAF312 and main metabolites in plasma



- **Genetic polymorphism**

Studies have showed that siponimod is mainly metabolised via CYP2C9. In study A2128, in subjects with CYP2C9*2*3 or CYP2C9*3*3 genotype, a 2 or 4-fold increase, respectively, in AUCinf and T½ compared with CYP2C9*1*1 was shown. Likewise, the pharmacokinetic parameters for the metabolites M3 and M5 are delayed or lower in subjects with CYP2C9*3*3 compared with CYP2C9*1*1. No marked Cmax differences between genotypes were observed.

Dose proportionality and time dependencies

- **Dose proportionality**

Dose proportionality across the tested range was determined in single-dose studies (Studies A2101, A2105 and A1101) and multiple-dose studies (studies A2105 and A2201).

- **Time dependency**

Study A2101 investigated single dose administration and study A2105 investigated multiple dose administration. Siponimod exhibits time independent PK (AUCinf after single dose is comparable to the AUCtau,ss after multiple dose). The decay in siponimod plasma concentration over time is bi-exponential. The effective half-life relevantly contributing to BAF312 accumulation is comprised between 22 h and 36 h and corresponds to the T1/2,α which could be observed after single and multiple dose administrations. AUC_{0-24} showed an accumulation index of approximately 2 across all doses after multiple daily dosing.

Intra- and inter-individual variability

Inter-subject variability was assessed in studies A2101, A2105, A1101 and A2128. Furthermore, a pooled analysis including healthy subjects in studies A2105 and A2118 and MS subjects in studies A2201 (RRMS) and A2304 (SPMS). The inter-subject variability of AUC was 10% to 60% in the single dose studies and increased with increasing dose in the multi dose study. The inter-subject variability was larger in the pooled data from SPMS and RRMS patients compared with healthy subjects. Based on popPK analysis, the coefficient of variation for Cl/F was 24.2% in SPMS patients, which is similar to the values of healthy

subjects indicating similar inter-individual variability. Based on estimates of PK-parameters for SPMS, RRMS and healthy subjects, the intra-subject variability is similar between populations.

Pharmacokinetics in the target population

Siponimod was tested in dermatomyositis (DM) and polymyositis (PM) patients as well as in RRMS patients in phase 2. However, patients with secondary progressive MS were only studied in the single pivotal phase 3 study A2304.

The concentrations in steady state in the target population were higher than in healthy volunteers. Thus, due to differences in study design and sampling times between studies in healthy subjects and the target population, direct comparisons are not possible. The simulated PK data are similar to the observed data based on healthy volunteers and RRMS patients. Health status was not a significant covariate in the model. This supports that data obtained in healthy volunteers can be extrapolated to the target population and RRMS patients.

Special populations

RRMS, polymyositis and dermatomyositis patients: In RRMS patients, the plasma concentrations were higher than in healthy subjects due to different sampling time. In patients with polymyositis or dermatomyositis the trough concentrations were 2-fold higher than in healthy volunteers, which could be caused by co-medication (CYP3A4 inhibitors), lower body weight and low sample size.

Impaired renal function (Study A2129): In severe renal impaired subjects, total and unbound AUC were slightly increased (by 23to 33%) compared to heathy matches subjects, whereas Cmax decreased by 8%. No dose adjustment is requested. Small differences in Cmax and AUC of the metabolite M3 between healthy and renal impaired subjects were observed. The metabolite M17 has not been measured in renal impaired subjects, however, it is expected that renal impairment would result in a relative lower level of M17 compared to the parent drug, as M17 is a cholesterol ester metabolite.

Impaired hepatic function (Study 2122): No relevant differences between groups of hepatic impairment were observed. However, for the metabolite M3, markedly increased values of Cmax and AUC were detected. As the affinity to the S1P1 receptor of the metabolite M3 is considered negligible compared to the mother compound, the increases in the metabolite concentrations is regarded as clinically insignificant.

Race: The evaluations of siponimod PK in the clinical study in Japanese subjects and the Phase 1/Phase 2 and Phase 3 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.

Gender: No clinical studies designed to detect possible gender differences were conducted. The popPK model indicated that some differences could be present between gender regarding lymphocyte count. However, the model showed high shrinkage and as such the predictions based on gender should be interpreted with caution. Overall, it is considered justified that no clinically relevant differences based on gender are present.

Weight: Differences in bodyweight did affect siponimod exposure. Effect of weight and CYP2C9 genotype was simulated in SPMS patients receiving a 2 mg daily dose and showed a 5-fold difference between lowest and highest median AUC,ss. However, within the normal weight range, the impact of body weight alone is not considered clinically relevant and no dose adjustment is considered warranted.

Children and elderly:

In the 2 PopPK analyses, age (range assessed: 18 to 61 years) was not identified as a covariate affecting siponimod CL/F. As hepatic and renal impairment do not impact siponimod PK, differences in siponimod PK are not expected between elderly and younger subjects.

No data in children or elderly patients has been generated. This is adequately reflected in the SmPC.

Pharmacokinetic interaction studies

In vitro: Siponimod showed weak inhibition of CYP3A4 (IC50 100 µM) and of CYP2C9 (IC50 230 µM) *in vitro*. Time dependent inhibition of CYP2C9 was demonstrated. Intestinal uptake of siponimod was studied in Caco-2 cells with well-known efflux pump inhibitors. The results pointed to passive permeation as the uptake mechanism without involvement of the efflux transporters P-gp, BCRP or MRP2. Siponimod was shown to inhibit OATP1B1 and OATP1B3 (IC50 1.65 µM and 2.88 µM, respectively). In a hepatic uptake study, it was demonstrated that siponimod hepatic uptake was soley driven by passive permeability without involvement of uptake transporters.

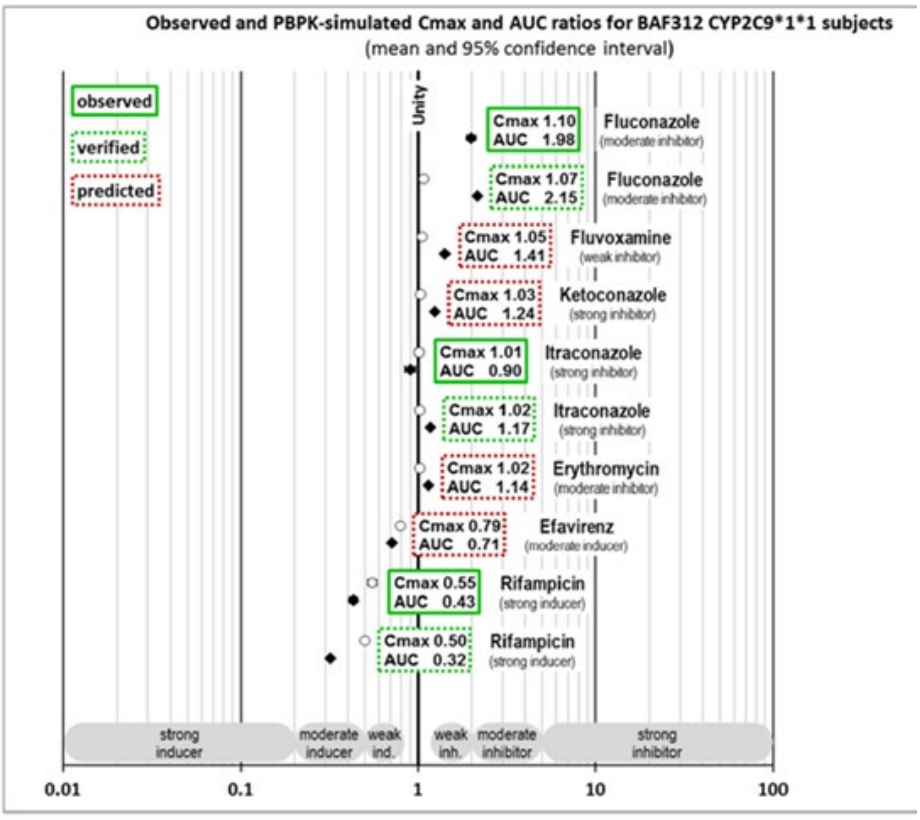
In vitro, the metabolite M3 showed weak inhibition of CYP2B6 (IC50 = 94 µM) and CYP2C9 (IC50 = 80 µM). M3 was an inhibitor of human BSEP and OCT1 with maximal inhibition of 38.5% and 32%, respectively and an inhibitor of OATP1B1 and OATP1B3 with IC50 of 3.7 µM and 4.1 µM, respectively. M17 showed no relevant inhibition of the transport activities of P-gp, BCRP, BSEP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2K at the tested concentrations.

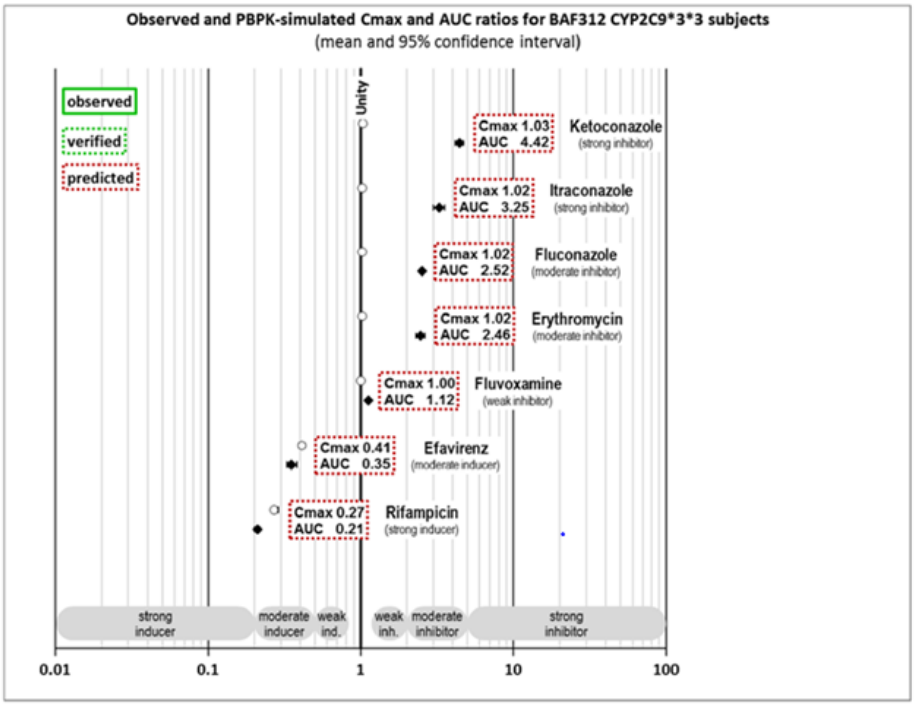
In silico: The Pop PK model for SPMS patients and PD data from study A2304 was used to explore whether or not smoking would affect siponimod PK as smoking is a potent CYP1A1 inducer; this showed that induction of CYP1A1 by smoking have no effect on siponimod PK. Individual plasma concentration-time profiles for smokers and non-smokers showed similar distributions.

Impact of the six different CYP2C9 genotypes on siponimod PK and the drug interaction potential in presence of perpetrators for CYP2C9 and CYP3A4 (itraconazole, fluconazole, ketoconazole, fluvoxamine rifampicin, erythromycin, and efavirenz) were evaluated in silico using SimCyp. Itraconazole, fluconazole and rifampicin were backed up by *in vivo* DDI data with siponimod. There was initially a mismatch between simulated and observed data for interaction with itraconazole, however PBPK simulation including both CYP3A4 and CYP1A1 metabolic pathways could better explain the observed *in vivo* results.

The simulations showed that strong CYP3A4 inhibitors (itraconazole and ketoconazole) in the CYP2C9 *3*3 genotype populations had increased DDI risk with a predicted AUC increase of 3.25 to 4.42-fold. This is adequately reflected in the SmPC. For the moderate CYP3A4 inhibitor erythromycin the *3*3 genotype had 2.5 fold higher AUC than the other genotypes.

Figure 4: Forest plots to summarize the DDI effects of perpetrators for CYP3A and CYP2C9 on BAF312





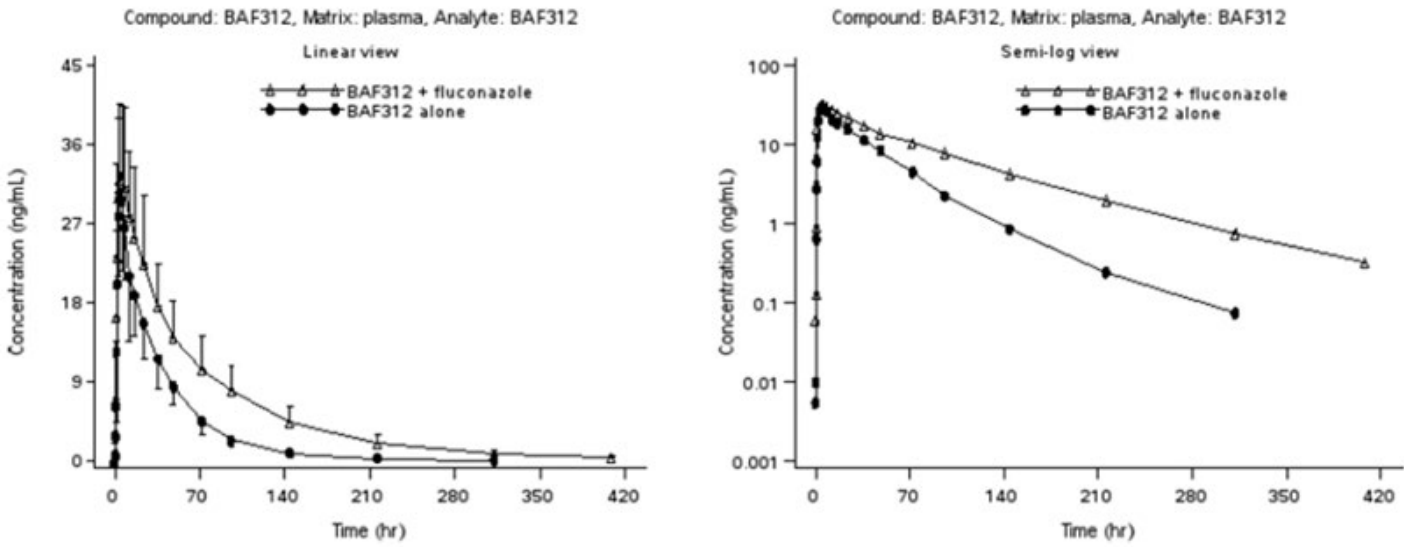
The AUCinf ratio (closed diamond) and Cmax ratio (open circle) of BAF312 were plotted with the respective perpetrator information at the right hand side. The data represented geometric mean with 90% confidence interval, which were taken from Table 6-11 to Table 6-17. The ratios in green closed, green broken and red broken boxes are the measured values, the predicted values with the current BAF312 model which was verified based on the clinical data, and the predicted values without corresponding measured data, respectively. The upper and lower panels show the data in sub-population carrying the CYP2C9 genotypes *1*1 and *3*3, respectively. The observed itraconazole data of the CYP2C9*1*2 population was included in the CYP2C9*1*1 forest plot.

When siponimod is co-administered with a moderate CYP2C9/moderate CYP3A4 dual inhibitor (e.g. fluconazole), the predicted net effect is between 1.78-2.15 fold for *1*1, *1*2, *1*3 and *2*3, the highest effect being estimated for CYP2C9 *2*2 patients, with a net effect of 2.73-fold. The combination of siponimod with moderate CYP2C9 or strong CYP3A4 inhibitor or moderate dual inhibitor should be avoided irrespective of the CYP2C9 genotype.

In vivo:

Study A2108: The potent CYP2C9 inhibitor fluconazole (200 mg qd) given concomitantly with a single dose of 4 mg siponimod increased the AUC of siponimod 2-fold and the Cmax by 10%.This effect is considered clinically relevant; hence dose reduction of siponimod when co-administered with fluconazole or other dual CYP3A4/CYP2C9 inhibitors is recommended and considered adequately reflected in the SmPC.

Figure 5: Arithmetic mean (SD) concentration-time profiles per treatment PK analysis set

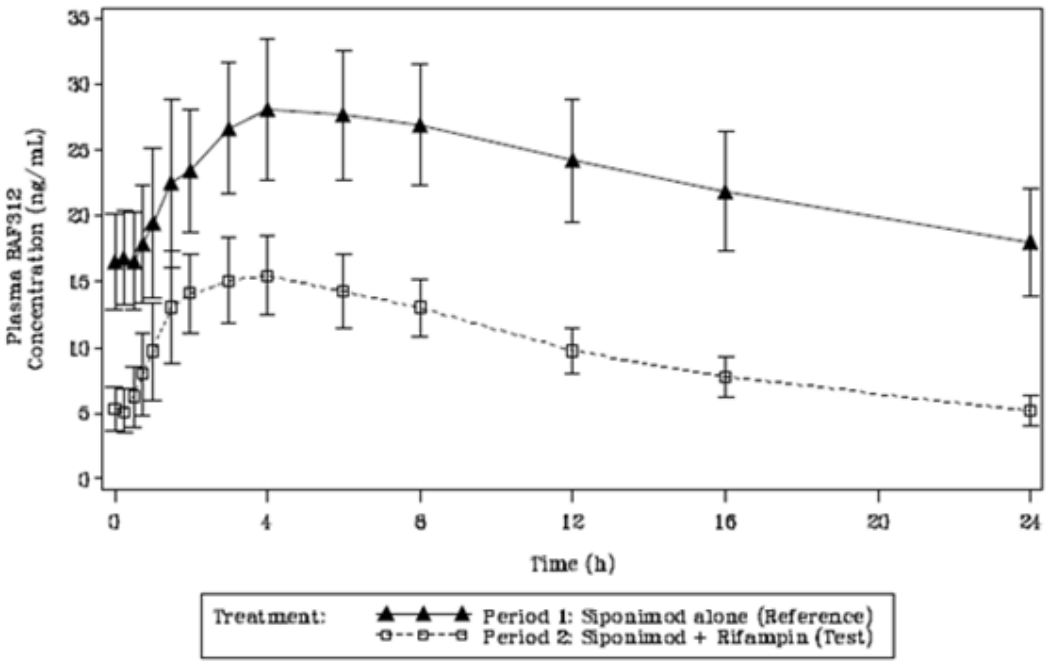


Study A2124: Co-administration of a single 0.25 mg dose of siponimod with itraconazole (a strong CYP3A4 inhibitor) at 100 mg bid decreased siponimod AUCs by 10% and 24% in subjects with the CYP2C9*1*2 and *1*3 genotypes, respectively. For the major metabolite M17 Cmax decreased by 28% and 38% and AUClast decreased by 58% and 77%, in subjects with the *1*2 and *1*3 genotypes, respectively.

Study A2125: In the clinical study with rifampin (a moderate CYP2C9/strong CYP3A4 inducer), 600 mg qd significantly decreased the steady-state exposure of siponimod (2 mg qd). The Cmax,ss of siponimod decreased by 45% while AUCtau,ss decreased by 57% in the presence of rifampin (*Figure 6*). This effect is considered clinically relevant hence concomitant use of siponimod with rifampin or other inducers of CYP3A4/CYP2C9 should be avoided due to concern of lack of efficacy. This is considered adequately reflected in the SmPC. The exposure of metabolite M3 Cmax,ss increased by 53% in presence of rifampin, but AUCtau,ss did not change.

Study A2121: Co-administration of 4 mg siponimod qd with an oral contraceptive did not cause significant changes to exposure of ethinylestradiol or changes in PD parameters. Levonorgestrel Cmax,ss and AUCtau increased by 18% and 28% when co-administered with siponimod for 27 days. This effect is not considered clinically relevant.

Figure 6: Arithmetic mean (SD) plasma concentration-time profiles of BAF312- Day 12 (Reference) and Day 24 (Test) for Cohort 2 (Pharmacokinetic analysis set)



q.d. = once daily
Period 1: Siponimod up-titrated from 0.25 to 2 mg q.d. (Days 1 through 12) (Reference).
Period 2: Siponimod 2 mg q.d. + Rifampin 600 mg q.d. (Days 13 through 24) (Test).
Below the limit of quantification (BLQ) values (<0.0500 ng/mL) have been set to zero.

2.4.3. Pharmacodynamics

Mechanism of action

Siponimod is an oral compound that acts on the S1P receptor and selectively targets 2 (S1P1 and S1P5) of the 5 known S1P receptors. Siponimod has immunomodulatory properties required for therapeutic approaches in multiple sclerosis.

T cells selectively require S1P1 activation for emigration from the thymus, and both T and B cells require this receptor for egress from peripheral lymphoid organs. Siponimod promotes a marked and long-lasting internalization and degradation of S1P1 receptors, thereby acting as a functional antagonist on S1P1. This makes lymphoid cells unresponsive to S1P signalling, thus depriving them of their capacity to egress from lymphoid organs (lymph nodes and Peyer's patches) and thereby preventing the recirculation of lymphocytes to blood and tissues including the CNS.

Siponimod does not deplete lymphocytes but results in redistribution away from the intravascular compartment. This effect results in a dose-dependent reduction of peripheral blood absolute lymphocyte count.

Primary and Secondary pharmacology

- **Primary pharmacology**

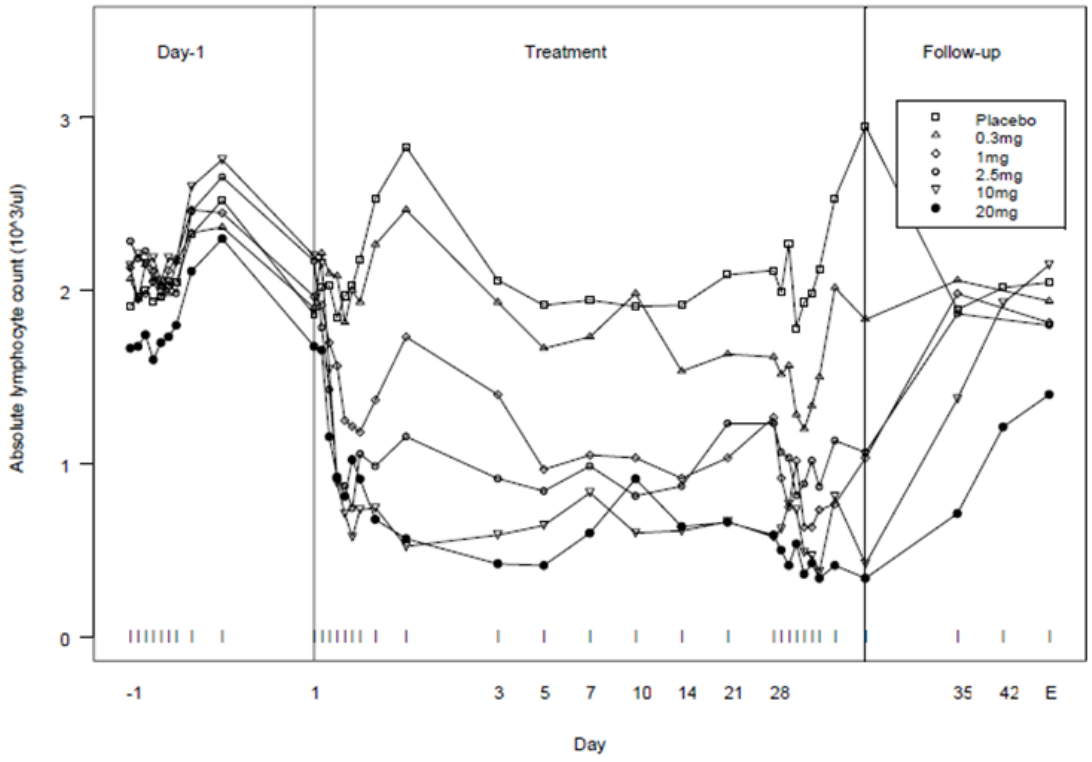
Absolute lymphocyte counts: In the single dose study (A2101), siponimod showed a dose dependent decline in absolute lymphocyte count between siponimod 0.3 to 10 mg. The recovery of lymphocytes was seen after 48 days, and due to a half-life of 27 to 57 hours, a once daily dose regimen was selected.

In the multiple dose study (A2105), there was a similar dose dependent decline in lymphocyte counts up to siponimod 10 mg as well as CD4+ and CD8+ cells. The recovery of CD4+ and CD8+ is almost complete 3 week post treatment.

In poor metabolisers the percentage of lymphocytes are provided and seems lower for extensive metabolisers than poor metabolisers, which is somewhat expected. In extensive metabolisers, the lymphocyte counts increased slightly as expected during treatment with a strong CYP2C9/3A4 inducer.

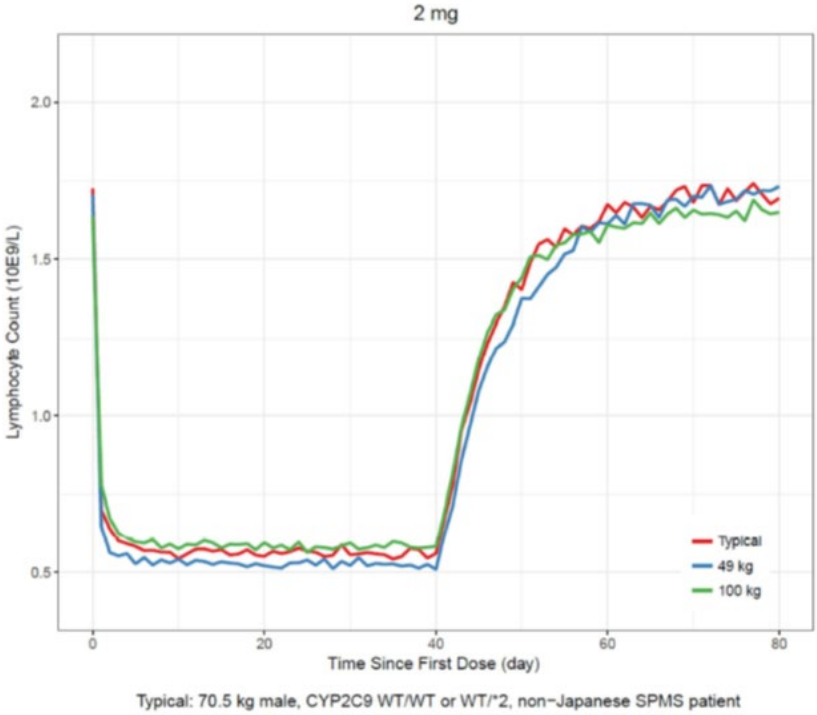
In pooled analysis, 73.3% had a lymphocyte counts between 0.2 to 1.2 x 10^9/L and 12.7% of the subjects had lymphocytes within the normal range. Even though the defined therapeutic absolute lymphocyte count is < 1.2 × 10^9/L, clinically relevant disease modifying effects remain present even with lymphocyte counts above 1.2 × 10^9/L. No individuals in the treatment with siponimod 2 mg experienced lymphocyte counts below 0.2 x 10^9/L.

Figure 7: Mean absolute lymphocyte count after multiple dose of siponimod in healthy subjects



The relationship between dose and lymphocyte counts were modelled in a PopPKPD analysis. This revealed a dose response relationship. It supported that weight did not impact lymphocyte count to a clinically relevant degree (*Figure 8*). Further, it revealed a small but not clinically relevant impact of Japanese origin and gender.

Figure 8: Simulated median absolute lymphocyte count profiles in SPMS patients following administration of 2 mg QD for 40 days by weight



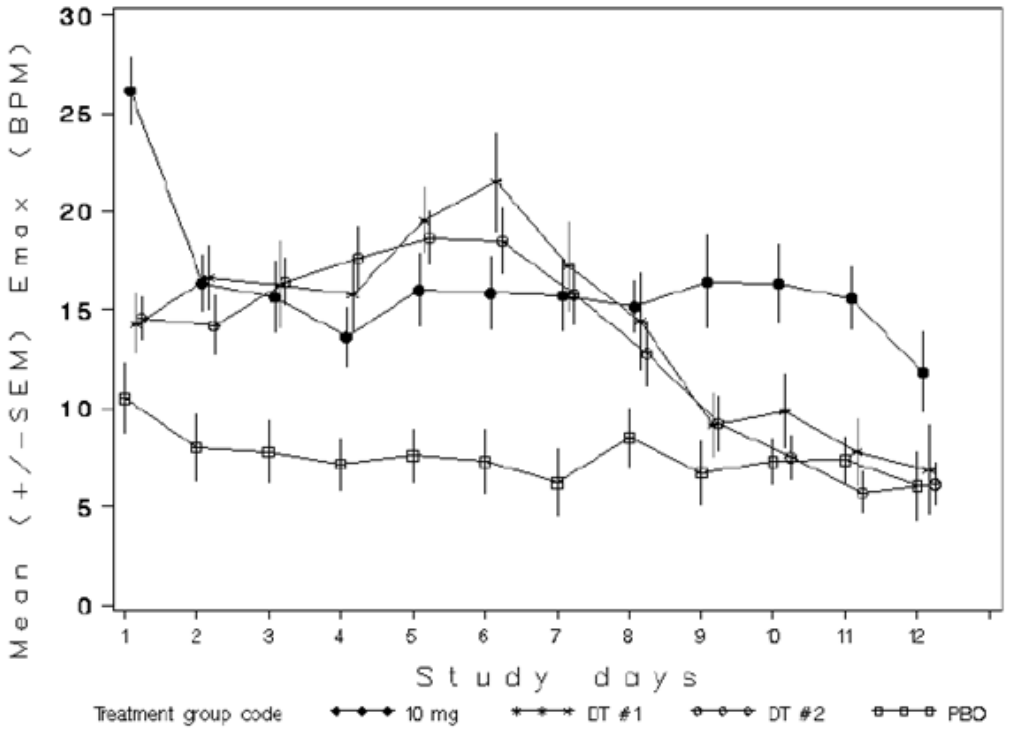
Efficacy of T cell-dependent and T cell-independent vaccines: In Study A2130, the proportions of responders at 4 weeks after vaccination by treatment group for each antigen demonstrated that the immune response and efficacy of the quadrivalent seasonal influenza vaccine was not compromised after short treatment interruption of 1 week prior until 4 weeks after vaccination. Concomitant use of the quadrivalent seasonal influenza vaccine and siponimod reduced the responder rate by 15% to 30%. In contrast, the PPV-23 vaccine can be co-administered with siponimod without compromising immune response and vaccination efficacy.

Pharmacodynamics of metabolites: Very week or no activity of M3 compared to the parent drug was found. In contrast, M17 contributed to around 3% to the pharmacological activity on S1P1 and S1P5.

- **Secondary pharmacology**

Heart rate: Siponimod has a negative chronotropic effect. Dose titration up to 10 mg showed a reduction in the negative chronotropic effect. Dose titration to 2 mg (the proposed dose for the majority of patients) was not evaluated in the dedicated dose titration study 2107, however as dose titration to 10 mg did not lead to further decrease in heart rate, it is indicated that the heart rate recovery is stabilised. Maximum heart rate decreased 16-20 bpm by dose titration, but the placebo corrected changes in heart rate were 4.1 bpm. The magnitude of the negative chronotropic effects at siponimod re-initiation appeared to be dependent on both the dose and the duration of treatment discontinuation. The SmPC recommends treatment to be re-initiated with a titration phase following discontinuation of treatment for 4 or more consecutive days.

Figure 9: Maximum decrease from baseline in hourly average heart rate for days 1-12



Note: A positive mean Emax corresponds to a decrease in HR from baseline.

In study A2119, no statistically significant differences in heart rate were seen between modified release formulations and the immediate release formulation, and the immediate release formulation was carried forward.

Cardiac Conduction: Siponimod has a negative dromotropic effect. Overall, across the clinical pharmacology studies, first and second degree AV blocks were seen, but no second degree AV blocks Mobitz type 2 were identified. One subject in the study A2111 experienced severe bradycardia of 25 bpm and a short period of asystole combined with presyncope and needed assistance from health professionals. This subject has a baseline HR of 60 BPM. In the SmPC it is recommended that patients with sinus bradycardia (heart rate <55 bpm), 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 (see SmPC section 4.4).

QTc interval: A thorough QT study was conducted (study A2118). No effect of siponimod on the QTc interval was detected. The metabolites, M3 and M5, showed a negative correlation with QTcF. The metabolite M17 was not assessed in this study, however QTc in patients exposed to long term treatment of siponimod is similar to the dedicated QTc study, metabolites are not expected to have significant effects on the QTc interval.

- **Pharmacodynamic interactions**

In study A2116 concomitant treatment with siponimod and propranolol decreased the heart rate with an average of 6 bpm compared with propranolol alone. Compared with placebo, the decrease in heart rate was markedly higher (12.3 to 14.7 bpm). This is adequately reflected in the SmPC.

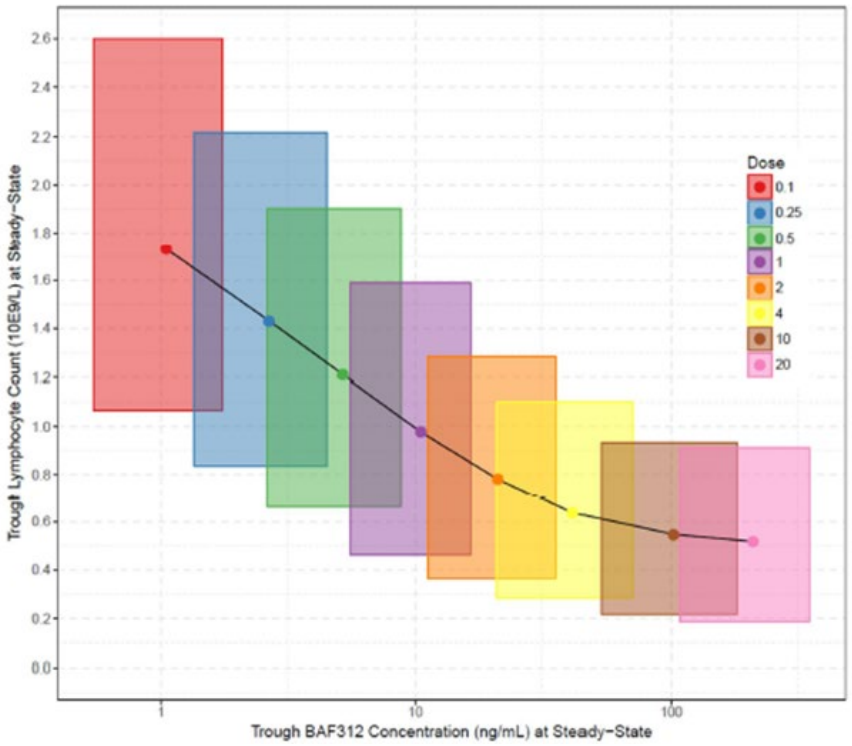
- **Genetic differences**

In Study A2128 patients with genotype CYP2C9*3*3 had around 3 bpm lower heart rate on each day of uptitration compare to genotype CYP2C9*1*1. This is in line with the pharmacokinetic results. In SmPC section 4.4, it is mentioned that siponimod should not be used in patients with genotype CYP2C9*3*3 due to increased plasma concentrations of siponimod which is endorsed.

Relationship between plasma concentration and lymphocyte count

The concentration-effect relationship was investigated in PK/PD simulations. *Figure 10* depicts the dose-dependent decrease in trough lymphocyte count simulated.

Figure 10: Median simulated trough siponimod concentration versus trough lymphocyte count in healthy volunteers by dose



The relationship between dose and lymphocyte counts were modelled in a PopPKPD analysis. This revealed a dose response relationship. It supported that weight did not impact lymphocyte count to a clinically relevant degree. Further, it revealed a small but not clinically relevant impact of Japanese origin and gender.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The clinical pharmacology program of siponimod contributing to PK data consisted of 15 phase 1 studies in healthy subjects or special populations. Additionally, three phase 2 studies in polymyositis and dermatomyositis patients, one phase 2 study in RRMS patients, and one phase 3 study in SPMS patients contributed with data to the PK programme.

The population PK model for siponimod is generally acceptable. A PBPK model was developed for prediction of drug-drug interactions of siponimod.

Besides one study (study A2102), the clinical studies were considered well conducted. The multiple dose studies (A2102) found up to 17 times higher plasma concentrations than anticipated in the 10 mg and 20 mg cohort, indicative of a more than 10 times higher doses than anticipated. The applicant informs that there was evidence of erroneous dosing.

Bioequivalence between the final market image and the market formulation was shown.

ADME

The median siponimod Tmax ranged from 3 - 6 hours. The absolute oral bioavailability of siponimod is approximately 84%. Siponimod concentration increases in an apparent dose proportional manner after multiple once-daily doses of siponimod 0.3 mg to 20 mg. Despite a delay in Tmax to 8 hours after a single dose, food intake had no effect on the systemic exposure of siponimod.

Siponimod is distributed to body tissues with a moderate mean volume of distribution of 124 litres. Protein binding of siponimod is >99.9% in healthy subjects and in patients with hepatic or renal impairment.

Siponimod is extensively metabolised, mainly by cytochrome P450 2C9 (CYP2C9), and to a lesser extent by cytochrome P450 3A4 (CYP3A4). Genetic polymorphism of CYP2C9 has a great influence on the overall metabolism, therefore knowledge of metaboliser status (extensive, intermediate or poor) is required before initiation of treatment. The influence of the genotypes *1/*3 and *2/*3 are reflected in the SmPC with reduction in dose to 1 mg QD maintenance treatment. The combination of siponimod with moderate or strong CYP3A4 inhibitors or moderate CYP2C9/CYP3A4 duel inhibitor should be avoided irrespective of the CYP2C9 genotype.

The pharmacological activity of the main metabolites M3 and M17 is not expected to contribute to the clinical effect and the safety of siponimod in humans. Large accumulation factors have been estimated for P29.6 and P30.5, but the metabolite to parent AUCtau,ss ratios were low, and the metabolites did only contribute marginally to the total exposure.

Siponimod is eliminated from the systemic circulation mainly due to metabolism and subsequent biliary/faecal excretion. The apparent elimination half-life of siponimod is approximately 30 hours. Steady state was reached after approximately 6 days of multiple once-daily administration of siponimod.

Special populations

No elderly patients were enrolled in clinical studies. Siponimod should be used with caution in patients aged 61 years and over.

The safety and efficacy of Mayzent in children and adolescents have not yet been established. Results from population pharmacokinetics suggest that gender based dose adjustment is not necessary. The single-dose pharmacokinetic parameters were not different between Japanese and Caucasian healthy subjects, indicating absence of ethnic sensitivity on the pharmacokinetics of siponimod.

No siponimod dose adjustments are needed in patients with mild, moderate or severe renal impairment. Siponimod must not be used in patients with severe hepatic impairment. No dose adjustments for siponimod are needed in patients with mild or moderate hepatic impairment.

A larger inter-subject variability was identified with increasing dose, in genotype CYP2C9*3*3 and in Caucasians (compared with Japanese). Based on pooled data from the target population and RRMS patients, the inter-subject variability was larger in MS patients compared with healthy subjects. Based on the PopPK model, the coefficient of variation for Cl/F was 24.2% in SPMS patients. This is similar to the values of healthy subjects suggesting similar inter-individual variability in SPMS patients and healthy subjects. Health status was not a significant covariate in the Pop PK model. This supports that data obtained in healthy volunteers can be extrapolated to the target population and RRMS patients.

Interactions

No clinical interaction studies were performed with siponimod as a perpetrator of DDI. No dedicated studies were conducted to evaluate siponimod as a substrate for transporters *in vitro.* Intestinal uptake of siponimod studied in Caco-2 cells indicated passive permeation is the uptake mechanism.

Metabolite M3 showed no significant inhibition or induction of any CYPs tested in-vitro. M3 was an inhibitor of human BSEP, OCT1 OATP1B1 and OATP1B3 *in vitro.* Metabolite M17 showed no relevant inhibition of the tested transporters.

Smoking is a potent CYP1A1 inducer and smoking status was shown by PK/PD analysis to have no impact on siponimod exposure on mean data from SPMS patients.

Impact of the six different CYP2C9 genotypes on siponimod PK and the drug interaction potential in presence of perpetrators for CYP2C9 and CYP3A4: itraconazole, fluconazole, ketoconazole, fluvoxamine rifampicin, erythromycin, and efavirenz were evaluated in silico using SimCyp. Itraconazole, fluconazole and rifampicin_predictions were backed up by *in vivo* DDI data with siponimod. There was initially a mismatch between simulated and observed data for the interaction with itraconazole, however PBPK simulation including both CYP3A4 and CYP1A1 metabolic pathways could better explain the observed *in vivo* results. The impact of ketoconazole, another strong CYP3A4 inhibitor, on siponimod exposure was predicted by SimCYP to be low for genotype *1*1 but high for genotype *3*3, a group of patients for whom siponimod is not indicated due to the increased plasma concentrations of siponimod. A similar result was obtained for erythromycin, a moderate CYP3A4 inhibitor.

In vivo, the potent CYP2C9 inhibitor fluconazole could increase the AUC of siponimod 2-fold and the Cmax by 10%. *In vivo*, itraconazole, a strong CYP3A4 inhibitor, decreased siponimod AUCs by 10% and 24% in subjects with the CYP2C9*1*2 and *1*3 genotypes, respectively. Concomitant administration of rifampin, a moderate CYP2C9/strong CYP3A4 inducer, significantly decreased the steady-state exposure of siponimodand concomitant use of siponimod and rifampin or other inducers of CYP3A4/CYP2C9 should be avoided. Co-administration with an oral contraceptive did not cause relevant changes to exposure of ethinylestradiol or PD parameters.

Siponimod is classified as a biopharmaceutics classification system (BCS) class II compound and practically insoluble in aqueous buffer pH 1 to 6.8. Potential effect of drugs which increased gastric pH was not investigated.

Pharmacodynamics

As a selective S1P receptor modulator, siponimod induces internalization and degradation of the S1P1 receptor and thereby acts as a functional antagonist on S1P1. The resulting absolute lymphocyte count (ALC) reduction in peripheral blood due to prevention of lymphocyte recirculation from lymphatic tissue to target organs constitutes the primary efficacy-related PD endpoint of siponimod.

Five pharmacodynamic studies were conducted: three studies dedicated to the negative chronotropic effect of siponimod, one study examining the T-cell dependent and independent antigen stimuli, and one dedicated QTc study. Furthermore, several pharmacokinetic studies contributed with data to the pharmacodynamic assessment. Data about possible genetic differences on PD response are limited. It is theoretically possible that genetic differences of the Sphingosine-1-phosphate receptor exist that could influence the efficacy and safety of siponimod. However, available scientific data do not suggest that such an effect would be clinically relevant.

Primary pharmacology

The single dose study showed a dose dependent decline in absolute lymphocyte count between 0.3 mg to 10 mg where the decline levelled off. The recovery of the lymphocytes was seen after 48 days, and

due to a half-life of 27 to 57 hours a once daily dose regimen was selected. One of the multiple dose studies also showed a dose related reduction in the mean ALC, mean ALC nadir and mean AUEC0-12h, over the dose range of BAF312 0.3 mg to 20 mg. The absolute lymphocyte counts recovered to the baseline value at end of study.

Following treatment with siponimod 2 mg (the proposed dose for the majority of patients) in multiple dose studies, an absolute lymphocyte count of 0.2 to 1.2 x 10^9/L was seen in 87.9% of the subjects. In subjects treated with siponimod 2 mg preceded by dose titration, lymphocyte counts between 0.2 and 1.2 x 10^9/L were seen in 73.3% of the subjects. Even though the defined therapeutic absolute lymphocyte count is < 1.2 × 10^9/L, clinically relevant disease modifying effects remain present even with lymphocyte counts above 1.2 × 10^9/L. No individuals in the treatment with siponimod 2 mg experienced lymphocyte counts below 0.2 x 10^9/L.

Regarding CD4+ and CD8+ cells, a dose-dependent reduction was observed subsequent to siponimod administration. Within 40 days, both the CD4+ and CD8+ counts appeared to normalize irrespective of siponimod dose. Besides subjects in the 20 mg dose group, all subjects in study A2105 demonstrated recovery of lymphocyte count by 14 days post-dose. Subjects receiving BAF312 20 mg have on average reached 83 % of the Day-1 value. In poor metabolisers (CYP2C9*2*3 and CYP2C9*3*3) the percentage of lymphocytes are lower compared with extensive metabolisers (CYP2C9*1*1). The relationship between dose and lymphocyte counts were modelled in a PopPKPD analysis. This revealed a dose response relationship. It supported that weight did not impact lymphocyte count to a clinically relevant degree. Nadir lymphocyte count depends on weight, gender ethnicity, healthy status, and CYP2C9 genotype. Lymphocyte recovery time depends on weight, gender, health status, and CYP2C9 genotype. Additional simulations for patients meeting more than one of the investigated characteristics (e.g. Japanese, female patient of 49 kg genotyped CYP2C9 *1/*3) showed a lymphocyte count of 0.31 x 10^9/L compared with 0.56 x 10^9/L in a typical patient. Furthermore, the recovery time to absolute lymphocyte counts of 1.0 x 10^9/L was 17 days for Japanese female patients of 49 kg genotyped 2*3* compared with 5 days in a typical patient.

The metabolite M3 was not pharmacologically active. In contrast, metabolite M17 contributed around 3% to the pharmacological activity on S1P1 and S1P5.

Secondary pharmacology

A negative chronotropic effect of siponimod was established based on 14 studies. The drop in heart rate was larger with increasing dose and levelled off at around siponimod 10 mg. A dose titration regimen up to siponimod 10 mg showed that the drop in heart rate was smaller during slow uptitration than initiation with siponimod 10 mg. Dose titration up to 2 mg (the proposed dose for the majority of patients) was not compared with initiation of siponimod 2 mg. A dose titration regimen is proposed in the SmPC. A drop in heart rate of 16-20 BPM was seen, but compared with placebo, the decrease in heart rate was 4.1 bpm. The magnitude of the negative chronotropic effects at BAF312 re-initiation appeared to be dependent on both the dose and the duration of treatment discontinuation. The 2 mg dose (the recommended treatment dose) showed a maximum absolute heart rate decrease of 14.2 bpm (90% CI: 12.0;16.5) with 72 hours pause and a decrease of 18.0 bpm (90% CI: 15.6;20.3) with 192 hours pause. Treatment should be re-initiated with a titration phase following discontinuation of treatment for 4 or more consecutive days.

Two modified release formulations were examined, but there were no differences in the negative chronotropic effect compared with the immediate release formulations. Therefore, the immediate release formulations were carried forward.

Besides bradycardia, asystole has been seen in a healthy well-trained subject with low baseline heart rate (60 bpm). As a recognition of the negative dromotropic effect, in the SmPC section 4.4, it is

recommended that patients with sinus bradycardia (heart rate <55 bpm), 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. Concomitant treatment with siponimod and propranolol decreased the heart rate with an average of 6 bpm compared with propranolol alone. Compared with placebo, the decrease in heart rate was markedly higher (12.3 to 14.7 bpm). Siponimod on top of propranolol was associated with a larger decrease in heart rate at day 20 compared with propranolol on top of siponimod treatment. This is adequately reflected in the SmPC.

The dedicated QTc study demonstrated no significant direct QT prolonging effect of siponimod and did not suggest an arrhythmogenic potential related to QT prolongation. A small increase in QTc was however seen with a peak at 3 hours post dose which corresponds to the Cmax. The upper boundary of the 90% CI did not exceed 10 ms. The applicant has included a warning in the SmPC section 4.4. The metabolites, M3 and M5, showed a negative correlation with QTcF. The metabolite M17 was not assessed in this study, however QTc in patients exposed to long term treatment of siponimod is similar to the dedicated QTc study, metabolites are not expected to have significant effects on the QTc interval.

2.4.5. Conclusions on clinical pharmacology

Methodologically, the clinical studies supporting this application were overall well conducted, and the pharmacokinetic models developed were in general considered acceptable. The PK of siponimod is considered adequately described. The pharmacological profile of siponimod in human studies has been adequately documented and meet the requirements to support the application. The proposed clinical dose of siponimod 2 mg preceded by 5 days up-titration is documented.

2.5. Clinical efficacy

The following indication was initially applied: Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS).

The clinical development program comprises two controlled studies evaluating the efficacy and safety of siponimod in MS patients:

- a phase 3 study (A2304, N=1651) testing one dose level of siponimod (2 mg) was performed in SPMS.

- a phase 2 dose - ranging study (A2201, N=297) was performed in RRMS.

Table 4: Completed and ongoing clinical studies in MS patients

Study	Population	Number of Patients	Treatments	Design	Treatment duration	Primary and secondary endpoints
A2304 Core Part (Phase 3)	SPMS	1651	2 mg or Placebo (2:1 randomisation)	Randomized, double-blind, multi-center, placebo controlled	Variable, <1 month to 37 months (median 18 months)	Time to 3mCDP, time to 3m confirmed 20% worsening on T25W, change in T2 lesion volume, time to 6mCDP, ARR, change in MSWS-12, change in brain

						volume, Gd-enhancing and new/enlarging T2 lesion counts, safety and tolerability
A2304 (Extension Part)	SPMS from Core Part of A2304	1220	2 mg	Open-label	Up to 23 months (at data cut-off of 31-Dec-2017)	Same as Core Part
A2201 (Phase 2)	RRMS	297	Period 1: Placebo 0.5 mg, 2 mg, 10 mg Period 2: Placebo, 0.25 mg 1.25 mg	Randomized, double-blind, multi-center, placebo controlled, adaptive dose ranging	Period 1: 6 months Period 2: 3 months	Number of CUAL, Gd-enhancing and new/enlarging T2 lesions counts, ARR,
A2201E1	RRMS from A2201	184	0.25 mg, 0.5 mg, 1.25 mg, 2 mg, 10 mg (dose blinded); 2 mg (open label)	Randomized, multi-center, dose-blinded study (no placebo) followed by open-label	5 years (median 63.6 months) median exposure 24 months (dose blinded) and 41 months (open-label)	Safety and tolerability Number of CUAL, Gd-enhancing and new/enlarging T2 lesion counts, ARR, disability progression, change in brain volume

2.5.1. Dose response study (Study A2201)

The dose-response relationship was elucidated in study A2201 in a different patient population (RRMS) and mainly with respect to MRI endpoints rather than clinical endpoints.

Methods

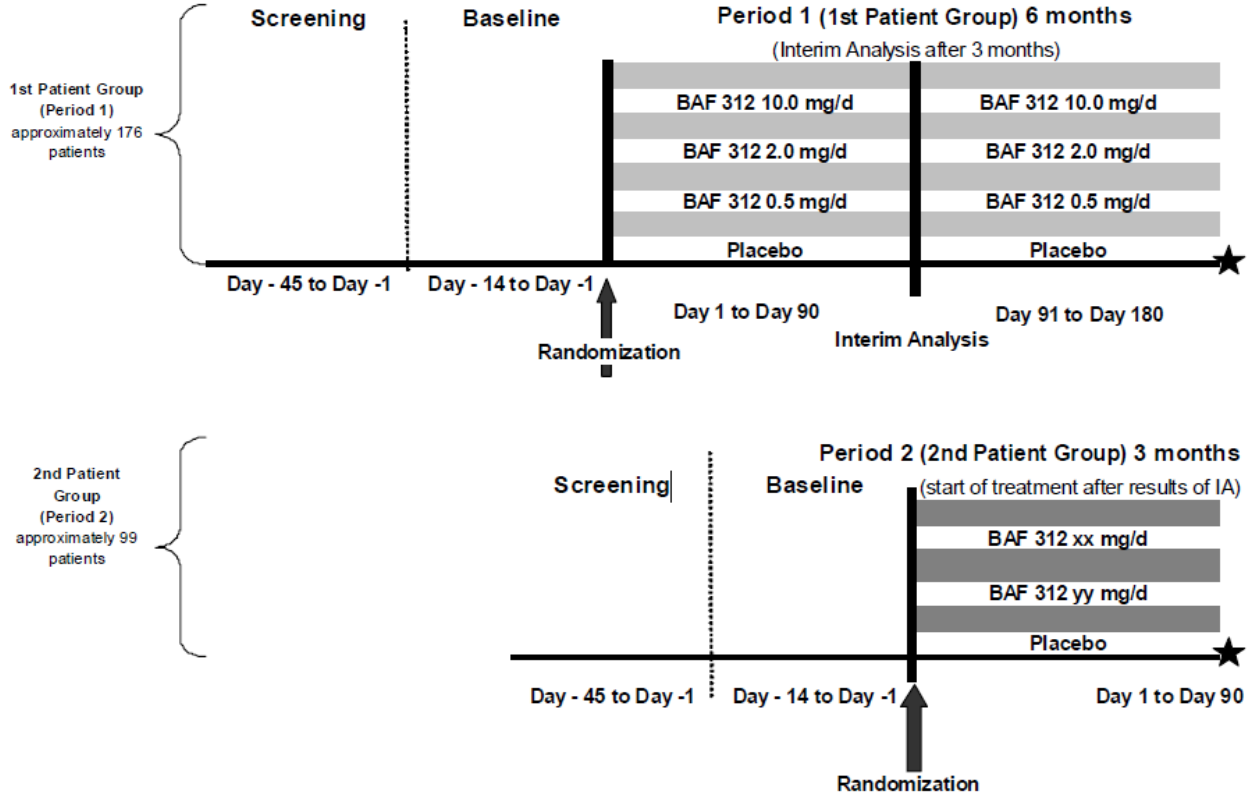
Study A2201 was a multi-center phase II adaptive dose-ranging, randomised, double-blind, parallel-group, placebo-controlled, study evaluating safety, tolerability and efficacy on MRI lesion parameters and determining the dose response curve of siponimod given orally once daily in patients with RRMS.

Two patient groups were tested sequentially, separated by an interim analysis (IA). The first group of patients (Period 1) was randomized in a 1:1:1:1 fashion to treatment with three doses of siponimod (10 mg, 2 mg and 0.5 mg given orally o.d.) or placebo for a period 6 months. After IA, the second group of patients (Period 2) was randomised (4:4:1) to two additional doses of siponimod, 1.25 mg and 0.25mg, as defined on the basis of the IA results, and placebo. These patients were treated for 3 months. Patients who completed the study were eligible to enter the Extension study that allows all placebo patients to be switched to siponimod, and patients already on a dose of siponimod to continue active treatment. A sample size of 275 randomised patients (250 completers) was targeted.

Males or females aged 18 to 55 years inclusive with a diagnosis of RRMS as defined by 2005 revised McDonald criteria, and a RRMS course with at least one documented relapse during the previous year or two documented relapses during the previous 2 years prior to randomisation, or a positive Gd-enhanced MRI scan at screening (in case the first MRI scan obtained at screening was negative, a second scan could be obtained 1 month later). Patients were to have an Expanded Disability Status Scale (EDSS) score of 0 to 5.0 inclusive, and to be neurologically stable with no evidence of relapse or corticosteroid treatment within 30 days prior to randomisation.

The primary endpoint was the number of combined unique active lesions (CUAL) defined as new Gd-enhanced lesions on T1-weighted, or new or newly enlarging lesions on T2-weighted MRI scans without double counting. Other endpoints included additional MRI outcomes and annualized relapse rate (ARR) at 3 and 6 months.

Figure 11: Study A2201 study design



Results

The study population had a mean age of 36 years, a median disease duration ranging from 4.7 to 7.6 years, and a mean EDSS baseline score of approximately 2.3.

Primary dose-response results

- The primary efficacy endpoint was met as demonstrated by a statistically significant dose-response relationship among the five doses of siponimod (10mg, 2mg, 1.25mg, 0.5mg and 0.25mg) and placebo during 3 months of treatment in patients with RRMS, measured by the number of CUAL lesions (p=0.0001 for the Emax model).

Table 5: Testing significance of candidate dose response models at 3 months (Full Analysis Set)

Model	T statistic	p-value (one-sided)*
Linear	1.75	0.0696
Emax (with ED50=1mg)	3.93	0.0001
Hill Emax 1 (with ED50=2mg and h=2)	2.53	0.0115
Hill Emax 2 (with ED50=3mg and h=3)	1.65	0.0858
Exponential (with delta=3.633)	1.20	0.1817

* Models with a p-value <0.025 are significantly different from a flat dose-response (i.e. no dose-response) model.
With ED50 the dose that gives half of the asymptotic maximum change over placebo, E_{max} the asymptotic maximum change in effect over placebo, h the Hill coefficient, delta the rate of increase.

- The estimated dose-response curve using the model specified in the primary analysis of the protocol estimated the dose which provides a 50% reduction over placebo as 0.38mg with a 95% confidence interval of 0.02 to infinity.
- Based on the dose-response curve at Month 3 from the Bayesian longitudinal model, the dose providing 50% reduction over placebo was estimated as 0.51mg, with a 95% confidence interval of 0.19 to 1.34. siponimod treatment reduced up to 80% of CUAL vs. placebo, with 10 and 2mg doses forming an upper plateau of the dose-response curve.
- The mean number of CUAL at Month 6 in the full analysis set was 0.4, 0.4, 0.9, and 2.0 for the siponimod 10mg, 2mg and 0.5mg groups and for the placebo group, respectively. The respective results in the per-protocol set were 0.4, 0.5, 1.8 and 1.9 for siponimod 10mg, 2mg, 0.5mg and placebo at Month 6.

Secondary variables

• ARR were 0.30, 0.20 and 0.61 for 10mg, 2mg and 0.5mg treatment groups respectively (only doses with 6-month data) vs. 0.58 for placebo. The analyses of ARR up to Month 6 showed superiority of the siponimod 2mg group compared to placebo.

• The proportion of relapse-free patients up to Month 6 was superior in the siponimod 2mg group compared to placebo.

• The numbers of new/newly enlarged T2 lesions at Month 3 compared to baseline were lower for the siponimod 10mg, 2mg, and 1.25mg treatment groups compared to placebo. The results seen at Month 6 showed a difference for the siponimod 10mg and the 2mg group compared to placebo.

• The mean number of new Gd-enhanced T1 lesions at Month 6 was lower in the siponimod groups than in the placebo group. The siponimod 10mg and 1.25mg groups at Month 3 and the siponimod 10mg and 0.5mg groups at Month 6 all demonstrated superiority over placebo.

• The effect on all post-baseline Gd-enhanced T1-weighted lesions was in line with the results obtained for new Gd-enhanced T1 lesions. The siponimod groups 10mg, 2mg, and 0.5mg after 6 months as well as 1.25mg after 3 months all demonstrated superiority over placebo. Superiority was also demonstrated for the siponimod 10mg, 2mg, and 0.5mg groups versus placebo at Month 3.

• The proportion of patients without any new MRI disease activity (CUAL) up to 3 and 6 months (sensitivity with weight) reached statistical significance in siponimod 2mg (p=0.020) and 1.25mg (p=0.001) groups at 3 months and in the siponimod 2mg group (p=0.022) at 6 months compared to placebo.

A2201E1: Supportive long-term data efficacy data (evaluated as secondary endpoints) were provided for 184 patients entering the extension of study A2201 (i.e. A2201E1), adding approximately 60 months

of treatment. Patients spent a median of 24 months in the dose-blinded phase followed by an open-label phase (duration approximately 3 years). In the dose-blinded phase, patients received the dose to which they were assigned to in the core part of A2201, while patients on placebo were randomised to one of the five doses in a blinded manner. All patients were switched to open-label siponimod 2 mg after the database lock of the core study. As to be expected for the RRMS population, EDSS remained relatively stable from core part throughout the extension part. A majority of patients remained free from events of 6m-CDP throughout the study. For relapse-related parameters ARR and proportion of patients free of confirmed relapses, the 1.25 mg and 2 mg dose group continued to perform better than the highest and the lowest dose groups during the dose-blinded part, while convergence could be observed during the open-label part when all subjects continued to receive 2 mg siponimod. The number of Gd-enhancing and new or enlarging T2 lesions remained low throughout the extension study lacking a clear dose-relation.

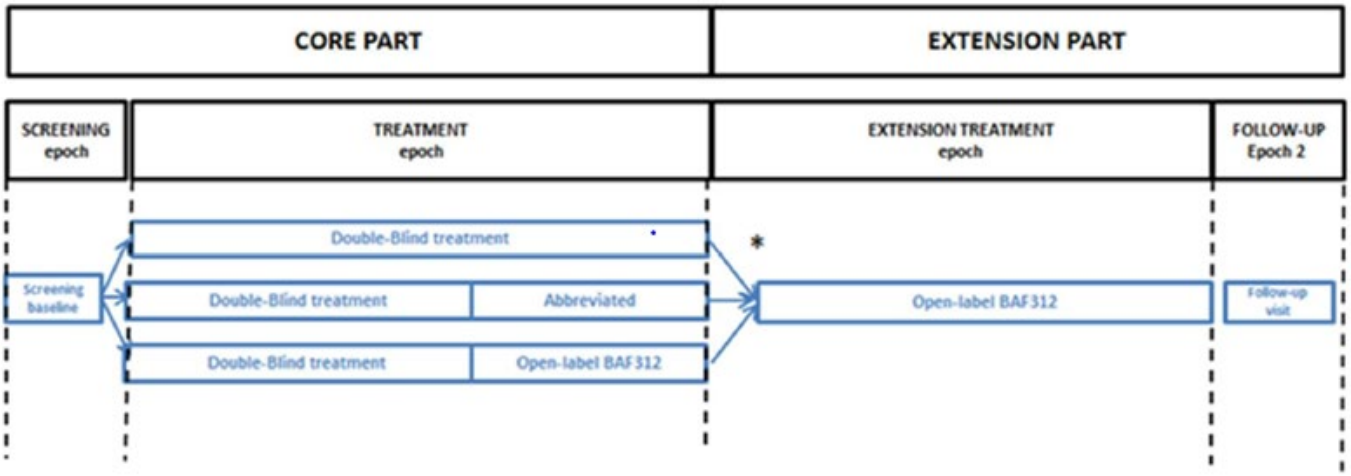
2.5.2. Main study (Study A2304)

Methods

This was the only study in the SPMS indication. The study design consisted of a Core Part and an Extension Part. The Core Part was a multicenter, randomised, double-blind, parallel-group, placebo-controlled, variable treatment duration study comparing the efficacy and safety of siponimod in patients with SPMS. Eligible patients were randomised to siponimod or placebo in a 2:1 ratio. The Core Part of the study was to be stopped approximately 3 years after the randomisation of the first patient. It was predicted that, by that time, the required number of 374 patients with 3-month confirmed disability progression (3m-CDP) (primary endpoint) would be observed and more than 95% of patients would have been randomised for 1 year or more.

During the Extension Part, eligible patients were to receive open-label siponimod. The Extension Part of the study was ongoing at the time of the interim report.

Figure 12: A2303 core and extended study design



Study Participants

Patients were recruited in 294 specialised centers in 31 countries across 5 continents. Approximately 78% of patients were recruited in the EU, and the study results are thus considered relevant for the European population.

Inclusion criteria (complete list)

1. Written informed consent obtained before any assessment was performed.
2. Male or female patients aged 18 to 60 years (inclusive) at screening.
3. Prior history of RRMS (2010 Revised McDonald criteria).
4. SPMS, defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses (Lublin and Reingold 1996, Lublin et al 2003, Rovaris et al 2006)
    - attestation by the investigator in a written statement that the disease had entered the progressive stage (according to the study definition) at least 6 months prior to enrollment.
5. Disability status at Screening with an EDSS score of 3.0 to 6.5 (inclusive).
6. Documented EDSS progression in the 2 years prior to study of ≥1 point for patients with EDSS <6.0 at screening, and ≥0.5 point for patients with EDSS ≥6.0 at screening. If documented EDSS scores were not available, a written summary of the clinical evidence of disability progression in the previous 2 years, and retrospective assessment of EDSS score from data up to 2 years prior to screening were to be submitted for central review. The investigator completed and submitted an 'evidence of disability progression form' for these cases; this form documented previous evidence from other sources such as previous neurological examination findings, medical history etc. to allow the central adjudication committee to assess if the patient was eligible. Of note: this criterion was not related to establishing SPMS diagnosis (as per inclusion criterion No. 4).
7. No evidence of relapse or corticosteroid treatment within 3 months prior to randomisation.

Main exclusion criteria (list not complete)

1. Medical conditions: Any medically unstable condition. History of malignancy within the past 5 years. Active infections or known to have acquired immune deficiency syndrome (AIDS) or positive human immunodeficiency virus (HIV) antibody. Active chronic disease of the immune system or with a known immunodeficiency syndrome. Significant cardiac disease including conduction and rhythm disorders or uncontrolled arterial hypertension. Severe respiratory disease. Diabetes mellitus unless well controlled and without organ complications. Stroke or TIA within 6 months. Macular edema during pre-randomisation phase. Patients with a history of macular edema were allowed to enter the study provided that they did not have macular edema at the ophthalmic examination at the Screening Visit Progressive neurological disorder. Severe autonomic nervous system dysfunction. Serious psychiatric disease. History of substance abuse.
2. Women who are pregnant, nursing (lactating) or women of child-bearing potential unless using highly effective methods of contraception during dosing and for 30 days after the last dose of siponimod
3. Patients unable to undergo MRI scans.
4. Homozygosity for CYP2C9*3 (tested at Screening), or refusal to test for CYP2C9*3 haplotype.
5. Clinically significant abnormal laboratory values prior to randomisation including AST (aspartate aminotransferase), ALT (alanine aminotransferase), gamma glutamyl transferase (GGT)>3 times upper limit of normal (ULN), bilirubin >1.5 ULN (unless Gilbert's syndrome), serum creatinine >1.7mg/dl, leucopenia<3.500/mm^3 or lymphopenia,800/mm^3

6. Patients positive for serological markers for hepatitis A, B, C, and E (acute or chronic infection).
7. Patients negative for varicella-zoster virus IgG antibodies at Screening.
8. Patients who received any live or live-attenuated vaccines within 2 months prior to randomisation.
9. Prohibited treatments: siponimod; fingolimod within 2 months prior to randomisation, or received fingolimod treatment for more than 6 months; intravenous immunoglobulin within 2 months prior to randomisation; dimethyl fumarate within 2 months prior to randomisation; natalizumab within 6 months prior to randomisation; immunosuppressive/chemotherapeutic medications (e.g., azathioprine, methotrexate) within 6 months prior to randomisation; cyclophosphamide within 1 year prior to randomisation; rituximab, ofatumumab, ocrelizumab or cladribine within 2 years prior to randomisation; alemtuzumab at any time; any mitoxantrone during previous 2 years prior to randomization or evidence of cardiotoxicity following mitoxantrone or a cumulative life-time dose of more than 60 mg/m2; teriflunomide within 2 years prior to randomization (unless teriflunomide plasma concentration was zero or without relevant biological significance) OR within 2 weeks prior to randomisation following successful accelerated elimination procedure as described in the product label; lymphoid irradiation, bone marrow transplantation or other immunosuppressive treatments with effects potentially lasting over 6 months, at any time. Certain heart-rate slowing medications. Potent inducers of CYP2C9.

Treatments

Siponimod (0.25, 0.5, 1, and 2 mg) and dose-matched placebo were provided as film-coated tablets that were identical in appearance. Patients were instructed to take the assigned study treatment (siponimod or matched placebo) tablets once daily during the Treatment Epoch, preferably at the same time each day. The protocol recommended that study medication be taken in the morning. Study treatment could be administered with or without food. The first dose was taken while the patient was in the clinic and specific monitoring procedures were required. The titration regimens are provided below:

Table 6: Titration and re-titration regimens

Target Dose (siponimod or matched placebo)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**
2 mg	0.25 mg	0.25 mg	0.5 mg	0.75 mg	1.25 mg	2 mg
1 mg	0.25 mg	0.25 mg	0.5 mg	0.75 mg	1 mg	1 mg

Patients with confirmed lymphocyte counts <0.2 x109/L at the 2 mg/day dose level underwent dose reduction to 1 mg/day.

Re-titration was required for patients who missed 4 or more consecutive doses while on maintenance dose or patients who missed one dose or more during dose titration.

Patients with 6-month CDP (6m-CDP) were informed of the potential options as follows:

- Continue blinded study treatment assignment (no change).
- Discontinue blinded study treatment and switch to open-label siponimod. These patients underwent dose titration to the 2 mg dose.
- Discontinue blinded study treatment and start any other MS treatment continuing under the abbreviated visit schedule.

For all 3 options, randomised treatment allocation remained blinded until the conclusion of the Core Part.

For treatment of MS relapses, a standard course of intravenous corticosteroids (up to 1000 mg/day methylprednisolone for 3-5 days) was permitted.

Objectives

Primary objective

- The primary objective was to demonstrate the efficacy of siponimod relative to placebo in delaying the time to 3m-CDP in patients with SPMS as measured by the EDSS.

Key secondary objectives

1) To demonstrate the efficacy of siponimod relative to placebo in delaying the time to 3-month confirmed worsening of at least 20% from Baseline in the Timed 25-Foot Walk Test (T25W).

2) To demonstrate the efficacy of siponimod relative to placebo in reducing the increase in T2 lesion volume from Baseline.

Additional secondary objectives

A. To evaluate the efficacy of siponimod relative to placebo in delaying the time to 6m-CDP as measured by EDSS.

B. To evaluate the efficacy of siponimod relative to placebo in reducing the frequency of confirmed relapses as evaluated by the ARR, and to evaluate time to first relapse and proportion of relapse-free patients.

C. To evaluate the effect of siponimod compared to placebo on the patient reported outcome Multiple Sclerosis Walking Scale (MSWS-12).

D. To evaluate the efficacy of siponimod compared to placebo with respect to inflammatory disease activity and burden of disease, as measured by conventional MRI: T1 Gd-enhancing lesions, new or enlarging T2 lesions, T1 hypointense lesions and percentage of brain volume change.

E. To evaluate the efficacy of siponimod relative to placebo on 3m-CDP as measured by EDSS in the following subgroups:

   - SPMS patients with or without superimposed relapses.
   - Rapidly evolving patients, defined as 1.5 point or greater EDSS change in the 2 years prior to study start, and in those not meeting this criterion.
   - Patients with moderate and severe disease course, as defined by Multiple Sclerosis Severity Score (MSSS) of 4 or more at baseline, and in those not meeting this criterion (Roxburgh et al 2005)

F. To evaluate the safety and tolerability of siponimod vs. placebo

Exploratory objectives

a. To evaluate the effect of siponimod compared to placebo on the following patient reported outcomes:

- The health-related quality of life (QoL) as measured by the Multiple Sclerosis Impact Scale (MSIS-29)
- The health-related QoL as measured by the European Quality of Life (EuroQol) – 5 dimensions (EQ-5D)

b. To explore efficacy of siponimod relative to placebo on defined cognitive tests: Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT) and Brief Visuospatial Memory Test Revised (BVMT-R)

c. To evaluate the efficacy of siponimod relative to placebo in the evolution of acute lesions into chronic black holes by MRI

d. To evaluate the efficacy of siponimod relative to placebo on the Multiple Sclerosis Functional Composite (MSFC) z-score

e. To evaluate the efficacy of siponimod relative to placebo in delaying the time to: 3-month confirmed worsening of at least 20% from baseline in the T25W or 3m-CDP as measured by EDSS score or 3-month confirmed worsening of at least 20% from baseline in the 9-Hole Peg Test (9-HPT) in either one of the hands (dominant or non-dominant)

f. To explore baseline characteristics which are associated with a positive treatment response to define clinically relevant responder subgroups

g. To explore the relationship between disability progression endpoints and drug concentration/lymphocyte count

h. To explore the relationship between selected safety parameters and drug concentration/lymphocyte count

i. To evaluate the pharmacokinetics (PK) of siponimod

j. To evaluate the effects of siponimod compared to placebo on 3m-CDP as measured by EDSS in the following subgroups: patients previously treated, or not, with interferon beta-1b and treatment-naïve and patients with prior treatment with disease-modifying drugs.

Outcomes/endpoints

The primary endpoint was the time to **3m-CDP** in patients with SPMS as measured by EDSS. The EDSS was assessed, based on neurological examination, by the Independent EDSS Rater every 3 months and in the case of a suspected MS relapse. The EDSS uses an ordinal scale to assess neurologic impairment in MS based on a neurological examination. Disability progression was defined as an increase from baseline of:

- 1 point in patients with a Baseline EDSS score of 3.0 to 5.0, or
- 0.5 point in patients with a Baseline EDSS score of 5.5 to 6.5.

Sustained disability progression for 3m-CDP was determined by confirming that the criterion was also met at visits 3 months later with any intervening EDSS values also meeting the criterion for change. EDSS scores used for confirmation of disability progression were to be obtained outside any ongoing relapse. In this context, the maximum duration of a relapse was defined as 90 days.

The first key secondary endpoint is **T25W** measured the time, in seconds, to walk 25 feet (7.62 meters). Two trials of the T25W were performed at each assessment and the T25W score was derived as the mean of both trials. Patients who were unable to complete both trials due to physical limitation were considered to have worsened at that visit. If only one trial was available, this was used in the assessment of disability progression, even if the other trial was not available due to physical limitation. A 3-month confirmed worsening of at least 20% from baseline in the T25W was defined as a decrease from baseline sustained for at least 3 months. The steps to identify 3-month confirmed worsening were similar to the process described for the 3m-CDP using EDSS.

The second key secondary endpoint is **change from baseline in the T2 lesion volume**. An MRI Manual that outlined technical implementation, image quality requirements, and MRI administrative procedures was provided to the study coordinator and MRI technician (or another designated person). All scans were also to be assessed by the central blinded MRI reading center for quality, completeness, and adherence to the MRI Manual. If a scan was incomplete or incorrectly performed, the study center was asked to repeat it as soon as possible. After completion of the quality check, all scans were analysed according to a standardized procedure.

Detection of progression

All available post-baseline EDSS scores (scheduled or unscheduled) were evaluated to assess if the change from baseline met the disability progression criterion. The first EDSS assessment that met the criterion defined the onset of tentative disability progression.

Confirmation of progression

Progression was confirmed if a subsequent scheduled visit at least 3 months after onset showed progression and every EDSS score (scheduled or unscheduled) obtained between the onset and confirmation visits also met the progression criterion. Only the EDSS assessments obtained at scheduled visits (including follow-up visits) and in the absence of relapse (confirmed or unconfirmed) were to be used for confirmation of progression.

By definition, a relapse could not last longer than 90 days. If the relapse end date was missing or indicated a duration longer than 90 days, a relapse duration of 90 days was assumed for determining whether the EDSS assessment was obtained in the absence of relapse. For patients with confirmed progression, the time to 3m-CDP was calculated from the date of Day 1 to the date of the CDP onset.

Relapses

MS relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality must have been present for at least 24 hours and occurred in the absence of fever (<37.5°C) or known infection.

The assessment, management, and reporting of MS relapse was done by the Primary Treating Physician. The treating physician assessed whether the neurological abnormality was consistent with the definition of MS relapse, and if so, the standard neurological examination (for the EDSS score) was to be performed by the Independent EDSS Rater.

A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS performed by the Independent EDSS Rater.

The following relapse variables were analysed:

- ARR (all relapses and confirmed relapses)
- Time to first relapse
- Proportion of patients free of relapses.

Sample size

The study was designed to have 90% power to detect a 30% reduction in the risk of 3m-CDP (hazard ratio of 0.70), using a log-rank test with 2-sided alpha level of 5% and 2:1 randomization of siponimod to placebo. Assuming a 2-year proportion with disability progression of 0.30 in the placebo group, a 2-year drop-out rate of 20%, and an enrolment rate of 100 patients per month, 1530 patients and an

overall study duration of approximately 42 months were required to observe at least 374 patients with disability progression, which would give the required power.

The protocol was amended to update the criterion for stopping the Core Part of the study from 374 patients with 3m-CDP had been observed (original plan) to approximately 3 years after randomization of the first patient and at least 374 events observed. At approximately 3 years, it was expected that more than 374 patients with 3m- CDP had been observed. This was expected to compensate for the slight power loss due to the alpha adjustment for the interim analysis and a power of at least 90% was expected at the end of the Core Part.

Randomisation and Blinding (masking)

Randomisation to one of the two treatment arms in a 2:1 ratio (Siponimod: Placebo) was stratified by country using a blocked randomisation. Some countries may have contributed few patients.

Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomisation until database lock of the Core Part, using the following methods:

1. Randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study with the following exceptions:

   DMC members, Independent Statisticians and Independent Programmers,

   PK analysts had access to the randomisation codes associated with patients from whom PK samples were taken, who kept the PK results confidential until database lock.

2. The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, appearance, taste, and odour.

Unblinding was permitted in the case of patient emergencies and at the conclusion of Core Part of the study.

There were three independent teams with access to different dataset to preserve the blind conduction of the trial. As per protocol, the first dose administrator/team was responsible for the dose initiation and had access to the first dose database. The primary treating physician/team, who was responsible for the clinical management of the patient including the assessment, management, and reporting of MS relapse (if needed) had access to the main database as per protocol. The EDSS rater was responsible for EDSS assessment and had only access to the Neurostatus e-scoring dataset.

Statistical methods

Analysis sets:

- All Screened Subjects Set (SCR): comprised all patients who were screened.
- Randomised Analysis Set (RAN): consisted of all randomised patients.
- **Full Analysis Set (FAS):** comprised all randomised patients with assigned treatments who took at least one dose of study medication. All available efficacy assessments were used, irrespective of the study treatment received. The FAS was used for all efficacy analyses.
- Modified Full Analysis Set (MFAS): comprised all randomised patients with assigned treatments who took at least one dose of study medication. If a patient prematurely discontinued study treatment and started a new MS-DMT or open-label siponimod, efficacy assessments were only used up to the start of the new MS-DMT or open-label siponimod.

- Per-protocol Set (PPS): consisted of all patients in the FAS who did not have any major protocol deviations that could have confounded the interpretation of analyses conducted on the FAS.
- Safety Set (SAF): comprised all patients who received at least one dose of study medication. Patients were analyzed according to the actual treatment received, using all available data up to and including 30 days after last dose of study drug or the day before start of open-label siponimod, whatever came first. The SAF was used for all safety analyses.
- Open-label Set (OLS): included all patients who received at least one dose of open-label siponimod in the Core Part.
- Follow-up Set (FUS): consisted of all patients who received at least one dose of study medication and had follow-up assessments (i.e., had off-drug evaluations/assessments after end of study drug). However, for patients who received at least one dose of open-label siponimod, off-drug evaluations/assessments were only included in this analysis if performed prior to the first dose of open-label siponimod; likewise, off-drug assessments after exposure to open-label siponimod were not included.
- Pharmacokinetic (PK) Set: included all patients with PK data.

Blinded sample size review:

A blinded sample size review was performed prior to the unblinded futility interim analysis. Prior to the completion of enrollment, a review of pooled disability progression data (based on EDSS) was performed to re-assess the assumptions of the disability progression sample size calculation. After the results of the blinded size became available it was decided to proceed as planned in the protocol.

Interim analysis:

Regular interim semi-blinded analyses of safety data were provided to the DMC (approximately twice a year). Also, one interim analysis for a futility assessment was provided. The protocol allowed, at the interim analysis, an assessment for stopping the trial early for efficacy to be made using an O'Brien-Fleming boundary using a Lan-DeMets alpha spending function. However, prior to the futility interim analysis being performed it was decided that even if this stopping boundary was reached the study was to continue in order to allow the collection of sufficient long-term safety and efficacy data. The futility interim analysis was to be performed when at least 50% of the required numbers of patients with 3m-CDP were available in the database. Novartis did not get access to the unblinded results while Core Part was ongoing. The DMC recommended that the study should proceed, i.e. it should not be stopped for futility.

Control of the type I error due to multiple endpoints:

The overall significance level for the primary endpoint is 0.05. The first hypothesis was performed at a two-sided significance level adjusted according to the O'Brien-Fleming alpha level correction which was calculated to be 0.0434. The alpha was adjusted since an interim analysis was performed.

A hierarchical testing procedure was implemented for the primary and key secondary endpoints, which were tested in the following order:

1. Time to 3m-CDP based on EDSS
2. Time to 3-month confirmed worsening of at least 20% from baseline in T25W
3. Change from baseline in T2 lesion volume

The second and third hypothesis tests were performed at a two-sided significance level of 0.05.

Additional secondary end points were evaluated at a nominal significance level of 0.05 without correction for multiplicity, or hierarchical testing.

Primary endpoint: 3m-CDP using the EDSS scale:

The null hypothesis tested that there was no difference in the time to 3m-CDP between the siponimod and placebo group versus the alternative hypothesis that there was a difference between the groups.

The hypothesis was tested using a Cox proportional hazards model with treatment, country, baseline EDSS (continuous scale) and SPMS group (with or without superimposed relapses in the 2 years prior to the screening) as covariates. The estimated hazard ratio (siponimod/placebo hazard rates) with 95% Wald confidence interval was obtained. The risk reduction in percent was calculated as (1 - hazard ratio) x 100.

The primary analysis of the time to 3m-CDP used all available data from all patients in the FAS, irrespective of premature discontinuation from study medication. Patients who did not reach 3m-CDP during the study were censored at the latest date known to be at risk (defined in the FAS as the date of the last EDSS assessment).

Supportive analysis for the primary endpoint

- Kaplan-Meier estimates (with 95% confidence intervals) were summarized at Month 12, Month 24, and Month 36. Kaplan-Meier curve were also presented. Log-rank tests were reported.
- The proportional hazard assumptions were evaluated using 1) graphical methods; 2) an interaction term between time and treatment.
- An analysis of 3m-CDP sustained until end of Core Part was performed post-hoc as a supportive analysis. An additional exploratory analysis was performed for the period from study start to the confirmation date of the 374th event of 3-month CDP.
- The FAS analysis was supplemented by analyses based on the PPS.
- The FAS analysis was also supplemented by an MFAS analysis. For the MFAS analysis, onset of disability progression could not have occurred after the first dose of MS-DMT (or open-label siponimod treatment).

Sensitivity analyses and handling of missing values/censoring/discontinuations for the primary endpoint

For the FAS, MFAS, and PPS, patients who did not have an EDSS assessment after the first dose of study drug were censored at Day 1.

Sensitivity analyses were performed on the FAS, using 3 predefined assumptions for determination of confirmed progression:

1. One sensitivity analysis assumed that all patients with a start of a tentative disability progression based on EDSS, who discontinued the Core Part prematurely within the 3-month confirmation interval, had confirmed progression based on EDSS.
2. A second sensitivity analysis assumed that all patients who discontinued the Core Part prematurely for reasons related to lack of efficacy without reaching the endpoint had confirmed progression based on EDSS at the time they stopped study participation.

3. A third sensitivity analysis assumed that all patients who discontinued the Core Part prematurely without reaching the endpoint had confirmed progression based on EDSS at the time they stopped study participation.

4. A fourth sensitivity analysis assumed that post-baseline EDSS assessments that were documented on the EDSS cover page but were not transferred in the database were considered to have met the disease progression.The EDSS data were collected in a vendor database, transferred to the Novartis database, and the transferred data were used for the statistical analysis. After reconciliation with the Novartis eCRF data, unresolved discrepancies were identified, including mislabeled visits and EDSS assessments documented on the eCRF cover page that were not loaded in the Novartis database. To evaluate robustness of the EDSS results, an additional sensitivity analysis was performed.

A number of protocol deviations and other irregularities occurred during the study. A pre-planned sensitivity analysis was performed to evaluate the potential bias introduced by subjects for whom the main investigator conducted EDSS assessment, or for whom the independent EDSS rater had access to the cardiac monitoring database. In this analysis, a Cox proportional hazards model excluding these patients for whom the EDSS rater had access to potentially unblinding information (identified based on the corresponding protocol deviation and during the MAA procedure) were performed. The comparison of the 3m-CDP in the potentially unblinded group of patients indicated an apparent much larger treatment effect than in the overall study population (HR approximately 0.4 as compared to an overall HR of approximately 0.8). A number of comprehensible factors that could have influenced or contributed to the observed imbalances in the CDP results were identified, e.g. a greater effect on CDP in the potentially affected subgroup of patients compared to the non-affected population and the overall population. Additional analyses also suggest that potential unblinding did not influence treatment decisions and ratings.

First key secondary variable: Time to 3-month confirmed worsening of at least 20% from baseline in T25W

A 3-month confirmed worsening of at least 20% from baseline in the T25W was defined as a decrease from baseline sustained for at least 3 months.

The hypothesis of no difference in T25W was tested using a Cox proportional hazards model. The Cox model included treatment, country/region, SPMS group (with-/without superimposed relapses in the 2 years prior to screening), baseline EDSS (continuous scale) and baseline T25W (continuous scale) as covariates. The hazard ratio was estimated, a log-rank test was performed, and Kaplan-Meier curves and estimates were presented. Kaplan-Meier and log-rank test analyses did not include patients with missing baseline assessments who were censored at baseline.

The FAS analysis was supplemented by analyses based on the MFAS and PPS as well as by sensitivity analyses.

Second key secondary variable: change from baseline in T2 lesion volume

All available data from the FAS were included in the primary analysis of the change from baseline in T2 lesion volume. For MRI assessments, not all patients had Month 24 assessments, and few were expected to have Month 36 assessments.

The change from baseline in T2 lesion volume (second key secondary variable) at Month 12, Month 24 and Month 36 was modeled using a mixed model for repeated measures (MMRM) with visit as a categorical factor and an unstructured covariance matrix. Covariates included treatment, country, age, SPMS group (with-/without superimposed relapses in the 2 years prior to screening), T2 volume at baseline (continuous scale), and number of T1 Gd-enhancing lesions at baseline (continuous scale). The

change from baseline was assumed to follow a normal distribution; the normality assumption of the residuals was tested.

The null hypothesis was that the difference between siponimod and placebo, averaged over Month 12 and Month 24, was zero. Difference between siponimod and Placebo, averaged over Month 12 and Month 24 was tested; these estimates and respective p-value were derived by appropriate contrast from the model. Parameters were estimated using restricted maximum likelihood (REML) methodology, whereby all available assessments contribute to parameter estimations. Similarly, differences in the change from baseline T2 lesion volume at both Month 12 and Month 24 between siponimod and placebo were tested using same model.

Relapse-related variables

The following relapse variables were analysed:

- ARR (all relapses and confirmed relapses)
- Time to first relapse
- Proportion of patients free of relapses

ARR was defined as the average number of relapses per year. ARR was analysed using a negative binomial regression model with the log-link function and treatment, country, continuous baseline EDSS, baseline number of T1 Gd-enhancing lesions and SPMS group (SPMS with/without superimposed relapses in the 2 years prior to screening) as covariates. Log (time in analysis period) was used as the offset variable to obtain the aggregate ARR when the number of relapses was used as the dependent variable in the model.

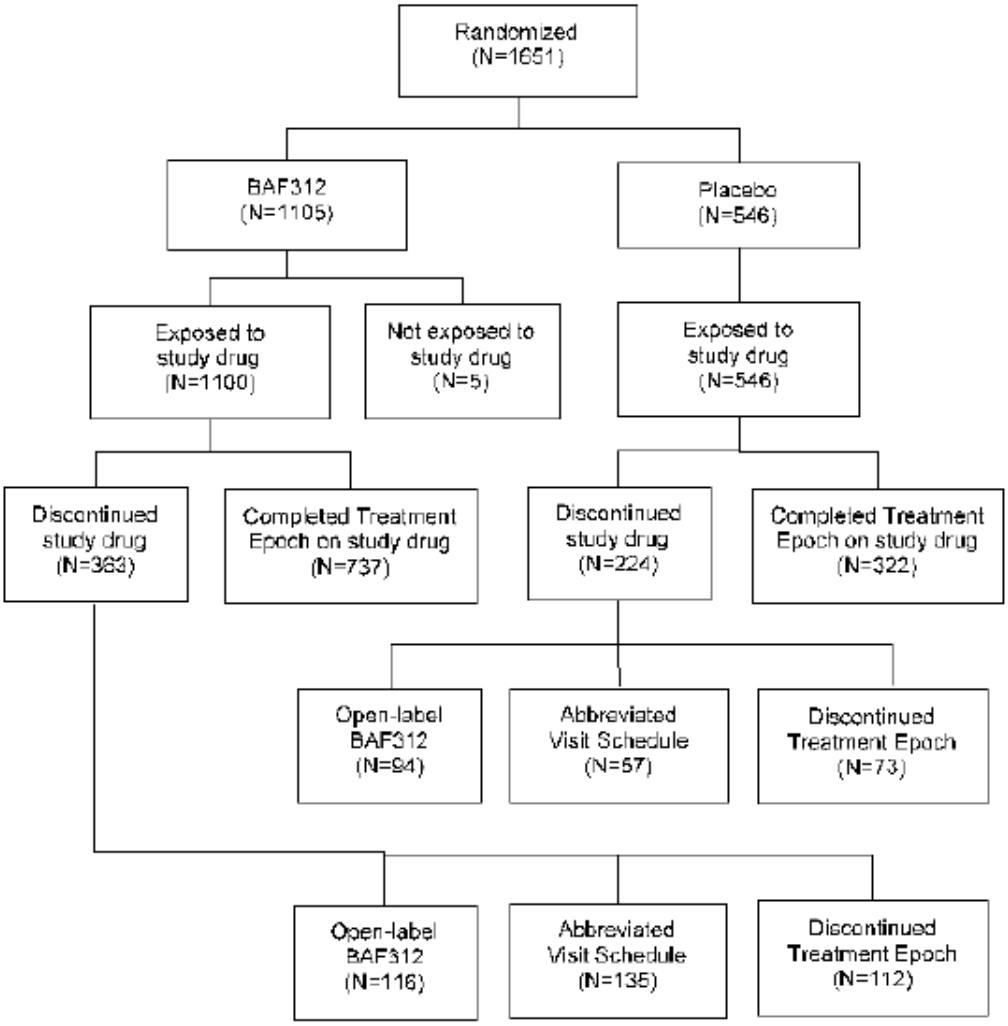
Negative binomial regression models were also used to analyse ARR by SPMS group (SPMS with/without superimposed relapses in the 2 years prior to screening).

Time to first relapse was defined as the time from Day 1 until the start of relapse symptoms. Patients without relapse were censored at the latest known date to be at risk. Analysis was done via a Cox proportional hazards model. Hazard ratio was estimated, a log-rank test was performed, and Kaplan-Meier curves and Kaplan-Meier estimates were presented.

Results

Participant flow

Figure 13: A2304 Study participant flow



A total of 2092 subjects were screened to participate in study A2304 and 1651 were enrolled and randomized. Five subjects were randomized to siponimod but not treated, and one subject had study procedures performed prior to providing informed consent; therefore, the Full Analysis Set (FAS) included 1645 subjects. The disposition of subjects is summarized in *Figure 13*.

More patients in siponimod arm (66.7%) than in placebo arm (59.0%) completed the Treatment Epoch on double-blind study drug. After prematurely discontinuing double-blind study drug (32.9% in the siponimod arm, 41.0% in the placebo arm), most patients (22.7% in the siponimod arm, 27.6% in the placebo arm) continued in the Treatment Epoch on open-label siponimod (this option was in principle only available for patients with a CDP event, although patients without 6m-CDP accessed siponimod rescue) or on the abbreviated visit schedule, in which they did not take study medication but could take a commercially available MS medication. Only 10.1% of siponimod patients and 13.4% of placebo patients discontinued Treatment Epoch directly from study drug. The most common reasons for

discontinuing the Treatment Epoch were "Subject / Guardian Decision,", "lack of efficacy", and "Adverse Event".

Conduct of the study

Protocol deviations:

Approximately 62% of the overall patient population had protocol deviations, predominantly in the following categories: key procedures not performed as per protocol (37.6% siponimod, 36.3% placebo) and other GCP deviations (28.6% and 28.0%, respectively).

Table 7: Protocol deviations, by deviation category – any protocol deviations (RAN)

	BAF312 N=1105 n (%)	Placebo N=546 n (%)	Total N=1651 n (%)
Subjects with at least one protocol deviation	693 (62.7)	333 (61.0)	1026 (62.1)
Protocol deviation category			
Key procedures not performed as per protocol	415 (37.6)	198 (36.3)	613 (37.1)
Other GCP deviation	316 (28.6)	153 (28.0)	469 (28.4)
Prohibited concomitant medication	74 (6.7)	38 (7.0)	112 (6.8)
Selection criteria not met	99 (9.0)	35 (6.4)	134 (8.1)
Subject not withdrawn as per protocol	3 (0.3)	2 (0.4)	5 (0.3)
Treatment deviation	85 (7.7)	38 (7.0)	123 (7.5)

A subject with multiple protocol deviations (PD) within a PD category is counted only once in the respective PD category.
Protocol deviation categories are presented in alphabetical order.

The "other GCP deviation" category mainly refers to:

- Blinding procedures not followed (without data integrity being affected). This occurred with similar incidence in each group (11.3%, 11.5% placebo). This deviation included incorrect access rights of the Primary Treating Physician/team to the first dose database.
- Dual database access by members of the first dose team but integrity of the study is not compromised. This occurred with similar incidence in each group (6.2% siponimod, 6.8% placebo). This deviation related to incorrect access rights of the First Dose Administrator/team to main database.
- Adjudication outcome (confirming evidence of progression in the medical history) was not available before randomization for 5.5% of siponimod patients and 6.0% of placebo patients.
- A low percentage of patients with 6m-CDP in each treatment were not re-consented (within 3 months of 6m-CDP) at the subsequent study visit (3.9% siponimod, 3.8% placebo), however, all patients subsequently signed the re-consent document.

Protocol deviations reported after initial database lock

The following protocol deviations were identified after initial Core Part database lock and included in the database at final core database lock: fampridine administration (either started or stopped) during the Core Part (9 patients (6 patients on siponimod, 3 on placebo) thus excluding them from the per protocol analysis) and missing serum pregnancy test at screening (4 patients, all on siponimod). There was no impact on safety for these patients. There were 7 patients for whom a potential unblinding issue was reported, however without impact on data integrity (6 patients on siponimod, 1 on placebo). Specifically, in 4/7 cases, the study nurse performed both main and blinded database tasks, and in 3/7 cases the

investigator had access to both the Core Part main database and Extension phase first dose database prior to Core Part database lock.

According to the original study report, for 13 patients (8 siponimod, 5 placebo), EDSS raters had access to the Core Part of the First Dose database while they conducted EDSS assessments during the Core Part of the study however, there was no evidence in the electronic trail that they ever accessed the first dose database.

According to the clinical study report amendment, a review was conducted to identify cases of dual database access and GCP01 protocol deviations (PDev) were assigned to the relevant cases before the original Core Study DBL. As part of an internal GCP inspection, conducted after finalisation of the CSR, the accountable vendor was requested to resend the list of granted/revoked access rights. This list was found to contain additional PDev not delineated in the original list.

According to the applicant's position and data provided during the OE, 213 patients could have been potentially affected by unblinded use of inappropriate dataset. According to table 14, there were three potential sources for unblinded EDSS assessments in the trial including an inappropriate access of EDSS rater to the first dose database (n=13) and/or the main database (n=57) and the inappropriate performance of EDSS assessment by main database user (n=3). According to the applicant, the inappropriate access by EDSS raters could have concerned 65 patients (*Table 8*).

Table 8: Number of patients potentially affected by sources of potential unblinding of EDSS rater and primary treating physician/team

		Number of patients affected		
	ID	**Siponimod N (%)**	**Placebo N (%)**	**All N (%)**
Potential unblinding of EDSS rater				
EDSS rater had access to First dose database	C1	8 (0.7)	5 (0.9)	13[1] (0.8)
Main database user performed EDSS rating[2]	C2	1 (0.1)	2 (0.4)	3 (0.2)
EDSS rater had access to Main database	C3	32 (2.9)	20 (3.7)	52 (3.2)
EDSS rater had access and entered data in Main database	C4	5 (0.5)	0 (0.0)	5 (0.3)
Potential unblinding of Primary treating Physician/team				
Main database user had access to First dose database	C5	55 (5.0)	36 (6.6)	91 (5.5)
Main database user had access and entered data in First dose database	C6	10 (0.9)	0 (0.0)	10 (0.6)
Other risk of blinding of the Main database user compromised[3]	C7	34 (3.1)	16 (2.9)	50 (3.0)

[1] 13 patients were rated in total by these 3 EDSS raters (assigned protocol deviation PROC47 in CSR) and excluded in CSR sensitivity analysis; 7 had scores actually rated while EDSS rater had access to First dose database

[2] Main user performed rating instead of the EDSS rater; not related to inappropriate database access. This category also includes 1 patient for whom EDSS rater signed an SAE form which could have led to unblinding.

3 e.g. patient 2071006: "ECG was reviewed by Principal Investigator not First dose administrator"; patient 4062001:" Blinded principal investigator assisted First dose administrator with performing Day 1, Day 4, and Day 7 Holter assessments" Classification: A patient can fall into several categories

Baseline data

These are summarised in Table 9, Table 10, Table 11, Table 12 and Table 13.

Disease history and baseline characteristics

With respect to MS disease history and baseline characteristics groups were generally balanced. Patient population enrolled was consistent with an early (median time since SPMS diagnosis 2.55 years and median age 49 years) moderately to severely disabled (median EDSS score of 6.0) population of SPMS. The SPMS population had a moderate to severe disease course (median MSSS=6 corresponding to 7th decile of disease severity) and nearly half of the population had focal inflammatory disease activity as reflected in the portion of patients with at least a relapse in the prior 2 years or at least one Gd-enhancing lesion at baseline.

Prior medications

Medications that were classified as MS-DMTs were pre-defined. As expected for patients with SPMS diagnosis, the majority had such therapies at any time prior to study entry: 77.8% in the siponimod group and 79.1% in the placebo group. The list of prior therapies was manually reviewed, and a subset further categorized as MS-DMTs (approved for the treatment of MS) or as off-label immunosuppressants and grouped by similar type in descending order in the siponimod group. The 3 most common prior treatments in each treatment group were interferon beta-1a, interferon beta-1b, and glatiramer acetate, and more than half of patients in each group had discontinued these due to lack of efficacy.

Table 9: Baseline demographic characteristics

Demographic variable	BAF312 N=1105	Placebo N=546	Total N=1651
Age groups - n (%)			
18-30	26 (2.4)	12 (2.2)	38 (2.3)
31-40	162 (14.7)	91 (16.7)	253 (15.3)
41-55	716 (64.8)	331 (60.6)	1047 (63.4)
>55	201 (18.2)	112 (20.5)	313 (19.0)
Age (years)			
n	1105	546	1651
Mean (SD)	48.0 (7.84)	48.1 (7.94)	48.0 (7.87)
Median	49.0	49.0	49.0
Min - Max	22 - 61	21 - 61	21 - 61
Sex - n (%)			
Female	669 (60.5)	323 (59.2)	992 (60.1)
Male	436 (39.5)	223 (40.8)	659 (39.9)
Race - n (%)			
Asian	31 (2.8)	18 (3.3)	49 (3.0)
Black or African American	7 (0.6)	3 (0.5)	10 (0.6)
Other	12 (1.1)	7 (1.3)	19 (1.2)
Unknown	5 (0.5)	5 (0.9)	10 (0.6)
White	1050 (95.0)	513 (94.0)	1563 (94.7)
Ethnicity - n (%)			
Hispanic or Latino	74 (6.7)	32 (5.9)	106 (6.4)
Not Hispanic or Latino	829 (75.0)	410 (75.1)	1239 (75.0)
Not reported	95 (8.6)	58 (10.6)	153 (9.3)
Unknown	107 (9.7)	46 (8.4)	153 (9.3)
Weight (kg)			
n	1084	534	1618
Mean (SD)	71.53 (15.685)	71.49 (16.005)	71.52 (15.786)
Median	70.00	70.00	70.00
Min - Max	40.0 - 142.1	38.5 - 145.3	38.5 - 145.3
Height (cm)			
n	1088	535	1623
Mean (SD)	169.24 (9.358)	169.44 (9.874)	169.31 (9.529)
Median	169.00	170.00	169.00
Min - Max	142.2 - 196.0	145.0 - 198.0	142.2 - 198.0
BMI (kg/m²)			
n	1070	525	1595
Mean (SD)	24.90 (4.842)	24.79 (4.769)	24.86 (4.817)
Median	24.12	24.15	24.13
Min - Max	15.1 - 52.2	15.5 - 53.3	15.1 - 53.3

Age is calculated from reference start date and date of birth. If due to privacy concerns, date of birth was not collected, age was imputed from year of birth.
Derived baseline weight, height and BMI are reported.

Table 10: MS disease history (RAN)

Patient characteristics	BAF312 N=1105	Placebo N=546	Total N=1651
Duration of MS since diagnosis (years)			
N	1103	546	1649
Mean (SD)	12.88 (7.912)	12.11 (7.484)	12.63 (7.779)
Median	11.95	11.21	11.67
Min – Max	0.1 - 44.4	0.4 - 39.4	0.1 - 44.4
Duration of MS since first symptom (years)			
N	1103	545	1648
Mean (SD)	17.12 (8.385)	16.23 (8.234)	16.83 (8.343)
Median	16.35	15.40	16.04
Min – Max	1.4 - 45.0	1.3 - 43.0	1.3 - 45.0
Time since conversion to SPMS (years)			
N	1103	546	1649
Mean (SD)	3.85 (3.609)	3.56 (3.284)	3.76 (3.506)
Median	2.57	2.52	2.55
Min – Max	0.1 - 24.2	0.1 - 21.7	0.1 - 24.2
Number of relapses in the last 2 years prior to screening			
N	1102	545	1647
Mean (SD)	0.7 (1.20)	0.7 (1.16)	0.7 (1.19)
Median	0.0	0.0	0.0
Min – Max	0 - 12	0 - 8	0 - 12
Number of relapses in the last 2 years prior to screening (categories) - n (%)			
0	712 (64.4)	343 (62.8)	1055 (63.9)
1	199 (18.0)	104 (19.0)	303 (18.4)
2-3	158 (14.3)	81 (14.8)	239 (14.5)
4-5	26 (2.4)	13 (2.4)	39 (2.4)
>5	7 (0.6)	4 (0.7)	11 (0.7)
Missing	3 (0.3)	1 (0.2)	4 (0.2)
Number of relapses in the last year prior to screening			
N	1104	545	1649
Mean (SD)	0.2 (0.54)	0.3 (0.57)	0.3 (0.55)
Median	0.0	0.0	0.0
Min – Max	0 - 4	0 - 4	0 - 4
Number of relapses in the last year prior to screening (categories) - n (%)			
0	878 (79.5)	416 (76.2)	1294 (78.4)
1	189 (17.1)	111 (20.3)	300 (18.2)
2-3	35 (3.2)	16 (2.9)	51 (3.1)
4-5	2 (0.2)	2 (0.4)	4 (0.2)
Missing	1 (0.1)	1 (0.2)	2 (0.1)
Time since the onset of the most recent relapse (months)			
N	1073	533	1606
Mean (SD)	61.75 (61.527)	54.25 (55.326)	59.26 (59.628)
Median	39.97	36.93	39.12
Min – Max	3.1 - 430.8	2.7 - 315.9	2.7 - 430.8

Duration of MS since diagnosis was derived as: (reference start date - MS diagnosis date)/365.25.
Duration of MS since first symptom was derived as: (reference start date - MS first symptom date)/365.25.
Time since onset of most recent relapse was derived as: (reference start date - most recent relapse onset date)/30.
Time since conversion to SPMS (years) was derived as: (reference start date - conversion to SPMS date)/365.25.

Table 11: Clinical MS baseline characteristics (RAN)

Baseline characteristics	BAF312 N=1105	Placebo N=546	Total N=1651
EDSS			
N	1105	546	1651
Mean (SD)	5.43 (1.076)	5.41 (1.026)	5.42 (1.059)
Median	6.00	6.00	6.00
Min – Max	2.0 - 7.0	2.5 - 7.0	2.0 - 7.0
EDSS (categories) - n (%)			
<3.0	6 (0.5)	2 (0.4)	8 (0.5)
3.0-4.5	312 (28.2)	148 (27.1)	460 (27.9)
5.0-5.5	165 (14.9)	100 (18.3)	265 (16.1)
6.0-6.5	620 (56.1)	295 (54.0)	915 (55.4)
>6.5*	2 (0.2)	1 (0.2)	3 (0.2)
MSSS			
N	1103	545	1648
Mean (SD)	5.83 (1.869)	5.95 (1.808)	5.87 (1.849)
Median	5.99	6.24	6.00
Min – Max	1.2 - 9.8	1.5 - 9.8	1.2 - 9.8
T25W (seconds)			
N	1095	544	1639
Mean (SD)	17.08 (20.829)	16.00 (22.101)	16.72 (21.259)
Median	10.30	9.55	10.05
Min – Max	2.9 - 228.0	3.3 - 290.9	2.9 - 290.9
9-HPT (seconds)			
N	1093	545	1638
Mean (SD)	34.05 (18.265)	34.52 (19.869)	34.21 (18.809)
Median	28.65	28.45	28.58
Min – Max	12.5 - 192.3	14.7 - 174.3	12.5 - 192.3
SDMT oral score			
N	1095	541	1636
Mean (SD)	38.9 (13.99)	39.6 (13.34)	39.1 (13.78)
Median	40.0	42.0	41.0
Min – Max	0 - 83	0 - 81	0 - 83

For continuous characteristics: n=number of patients with non-missing baseline measurement; for categories: a patient may only be counted in one of the categories.
* At baseline three patients had EDSS = 7.0. Patient PID A2304-1067-005 had screening EDSS = 6.5; PID A2304-7006-002 had screening EDSS = 7.0, PID A2304-9057-004 had screening EDSS = 5.0.

Table 12: MRI baseline characteristics (RAN)

Baseline characteristics	BAF312 N=1105	Placebo N=546	Total N=1651
Number of Gd-enhancing T1 lesions			
n	1070	529	1599
Mean (SD)	0.9 (3.55)	0.7 (3.55)	0.8 (3.55)
Median	0.0	0.0	0.0
Min - Max	0 - 55	0 - 65	0 - 65
Number of Gd-enhancing T1 lesions (categories) - n (%)			
0	833 (75.4)	415 (76.0)	1248 (75.6)
≥1	237 (21.4)	114 (20.9)	351 (21.3)
Missing	35 (3.2)	17 (3.1)	52 (3.1)
Volume of T2 lesions (mm^3)			
n	1074	531	1605
Mean (SD)	15631.8 (16267.91)	14694.0 (15619.84)	15321.5 (16057.60)
Median	10286.0	9994.0	10083.0
Min - Max	23 - 116664	0 - 103560	0 - 116664
Volume of unenhanced T1 lesions (mm^3)			
n	1070	529	1599
Mean (SD)	6757.3 (8682.22)	5994.1 (7959.58)	6504.8 (8455.14)
Median	3533.5	3288.0	3462.0
Min - Max	0 - 61537	0 - 62149	0 - 62149
Normalized brain volume (cc)			
n	1071	531	1602
Mean (SD)	1422.0 (86.23)	1424.5 (87.59)	1422.8 (86.67)
Median	1420.5	1425.2	1422.3
Min - Max	1136 - 1723	1199 - 1691	1136 - 1723

For continuous characteristics: n=number of patients with non-missing baseline measurement; for categories: a patient may only be counted in one of the categories.

Table 13 Selected MS-DMT and off-label immunosuppressants, by preferred term (RAN)

Preferred term	BAF312 N=1105 n (%)	Placebo N=546 n (%)	Total N=1651 n (%)
Any MS disease modifying therapy	**860 (77.8)**	**432 (79.1)**	**1292 (78.3)**
MS-DMTs (Approved for the treatment of MS)			
INTERFERON BETA-1A	448 (40.5)	240 (44.0)	688 (41.7)
INTERFERON BETA-1B	315 (28.5)	138 (25.3)	453 (27.4)
INTERFERONS	31 (2.8)	17 (3.1)	48 (2.9)
INTERFERON BETA	5 (0.5)	5 (0.9)	10 (0.6)
INTERFERON	2 (0.2)	0	2 (0.1)
PEGINTERFERON BETA-1A	1 (0.1)	1 (0.2)	2 (0.1)
GLATIRAMER ACETATE	285 (25.8)	157 (28.8)	442 (26.8)
NATALIZUMAB	76 (6.9)	35 (6.4)	111 (6.7)
MITOXANTRONE HYDROCHLORIDE	54 (4.9)	17 (3.1)	71 (4.3)
MITOXANTRONE	48 (4.3)	24 (4.4)	72 (4.4)
DIMETHYL FUMARATE	24 (2.2)	8 (1.5)	32 (1.9)
FUMARIC ACID	1 (0.1)	1 (0.2)	2 (0.1)
TERIFLUNOMIDE	16 (1.4)	5 (0.9)	21 (1.3)
FINGOLIMOD HYDROCHLORIDE	12 (1.1)	6 (1.1)	18 (1.1)
FINGOLIMOD	8 (0.7)	1 (0.2)	9 (0.5)
DACLIZUMAB	4 (0.4)	2 (0.4)	6 (0.4)
Off-label immunosuppressants			
AZATHIOPRINE	61 (5.5)	39 (7.1)	100 (6.1)
CYCLOPHOSPHAMIDE	49 (4.4)	23 (4.2)	72 (4.4)
CICLOSPORIN	1 (0.1)	0	1 (0.1)
RITUXIMAB	3 (0.3)	0	3 (0.2)
METHOTREXATE	9 (0.8)	7 (1.3)	16 (1.0)
MYCOPHENOLATE MOFETIL	13 (1.2)	6 (1.1)	19 (1.2)

A patient can be counted in more than one MS disease modifying therapy (MS-DMT) preferred term.
NovDTD version 14.3 version was used for the reporting of prior medications.
For medication reported under the preferred term=Interferon beta, it was not possible to assess from verbatim if IFN-B1a or IFN-B1b had been administered.
MS-DMT include prior medications which have been further classified into MS-DMT based on a pre-specified list of preferred terms.

Numbers analysed

Patients in the FAS were analysed according to the randomised treatment assignment following the intention-to-treat principle (modified ITT version as only randomised patients who took at least one dose of study medication were included), using all available efficacy assessments, irrespective of the study treatment received. This means that efficacy data obtained while patients were receiving open-label siponimod or receiving other MS-DMT while on the abbreviated visit schedule were also included in the analyses of the treatment groups as randomised.

The PPS was used for sensitivity analyses of the primary and key secondary efficacy variables and consisted of all patients in the FAS who did not have any major protocol deviations that could have confounded the interpretation of efficacy analyses. Overall, 85 randomised patients were excluded from the PPS: 62 in the siponimod group and 23 in the placebo group; while an additional 179 patients had data excluded from PP analyses from the date of the deviation onwards. In addition, any efficacy data assessed after permanent study drug discontinuation were excluded.

Table 14: Population included in the different Analysis sets

Analysis set	BAF312	Placebo	Total
Randomized Set (RAN)	1105	546	1651
Full analysis Set (FAS)	1099	546	1645
Modified full analysis Set (MFAS)	1099	546	1645
Per-protocol Set (PPS)	1037	523	1560
Safety Set (SAF)	1099	546	1645
Open-label Set (OLS)	116	94	210
Follow-up Set (FUS)	648	304	952

A definition of eligibility criteria for each analysis set is provided in the statistical methods.

Outcomes and estimation

Primary efficacy endpoint

Time to 3-month Confirmed Disability Progression

The primary efficacy objective was to compare siponimod versus placebo in delaying the time to 3m-CDP in patients with SPMS as measured by the EDSS. A 3m-CDP required that the EDSS score at progression, the 3-month confirmatory EDSS score and any EDSS scores obtained in between met the disability progression criteria. The confirmatory EDSS score could not have been recorded during an MS relapse. There was no imputation for patients who discontinued without having a confirmed progression.

Siponimod showed a 21.2% risk reduction compared to placebo for time to 3m-CDP based on EDSS that was statistically significant (hazard ratio 0.79, 95% CI (0.65-0.95) p=0.0134), as summarised below:

Table 15: Time to 3-month CDP based on EDSS - Cox proportional hazards model (FAS)

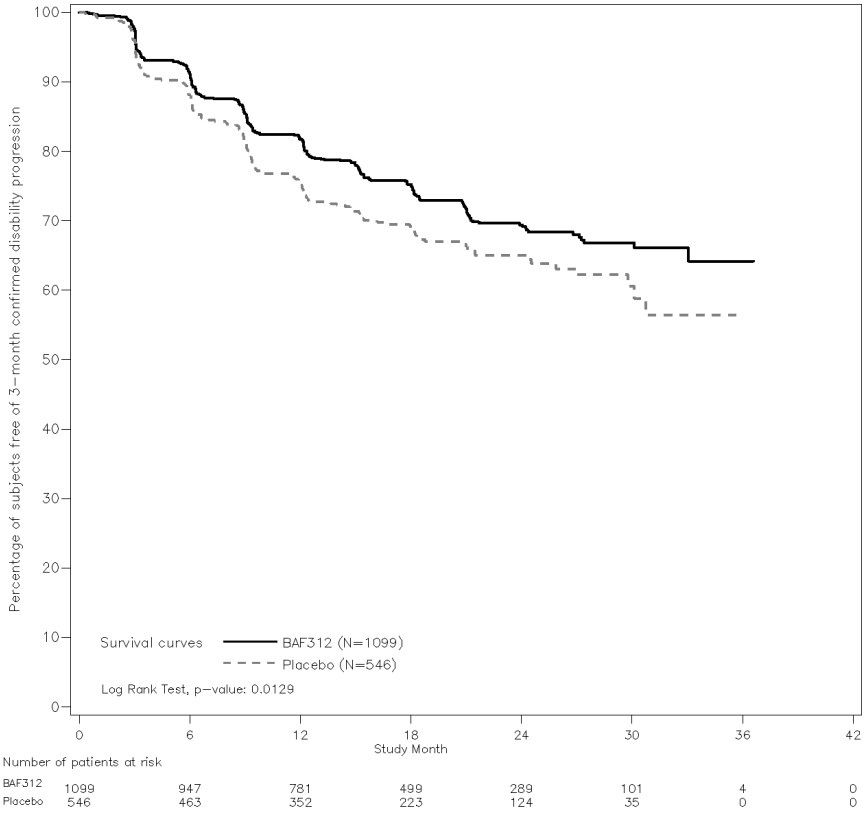
			Comparison: BAF312 vs Placebo #		
Treatment	n/N'	(%)	Risk reduction	Hazard ratio (95% CI)	p-value
BAF312 (N=1099)	288/1096	(26.3)	21.2%	0.79 (0.65; 0.95)	0.0134
Placebo (N=546)	173/545	(31.7)			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates).
Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-hazard ratio) * 100.
For 3 siponimod patients and 1 placebo patient, information on the number of relapses in the last 2 years could not be derived (missing).

For the FAS, Kaplan-Meier estimates for the percentage of patients free of 3m-CDP events were provided at Months 12, 24, and 36. Kaplan-Meier curves showed difference between siponimod and placebo, in favour of siponimod. The log rank test was statistically significant, indicating a delay in the time to 3m-CDP in the siponimod group (p=0.0129). The percentage of patients free of 3m-CDP events for the siponimod arm was 81.82 %, 69.39 % and 64.17 % for the year 1, 2, and 3, respectively. For the placebo arm, the corresponding estimates were 75.32 %, 65.03 % and 56.41 % for the year 1, 2 and 3, respectively. Kaplan-Meier estimates indicated that the time to first quartile (25%) of patients experiencing 3m-CDP events was 541 days, 95 % CI (455; 627) and 363 days, 95

% CI(281; 457) for the siponimod and placebo arm, respectively (an approximate difference of 6 months).

Figure 14: Percentage of subjects free of 3-month confirmed disability progression based on EDSS - Kaplan Meier curves (FAS)



- Last known date to be at risk is defined as the last EDSS assessment date in core part.
- Subjects without baseline EDSS assessment are excluded from the analysis.

Sensitivity analyses

The primary analysis based on the Cox proportional hazards model for time to 3m-CDP was repeated on the PPS and MFAS, and four sensitivity analyses of time to 3m-CDP were done for the FAS using the Cox proportional hazards model and Kaplan-Meier estimates as detailed in the method section.

Table 16: Primary analysis and sensitivity analysis for the 3-month CDP – Cox proportional hazards model

Analysis	BAF312 n/N'	Placebo n/N'	Comparison: BAF312 vs Placebo	
			Risk reduction	p-value
Primary analysis (FAS)	288/1096	173/545	21.2%	0.0134
Primary analysis (PPS)	249/1034	161/522	24.1%	0.0066
Primary analysis (MFAS)	288/1096	172/545	20.9%	0.0153
Sensitivity analysis 1	309/1096	192/545	24.1%	0.0028
Sensitivity analysis 2	308/1096	179/545	18.7%	0.0282
Sensitivity analysis 3	448/1096	259/545	17.8%	0.0123
Sensitivity analysis 4	288/1096	173/545	21.3%	0.0133

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates).
Sensitivity analysis 1: patients who discontinued the Treatment Epoch prematurely and had tentative progression at the end of the Core Part were categorized as having confirmed progression at the start date of the tentative progression
Sensitivity analysis 2: patients who discontinued the Treatment Epoch prematurely for reasons related to lack of efficacy or progressive disease without reaching the endpoint were categorized as having confirmed progression at the time they prematurely discontinued the Treatment Epoch.
Sensitivity analysis 3: patients who discontinued the Treatment Epoch prematurely without reaching the endpoint were categorized as having confirmed progression at the time they discontinued the Treatment Epoch prematurely.
Sensitivity analysis 4: post-baseline EDSS assessments that were documented on the EDSS cover page, but were not transferred in the database were considered to have met the disease progression criteria.

Patients at sites where the EDSS rater had temporary access to potentially unblinding information were excluded from an additional analysis of time to 3-month CDP, using the primary analysis model on the FAS. Excluding data from the 213 patients potentially unblinded (resulting in n=1432 patients definitely not unblinded), the HR was 0.85 95% (0.69-1.05). Excluding data only from the 65 patients for whom EDSS blinded assessment could have been compromised (n=1576), the HR was 0.80 95%CI (0.66-0.97).

Key secondary endpoints

The two key secondary endpoints (in sequence of hierarchical testing) were:

- time to 3-month confirmed worsening of at least 20% from baseline in T25W
- change from baseline in T2 lesion volume

Time to 3-month confirmed worsening of at least 20% from baseline in T25W

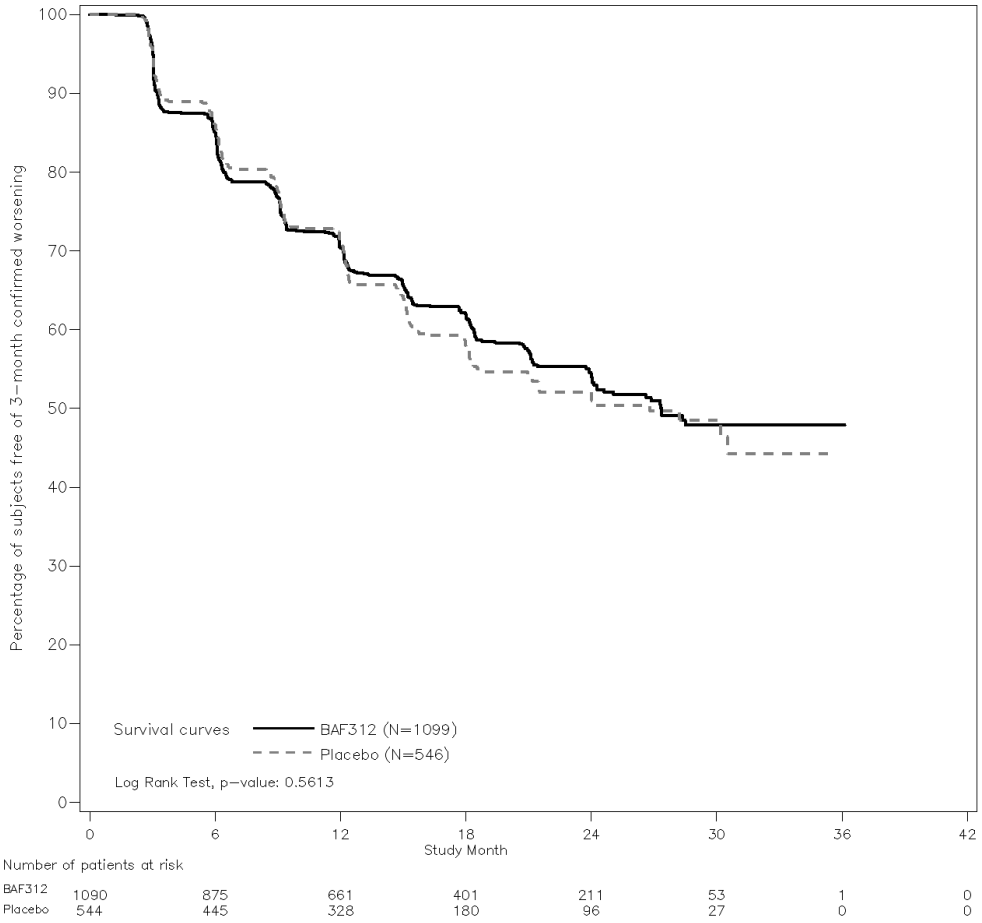
This first key secondary endpoint in the hierarchy did not reach statistical significance (p=0.4398) achieving only a 6.2% risk reduction in favour of siponimod. As specified in the methods section, the FAS analysis was supplemented by analyses based on the MFAS and PPS as well as by sensitivity analyses that did not reach statistical significance.

Table 17: Time to 3-month confirmed worsening in T25W of at least 20% from baseline – Cox proportional hazards model (FAS)

			Comparison: BAF312 vs Placebo£		
Treatment	n/N'	(%)	Risk reduction	Hazard ratio (95% CI)	p-value
BAF312 (N=1099)	432/1087	(39.7)	6.2%	0.94 (0.80; 1.10)	0.4398
Placebo (N=546)	225/543	(41.4)			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates)
£ Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, baseline T25W, and SPMS group (with/without superimposed relapses, baseline definition) as covariates.
Risk reduction is derived as (1-hazard ration) * 100

Figure 15: Percentage of subjects free of 3-month confirmed worsening of at least 20% from baseline in the timed 25'foot walk test (T25W) - Kaplan Meier curves (FAS)



- Last known date to be at risk is defined as the last T25W assessment in the core part.
- Subjects without baseline T25W assessment are excluded from the analysis.

Change from baseline in T2 lesion volume

Since the preceding key secondary endpoint in the hierarchy was not met, statistical significance for this endpoint could formally not be claimed. With this caveat, differences in the change from baseline in T2

lesion volume at both Month 12 and Month 24 and the average over these two time-points were observed between siponimod and placebo groups.

Table 18: Change from baseline in T2 lesion volume (mm3) by time point (Month 12 and 24) – repeated measures model (FAS)

	Adjusted means (SE)		Comparison of adjusted means BAF312 vs Placebo			
Time point	BAF312 (N=1099) (N'=995)	Placebo (N=546) (N'=495)	Difference	SE	95% CI	p-value
Month 12	204.9 (67.47)	818.0 (87.29)	-613.1	95.39	(-800.2 ; -426.0)	<0.0001
Month 24	162.9 (73.90)	940.4 (97.20)	-777.5	108.62	(-990.6 ; -564.4)	<0.0001
Average over Month 12 and Month 24	183.9 (66.33)	879.2 (85.43)	-695.3	92.79	(-877.3; -513.3)	<0.0001

N'=number of subjects included in the analysis (i.e. with at least MRI scan post-baseline and non missing covariates)
Obtained from fitting a repeated measures model (model assumes normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country/region, baseline T2 lesion volume, number of T1 Gd-enhancing lesions at baseline, SPMS group (with/without superimposed relapses, baseline definition). Adjusted mean refers to the change from baseline in T2 lesion volume.

Additional secondary endpoints

A. Time to 6-month CDP

Siponimod treatment delayed the time to 6m-CDP compared to placebo. A risk reduction of 25.9% in 6m-CDP was observed for siponimod (218/1096 events) compared to placebo (139/545 events) (HR 0.74, 95%CI (0.60, 0.92) p=0.0058).The percentage of patients free of 6m-CDP events for the siponimod arm was 86.51%, 76.41% and 75.27% for the year 1, 2, and 3, respectively. For the placebo arm, the corresponding estimates were 78.30%, 71.48% and 70.07% for the year 1, 2 and 3, respectively. Analyses of time to 6m-CDP were repeated on the PPS showing a 29.4% risk reduction in 6-month disability progression for siponimod compared to placebo (HR 0.71, 95%CI (0.56-0.88), p=0.0021). Time to 6m-CDP sustained until last observation in core part was also analysed using the Cox proportional hazards model. This supportive analysis showed a risk reduction of 22.0% for siponimod relative to placebo (p=0.0349). Finally, when excluding data from the 213 potentially unblinded patients, the HR was 0.77 with a 95% CI of (0.61-0.97) in the remaining (n=1432) patients that could not have been unblinded.

B. Relapse Related-Variables

Annualised relapse rate (ARR)

Analyses of relapse were done for confirmed relapses and all relapses (confirmed and unconfirmed). The adjusted group-based (aggregate) ARRs showed low incidence of relapses in the study population (*Table 19).* Analysis of adjusted ARR using negative binomial model for confirmed relapses showed a 55.5% rate reduction for confirmed relapses for siponimod compared to placebo (ARR ratio 0.445, p<0.0001).

Excluding data from the 213 patients potentially unblinded (resulting in n=1432 patients definitely not unblinded), analysis of adjusted ARR using negative binomial model for confirmed relapses showed a 58.1% rate reduction for confirmed relapses for siponimod compared to placebo (ARR ratio 0.419, p<0.0001).

Table 19: ARR for confirmed relapses – negative binomial regression (FAS)

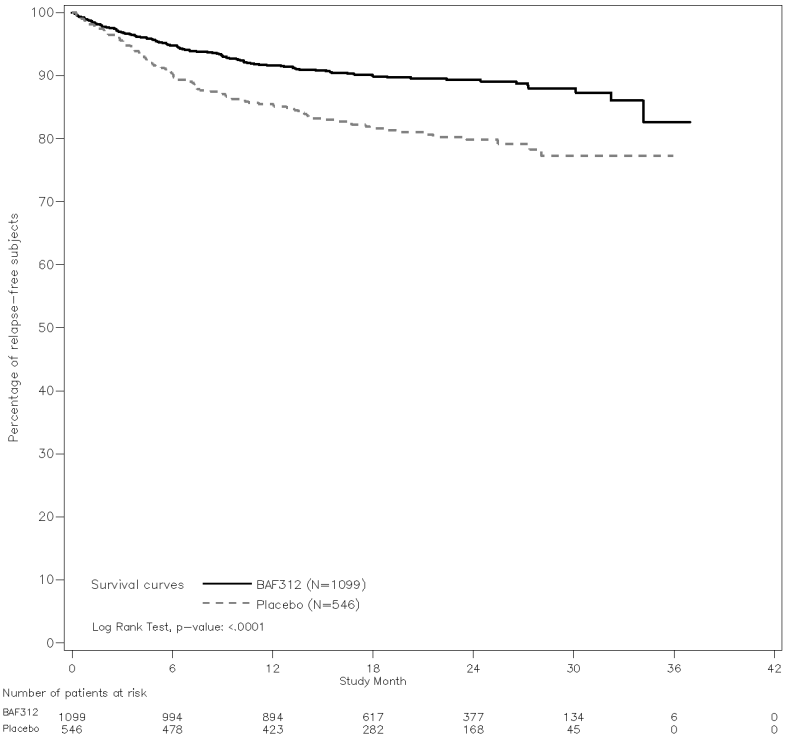
		Between-treatment comparison BAF312 vs Placebo§		
Treatment	Adjusted ARR (95% CI)§	Rate reduction	ARR ratio (95% CI)	p-value
BAF312 (N=1099)	0.071 (0.055;0.092)	55.5%	0.445 (0.337;0.587)	<0.0001
Placebo (N=546)	0.160 (0.123;0.207)			

Analysis period: from first day of study drug up to end of core part.
§ Obtained from fitting a negative binomial regression model adjusted for treatment, country/region, baseline EDSS, baseline number of T1 Gd-enhancing lesions, and SPMS group (with/without superimposed relapses, baseline definition) (offset: time in analysis period in years)

Time to first relapse

The analysis of time to first confirmed relapse showed a risk reduction of 46.4% that favoured siponimod (113/1061 events) compared to placebo (100/528) (HR 0.54, 95%CI (0.41, 0.70) p<0.0001). The risk reduction of 48.3% observed for the PPS (hazard ratio: 0.52; 95%CI (0.39-0.69) p<0.0001) was consistent with the results observed for the FAS. Kaplan-Meier curves depicting the percentage of patients who were free of confirmed relapse showed a difference between siponimod and placebo in the percentage of patients free of confirmed relapse *(Figure 16)*.

Figure 16: Percentage of relapse-free (confirmed relapse) subjects –Kaplan-Meier curves (FAS)



- Relapses up to end of core part are included

Proportion of patients with relapse

Relapses were observed in a lower percentage of patients treated with siponimod (184/1029=16.7%) compared to placebo (142/546=26.0%). The proportion of patients with confirmed relapses (113/1099=10.3% for Siponimod arm and 102/546=18.7% for placebo) is difficult to interpret in an event-driven study design with highly variable study duration across patients.

C. Multiple Sclerosis Walking Scale (MSWS-12)

Walking ability (ambulation) was self - assessed by the patients using the MSWS-12. Total transformed scores on the MSWS-12 ranged from 0-100 with higher scores reflecting greater impairment. There was no significant difference between treatment groups.

Table 20: Change from baseline in MSWS-12 converted score, by time point (Month 12 and 24) repeated measures model (FAS)

	Adjusted means (SE)		Comparison of adjusted means BAF312 vs Placebo			
Time-point	BAF312 (N=1099) (N'=1022)	Placebo (N=546) (N'=516)	Difference	SE	95% CI	p-value
Month 12	1.53 (0.678)	3.36 (0.908)	-1.83	1.030	(-3.85; 0.19)	0.0764
Month 24	4.16 (0.848)	5.38 (1.167)	-1.23	1.359	(-3.89; 1.44)	0.3671

N'=number of subjects included in the analysis (i.e. with a baseline and at least one post-baseline MSWS-12 converted score)
Obtained from fitting a repeated measures model (assumes normally distributed data) with visit as categorical factor. Model was adjusted for treatment, region/country, baseline MSWS-12 converted score. Adjusted means refers to the change from baseline in MSWS-12.

D. MRI related variables

T1 Gd-enhancing lesions

At baseline, approximately 76% of patients in each group did not have T1 Gd-enhancing lesions (Table 12). With regard to all post-baseline scans, 89.4% of siponimod patients and 66.9% of placebo patients were free of T1 Gd-enhancing lesions (Table 21). The same trends were observed in the PPS.

Table 21: Proportion of patients free of T1 Gd-enhancing lesions, by time point (Month 12 and 24) – summary statistics (FAS)

Endpoint Time-point	BAF312 N=1099 n/m	Placebo N=546 n/m
Proportion of patients free of T1 Gd-enhancing lesions (in this scan)		
Month 12	954/1019 (93.6)	391/507 (77.1)
Month 24	593/622 (95.3)	250/304 (82.2)
Proportion of patients free of T1 Gd-enhancing lesions (all post-baseline scans)		
All post-baseline scans	917/1026 (89.4)	341/510 (66.9)

n=number of subjects who are free of lesions.
For all post-baseline scans, m=number of subjects with at least one post-baseline result
At time-points evaluated on a single MRI scan, m=number of subjects with result in this scan.

The mean number of lesions per scan was low in each treatment group. Statistically significant differences, favoring siponimod, were seen for number of T1 Gd-enhancing lesions at Month 12 and Month 24 (p<0.0001).

Table 22: T1 Gd-enhancing lesions per patient per scan, by time point (Month 12 and 24) – repeated measures negative binomial regression (FAS)

	Adjusted mean (95% CI)§		Between-treatment comparison§ BAF312 vs Placebo			
Time-point	BAF312 (N=1099) (N'=996)	Placebo (N=546) (N'=496)	Rate reduction	Rate ratio	(95% CI)	p-value
Number of T1 Gd-enhancing lesions (in this scan)£						
Month 12	0.080 (0.058;0.111)	0.640 (0.488;0.839)	87.4%	0.126	(0.083;0.191)	<0.0001
Month 24	0.074 (0.040;0.138)	0.418 (0.288;0.607)	82.2%	0.178	(0.087;0.362)	<0.0001

N'=number of patients included in the analysis (i.e. with at least one MRI scan post baseline and non-missing values for the covariates included in the model).
Adjusted mean (or rate) refers to the adjusted number of lesions per subject per scan.
Rate reduction is derived as (1- rate ratio) * 100.
§ Obtained from fitting negative binomial regression model adjusted for treatment, age, baseline number of T1 Gd-enhancing lesions (offset=number of scheduled MRI scans).
£ A repeated measures regression model was implemented with visit as a categorical factor

New/newly enlarging T2 lesions

The proportions of patients free of new or enlarging T2 lesions compared to the previous scan were 62.2% and 78.8% for siponimod and 46.2% and 50.7% for placebo patients at Months 12 and 24, respectively. For all post-baseline scans (performed annually), 56.9% of siponimod patients and 37.3% of placebo patients were free of new or enlarging T2 lesions (*Table 23*).Similarly, siponimod showed a prominent effect on the reduction of the mean number of new/newly enlarging T2 lesions at Month 12 (relative to baseline) and Month 24 relative to Month 12 (*Table 24*:).

Table 23: Proportion of patients free of new or enlarging T2 lesions, by time point (Month 12 and 24 relative to previous time point) – summary statistics (FAS)

Endpoint Time-point	BAF312 N=1099 n/m	Placebo N=546 n/m
Proportion of patients free of new or enlarging T2 lesions (in this scan relative to previous scan)		
Month 12 (relative to baseline)	636/1023 (62.2)	235/509 (46.2)
Month 24 (relative to Month 12)	493/626 (78.8)	154/304 (50.7)
Proportion of patients free of new or enlarging T2 lesions (overall)		
All post-baseline scans	584/1026 (56.9)	190/510 (37.3)

n=number of subjects who are free of lesions.
At last assessment time-points, m=number of subjects at least one post-baseline result
At time-points evaluated on a single MRI scan, m=number of subjects with result in this scan.

Table 24: New or enlarging T2 lesions, by time point (Month 12 and 24 relative to previous time point) – repeated measures negative binomial regression (FAS)

	Adjusted mean (95% CI)§		Between-treatment comparison§ BAF312 vs Placebo			
Time-point	BAF312 (N=1099) (N'=997)	Placebo (N=546) (N'=496)	Rate reduction	Rate ratio	(95% CI)	p-value
Month 12 (relative to baseline)	1.003 (0.858;1.172)	3.776 (3.148;4.528)	73.4%	0.266	(0.215;0.328)	<0.0001
Month 24 (relative to Month 12)	0.489 (0.371;0.644)	3.437 (2.800;4.220)	85.8%	0.142	(0.103;0.196)	<0.0001

N'=number of patients included in the analysis (i.e. with at least one MRI scan post first dose and non-missing values for the covariates included in the model).
Adjusted mean (rate) refers to the adjusted number of lesions per patient per year. The rate ratio is the ratio of adjusted means (or rate) of BAF312 versus Placebo. Rate reduction is derived as (1 - rate ratio) *100.
§ Obtained from fitting a repeated measures negative binomial regression model with visit as a categorical factor. Model was adjusted for treatment, region/country, age, baseline number of Gd-enhancing T1 weighted lesions (offset=time between visits).

All post-baseline visits up to and including Month 24 have been included.

T1 hypointense lesions

Increase from baseline in the volume (mm3) of T1 hypointense lesions, was smaller in the siponimod group at Month 12 (541 mm3) than in the placebo group (635.7 mm3). For number of new T1 hypointense lesions (relative to previous scheduled scan), mean number of new lesions was 1.5 in the siponimod group at Month 12 and 3.3 in the placebo group, and showed differences between groups (favoring siponimod) also at Months 24 (mean number of new T1 hypointense lesions 0.5 siponimod 2.4 for placebo, compared to Month 12).

Percent Brain Volume Change (PBVC)

The PBVC relative to baseline was -0.283% for siponimod and -0.458% for placebo at Month 12 (p<0.0001). The decrease in PBVC was also lower in patients treated with siponimod at Month 24 (p=0.0196). The relative reduction by time point was 38.21% (0.175/0.458) at Month 12 and 15.26% (0.128/0.839) at Month 24.

Table 25: PBVC relative to baseline, by time point (Month 12 and 24) – repeated measures model (FAS)

	Adjusted means (SE)		Comparison of adjusted means BAF312 vs Placebo			
Time-point	BAF312 (N=1099) (N'=894)	Placebo (N=546) (N'=436)	Difference	SE	95% CI	p-value
Month 12	-0.283 (0.0264)	-0.458 (0.0341)	0.175	0.0367	(0.103; 0.247)	<0.0001
Month 24	-0.711 (0.0356)	-0.839 (0.0476)	0.128	0.0549	(0.021; 0.236)	0.0196

N'=number of subjects included in the analysis (i.e. with at least MRI scan post-baseline and non-missing covariates)
Obtained from fitting a repeated measures model (for normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country/region, age, normalized brain volume at baseline, number of T1 Gd-enhancing lesions at baseline, T2 volume at baseline, and SPMS group (with/without superimposed relapses, baseline definition).
Adjusted mean refers to PBVC relative to baseline.

All post-baseline visits up to and including Month 36 have been included.

Exploratory efficacy results

Results of exploratory endpoints according to the statistical plan:

a) Patient-reported outcomes
   - Multiple Sclerosis Impact Scale (MSIS-29): A higher score on the MSIS-29 was indicative of greater impact of MS on day to day life. In the FAS analysis, for physical impact scores, the adjusted mean differences of -2.89 at Month 12 was significant (p=0.0034), favoring siponimod, but significance was not achieved at Month 24 (p=0.3000). For psychological impact scores, statistical significance was not achieved at Month 12 or Month 24 (0.0604 and 0.6703, respectively).
   - EQ-5D: The EQ-5D included a health state classification and a VAS thermometer. For the EQ-5D utility scores, the small adjusted mean difference between treatment groups of 0.025 at Month 12 showed a statistically significant difference (p=0.0392) favoring siponimod, but significance was not reached at Month 24 (p=0.0913). For the VAS thermometer score, statistical significance for the adjusted mean differences was not achieved at Month 12 or Month 24 (p=0.0722, p=0.4712, respectively).

b) Cognitive function
   - Symbol Digit Modalities Test (SDMT) oral score: The score was based on number of correct answers in 90 seconds. At Month 12, the comparison of adjusted mean change in correct responses between siponimod and placebo showed a small but significant difference of 1.085 (p=0.0132), which increased to 2.303 at Month 24 (p=0.0002) showing that patients on siponimod had more correct answers in 90 seconds. The difference in adjusted means over all time-points was 1.384 (p=0.007). There was no worsening in the siponimod group at Month 12 and Month 24, whereas, in the placebo group a worsening of mean scores was observed at each time point.
   - Paced Auditory Serial Addition Test (PASAT): The number of correct answers from the PASAT test was recorded (possible range 0-60). The adjusted means were not statistically different between groups.
   - Brief Visuospatial Memory Test Revised (BVMT-R): The analysis of total recall and delayed recall scores did not show meaningful differences between treatment groups.

c) Evolution of acute lesions into chronic black holes: The average patient-level rates of T1 Gd-enhancing lesions that evolved into hypointense lesions were similar in each group at Month 12 (0.63 siponimod, 0.60 placebo) and Month 24 (0.75 siponimod, 0.74 placebo). The percentages of patients who had at least 1 T1 Gd-enhancing lesion that evolved into a T1 hypointense lesion were (siponimod and placebo, respectively): 77% and 68% at Month 12 and 73% and 86% at Month 24.

d) MSFC**:** The MSFC z-scores were calculated from the subscale results (T25W, 9-HPT, and PASAT). The scores for these 3 components were combined to create a single score that was used to detect changes over time. Change from baseline in MSFC z-scores, and in the individual subscale scores (adjusted means) did not show significant differences between siponimod and placebo.

e) Disability progression based on composite endpoint: The analysis of time to 3m-CDP based on the composite endpoint showed a risk reduction of 9.1%; however, the difference between groups was not statistically significant (p=0.1775).

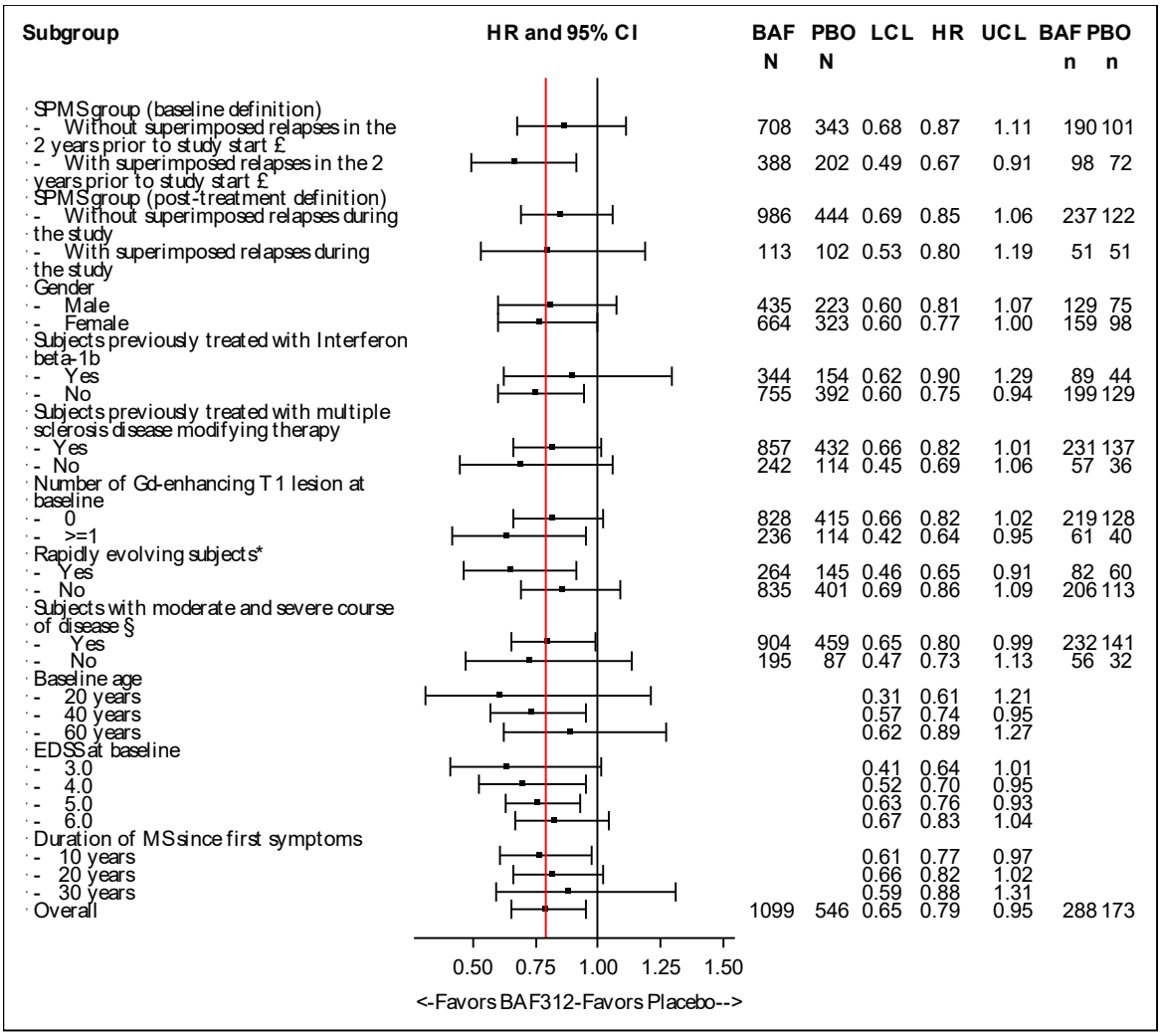
Additionally, the MAH explored Low contrast visual acuity (LCVA): The analysis of change from baseline in LCVA by visit showed small differences that did not reach statistical significance (p=0.3656 and p=0.8774 at Months 12 and 24, respectively) for comparisons of adjusted means.

Subgroup analyses

As an, additional secondary objective, the applicant evaluated efficacy of siponimod relative to placebo on 3-months CDP (3m-CDP) based on EDSS for three pre-defined subgroup analyses, namely SPMS

group, rapidly evolving MS and MS severity course. Additionally, the applicant presented subgroup analyses for other baseline demographic and MS-related features. Finally, the applicant presented subgroup analysis for SPMS group based on-trial relapses (post-baseline definition). Effect of siponimod was more pronounced for younger patients, moderately disabled patients, those with rapidly evolving MS and patients presenting makers of focal inflammatory activity (either relapses in the 2 prior years or *Gd-enhancing T1 lesions at baseline) (Figure 17).*

Figure 17: Time to 3-month CDP based on EDSS – Forest plot displaying hazard ratios, by subgroup (FAS)

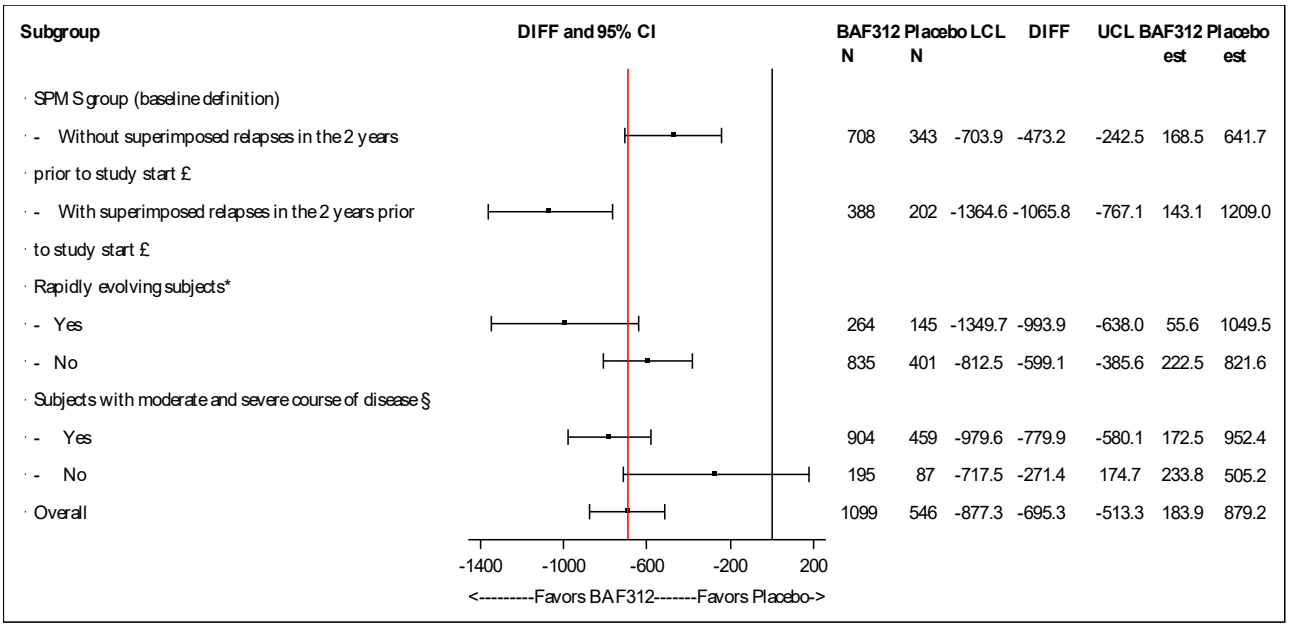


N is the number of subjects in the subgroup; n is the number of subjects in the subgroup with confirmed disability progression. HR = hazard ratio. LCL/UCL = Lower/Upper limit of the HR 95% confidence interval
Results using a Cox proportional hazard model with treatment, country/region, baseline EDSS, SPMS group (with-/without superimposed relapses, baseline definition) and the subgroup (if other than SPMS group) as covariates.
£ Date of study start corresponds to the date of screening visit.
§ Moderate or severe course of disease is defined as Global MSSS of 4 or more at baseline.
* Rapidly evolving subjects are defined as subjects with 1.5 or greater EDSS change in the 2 years prior to or at study start and disability progression in the 2 years prior to study start was not adjudicated.
Subjects previously treated with Interferon beta-1b (IFNB)/disease modifying therapy (MS-DMT) are defined as subjects who received and stopped IFNB/MS-DMT prior to first dose of study treatment

Change from baseline in T2 lesion volume

Subgroup analyses for the three main subgroups specified in the SAP for the 3m-CDP based on EDSS were also performed for the change from baseline in T2 lesion volume. With the caveat that the statistical significance for the main effect for this secondary outcome could not be formally claimed as the preceding key secondary endpoint in the hierarchy was not met, results from subgroup analyses were in the same direction as the primary endpoint suggesting a larger effect on those with a rapidly evolving MS and/or superimposed relapses in the 2 years prior to study start (Figure 18).

Figure 18: Change from baseline in T2 volume (mm3) – Forest plot displaying treatment differences in adjusted means from a repeated measures model, by subgroup (FAS)

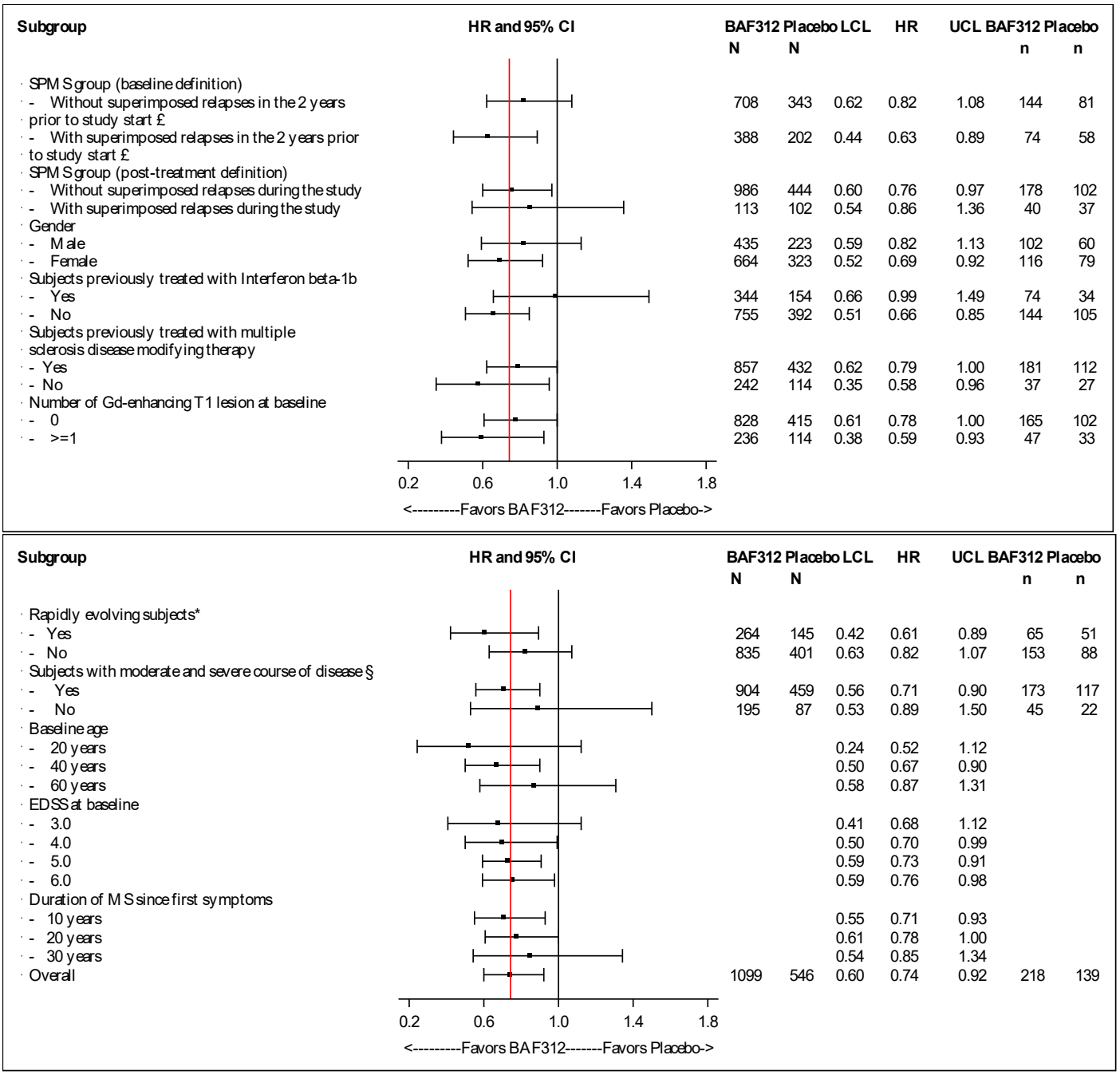


N is the number of subjects in the subgroup; n is the number of subjects in the subgroup with confirmed disability progression. HR = hazard ratio. LCL/UCL = Lower/Upper limit of the HR 95% confidence interval
Results using a Cox proportional hazard model with treatment, country/region, baseline EDSS, SPMS group (with-/without superimposed relapses, baseline definition) and the subgroup (if other than SPMS group) as covariates.
£ Date of study start corresponds to the date of screening visit.
§ Moderate or severe course of disease is defined as Global MSSS of 4 or more at baseline.
* Rapidly evolving subjects are defined as subjects with 1.5 or greater EDSS change in the 2 years prior to or at study start and disability progression in the 2 years prior to study start was not adjudicated.

Time to 6-month CDP (post-hoc)

The applicant presented post-hoc subgroup analyses for the 6m-CDP using EDSS and results were in the same direction as the ones reported for the 3m-CDP using EDSS (*Figure 19*).

Figure 19: Time to 6-month CDP based on EDSS – Forest plot displaying hazard ratios, by subgroup (FAS)



N is the number of subjects in the subgroup; n is the number of subjects in the subgroup with confirmed disability progression. HR = hazard ratio. LCL/UCL = Lower/Upper limit of the HR 95% confidence interval
Results using a Cox proportional hazard model with treatment, country/region, baseline EDSS, SPMS group (with-/without superimposed relapses, baseline definition) and the subgroup (if other than SPMS group) as covariates.
£ Date of study start corresponds to the date of screening visit.
§ Moderate or severe course of disease is defined as Global MSSS of 4 or more at baseline.
* Rapidly evolving subjects are defined as subjects with 1.5 or greater EDSS change in the 2 years prior to or at study start and disability progression in the 2 years prior to study start was not adjudicated.
Subjects previously treated with Interferon beta-1b (IFNB)/disease modifying therapy (MS-DMT) are defined as subjects who received and stopped IFNB/MS-DMT prior to first dose of study treatment

ARR

Negative binomial regression models were also used to analyse ARR by SPMS group (SPMS with/without superimposed relapses in the 2 years prior to screening). Patients with superimposed relapses in the 2

years before baseline, who were treated with siponimod, had a 42.1% rate reduction in confirmed relapses relative to placebo (ARR ratio=0.579: 95%CI (0.3990-0.839); p=0.0039). Patients without superimposed relapses in the 2 years before baseline, who were treated with siponimod, had a 65.3% rate reduction in confirmed relapses relative to placebo (ARR ratio=0.347; 95%CI (0.229-0.525) p<0.0001).

Ancillary analyses

As an attempt to disentangle the effect of Siponimod on disability progression driven by the effect on relapses, the applicant used different statistical methods

1. Subgroup analyses

As reported in the forest plots for subgroup analyses (*Figure* 17 and *Figure 19*), the HRs for 3m-CDP based on EDSS were 0.67 95% CI (0.49-0.91) and 0.87 95%CI (0.68-1.11) for SPMS with and without superimposed relapses in the 2 years prior to inclusion, respectively. Similar findings were reported for 6m-CDP based on EDSS for SPMS patients with [HR=0.63 95% CI (0.44-0.89)] and without superimposed relapses in the 2 years prior to inclusion [HR=0.82 95%CI (0.62-1.08)].

In addition to the baseline relapse activity, the applicant provided results based on post-baseline relapses over the trial. The HRs for 3m-CDP based on EDSS were 0.80 95% CI (0.53-1.19) and 0.85 95%CI (0.69-1.06) for SPMS with and without on-study relapses, respectively. Similar findings were reported for 6m-CDP based on EDSS for SPMS patients with [HR=0.86 95% CI (0.54-1.36)] and without on-trial relapses [HR=0.76 95%CI (0.60-0.97)].

During the OE, the applicant provided additional estimates for 3m-CDP and 6m-CDP based on EDSS for different subgroups using the presence/absence of baseline Gd-enhancing lesions and relapse in the two years prior inclusion as criteria for subgroups definition. There were no differences between siponimod and placebo in CDP based on EDSS for half of the population who had neither relapse prior 2 years nor Gad lesion at baseline Table 26. In patients with active disease (defined as presence of relapses in the 2 years prior to screening or presence of T1 Gad lesion at baseline dark grey in Table 26), reflecting the target population of the proposed indication, the hazard ratio for siponimod (BAF312) compared to placebo for both 3m-CDP (primary endpoint) and 6m-CDP (secondary endpoint) was significantly less than 1.00.

Table 26: Subgroup analyses based on different definition criteria of active SPMS

Analysis Population	**3m-CDP HR (95%CI) p-value**	**6mCDP HR (95%CI) p-value**	**N included in the model* (%)**
Active - w relapse in the prior 2 years	0.70 (0.51 ; 0.96) p=0.0280	0.64 (0.45 ; 0.92) p=0.0151	590 (35.9%)
Active – w Gad lesion at baseline	0.65 (0.43 ; 1.00) p=0.0506	0.57 (0.36 ; 0.92) p=0.0203	349 (21.2%)
Active – w relapses in the prior 2 years **and/or** Gad lesion at baseline	0.69 (0.53 ; 0.91) p=0.0094	0.63 (0.47 ; 0.86) p=0.0040	778 (47.3%)
Active – w relapses in the prior 2 years **and** Gad lesion at baseline	0.67 (0.36 ;1.27) p=0.2175	0.56 (0.27 ; 1.14) p=0.1091	161 (9.8%)
No relapses in the prior 2 years and no Gad lesion at baseline	0.93 (0.71 ; 1.23) p=0.6215	0.87 (0.64 ; 1.19) p=0.3762	827 (50.3%)

*Cox model run on the subgroup, with baseline EDSS, presence of relapses in the 2 years prior to inclusion (when applicable) and country covariates. Only patients with non-missing covariates are included. Gad=gadolinium-enhancing

2. Effect independent of relapses in overall population using a re-baselined EDSS after a relapse

The applicant evaluated the impact of lack of recovery of a relapse (confirmed and unconfirmed) on time to 3m-CDP based on EDSS. For this analysis, onset of progression could not occur during a relapse and, if the EDSS value did not return to baseline EDSS after a relapse, the increased EDSS value after relapse resolution was used to establish a new EDSS baseline value. Using this "re-baselining" definition of 3m-CDP, 23.7% (261/1099) of patients in the siponimod group, and 25.5% (139/546) in the placebo group did show 3m-CDP. This corresponds to a non-significant relative risk of 0.93 with 95% CI (0.78; 1.12).

3. Principal stratum analysis of effect in non-relapsing patients

Upon request, the applicant provided additional analyses addressing two estimands using the ICH E9 R1 addendum framework using multiple imputation based on the control arm.

The principal stratum analysis is a theoretical way to calculate the probability of belonging to the "never relapsing" stratum by making several assumptions including:

1. Siponimod cannot cause relapses
2. The probability of belonging to a particular stratum ("never relapsing", "only relapsing on placebo", "always relapsing", "relapsing only on siponimod") does not depend on being a drop-out when EDSS at baseline and previous relapses are taken into account.
3. The probability of 3m-CDP is independent of being a drop-out when EDSS at baseline, previous relapses; treatment and stratum are taken into account.
4. Patients who discontinued the treatment epoch before the time point considered (12,18 or 24 months) were assumed to be exchangeable with non-missing patients conditional on EDSS at baseline (above/below 6) and prior study relapses.

Since the calculations are iterative, a starting set of values were chosen based on available information (prior distribution). The starting values do influence the results, and some of those values were challenged in sensitivity analyses.

The subgroup of patients that would not relapse regardless of treatment assignment (siponimod or placebo) can be considered as the "true non-relapsing" patients as they would not relapse under any treatment. In the principle stratum analysis, the relative risk for 3m-CDP was between 0.80 and 0.86 (*Table 27*) however with wide confidence intervals.

Table 27:Confirmed disability progression based on EDSS – Relative risk in non-relapsing patients - Principal stratum analysis

Endpoint	Principal stratum of non-relapsers* Estimates of relative risk (posterior median and 95% credible interval)		
	12 months cut	18 months cut	24 months cut
3 months CDP	0.80 (0.56; 1.08)	0.86 (0.57; 1.24)	0.82 (0.48; 1.32)
6 months CDP	0.67 (0.44; 0.93)	0.71 (0.42; 1.09)	0.71 (0.37; 1.21)

*patients who would not relapse over the specified period of time on study regardless treatment assignment.

In addition to the principal stratum analysis, the question of treatment effect on disability progression independent of an effect on relapses in the overall population was addressed using the hypothetical strategies described below. Two hypothetical estimands are defined in scenarios, which reflect the question of interest:

1. under the hypothetical condition that no relapse would occur (hypothetical prescriptive), and

2. that relapses would occur in an identical rate (same risk of experiencing intercurrent relapses) in both treatment groups (hypothetical natural).

Estimation of treatment effect on disability progression before first relapse can be achieved by a Cox proportional hazard model applied to data with censoring at the time of first relapse. Such approach led to HRs of 0.87 (95%CI: 0.71; 1.08) and 0.78 (95%CI: 0.61; 0.98) for 3- and 6m-CDP respectively. Similar HRs were obtained under the second scenario (Table 28:).

Table 28: Estimation of effect of siponimod on CDP in all SPMS patients independent of treatment effect on relapses – HR and 95% CI – Study A2304

Endpoint	Cox model with censoring at time of first relapse	Cox model with IPCW*	Simulations based on empirical distribution
3 months CDP	0.872 (0.705 ; 1.079)	0.856 (0.703 ; 1.043)	0.821 (0.678 ; 0.990)
6 months CDP	0.776 (0.613 ; 0.982)	0.771 (0.619 ; 0.961)	0.774 (0.626; 0.963)

*Inverse Probability Censoring Weigh
Cox models included baseline EDSS score and presence of relapse in the 2 years prior to study as covariates

Summary of main study

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

Table 29: Summary of Efficacy for trial CBAF312A2304

Title: A multicenter, 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		
Study identifier	BAF312A2304 (EudraCT number 2012-003056-36)	
Design	Multicenter, randomized, double-blind, parallel-group, placebo-controlled (randomization 2:1 siponimod:placebo). Possibility to switch to open-label active treatment after 6-month confirmed disability progression and remain in the study. Patients offered to continue in study extension on open-label active treatment after primary analysis cut-off point.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Variable duration (end of study was defined when at least 374 3-month CDP events were reached and at least 12 months after last patient was randomized) Not applicable Maximum 7 years
Hypothesis	Superiority	
Treatments groups	BAF312	Siponimod 2 mg/day - 1105 patients randomized (1099 treated)

	Placebo		Placebo - 546 patients randomized and treated
Endpoints and definitions	Primary endpoint	Time to 3-month CDP	Time to 3-month Confirmed Disability Progression (3mCDP) defined as an increase from baseline of EDSS score of: - 1 point in patients with a Baseline EDSS score of 3.0 to 5.0, or - 0.5 point in patients with a Baseline EDSS score of 5.5 to 6.5. Criteria must be met at visits at least 3 months after onset and at any interim assessment. Confirmation cannot be during a relapse
	Key Secondary endpoint	Time to 3-month confirmed worsening of T25W	Time to 3-month confirmed worsening of Timed 25 Walking test by 20% compared to baseline. Criteria must be met at visits 3 months after onset and at any interim assessment. Confirmation cannot be during a relapse.
	Key Secondary endpoint	Change from baseline in T2 lesion volume	
	Secondary endpoint	Time to 6-month CDP	Time to 6-month Confirmed Disability Progression (6mCDP). Progression defined as for 3 month CDP. Criteria must be met at visits 6 months after onset and at any interim assessment. Confirmation cannot be during a relapse.
	Secondary endpoint	Annualized relapse rate (ARR)	Defined as the average number of confirmed relapses per year. Confirmed relapse: associated with an increase of at least 0.5 points on the EDSS score, or an increase of 1 point in two Functional System scores or 2 points in one Functional System score
	Secondary endpoint	Change in Multiple Sclerosis Walking Scale (MSWS-12)	Patient Reported Outcome
	Secondary endpoint	Change in other measures by conventional MRI	Number of Gd enhancing T1 lesions Number of new or enlarging T2 lesions T1 hypointense lesions Percentage of Brain volume change
Database lock	15-Aug-2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS) (with intend to treat principle) All randomized patients receiving at least one dose of study medication (5 patients excluded from FAS never took medication and 1 patient excluded due to delayed informed consent)		
	Treatment group	BAF312	Placebo
	Number of subject	1099	546

Descriptive statistics and estimate variability	% pts free of 3m-CDP at 12 months (Kaplan-Meier estimate)	81.82	75.32
	Variability statistic (95%CI)	(79.47; 84.18)	(71.59; 79.04)
	% pts free of 3m-CDP at 24 months (Kaplan-Meier estimate)	69.39	65.03
	Variability statistic (95%CI)	(66.24, 72.54)	(60.54, 69.53)
	% pts free of 3m-CDP at 36 months (Kaplan-Meier estimate)	64.17	56.41
	Variability statistic (95%CI)	(58.95, 69.40)	(48.55, 64.28)
Effect estimate per comparison	Primary endpoint	Comparison	BAF312 - Placebo
		Hazard ratio	0.79
		95%CI	(0.65; 0.95)
		P-value	0.0134
Notes	Cox proportional hazard model was adjusted for country, baseline EDSS score and presence of relapses in the 2 years prior to inclusion. Patients with missing covariates were excluded from the model. Primary analysis was supplemented by sensitivity analyses (Per-protocol set, various handling of censored data, log-rank test). All yield similar conclusion.		
Analysis description	**Analysis of first key secondary endpoint T25W**		
Analysis population and time point description	Full analysis set (with intend to treat principle) Due to the nature of analysis (time-to) no time point defined		
	Treatment group	BAF312	Placebo
	Number of subjects	1099	546
Descriptive statistics and estimate variability	% pts free of 3-month confirmed worsening in T25W at 12 months (Kaplan-Meier estimate)	70.51	71.53
	Variability statistic (95%CI)	(67.71, 73.31)	(67.61, 75.45)
	% pts free of 3-month confirmed worsening in T25W at 24 months (Kaplan-Meier estimate)	54.53	52.07
	Variability statistic (95%CI)	(51.06, 58.00)	(47.14, 57.00)
	% pts free of 3-month confirmed worsening in T25W at 36 months (Kaplan-Meier estimate)	47.90	44.21
	Variability statistic (95%CI)	(43.60,52.20)	(36.55, 51.87)
Effect estimate per comparison	First key Secondary endpoint	Comparison groups	BAF312 - Placebo
		Hazard ratio	0.94
		95%CI	(0.80; 1.10)
		P-value	0.4398
Notes	Cox proportional hazard model was adjusted for country, baseline EDSS score, baseline T25W and presence of relapses in the 2 years prior to inclusion. Patients with missing covariates were excluded from the model. This key secondary endpoint did not reach statistical significance; additional endpoints were evaluated at nominal statistical significance level of 0.05 without correction of multiplicity or hierarchical testing. Nominal p-values for the other secondary endpoints are provided below, as they contribute to the understanding of the totality of the evidence of the treatment effect of siponimod in SPMS.		

Analysis description	**Analysis of second key Secondary endpoint Change from baseline in T2 lesion volume**		
Analysis population and time point description	Full analysis set (with intend to treat principle)		
	Treatment group	BAF312	Placebo
	Number of subjects	1099	546
Estimates per treatment group and Estimate variability	Average change from baseline over Month 12 and Month 24 assessment	183.9mm3	879.2mm3
	Variability statistic (SE)	66.33	85.43
Effect estimate per comparison		Comparison groups	BAF312 - Placebo
		difference	-695.3
		95%CI	(-877.3; -513.3)
		P-value	<0.0001
Notes	Obtained from fitting a MMRM (model assumes normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country, age, baseline T2 lesion volume, number of T1 Gd-enhancing lesions at baseline and presence of relapses in the 2 years prior to inclusion.		
Analysis description	**Analysis of relevant secondary endpoints**		
Analysis population and time point description	Full analysis set (with intend to treat principle)		
	Treatment group	BAF312	Placebo
	Number of subjects	1099	546
Descriptive statistics, Estimate by treatment group, estimate variability	% pts free of **6mCDP** at 12 months (Kaplan-Meier estimate)	85.51	78.30
	Variability statistic (95% CI)	(83.37; 87.66)	(74.73; 81.87)
	% pts free of 6mCDP at 24 months (Kaplan-Meier estimate)	76.41	71.48
	Variability statistic (95% CI)	(73.53,	(67.29, 75.67)
	% pts free of 36mCDP at 36months (Kaplan-Meier estimate)	75.27	70.07
	Variability statistic (95% CI)	(72.15,	(65.52, 74.62)
	ARR (confirmed) Negative binomial regression model	0.071	0.160
	Variability statistic (95% CI)	(0.055, 0.092)	(0.123, 0.207)
	Change from baseline of **MSWS-12** (average over all visits)	2.69	4.46
	Variability statistic (SE)	0.627	0.835
	Number of **Gd-enhancing T1 lesions per scan** (cumulative number up to Month 24)	0.081	0.596
	Variability statistic (95%CI)	(0.065,	(0.469; 0.758)

	New or enlarging T2 lesions compared to previous assessment (average over all visits)	0.700	3.603
	Variability statistic (95%CI)	(0.581,	(3.027, 4.288)
	PBVC relative to baseline (average over month 12 and 24)	-0.497	-0.649
	Variability statistic (SE)	0.0286	0.0373
Effect estimate per comparison	Time to 6-month CDP	Comparison	BAF312 vs Placebo
		Hazard ratio	0.74
		95%CI	(0.60, 0.92)
		P-value	0.0058
	ARR (confirmed)	Comparison	BAF312 vs Placebo
		ARR ratio	0.445
		95%CI	(0.337, 0.587)
		P-value	<0.0001
	MSWS-12 change from baseline	Comparison	BAF312 vs Placebo
		Difference	-1.77
		95%CI	(-3.59; 0.05)
		P-value	0.0571
	Number of Gd-enhancing T1 lesions per scan	Comparison	BAF312 vs Placebo
		Rate ratio	0.137
		95%CI	(0.098; 0.190)
		P-value	<0.0001
	Number of new or enlarging T2 lesions	Comparison	BAF312 vs Placebo
		Rate ratio	0.194
		95%CI	(0.155; 0.244)
		P-value	<0.0001
	PBVC relative to baseline	Comparison	BAF312 vs Placebo
		Difference	0.152
		95%CI	(0.071; 0.232)
		P-value	0.0002
Notes	. Only patients with available data and covariates were included in the models for comparison. Estimates by treatment group were obtained from adjusted models (negative binomial, MMRM)		

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

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive study(ies)

Not applicable.

2.5.3. Discussion on clinical efficacy

Study A2201

This phase 2 dose-finding study (A2201, N=297) was performed in patients with RRMS investiating 5 different doses of siponimod and placebo in two subsequent periods. The patient population included was rather young (mean age 36), with a preponderence of women, and a median disease duration ranging from 4.7 to 7.6 years having rather mild functional impairment (mean baseline EDSS 1.95-2.41), with active disease as indicated by a median number of one relapse in the last year and two in the last 2 years. Thus, the dose-response relationship was elucidated in a different patient population (RRMS) using endpoints indicative of acute focal inflammatory activity mainly with respect to MRI rather than clinical endpoints. The statistical approach (MCP-mod) used for assessing the dose response is considered appropriate. A dose titration scheme was implemented for Period 2 (but not in Period 1) based on safety reasons (to mitigate first-dose bradycardia) and the applicant clarified that efficacy is not compromised by the slight delay in reaching steady state over a 5 days titration interval. The RRMS study provides information as to which doses may affect the inflammatory component of MS. Nevertheless, effects on MRI measures in RRMS do not necessarily predict effect on disease progression in SPMS without focal inflammatory activity. There were 23 protocol deviations (PDev) in regard to MRI performance while patients were on steroid therapy or within 14 days after discontinuation of steroids. It was clarified that PDev of such cases were observed in all dose groups, while only one of these PDs indeed affected one of the scans used for the primary endpoint. A sensitivity analysis on the number of patients with PDev/scans performed during or within 14 days of steroids was reassuring that this PDev did not affect the overall efficacy results. For the extension study A2201E1, several limitations need to be considered for data interpretation, including the lack of a placebo group, the small group sizes per treatment arm, and the variable treatment interruption between the core and the extension part. This was due to a delay in approval of a protocol amendment aiming to incorporate the dose titration regimen and hence concerned patients included in Period 1 of the core part (i.e. those assigned to 10 mg, 2 mg, and 0.5 mg siponimod). Patients from Period 1 had dose interruptions of up to 10 months, which was clarified to have had an impact on inflammatory activity. However, an effect could be regained after re-initiation of treatment.

Study A2304

Only one pivotal study (A2304) testing one dose level of siponimod (2 mg) was performed in SPMS. However, the study was large (N=1651).

Eligibility criteria and study population: patients were recruited in 31 countries across 5 continents. 78% of patients were recruited in the EU, and the study results are thus considered relevant for the European population. Regarding eligibility criteria, 653 out of 1651 patients (39 %) were included based on a written statement of the clinical evidence of disability progression in the previous 2 years and retrospective assessment of EDSS scores from data up to 2 years prior to screening (inclusion criterion No.6). Approximately one third of these patients (n=170) were lacking adjudications at the time of randomisation. 94 of these 170 patients were identified during the enrolment period and reported as PDev in the clinical study report. Additional 76 patients were identified just prior to database lock and confirmed to be eligible in retrospect but not handled as PDev. According to the applicant, patients with late adjudications were not treated differently in the FAS analyses. In addition, 13 patients were identified to have been randomised without any documented evidence of disability progression in the 2 years prior to enrolment available (neither through EDSS scores in the medical history nor through central adjudication). Although the late adjudication for these 170 patients and the lack of adjudication for these 13 patients (7 from the active treatment arm and 5 from the placebo arm) are concerns with regard to

the reliability of the study conduct, the CHMP agreed that it does not influence study results as evidence of progression in the 2 years prior study entry was retrospectively confirmed and a sensitivity analysis of the primary endpoint excluding the 13 patients with lack of adjudication was in line with the primary analysis.

According to the guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2), for demonstration of prevention of disability progression independent of relapses in SPMS, it is recommended to target only SPMS patients without a recent relapse and no MRI activity suggestive of active inflammation. Although 22% of the patients had not been on immunomodulatory treatments prior to the study, which is a representative number for the European population, several aspects of the eligibility criteria challenge the representativeness for the full spectrum of SPMS. In this study only patients with a relapse within 3 months prior to randomisation were specifically excluded. Approximately 50% of the patients had either at least one relapse in the previous 2 years of inclusion or one or more Gd-enhancing lesion at baseline. A population mainly based on patients with few or no recent relapses would have been preferable. Moreover, the median age of study population was 49 years and the median time to SPMS conversion was 2.55 years. In addition, even in the presence of new or enlarging T2 lesions and relapses, only 30% of placebo and 25% of siponimod patients experienced 6m-CDP based on EDSS after 3 years in the trial which may indicate a relatively early phase of SPMS where biological redundancy has not yet been extenuated by extensive CNS damage.

Randomization: The only parameter used as stratification factor at randomisation was 'countries'. The use of region (North America, Europe, Japan, rest of the world) instead of country and EDSS at baseline (for example above/below 6) and as stratification factors at randomisation would have been preferable. Moreover, since patients with recent (> 3 months) relapses were not excluded and since the number of previous relapses may be correlated with the probability of having relapses in the future, it would have been preferable to also include this factor in the stratification at randomisation.

Blinding: Regarding blinding of treatment assignment it should be noted that not only DMC members and independent statisticians/programmers had access to unblinded data but also the PK analysts. Apart from blinding of treatment assignment, measures were taken to ensure blinding of EDSS raters to all other clinical information (e.g. bradycardia). Evaluation of the primary endpoint was assessed and managed by EDSS raters in the separate NESC database not accessible by other study staff. Furthermore, two separate databases were set up for the main data and the dose initiation data to preserve the blind. However, there were raters, nurses, and investigators with access to the first (titration phase, ECG data) and main (containing e.g., AEs) databases with potentially unblinding information. The applicant subsequently performed the primary endpoint analysis (3m-CDP) including only patients who could have been compromised (n=213), which resulted in a much larger apparent effect size (HR ~ 0.4) as compared to overall HR (~ 0.8).

The applicant was asked to explain the difference observed in HRs between the potentially unblinded subgroup and the definitely non-unblinded patients. During the procedure, the applicant identified a number of factors that could have influenced or contributed to the observed imbalances in the CDP results including differences in baseline characteristics (more inflammation and lower EDSS scores in this non-randomized subpopulation as compared to the full population), a larger relapse rate in the potentially unblinded subgroup compared to the overall population (considering the mechanism of action, this subpopulation could have experienced a greater reduction in 3m-CDP) and change in the statistical model dependence ('country' deleted as covariate). The following analyses were additionally supportive:

The overall HR for the 6m-CDP based on EDSS, a more robust endpoint of disability progression, was 0.74 [95%CI (0.60-0.92)] and HR after excluding 213 patients potentially unblinded was 0.77 [95% CI (0.61-0.97)]. Moreover, the applicant identified different types of potential unblinding over the trial.

Specifically, for EDSS assessment, the integrity of EDSS data for 65 patients could have been compromised. The HR for the 3m-CDP based on EDSS excluding these 65 patients was 0.80 95%CI (0.66-0.97). Beyond the interpretation of the statistical significance of the observed differences in the change of T2 lesions volume (second key secondary endpoint), a relevant aspect in this context is that MRI results were analysed in a centralized reading center and therefore, the potential unblinding due to the "unappropriated database access" should not have affected the robustness of these results.

Moreover, the applicant presented additional analyses suggesting that potential unblinding did not influence treatment decisions and ratings. Additional analyses based on heart rate changes on Day 1 (first-dose database potentially accessible for some EDSS raters) lacked a pattern on 3m-CDP or 6m-CDP outcomes in the potentially affected population that would have indicated intentional unblinding. Moreover, the option of switching patients to open-label rescue therapy following 6m-CDP was analysed, which could have probably triggered the result of the potentially unblinded 213 patients. However, no pattern indicative of intentional unblinding of the assessment of EDSS progression for the intention to switch patients to active treatment was found in the potentially affected subset of patient.

Considering all of the above, the CHMP was of the opinion that, although it still remained difficult to totally negate any bias due to potential unblinding, the provided arguments underline that it was unlikely that the subgroup results of the patients potentially affected is solely due to a systematic bias due to unblinding. In addition, since unblinding of EDSS raters would provide the main risk for bias of the primary endpoint, the analysis excluding the 65 patients whose EDSS rater could potentially have been unblinded was considered to cover the most relevant scenario. In this analysis, the results of the 3m-CDP and of the 6m-CDP remained statistically significant.

Protocol amendments: The set-up for EDSS data capture was changed during the course of the study. This is of concern, since the reliability of the EDSS data - and the blinding of the EDSS rater to other clinical information - is essential. Algorithms to perform data control for inconsistencies in the EDSS assessments were implemented at different time points during the study. According to the GCP inspection (Inspection Request 301), 4010 (26.4 %) EDSS examinations were corrected. In some case up to 1.5 years had passed between the correction of the EDSS record and the actual visit.

Primary endpoint (including statistical analysis): The primary endpoint was 3m-CDP measured by the EDSS while 6m-CDP is the preferred endpoint in the guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2). It is acknowledged that 6m-CDP is used as a secondary endpoint (not controlled for multiplicity), however the study was powered for the 3m-CDP. The definition of onset of disease progression and confirmation of disease progression are agreed. The Cox proportional hazard model to calculate the primary endpoint contains several explanatory variables: treatment, country, baseline EDSS (continues scale) and SPMS group (with or without superimposed relapses at baseline). The only parameter used as stratification factor at randomisation was 'countries'. According to the Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013), the use of additional covariates not included during the stratification at randomisation needs to be justified. The estimand proposed by the applicant is clinically relevant, but it would be difficult to justify that study discontinuations would be "missing at random" (non-informative censoring). Furthermore, the effect of other MS-DMT therapies including open-label siponimod can mask or exaggerate the treatment effect. Of note, intermediate missing EDSS values were not imputed by the applicant. The applicant presented sensitivity analysis considering other imputation rules and the results were concordant with those presented for the primary analysis.

Effect independent on relapses: To assess the treatment effect on CDP independent on relapses, the applicant presented results using several methodological strategies including subgroup analyses, a "re-baselining" definition of 3m-CDP based on EDSS. Upon request, the applicant provided additional

analyses addressing two estimands using the ICH E9 R1 addendum framework using multiple imputation based on the control arm (see next section of discussion).

First key secondary endpoint: The applicant used additional covariates not included during the stratification at randomisation. However, the applicant presented a justification and sensitivity analysis to assess the impact of the covariates on the results. The results of the sensitivity analyses are consistent with those of the primary analysis.

Second key secondary endpoint: The selection of a MMRM for estimating the change from baseline in T2 lesion volume was calculated using a mixed model for repeated measurements was endorsed. Missing data in the model is assumed to be at random.

Secondary relapse related endpoints: Relapse related endpoints were not considered key secondary endpoints and were not controlled for multiplicity. A negative binomial model was used to analyse ARR. Missing data is considered to be at random and patients who withdrawn early from the study only contribute during the observational period. The applicant presented sensitivity analysis were different imputation rules were implemented and the results were similar to those obtained during the primary analysis. The Cox proportional hazard model was used to calculate the time to first relapse.

Efficacy data and additional analyses

Participant flow: treatment discontinuations and missing data

A total of 1099 and 546 patients received siponimod and placebo, respectively, and were analysed in the FAS. Discontinuations from the treatment epoch/trial were 18% and 22% for siponimod and placebo, respectively, while discontinuations from double-blind treatment were overall higher (41% on placebo and 33% on siponimod). Discontinuation due to a lack of efficacy/disease progression summed up to 12.4% of subjects on siponimod and 19.7% of subjects on placebo. Uncertainty relates to a high number of subjects in both groups (10.3% and 13%), who discontinued due to subject/guardian decision, assuming that the "decision" may also have been driven by lack of efficacy, which cannot be clarified with the available information.

The applicant subsequently presented information regarding the follow-up time for different groups of patients: among those who completed the blinded study phase, there were patients who did not experience a 3m-CDP but had relapses (siponimod: 51 and placebo: 27). Furthermore, there were patients who suffered relapses before the 3m-CDP (siponimod: 40 and placebo: 43). For the patients censored due to administrative censoring and who did not take any active DMT, there were some patients who experienced relapses (siponimod: 1 and placebo: 2). For those lost to follow-up, there were some who experienced relapses with or without onset of progression (siponimod: 4 and placebo: 10 in each group). For patients who took other DMTs after discontinuation, relapses were observed in patients who had administrative censoring (siponimod: 2 and placebo: 2).

Results for the primary endpoint: In the pivotal study, 26.3% (288/1096) and 31.7% (173/545) in the siponimod and placebo arm experienced a 3m-CDP in EDSS. The hazard ratio (siponimod/placebo) was estimated to 0.79 with 95% CI (0.65;0.95). The risk of 3m-CDP at a given point in time was approximately 21% lower for patients in the siponimod group compared to the placebo group, the absolute difference in event rates between the siponimod and the placebo arm at the end of the study was 5 percentage points, which may not be considered particularly compelling in regard to a single pivotal trial. The clinical relevance of the observed effect has been further explained by the applicant in the course of this procedure: The Kaplan-Meier percentiles show that the longer-term benefit of siponimod over placebo could be equated with an improvement of about 25-30% in time to 3m-CDP and of more than 50% increase in time to 6m-CDP. In other words, the time to disease progression could be expected to be prolonged with siponimod. It needs to be noted that the majority of patients actually did

not progress over the trial. The percentage of patients free of 3m-CDP events for the siponimod arm was 81.82 %, 69.39 % and 64.17 % for the year 1, 2, and 3, respectively. For the placebo arm, the corresponding estimates were 75.32 %, 65.03 % and 56.41 % for the year 1, 2 and 3, respectively. Moreover, even in the presence of on-trial new T2 lesions and relapses which could have contributed to increased EDSS due to an incomplete of recovery (see estimates using re-baselining definition of 3m-CDP) only 30% of placebo and 25% siponimod patients experienced 6m-CDP for 3 years over the trial. This may suggest that biological redundancy is not extenuated, which usually happens in RRMS and in early SPMS (median time to SPMS conversion was 2.55 years).

The results on primary endpoint in patients with active disease are:

24.9% (128/515) and 34.6% (91/263) in the siponimod and placebo arm, respectively, experienced a 3m-CDP in EDSS. The hazard ratio (siponimod/placebo) was estimated at 0.69 with 95% CI (0.53;0.91). The primary endpoint in the restricted target population was therefore met (p=0.0094).

Key secondary endpoints: No effect of siponimod was demonstrated on the first key secondary endpoint 'time to 3-month confirmed worsening of at least 20% from baseline in T25W'. In regard to the analysis of the first key secondary endpoint, clarification was provided that results of the T25W were not compromised by allowed comedication of (dal) fampridine in 20% of subjects in either group. It could finally not be clarified why post-baseline results for the placebo arm were less variable compared to the siponimod arm. In sum, the high variability in the outcome on the T25W test in this more advanced MS patient population (more than 50% of the patients needed at least one walking aid) has limited the ability to detect changes and a treatment effect.

As for the next key secondary endpoint in the hierarchy, the change from baseline in T2 lesion volume, there appeared to be a treatment effect of siponimod, even if superiority could formally not be claimed. With this caveat, the 80% reduction in the average change from baseline T2 lesion volume over Month 12 and Month 24 observed between siponimod and placebo groups should not be ignored not only in the particular context of the potential unblinding affecting primary endpoint but also in the context of the included SPMS population. The magnitude of the relative difference (80% reduction in T2 volume change) in relation to the primary endpoint (21% reduction in the rate of 3m-CDP) suggested a prominent therapeutic effect of siponimod on SPMS via the reduction of focal inflammatory activity in the CNS.

Other secondary endpoints: a risk reduction of 25.9% in 6m-CDP was observed for siponimod compared to placebo (HR 0.74, 95% CI 0.60-0.92, p=0.0058), a rate reduction that was roughly maintained after the exclusion for the 213 potentially unblinded patients. It should be noted that 15% of patients of each group (43/288 siponimod and 26/173) with 3m-CDP did not have another EDSS score (6-m confirmation score) performed. In an additional 27 siponimod and 8 placebo patients, CDP was not confirmed at 6 months. These findings demonstrate that 3m-CDP and 6m-CDP are not necessarily interchangeable. In fact, the 6m-CDP endpoint is considered the more reliable endpoint with regard to the longer observation period in line with the guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2). Therefore, the importance of the 6m-CDP endpoint, although formally a secondary endpoint in this study, should not be neglected.

The results on 6-month CDP in patients with active disease are:

19% (98/515) and 28.1% (74/263) in the siponimod and placebo arm, respectively, experienced a 6m-CDP in EDSS. The hazard ratio (siponimod/placebo) was estimated at 0.63 with 95% CI (0.47;0.86). The nominal p-value of this secondary endpoint is 0.0040.

In line with the results for T2 lesion volume, a 55.5% rate reduction for confirmed relapses for siponimod compared to placebo was observed in the trial which reinforces the effect of siponimod in SPMS via reduction of focal inflammatory activity. There was no effect on self-assessed walking ability (MSWS-12) in line with the lack of an effect on the T25W. Analysis of composite scores based on disease-relevant

endpoints such as e.g. T25W, 9-HPT, and PASAT did not indicate an effect of siponimod. Overall, there were no significant differences in other exploratory results including patient-reported outcomes (quality of life) and other domain-specific disability scores including cognitive and visual endpoints.

The significant difference of 2.303 letters at Month 24 (p=0.0002) for the SDMT should be interpreted with caution, particularly in the context of absence of correction for multiplicity in the exploratory testing in the trial and studies that suggest that 4 symbols or at least 10% are the minimum clinically relevant difference for patients with MS (the median baseline SDMT in the trial was 41).

Effect independent of relapses: Most of the study patients (n= 785) had previously been treated with a MS-disease modifying therapy. Patients without prior treatment seemed to have had slightly more inflammation (40% had relapses in the 2 years prior screening in contrast to 34.5% of those with prior DMT treatment) and slightly less advanced disease (lower baseline EDSS scores).

According to the guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2), the occurrence of relapse activity needs to be assessed during the study and taken into account when determining confirmed progression of disability. The occurrence of relapses during study A2304 needs to be interpreted cautiously given that patients had a variable duration on study due to the event-driven design. However, given that a number of confirmed and unconfirmed relapses occurred during the study (n=184, 16.7 % and n=142, 26.0 % in the siponimod and placebo arm, respectively). However, the annualized relapse rate during study was quite low (0.16 in the placebo arm based on confirmed relapses).

The applicant performed several analyses to determine the effect of siponimod independent of relapses. In the pre-planned comparison among patients with and without relapses during the last two years before study entry, the HR for patients without pre-study relapses was 0.87, 95 %CI (0.68; 1.11) for 3m-CDP while the HR was 0.67 95%CI (0.49-0.91) for those with pre-study relapses. Similar findings were reported for 6m-CDP: HR 0.63, 95% CI (0.44-0.89), for those with pre-study relapses and HR 0.82, 95% CI (0.62-1.08) for those without them. Given the limitation that the presence of a pre-study relapse is not necessarily predictive of presence of on-study relapse activity (and vice versa), these results show that the effect of siponimod on disability worsening is larger in patients with relapses. The effect of siponimod on CDP based on EDSS in approximately half of the population who had neither at least one relapse prior 2 years nor Gad lesion at baseline was small. The subgroup analysis for patients with rapidly evolving disease activity also showed a lower treatment effect for patients with low activity (HR 0.86, 95% CI (0.69; 1.09). From the subgroup analyses, the effect on T2 lesion volume appears to be more pronounced in patients with relapses. The applicant also performed an analysis to investigate the difference in time to progression for patients with and without on-study relapses. The HR for is 0.85 (0.69; 1.06). This analysis is however of limited informative value since this is a post randomisation variable. Analyses based on post-randomisation events are confounded when both outcomes, relapses and confirmed disability progression, are affected by the drug treatment under evaluation. Using the "re-baselining" definition of 3m-CDP, a non-significant relative risk of 0.93 with 95% CI (0.78; 1.12) was found.

The applicant also provided a principal stratum analysis according to the ICH E9 R1 addendum framework using multiple imputation based on the control arm. This allows, in a theoretical way, to calculate the probability of belonging to the "never relapsing" stratum by making several strong assumptions including:

1. Siponimod cannot cause relapses
2. The probability of belonging to a particular stratum ("never relapsing", "only relapsing on placebo", "always relapsing", "relapsing only on siponimod") does not depend on being a drop-out when EDSS at baseline and previous relapses are taken into account.

3. The probability of 3m-CDP is independent of being a drop-out when EDSS at baseline, previous relapses; treatment and stratum are taken into account.
4. Patients who discontinued the treatment epoch before the time point considered (12,18 or 24 months) were assumed to be exchangeable with non-missing patients conditional on EDSS at baseline (above/below 6) and prior study relapses.

The principal stratum analysis indicates that the risk of progression could be about 14 - 20 % (29 – 33 %) lower for siponimod compared to placebo for patients who will never relapse based on the 3m-CDP endpoint.

The assumptions concerning missingness, are not testable since it is not possible to exclude that other variables also play a major role in the probability of DP (for instance the presence of Gd-enhancing lesions at baseline or a prominent accumulation of new or enlarging T2 lesions prior study inclusion). The monotonicity assumption is relaxed in the sensitivity analysis and it seems that the results do not vary much when this assumption is not made.

To assess the treatment effect on CDP independent on relapses, the applicant estimated the difference in time to 3m-CDP by assuming that relapses would not occur. Patients who experienced a relapse were censored at the first relapse occurrence. Since censoring is informative (depends on treatment effect), IPCW is used to correct for bias. However, IPCW relys on the assumption that the probability of observing a relapse is completely described by the covariates (baseline characteristics) included in the model. This is a strong assumption since the variables determining the probability of relapses are unknown. Censoring patients at the first relapse also assumes that the rate of progressive disability accumulation before the first relapse reflects the rate of disability accumulation over the whole course of the disease excluding periods affected by relapsing event. While patients who experienced relapses before inclusion in the study are included, it is not possible to determine whether this assumption is correct.

The applicant also implemented a hypothetical estimand where the effect of siponimod is estimated in a situation where relapses had not occurred. The results of the HR varied around 0.82-0.87 for the 3m-CDP endpoint with large CIs including 1 for the 3m-CDP endpoint and was found to be more stable for the 6m-CDP endpoint (0.77). However, these analyses are based on quite strong and untestable assumptions. In this particular context, the assumption that probability of 3m-CDP can be fully predicted from EDSS at baseline and previous relapses is a strong assumption to maintain.

It is acknowledged that the applicant presented several analyses in order to estimate the effect of siponimod independent of relapses. However, it remains very challenging to disentangle the effect of siponimod on relapses and on general disease progression. Nevertheless, the results of the different analyses were consistent.

Additional expert consultation

At the SAG Neurology meeting held on 7 November 2019, the applicant proposed indication under discussion was as follows:

"Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS)."

1. **Do the experts consider that the patients included in the pivotal study are representative of the proposed indication (Secondary Progressive Multiple Sclerosis (SPMS))?**

The SAG experts considered that the patients included in the pivotal study represent only partly the full spectrum of patients to be included in the proposed indication – SPMS. In clinical practice, a significant percentage of the SPMS patients are with higher EDSS scores, are of older age and have longer disease duration than the ones, recruited in the presented clinical trial.
The recruited population is representative of the "early" phase of the SPMS, and the phase when the transition from RRMS course happens.

2. Do the experts consider that the observed frequency of relapses in the placebo treated patients reflect what is expected for untreated patients with SPMS?

SAG experts considered that the observed frequency of relapses in the placebo group is representative of an "early stage" of SPMS (and not of the "late stage" SPMS in which it is expected to be lower), but the SAG experts found this question difficult to answer without a clear knowledge if the previous DMT was effectively stopped early enough to not have an effect on the baseline inflammatory activity during the trial.

Having approx. 80% of the patients on DMT before inclusion in the trial (notwithstanding the washout period applied) underlines the concerns, as it is practically impossible to exclude potential remaining effects of these therapies on the course of the observed disease progression, relapses and inflammatory activity.

3. How are patients with SPMS currently treated in clinical practice? How are SPMS patients experiencing focal inflammatory activity handled in clinical practice?

There are significant regional differences, influenced by a variety of factors, including reimbursements and availability.

In some countries patients below EDSS=6.5 are treated with therapies applicable for Relapsing MS (RMS), off-label or even with other off-label alternatives (rituximab, mitoxantrone, cyclophosphamide, methotrexate). In other countries, patients transitioning from RRMS to SPMS usually either continue ongoing DMTs or are reinstated on treatment (DMTs for RMS) if they have evidence for focal inflammatory activity (either a new relapse or clear MRI activity registered either with evidence of new T2 lesions or gadolinium-enhancing lesion).
The SAG experts agreed that in many situations, clinicians tend to delay the diagnosis of SPMS as long as they consider that a risk of significant inflammatory activity remains, making patients eligible for therapies licensed for relapsing MS.
The patient representatives confirmed the above situation and expressed a desire for a therapy that targets the described population, currently considered as transitional or "early" SPMS. They also highlighted that the current tendency to delay the diagnosis of SMPS makes it ever more difficult to gather data in the "transitioning" population.

Is this phenotype readily identifiable by clinicians treating MS, and if so is the study population representative of these patients?

The SAG experts agreed that this phenotype could be representative of an "early stage" SPMS cohort, which in practice will be possible to identify with close clinical monitoring and use of periodic standardized MRI scans. However, SAG experts insisted that the ease of diagnosis may vary with different settings, mainly due to difficulties, related to access to standardized high-quality MRI. It was also highlighted that EDSS scoring may be less sensitive to some aspects of clinical worsening (mainly cognition) and may also vary among raters depending on their training.

Some SAG experts expressed the opinion that it may not be that easy to precisely identify this population (and differentiate from RRMS patients with controlled disease), especially taking into account the remnant effect of DMT.

4. Do the experts consider that the pharmacological profile of siponimod supports a treatment effect on disability progression in SPMS?

While the ability of siponimod to cross the blood-brain barrier could in theory support a central effect on the compartmentalized inflammation (associated with diffuse injury of the normal-appearing white and grey matter) that is also present in SPMS patients (beside focal inflammation), the SAG experts agreed that there were no convincing experimental nor clinical data supporting such an effect for siponimod.
The presented data on brain atrophy were not considered as convincing with this regard as these findings could be explained by the effect on the still present new focal inflammatory activity, rather than by an effect on the compartmentalized one or by a neuroprotective activity.

5. **Do the experts consider that an effect of siponimod independent of relapses has been shown and is clinically relevant? If it is assumed that an effect on progression of disability cannot fully be separated from an effect on relapses, do the experts consider that the observed treatment effect on disability progression in the overall study population and the population not affected by potential unblinding, respectively, supports efficacy in SPMS?**

   The SAG experts found it very difficult to express a position on the effects of potential unblinding on the observed efficacy, although a majority expressed concerns and considered that this situation contributes to weaken the robustness of data provided.

   The SAG experts agreed that the data provided some evidence for a positive effect of siponimod in "early stage" SPMS patients, but considered that this benefit was very difficult to disentangle from an effect on focal inflammatory activity. Thus a majority agreed that provided data were insufficient to support an effect independent of relapses, as well as for an effect in patients with higher EDSS.

   Collectively, there was a consensus among SAG experts that the data are insufficient to justify the use of siponimod in the whole SPMS population.

   The SAG experts discussed the need for a second confirmatory trial and they stated that should such a trial be considered, its focus should fall on the "later" stage of SPMS. Such additional evidence will be needed to justify a discussion on an approval in the "broad" SPMS indication. Currently, the benefit/risk ratio cannot be evaluated in the "later" SP stages, a patient population that may also be more sensitive to treatment side effects (older age, with more comorbidities, and more neurological deficits, longer disease duration).

   The SAG experts found that the available data could allow the use of siponimod in a restricted population of "early active SPMS stage » patients, but would not support a broader SPMS indication, due to an incomplete representation in the study population of the "later" SPMS stage population, representing a large proportion of this MS form, observed in clinical practice.

   Regarding the precise definition of the potential indication, the SAG was split.

   A majority of the experts would consider the use of siponimod in a restricted patients population defined on the basis of the inclusion criteria of the EXPAND trial but excluding the low EDSS scores (e.g. EDSS below 4) considering that diagnosis of SPMS in this disease phase is rather uncertain). Others would also include these patients, considering they may have a chance for experiencing larger benefits and lower risks. The SAG experts agreed that any definition of the potential target population will have to take into account the persistence of focal inflammatory activity in SPMS patients, but potentially also keeping in mind safety-related considerations.

2.5.4. Conclusions on the clinical efficacy

A single pivotal study was performed in SPMS but included a sizeable study population. Although, the primary endpoint was met, there were considerable concerns regarding data quality and blinding of the study. In this regard, the applicant identified a number of factors that could have influenced or contributed to the observed imbalances in the CDP results. The CHMP was of the opinion that, although,

it still remains difficult to totally negate any bias due to potential unblinding while agreeing that none of the outlined factors alone or in combination could completely explain this imbalance, the arguments provided by the applicant underline that it is unlikely that the subgroup results of the patients potentially affected are solely caused by systematic bias due to unblinding. This was also considered in the context of the analyses presented for the 6m-CDP, a more robust marker for CDP, and additional analyses suggested that potential unblinding did not influence treatment decisions and ratings. In addition, the analysis excluding 65 patients whose EDSS raters could have potentially unblinded was considered to cover the most relevant scenario. In this analysis, the results of the 3m-CDP and of the 6m-CDP remained statistically significant. Therefore, this issue was considered solved.

Although the applicant provided several pre-planned and post-hoc analyses, efficacy of siponimod independent of relapses could not be convincingly shown. In fact, the effect of siponimod on disability progression appeared small in patients without relapses and without focal MRI activity.

All above considered, The CHMP is of the opinion that efficacy of siponimod has been demonstrated in patients with SPMS with active disease evidenced by relapses or imaging feature of inflammatory activity.

2.6. Clinical safety

The overall safety database of siponimod consists of two randomized, controlled studies; a Phase 3 study (Study A2304) in SPMS patients with a core part and extension part and a Phase 2 study (Study A2201) with its long-term extension study (Study A2201E1) in patients with RRMS (see Table 30). The cut-off date for data collection was 31-December-2017.

These data are supported by phase I studies in healthy and special populations.

The study in the RRMS population (Study A2201 and the A2201E1) comprised patients with an EDSS score of 0 to 5.0 aged 18 to 55 years. The patients had at least one documented relapse during the year prior to study entry or two documented relapses during the two years prior to study entry or a Gd-enhancing MRI scan at screening.

The study in the SPMS population (Study A2304) comprised patients with an EDSS score of 3 to 6.5 aged 18 to 60 years. Patients in this study had documented EDSS progression in the two years prior to study entry of ≥1 point for patients with EDSS < 6.0 at screening, and ≥0.5 point for patients with EDSS ≥ 6.0 at screening.

Table 30: Overview of Phase 2 and 3 clinical studies that contributed key safety data

Study	Study objective, population	Total No. of patients	Treatment duration	Treatment dose/day
Phase 3 controlled study				
A2304, Core part (CP)	Phase 3, double-blind, randomized, multicenter study evaluating efficacy and safety of siponimod vs. placebo in patients with **SPMS**	**1651** Siponimod 1105, Placebo 546	Flexible <1 up to 37 months	Siponimod 2.0 mg (or reduced to 1 mg dose based upon APLC levels)* , Placebo, once daily
Phase 2 study / dose selection				

A2201	Phase 2, double-blind, randomized, multi-center, dose-ranging study evaluating safety, tolerability (including cardiac events and blood pressure effects) and efficacy of siponimod vs. placebo in patients with **RRMS**	**297** Siponimod 235, Placebo 62	Period 1: 6 months Period 2: 3 months	Spionimod (5 dose levels 0.25, 0.5, 2, 1.25, 2, 10 mg) or placebo once daily
Long-term safety				
A2304 **Extension part** (EP) #	Open-label in patients with **SPMS** from Core Part of A2304	**1220** enrolled as of 31.12.2017 (cut-off)	Ongoing, up to an additional 84 months*	Siponimod 2.0 mg, once daily
A2201E1	An extension study to the A2201 study to evaluate long-term safety, tolerability and efficacy of siponimod given orally once daily in patients with **RRMS**	184 dose- blinded phase 159 open- label phase	2 years additional 3 years or more	Dose blind phase: 5 dose levels of siponimod (0.25, 0.5, 1.25, 2, 10 mg) once daily Open-label phase: 2 mg once daily

Mean duration of exposure as of 31-Dec-2017 was 19 months

* or reduced to 1 mg based on confirmed absolute peripheral lymphocyte count (APLC) <0.2 x10^9/L

Patient exposure

Exposure in the controlled pool

Exposure to siponimod in the clinical program was extensive with 1784 MS patients treated with at least one dose of siponimod (dose ranges from 0.25 to 10 mg once daily). Of these, over 1737 MS patients were treated with at least one dose of siponimod 2 mg, the proposed dose for registration, or higher. The cumulative exposure of clinical trial MS patients to siponimod is estimated at 4650 patient-years.

In **Study A2304** (core part) a total of 1651 SPMS patients were randomized (1105 Siponimod, 546 Placebo), in the extension of study A2304 1220 SPMS patients from the core part were enrolled (up to 31.12.2017, study is ongoing). Patients randomized to siponimod had similar mean exposure to double-blind study drug (18.54 months) compared to placebo (18.04 months). Acknowledging the 2:1 randomization ratio, cumulated exposure to siponimod was 1673.8 patient-years versus 809.1 patient-years in placebo. Most patients in each group (80.4 % siponimod, 78.8% placebo) had at least 12 months of exposure to double-blind study drug; however, less than 30% of patients in either group had at least 24 months of exposure, this was due to the event-driven study design leading to variable exposure duration for different patients. Exposure duration in this study was variable for individual patients, ranged from less than 1 month to more than 36 months. The **Extension Part** of study A2304 will allow patients to continue treatment with open label siponimod and aims to provide additional long-term safety data as well as additional information on efficacy measures.

Table 31: Duration of exposure to double-blind study drug (Safety Set, SAF)

Duration of Exposure to study drug	**BAF312** **N=1099**	**Placebo** **N = 546**
Cumulative exposure - n (%)		
>= 1 day	1099 (100)	546 (100)
>= 7 days	1089 (99.1)	545 (99.8)
>= 1 month	1073 (97.6)	540 (98.9)
>= 3 months	1043 (94.9)	529 (96.9)
>= 6 months	1007 (91.6)	511 (93.6)
>= 12 months	884 (80.4)	430 (78.8)
>= 24 months	322 (29.3)	142 (26.0)
>= 36 months	6 (0.5)	1 (0.2)
Exposure in months		
n	1099	546
Mean	18.54 (8.386)	18.04 (7.766)
SD	18.07	17.67
Min-Max	0.0-36.8	0.2-36.1
Patient-time (patient-years)	**1673.8**	**809.1**

Each patient is counted in the category of maximum duration as well as in each lower category. The duration of exposure (days) to study drug is derived as (last dose date – first dose date) +1. One month is defined as 30 days. Patient years is (the sum of the number of days of exposure for all patients in the group)/365.25.

Study A2201 included 297 RRMS patients (235 Siponimod, 62 Placebo) and its extension (A2201E) with 343 RRMS patients, 184 dose blinded, 159 open label). With a median duration of exposure to siponimod of 63.6 months (more than 5 years), study 2201 including its extension contributes mainly to the characterization of the long-term safety and tolerability profile of siponimod in RRMS patients. Study A2201 contributed exposure up to 6 months in the controlled pool, while patients in Study A2304 Core Part were exposed for significantly longer (mean exposure to siponimod and placebo was 18.54 and 18.04 months, respectively). Mean duration of exposure to siponimod was comparable in males and females in the age groups of 31 to 45 years, 46 to 55 years and >55 years of age. A summary of exposure to double-blind study drug is provided in *Table 32*.

Table 32:Duration of exposure to study drug 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 2 mg 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	3.05	5.52	3.06	17.73	4.63	16.51
SD	0.51	1.39	0.40	8.50	2.33	8.20
Min	0.03	0.39	1.22	0.03	0.03	0.20
Q1	2.99	5.72	3.02	12.12	3.05	10.58
Median	3.15	5.95	3.15	17.36	5.91	16.10
Q3	3.25	6.21	3.22	23.92	6.21	23.36
Max	3.78	6.60	3.58	36.24	6.87	35.58
Patient-time (patient-years)	12.94	19.78	10.70	1696.11	19.28	835.28

Patient-years is the sum of the exposure in days over patients / 365.25.
In the controlled pool one month is calculated as 365.25/12 days (i.e. 30.4375 days). In the Study 2304 analysis, one month was equal to 30 days.

Most patients in the siponimod 2 mg and placebo groups (75.3% siponimod 2 mg, 68.9% placebo) had at least 12 months of exposure to double-blind study drug. Approximately half of the patients were exposed for 18 months and approximately one quarter were exposed for 24 months.

Mean exposure to siponimod 2 mg was 18.33 months and 17.35 months for males and females, respectively. Mean exposure to placebo was 16.72 months and 16.38 months for males and females, respectively. The siponimod 2 mg group was comprised of approximately 60% female and 40% male patients. Mean exposure to siponimod 2 mg was comparable in males and females in the age groups of 31 to 45 years, 46 to 55 years and > 55 years of age.

The mean exposure to siponimod 2 mg was 17.98 months for extensive CYP2CP metabolizers (WT/WT;*2/WT;*2/*2) and 16.66 months for poor siponimod metabolizers (*3/WT;*2/*3). The majority of patients in the siponimod 2 mg (84.3%) and (86.2%) placebo groups were extensive metabolizers. Patients randomized to siponimod received doses of 2 mg daily irrespective of genotype (for details see *pharmacology* section and s*afety in special populations*).

Exposure in the long-term safety pools

In addition, approximately 19 months of safety and clinical efficacy data on the use of siponimod 2 mg in SPMS patients was provided from the ongoing Extension Part of Study A2304 (Study A2304 EP, up to the data cut-off of 31-Dec-2017). In this open-label extension part of the Core Part of study A2304 1220 SPMS patients were enrolled, the study is ongoing, up to an additional 84 months (7 years).

Long-term safety and efficacy data in patients treated with siponimod are applicable by more than 5 years (811.8 patient-years) total exposure data from the Phase 2 extension Study A2201E1 in patients with RRMS. Data covering 2 years from the dose-blinded phase of the study (when patients were treated with one of the 5 siponimod doses tested during Study A2201) and approximately 3 additional years from the open-label phase (when patients were treated with 2 mg siponimod) were provided.

The median exposure to siponimod was similar for both long-term groups and was approximately 32 months at the cut-off date of 31-Dec-2017. There were 1024 (59.0%) patients exposed to siponimod for at least 2 years, 776 (44.7%) patients exposed for at least 3 years and 127 (7.3%) patients exposed for at least 5 years in the broad exposure long-term pool (Table 33:).

The number of patients exposed for more than 5 years in the Long-term pool broad (1) was larger with 127 patients compared to 46 patients in the Long-term pool (2). The differences in the number of patients exposed for 2 years or longer in the in the two long-term pools are mostly accounted for by the additional patients from the A2201 study included in the broad (1) pool, rather than differences between pools in the proportions of early withdrawals.

Mean duration of exposure to siponimod in the long-term pools was comparable in males and females in the age groups of 31 to 45 years, 46 to 55 years and >55 years of age.

Mean duration of exposure in the siponimod 2-10 mg (broad (1)) group was 32.14 months and 31.14 months for the extensive and poor metabolizer subgroups (CYP2C9 genotype), respectively. Mean duration of exposure in the siponimod 2-10 mg (2) group was 30.54 months and 29.38 months for the extensive and poor metabolizer subgroups, respectively. Mean duration of exposure was comparable in each CYP2C9 genotype subgroup.

Table 33: Duration of exposure to study drug by treatment - Long-term Safety Pools (Safety Set)

Duration of Exposure to study drug	**BAF312 2-10 mg broad (1)** **N = 1737**	**BAF312 2-10 mg (2)** **N = 1737**
Any exposure - n (%) Cumulative exposure - n (%)	1737 (100)	1737 (100)
>= 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	1449 (83.4)	1441 (83.0)
>= 18 months	1330 (76.6)	1321 (76.1)
>= 24 months	**1024 (59.0)**	1008 (58.0)
>= 30 months	916 (52.7)	901 (51.9)
>= 36 months	**776 (44.7)**	756 (43.5)
>= 4 years	348 (20.0)	254 (14.6)
>= 5 years	**127 (7.3)**	46 (2.6)
>= 6 years	18 (1.0)	12 (0.7)
Exposure in months		
n	1737	1737
Mean	31.9161	30.3011
SD	18.34882	16.68774
Min	0.033	0.033
Q1	19.2850	18.5300
Median	32.3940	31.6390
Q3	45.6670	42.8750
Max	75.006	75.006
Patient-time (patient-years)	4619.837	4386.075

(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 patients treated in both the core and extension study/part, duration of exposure is calculated as the sum of exposure duration in the core and extension without counting the off-drug period in- between.

Studies in other indications

Three exploratory clinical studies were conducted in 49 patients with polymyositis/dermatomyositis: Study CBAF312A2202 (polymyositis or dermatomyositis), Study CBAF312X2205 (polymyositis), and Study CBAF312X2206 (dermatomyositis). These indications are not being pursued further. Apart from the MS indication, there is one study ongoing; CBAF312X2207, which was initiated and enrolled one patient before the data cut-off point (31-Dec-2017). The study is a randomized, placebo-controlled trial to evaluate the efficacy and safety of siponimod in patients with stroke due to intracerebral hemorrhage. No death, serious adverse events (SAEs) or adverse events (AEs) were reported up to the 31-Dec-2017 cut-off date. This study is not evaluated further here.

All analyses were performed on the safety set (SAF) defined as: all patients who were enrolled and took at least one dose of study drug.

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

1.Controlled pool (S-db1): (0.25mg, 0.5mg, 1.25mg, 2mg, 10mg, placebo)

Patients included in the pool: patients in the placebo-controlled double-blinded treatment epoch of studies A2201 and A2304 from all doses.

Records included in the pool: data collected during the double-blinded treatment period including a 30-day follow-up period were included, but not during open-label siponimod treatment.

Motivation for the pool: This pool is used to compare the effect of each dose of siponimod compared to placebo during controlled part of the studies, especially the incidence of the adverse events listed as potential risks. The pool is also used to assess the comparability of the exposure between dose groups, and subgroups of interests as age group, gender, race and genotype

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

Patients included in the pool: all patients receiving at least once siponimod 2 mg or 10 mg.

Records included in the pool:

a) Data collected during the treatment period when they were 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 CP 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 2mg to 1mg (permitted per protocol due to low lymphocyte counts or tolerability). Similarly, for patients who received the 10 mg dose and then switched to 2mg (and subsequently from 2 mg to 1 mg dose), data collected while receiving reduced dose.

Motivation for the pool: This pool is used to assess the long-term effects of siponimod under the target dose of 2 mg or higher. It is also used to assess the occurrence of the potential risk appearing during the dose titration and re-titration.

3. Titration pool (S-db3): Focus on the initiation and up-titration period

The Titration pool includes patients who underwent dose titration from placebo or no-treatment to siponimod 2 mg either at dose initiation in the core studies (A2201 and A2304) and/or extension study (A2201E1) or Extension Part of A2304, or during dose restart after an interruption of siponimod treatment of 4 consecutive days or more. Dose restarts after interruption of 4 days or more included restarting siponimod after stopping/completing the Core Part of A2304 and then receiving siponimod in the Extension Part (majority of dose restarts), and restarting siponimod after interruption, related to e.g. safety event or per protocol.

4. Long Term Safety Pool (S-db4) (2mg/10mg - broad)

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

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

Motivation for the pool: This pool is used to assess the long-term effects of siponimod for patients getting at least once in the target dose of 2 mg or higher. It is similar to the second long-term pool (S-db2), but also covers the data for these patients under different dose of siponimod before they switched.

Total patient exposure is considered acceptable for the different siponimod dosing groups. Long-term safety data have been collected in accordance with requirements of ICH E1 guidance (CPMP/ICH/375/95) and the numbers of patients exposed for more than 6 months and more than 1 year were sufficient.

Demographics

The demographics of the safety population is shown below for patients in the controlled studies. The demographics were essentially similar in the extension studies (data not shown).

Table 34: Demographics by treatment - Controlled pool (Safety Set)

	BAF312 0.25mg	**BAF312 0.5mg**	**BAF312 1.25mg**	**BAF312 2 mg**	**BAF312 10 mg**	**Placebo**
Characteristics	**N=51**	**N=43**	**N=42**	**N=1148**	**N=50**	**N=607**
Age groups (years) -n (%)						
18-30	10 (19.6)	10 (23.3)	12 (28.6)	38 (3.3)	13 (26.0)	32 (5.3)
31-45	33 (64.7)	26 (60.5)	26 (61.9)	391 (34.1)	31 (62.0)	219 (36.1)
46-55	8 (15.7)	7 (16.3)	4 (9.5)	519 (45.2)	6 (12.0)	244 (40.2)
>55	0	0	0	200 (17.4)	0	112 (18.5)
Age (years)						
n	51	43	42	1148	50	607
Mean	37.4	36.0	35.4	47.5	36.4	46.8
SD	8.39	8.79	8.87	8.17	8.43	8.86
Min	23	21	19	19	20	19
Median	36.0	35.0	35.0	48.0	37.0	48.0
Max	53	55	55	61	53	61
Sex -n (%)						
Male	9 (17.6)	13 (30.2)	11 (26.2)	450 (39.2)	20 (40.0)	239 (39.4)
Female	42 (82.4)	30 (69.8)	31 (73.8)	698 (60.8)	30 (60.0)	368 (60.6)
Race -n (%)						
White	50 (98.0)	42 (97.7)	41 (97.6)	1093 (95.2)	48 (96.0)	572 (94.2)
Asian	0	0	0	30 (2.6)	0	18 (3.0)
Black or African American	1 (2.0)	0	1 (2.4)	8 (0.7)	0	4 (0.7)

Other	0	1 (2.3)	0	12 (1.0)	2 (4.0)	8 (1.3)
Unknown	0	0	0	5 (0.4)	0	5 (0.8)
Ethnicity -n (%)						
Hispanic/Latino	1 (2.0)	1 (2.3)	1 (2.4)	75 (6.5)	1 (2.0)	33 (5.4)
Not Hispanic/Latino	50 (98.0)	42 (97.7)	41 (97.6)	871 (75.9)	49 (98.0)	470 (77.4)
Not Reported	0	0	0	95 (8.3)	0	58 (9.6)
Unknown	0	0	0	107 (9.3)	0	46 (7.6)
CYP2C9 Genotype -n (%)						
WT/WT, *2/WT, *2/*2	47 (92.2)	35 (81.4)	36 (85.7)	968 (84.3)	41 (82.0)	523 (86.2)
*3/WT, *2/*3	4 (7.8)	7 (16.3)	6 (14.3)	176 (15.3)	9 (18.0)	83 (13.7)
Missing	0	1 (2.3)	0	4 (0.3)	0	1 (0.2)
BMI (kg/m2)						
n	50	42	40	1115	48	586
Mean	24.27	24.91	25.75	24.95	23.93	24.70
SD	5.157	5.825	7.427	4.903	3.218	4.790
Min	17.1	16.4	17.8	15.1	16.8	15.5
Median	22.54	23.75	23.82	24.15	23.87	24.03
Max	40.2	46.6	52.4	52.2	30.9	53.3

Age is calculated from reference start date and date of birth. If due to privacy concerns, date of birth was not collected, age was imputed from year of birth.

Adverse events

Treatment-emergent adverse events (TEAEs) comprise all adverse events, which occurred during the trials.

There were more adverse events in the in siponimod groups than in the placebo group, and the incidence of adverse events increased with increasing dose of siponimod:

Table 35: Incidence rate of treatment emergent adverse events (TEAE), by preferred term – n (%) of patients with events – Controlled pool (Safety Set)

Preferred term	**BAF312 0.25 mg** N=51 n (%) OR* (95% CI)	**BAF312 0.5 mg** N=43 n (%) OR* (95% CI)	**BAF312 1.25 mg** N=42 n (%) OR* (95% CI)	**BAF312 2 mg** N=1148 n (%) OR* (95% CI)	**BAF312 10 mg** N=51 n (%) OR* (95% CI)	**Placebo N=607** N (%)
Number of patients with at least one AE	41 (80.4) 0.9 (0.5, 1.9)	37 (86.0) 1.4 (0.6, 3.4)	30 (71.4) 0.6 (0.3, 1.1)	1029 (**89.6)** 2.0(1.5, 2.6)	48 (96.0) 5.4 (1.3, 22.7)	495 (**81.5**)

*Odds ratio

TEAEs were reported for a greater percentage of patients in the siponimod 2 mg group (89.6%) than in the placebo group (81.5%) in the controlled pool (Table 35), while the incidence was 91.7% in the siponimod 2-10 mg broad group for the long-term safety pool. TEAEs in the siponimod 2 mg group were reported most frequently in the SOC of infections and infestations (48.6% siponimod 2 mg, 49.6% placebo) followed by nervous system disorders (38.6% siponimod 2 mg, 32.1% placebo) (Table 36 :).

Table 36 : Frequency of treatment emergent adverse events and serious adverse events by age categories and treatment – Controlled safety pool

Safety event categories	Age[1] <65 years BAF312 2mg n (%) N=1148	 Placebo n (%) N=607
Total AEs	1029 (89.6)	495 (81.5)
AE leading to drop-out (discontinuation)	92 (8.0)	30 (4.9)
Serious AEs - Total	193 (16.8)	74 (12.2)
- Deaths (fatal outcome)	2 (0.2)	3 (0.5)
- Grade 4 (life threatening)	22 (1.9)	7 (1.2)
- Grade 3 (severe, medically significant, hospitalization, disabling)	84 (7.3)	35 (5.8)
- Grade 2 (moderate, minimal, local or non-invasive intervention)	57 (5.0)	20 (3.3)
- Grade 1 (mild, asymptomatic, clinical or diagnostic observation)	30 (2.6)	12 (2.0)
Psychiatric disorders [2]	171 (14.9)	88 (14.5)
Nervous system disorders [2]	443 (**38.6**)	195 (**32.1**)
Accidents and injuries [3]	231 (20.1)	112 (18.5)
Cardiac disorders [2]	145 (12.6)	62 (10.2)
Vascular disorders [2]	169 (14.7)	67 (11.0)
Central nervous system vascular disorders [3]	22 (1.9)	10 (1.6)
Infections and infestations [2]	558 (**48.6**)	301 (**49.6**)
Anticholinergic syndrome [3]	205 (17.9)	108 (17.8)
Quality of life decreased [4]	0	0
Hypotension [5]	103 (9.0)	46 (7.6)
Bone and joint injuries [6] (including fractures)	55 (4.8)	23 (3.8)
Ataxia [4]	5 (0.4)	2 (0.3)
Fall [4]	128 (11.1)	62 (10.2)

A patient with multiple adverse events within a category is counted only once in the row.
A patient with multiple occurrences of different grades of an AE under each treatment is counted only the worst grade in this AE category for that treatment.
N is the number of patients in the treatment group at risk, n is the number of patients with at least one event in the treatment group and age category.
Treatment emergent: up to and including 30 days of last double-blind dose of study drug or start of open-label BAF312, whichever comes first.
[1] Age at inclusion
[2] System Organ Class (SOC)
[3] Standardised MedDRA Queries (SMQs) (Broad)
[4] Preferred Term
[5] Novartis MedDRA Query including: Blood pressure decreased, Blood pressure systolic decreased, Blood pressure diastolic decreased, Blood pressure fluctuation, Hypotension, Orthostatic hypotension, Dizziness, Dizziness postural, Dizziness exertional, Presyncope, Syncope, Depressed level of consciousness, Loss of consciousness
[6] High Level Group Term

The most commonly reported adverse events by preferred term in the siponimod group with a higher frequency than in the placebo group (% siponimod group vs. % placebo group) were headache (15% vs. 13%), hypertension (11% vs. 7%), dizziness (7% vs. 5%), nausea (7% vs. 4%), ALT increased (6%

vs. 1%), and bradycardia (5% vs. 3%). The TEAEs reported in ≥3 % of patients in the siponimod 2 mg group are presented in Table 37.

Table 37: Incidence of most frequent treatment emergent adverse events (TEAE) (>=3% in siponimod 2mg group), by preferred term – n (%) of patients with events – Controlled Pool (Safety Set)

	BAF312 0.25mg N=51 n (%)	**BAF312 0.5mg N=43 n (%)**	**BAF312 1.25mg N=42 n (%)**	**BAF312 2 mg N=1148 n (%)**	**BAF312 10mg N=50 n (%)**	**Placebo N=607 n (%)**
Number of patients with at least one AE	41 (80.4)	37 (86.0)	30 (71.4)	1027 (89.6)	48 (96.0)	494 (81.5)
All deaths	0	0	1 (2.4)	3 (0.3)	0	4 (0.7)
On-treatment deaths	0	0	1 (2.4)	1 (0.1)	0	1 (0.2)
SAEs	0	7 (16.3)	2 (4.8)	193 (16.8)	2 (4.0)	74 (12.2)
AEs leading to discontinuation	1 (2.0)	5 (11.6)	1 (2.4)	92 (8.0)	10 (20)	30 (4.9)
AEs leading to study drug interruption	0	1 (2.3)	0	80 (7.0)	2 (4.0)	17 (2.8)
AEs requiring concomitant medication or non-drug therapy	25 (49.0)	29 (67.4)	25 (59.5)	796 (69.3)	27 (54.0)	406 (66.9)
Headache	**4 (7.8)**	**9 (20.9)**	**5 (11.9)**	**173 (15.1)**	**22 (44.0)**	**76 (12.5)**
Nasopharyngitis	8 (15.7)	8 (18.6)	9 (21.4)	154 (13.4)	7 (14.0)	87 (14.3)
Urinary Tract Infection	2 (3.9)	2 (4.7)	3 (7.1)	135 (11.8)	2 (4.0)	83 (13.7)
Fall	0 (0)	0 (0)	0 (0)	128 (11.1)	0 (0)	62 (10.2)
Hypertension	**1 (2.0)**	**1 (2.3)**	**1 (2.4)**	**121 (10.5)**	**1 (2.0)**	**44 (7.2)**
Fatigue	0 (0)	1 (2.3)	4 (9.5)	105 (9.1)	8 (16.0)	56 (9.2)
Upper Respiratory Tract Inf.	0 (0)	3 (7.0)	1 (2.4)	95 (8.3)	2 (4.0)	48 (7.9)
Dizziness	**0 (0)**	**5 (11.6)**	**1 (2.4)**	**80 (7.0)**	**13 (26.0)**	**32 (5.3)**
Influenza	4 (7.8)	1 (2.3)	1 (2.4)	78 (6.8)	2 (4.0)	44 (7.2)
Nausea	**3 (5.9)**	**2 (4.7)**	**3 (7.1)**	**77 (6.7)**	**8 (16.0)**	**21 (3.5)**
Diarrhoea	1 (2.0)	1 (2.3)	0 (0)	72 (6.3)	1 (2.0)	26 (4.3)
ALT Increased	**1 (2.0)**	**0 (0)**	**1 (2.4)**	**69 (6.0)**	**4 (8.0)**	**8 (1.3)**
Back Pain	1 (2.0)	3 (7.0)	2 (4.8)	70 (6.1)	3 (6.0)	47 (7.7)
Pain In Extremity	2 (3.9)	2 (4.7)	1 (2.4)	61 (5.3)	1 (2.0)	21 (3.5)
Bradycardia	**2 (3.9)**	**2 (4.7)**	**0 (0)**	**53 (4.6)**	**14 (28.0)**	**16 (2.6)**
Arthralgia	0 (0)	2 (4.7)	1 (2.4)	52 (4.5)	0 (0)	37 (6.1)
Depression	3 (5.9)	0 (0)	1 (2.4)	51 (4.4)	0 (0)	32 (5.3)
Oedema Peripheral	1 (2.0)	0 (0)	0 (0)	50 (4.4)	2 (4.0)	14 (2.3)
Melanocytic Naevus	0 (0)	1 (2.3)	1 (2.4)	49 (4.3)	2 (4.0)	19 (3.1)
GGT increased	2 (3.9)	0 (0)	0 (0)	46 (4.0)	3 (6.0)	6 (1.0)
Muscle Spasticity	0 (0)	0 (0)	0 (0)	45 (3.9)	0 (0)	24 (4.0)
Constipation	0 (0)	0 (0)	0 (0)	42 (3.7)	2 (4.0)	23 (3.8)
Cough	3 (5.9)	4 (9.3)	1 (2.4)	40 (3.5)	4 (8.0)	19 (3.1)
Insomnia	1 (2.0)	0 (0)	0 (0)	38 (3.3)	0 (0)	20 (3.3)
Muscle Spasms	0 (0)	0 (0)	1 (2.4)	37 (3.2)	0 (0)	19 (3.1)
Bronchitis	0 (0)	3 (7.0)	1 (2.4)	37 (3.2)	0 (0)	16 (2.6)
Contusion	0 (0)	1 (2.3)	1 (2.4)	35 (3.0)	0 (0)	17 (2.8)

A patient with multiple occurrences of an AE under each treatment is counted only once in this AE category for that treatment. Preferred terms are sorted in descending frequency of AEs based on BAF312 2 mg.
N is the number of patients in the treatment group at risk, n is the number of patients with at least one event in the treatment group. Incidence % is calculated by n/N.

AEs of special interest

Adverse events of special interest (AESI) were defined as events of potential risk of occurrence based on the current available preclinical and clinical data, the class effect, and the potential mechanism of action of siponimod. The AEs of interest are those arising from known mechanism of action and pharmacologic effects of S1P receptor modulators. Based on prior experience with the class of S1P receptor modulators the focus is on the following AEs observed in siponimod clinical studies: infections (Varizella Zoster Virus (VZV) reactivation, herpes zoster), lymphopenia, macular edema, abnormal hepatic enzymes, malignancies (skin neoplasms), hypertension, seizures, thromboembolic events, respiratory disorders, peripheral edema/ swelling and bradyarrhythmias associated with treatment initiation.

Specific safety monitoring procedures were included in the clinical trial protocols to ensure early detection and provide guidance on management of adverse events (AEs) of specific interest: bradyarrhythmic events, infections, neoplasms, eye disorders, laboratory changes and pulmonary function tests (PFTs).

Infections

The most common infections in the siponimod 2 mg group were nasopharyngitis (13.4% vs 14.3% placebo), urinary tract infection (11.8% vs 13.7% placebo) and upper respiratory tract infection (8.3% vs 7.9% placebo). Fungal skin infections were reported in 0.9% of siponimod 2 mg patients and 0.2 % of placebo patients. Fungal infections were reported for a similar percentage of patients in the siponimod 2 mg and placebo groups (3.7% and 3.1%). No imbalance in lower respiratory tract infections (4.1% vs 4.0 %) and urinary tract infections (14.0% vs 16.1%) was observed in the siponimod 2 mg patients compared to placebo group (based on risk search terms defined by high level group term).

Herpes zoster reactivations occurred more often in the siponimod (3.0%) than in the placebo group (0.7%). The SmPC adequately advices to ascertain that patients have previously been infected with or vaccinated against herpes zoster before initiation of treatment with siponimod.

Serious infections:

As is also addressed in the section of serious adverse events, cases of serious infections occurring with a lower frequency than tabulated above comprised: herpes zoster meningitis, encephalitis viral, sepsis, septic shock, pneumonia, pyelonephritis, chronic pyelonephritis, cellulitis, and two upper respiratory tract infections. Noteworthy, there were no incidences of PML but a case of cryptococcal meningitis was reported.

Lymphopenia

Reductions in circulating lymphocyte counts are expected with siponimod due to its mode of action. Siponimod causes a dose-dependent reduction in peripheral lymphocyte count to 20 – 30 % of baseline values due to reversible sequestration of lymphocytes in lymphoid tissues. Clinical pharmacology studies have shown that lymphocyte counts are already reduced on Day 1 of treatment. In clinical pharmacology studies, a sharp decrease in the lymphocyte count upon treatment initiation was observed, then values remained at a plateau during the chronic treatment followed by a return to baseline starting promptly after treatment discontinuation (Day 39).

Lymphocytopenia is a pharmacodynamic effect of siponimod, and as such not an adverse event. However, 3% of the siponimod treated patients in the controlled pool and 10% in the long-term pool developed severe lymphopenia, which, however, did not translate into increased infections others than those labelled.

In comparison to fingolimod the half-life of siponimod is much shorter (approximately 30 h versus 200 h for fingolimod). Lymphocyte counts begin to recover within some days of stopping therapy, returning to

normal values (≥ 1.0 x10^9/L) within 10 days (2-4 weeks) of stopping chronic therapy in most subjects. Drug effects are therefore likely to cease more rapidly after discontinuation than in the case of fingolimod, where the return to 80% of the baseline lymphocyte counts after discontinuation of 0.5 mg fingolimod may take up to 48 days.

A dose-effect of siponimod on the change from baseline in the lymphocyte count was observed at day 7, month 1, month 3 and month 6. Patients receiving different doses (10 mg, 2 mg, 1.25mg) experienced a decrease in absolute lymphocyte counts to <0.2x10^9/L on at least one occasion during the course of the study at frequencies of 36.2% (10 mg), 3.3% (2 mg), and 2.4% (1.25 mg).

For the siponimod treated group, there was a higher proportion of patients (52.9%) with at least one measured lymphocyte count in the lowest category (<0.4 × 109/L) at any time on treatment that experienced one or more infections. This is compared to 45.0% of patients with infections with at least one lymphocyte count of 0.4 - 0.6 × 109/L and 42.3% of patients with infections with lymphocyte counts >0.6 × 109/L. This trend was consistent across all types of infections classified according to the organ-related high level term.

Lymphopenia was reported as AE in 8 patients (16.0%) in the siponimod 10 mg group, in 18 siponimod 2 mg patients (1.6%) and no placebo patients in the controlled pool.

For the long-term pool, absolute lymphocyte counts showed the same pattern as that seen in the controlled pool. The counts were reduced at Day 28 for siponimod 2-10 mg and remained reduced from Day 28 until the end of the time period recorded. Almost all patients in the long-term pool S-db4 (broad) had lymphocyte counts decreased below the normal range (98.7%; all grades), with CTC grade 4 decreases (<0.2 x10^9/L lymphocytes) observed in 10.4% of patients. Generally, a higher incidence of lymphopenia AEs were reported in the Long-term pool S-db4 (broad) compared to the Controlled pool (11.6% vs. 1.6%). However, it should be noted that, for study blinding purposes, the absolute total white blood cell (WBC), neutrophil and lymphocyte counts were blinded from the sponsor and the investigator during the controlled period of the studies. Results were only communicated to the site in case of a notable abnormality (for lymphocytes <0.2 x10^9/L) that could have required a dose change.However, even for patients with the lowest lymphocyte counts no substantial difference in the incidence of_infections was detected in comparison to the placebo group. More remarkable is the low infection rate, including lower incidence of infections in comparison to placebo (49.3%), for those patients with lymphocyte counts > 0.6 × 10^9/L.

In special situations of study A2304 less than the full 2 mg dose was to be administered, i.e. subjects with confirmed lymphocyte counts <0.2 x10^9/L and in patients with CYP2C9*2*3 or CYP2C9*1*3 (poor and intermediate metabolizer) genotype (please refer to clinical pharmacology section).

During study A2304, patients with confirmed lymphocyte counts <0.2 x10^9/L at the 2 mg/day dose level (or placebo) underwent dose reduction to 1 mg/day during double-blind treatment and this dose was to be maintained irrespective of re-increase in lymphocyte counts. The same proceeding was applied in patients on open-label siponimod. In case that lymphocyte counts remained at 0.2x10^9/L or dropped even further under the 1 mg dose, dose interruption became necessary and treatment was not to be re-initiated (using dose titration) until level reached 0.6 x10^9/L. Adequate information on the mode of routine monitoring of WBC counts and lymphocyte counts in section 4.4 have been included. Please also refer to assessment of laboratory findings.

Macular edema:

Macular edema is a class effect of S1P receptor modulators. The pathophysiological mechanism is based upon the interaction between the modulator and the S1P1 receptor present on endothelial cells. Clinical signs associated with macular edema can be visual acuity defect, but not systematically.

The applicant reported that in the controlled pool of patients in MS trials, macular edema (including cystoid macular edema) appeared as a TEAE in 20 (1.7%) patients in the siponimod 2 mg group and in one patient (0.2%) in the placebo treatment group.

In the long-term safety pool (broad) five additional cases of macular oedema occurred. Of the 5 patients, one patient was reported with asymptomatic retinal edema (grade 1).

Macular edema was reported as an SAE for 3 (0.3%) patients in the siponimod 2 mg group and in none of the patients in the other treatment groups in the controlled pool.

In 8 siponimod patients (9 eyes), macular edema was associated with new visual impairment. Fluorescein angiography was not routinely performed, but in patients who had the assessments retinal capillary leakage was detected in 12/38 siponimod patients (16/76 eyes) and 1/7 placebo patients (2/14 eyes).

Recurrence of macular edema upon re-challenge with siponimod is likely. Continuation of siponimod in patients with macular edema has not been evaluated. It is recommended siponimod to be discontinued if a patient develops macular edema. Siponimod should be used with caution in patients with a history of uveitis or diabetes mellitus due to a potential increase in the risk of macular edema. Regular ophthalmological examinations should be conducted in these patients to detect macular edema. These instructions are addressed in the SmPC.

Cardiac events

Effects on heart

Siponimod decreases the heart rate and may lead to bradyarrhythmias, especially during the initiation of the treatment. During dose initiation, 7.4% of the siponimod treated patients experienced bradyarrhythmias and bradycardia as compared to 2.9% in the placebo group. Of these, 18 patients (1.6%) had conduction defects including first degree AV or second degree Mobitz type I AV block, or ECG QT prolonged. Noteworthy, there were no second degree AV Mobitz type II or third degree AV block. The bradyarrhythmic effect is most pronounced 0-8 hours post-dosing and during the first 7-10 days after treatment initiation. Patients with second degree Mobitz type II AV block, third degree AV block, sino-atrial heart block or sick-sinus syndrome should not use siponimod, if they do not wear a pacemaker. Patients who in the previous 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischaemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure should not use siponimod. Finally, the SmPC adequately addresses the uncertainties of siponimod treatment in patients taking medications with strong influence on cardiac conduction or function and recommends that a cardiologist should be consulted before initiation of siponimod. A short instruction /summary to prescribing physician on treatment possibilities in case of severe bradycardia is also included. As it is unknown which patients who will experience a symptomatic reduction in heart rate, patients should not drive or operate machines during the first day of treatment initiation with siponimod.

Effects on blood pressure:

Small increases in blood pressure are noticeable during treatment with siponimod both during the placebo-controlled studies and during the extensions. The increase occurred mainly during the first year of treatment.

The increase in blood pressure was reflected by more TEAEs of hypertension in the siponimod group than in the placebo group (12% vs 9%). However, there was a similar incidence of new systolic blood pressure (SBP) > 180 mmHg (0.4% vs. 0.3%) and a similar incidence of new diastolic blood pressure (DBP) > 110 mmHg (0.9% vs. 0.5%) in the siponimod and placebo groups, respectively.

Even if blood pressure is only moderately increased, it appears to be dose and duration dependent. The risk needs to be taken into account for long-term treatment; this is addressed in the SmPC.

Two patients in the siponimod group were diagnosed with 'Retinopathy hypertensive' as compared to none in the placebo group. The applicant has clarified that these events did not appear related to treatment with siponimod.

Cholesterol

Mean total cholesterol levels in the siponimod 2 mg group tended to gradually increase from baseline until Month 18 when mean cholesterol in the siponimod 2 mg group had increased by 0.396 mmol/L compared to placebo -0.014 mmol/L. Change from baseline to last assessment on study drug was 0.350 mmol/L for 2 mg siponimod. Mean triglyceride change from baseline in the 2 mg siponimod group also slightly increased from baseline until Month 9 to 0.1609 mmol/L.

The proportion of patients with abnormally high total cholesterol was higher in 2 mg siponimod (35.6% All grades) compared to placebo (23.9%). Similarly, the proportion of patients with abnormally high triglycerides was higher in the 2 mg siponimod group (35.8% All grades) compared with placebo (29.0%). There was no significant imbalance in the incidence of TEAEs relevant for the laboratory findings above, specifically hypercholesterolemia was reported in 2.4% of patients in the siponimod 2mg group compared to placebo group (2.0%); hyperlipidemia 0.4% vs. 0.2% and hypertriglyceridemia 0.2% vs. 0.3%, respectively. The findings were comparable between the controlled and long-term pools.

Thromboembolic events

Results in the Controlled pool and in the Long-term pool do not indicate that siponimod leads to thromboembolic complications. However, as the drugs in this class lead to increased blood pressure in some patients, thromboembolic events may occur at an increased frequency after longer-term treatment. Therefore, thromboembolic events are included in the RMP as an important potential risk.

Liver-related adverse events

As noted with other S1P receptor modulators, increased liver transaminases (mostly ALT elevation) were the most commonly reported AEs of interest in patients treated with siponimod and were reported as TEAEs in 13. 2% of siponimod patients and 4.0% of placebo patients in the controlled. Only few patients showed elevations of > 5 x ULN, 1 patient had ALT>10xULN. 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.

Increased GGT was the next most common TEAE, reported for 6.0% and 4.0% of patients in the siponimod 10 mg and 2 mg groups and for 1.0% of patients in the placebo group.

No case of serious hepatotoxicity (Hy's law) or liver failure was observed in any of the siponimod or placebo groups.

The mechanism by which siponimod may cause liver enzyme elevation is unknown. A further unexplained finding was a greater incidence of liver transaminase elevation in males compared to females, a gender

effect which has been seen also with fingolimod, another S1P receptor modulator. However, no explanation to these findings could be found.

A similar total siponimod plasma exposure was observed in hepatically and renally impaired patients compared to healthy subjects, with a trend for a higher unbound siponimod exposure in hepatically impaired patients. Initiation of treatment with siponimod in case of pre-existing hepatic abnormalities should be made with caution and patients should be closely monitored during treatment.

Since siponimod is mainly eliminated via hepatic metabolism and excretion via bile into faeces, hepatic impairment is expected to influence the clearance of siponimod. AST, ALT and bilirubin were tested during the model development process analysing phase 1 and phase 2 studies only. Patients who develop symptoms suggestive of hepatic dysfunction during treatment should have liver enzymes checked and siponimod should be discontinued if significant liver injury is confirmed. Severe liver impairment (Child-Pugh class C) is therefore a contraindication in the SmPC.

Seizures

Seizures, based on risk search terms defined by the SMQ (broad) Convulsions, were reported as TEAEs in 17 (1.5%) siponimod 2 mg patients and 3 (0.5%) placebo patients in the Controlled pool.

Nine (of 17) patients had *de novo* events. Time to onset for the *de novo* events ranged from 44 to 899 days: (< 3 months – 2 patients, 3 to 6 months – 2 patients, > 6 months – 5 patients). Of the 9 de novo seizure/epileptic seizure events, concomitant anti-epileptic medication was administered in seven patients. In the other two cases (seizure and simple partial seizures) no anti-epileptics were used. Siponimod therapy was continued in 8 patients and no recurrence of the events was reported. Study drug was discontinued in only one patient, with generalized tonic-clonic seizure.

In the three placebo patients with reported seizure related event, one patient who had de novo epilepsy was started on anti-epileptic medication and was subsequently seizure–free under antiepileptic medication. In the other two cases: final diagnosis was not confirmed in one case (reported to have "cerebral signs of possibly epileptic potentials") and in the third case, the patient had a prior history of seizures.

It has been observed that the risk of epilepsy and epileptic seizures is generally higher in patients with a longer MS disease duration than in the overall population. Epileptic seizures are also included as an ADR for various classes of MS therapies, such as interferons, fampridine and fingolimod. By now, the cause of the apparent increase in seizures on siponimod appears rather ambiguous. The applicant confirms to monitor seizures continuously through routine pharmacovigilance and to further characterize the risk (frequency, nature, and severity of risk) in the post-approval setting.

Suicidal behaviour:

Suicidal attempt/ideation/behaviour was found to be increased in patients treated with siponimod (1.6%, n=18) as compared to patients treated with placebo (0.7%, n=4) in the controlled pool. However, causality with siponimod treatment could not have been established given that 15/18 cases in the siponimod group and 3/4 cases in the placebo group were confounded by relevant medical history of depression or anxiety and/or concomitant medication.

New malignancies

Malignancies, based on risk search terms defined by the SMQ Malignant or unspecified tumors, were reported as TEAEs in 21 (1.8%) patients [Odds ratio 0.8 vs Placebo (95% CI 0.4, 1.6)] and 1 (2.3%) patient [Odds ratio 1.0 vs Placebo (95% CI 0.1, 7.9)] receiving siponimod 2 mg and 0.5 mg respectively compared to 14 (2.3%) placebo patients. The majority of reported neoplasms consisted of skin malignancies (based on risk search terms defined by customized NMQ) and were of comparable incidence

in the siponimod 2 mg (1.3%, 15 patients) and placebo (1.3%, 8 patients) groups. No increase in the IR (per 100 PY) of malignancy-related events was observed in the long-term safety pools [1.2 (95% CI 0.9, 1.6)] as compared to the controlled pool [1.2 per 100 PY (95% CI 0.8, 1.9)].

Basal cell carcinoma was the most common neoplasm and there was no increase in IR observed in the long term pool (0.6 per 100 PTY (95% CI 0.4, 0.9) as compared to controlled pool (0.7 per 100 PTY (95% CI 0.4, 1.2). It should be noted that active dermatological screening was continued yearly in the A2304 EP.

During the core and extension studies, there were four patients diagnosed with malignant melanoma in the siponimod group as compared to none in the placebo group including a patient, who received his last dose of siponimod 609 days before the diagnosis of malignant melanoma. The applicant has included 'Malignancies' as an important potential risk in the RMP, this is considered appropriate. More importantly, skin malignancies are now included as a warning in the SmPC section 4.4.

However, the number of events of any type of malignancy to date, and the duration of follow-up, is relatively limited and does not permit firm conclusions at this time on any potential long-term risk of the immunomodulatory therapy. Hence, patients with known active malignancies should not initiate siponimod therapy.

Serious adverse event/deaths/other significant events

Deaths:

As of 31-Dec-2017, there were 18 patient deaths (plus one death during the screening period). Among the 18 deaths, 8 deaths were reported during the controlled trials; 4 placebo patients and 4 siponimod patients.

The cause of death in the four patients receiving siponimod were acute myocardial insufficiency, suicide, urosepsis, and malignant melanoma in patients receiving siponimod. The cause of death in the four patients receiving placebo were haemorrhagic stroke, lung adenocarcinoma, unknown, and gastric cancer.

Table 38: Patient deaths in the siponimod clinical program

Study / Treatment received	**Primary preferred term** **(Event contributing to death)**	**Study Day relative to start date of study medication**	**Number of days since last dose of study medication**	**Causality (per investigator)**
Controlled Pool				
A2201/ 1.25mg	Cardiac arrest** (Acute myocardial insufficiency)	79	27	Yes / suspected
A2304	Completed suicide **	257	2	No
A2304	Urosepsis #	347	72	No
A2304	Malignant melanoma (multiple organ dysfunction syndrome)	278	31	Yes
Placebo				

A2304	Haemorrhagic stroke ** (cardio-respiratory arrest)	151	15	No
A2304	Lung adenocarcinoma **	785	50	Yes
A2304	Death (unknown reason)	825	232	No*
A2304	Gastric cancer **	672	204	No
Long-term Pool				
A2201/ 1.25mg	Craniocerebral injury**	1859	17	No
A2304/ 2 mg	Amyotrophic lateral sclerosis	1155	105	No
A2304/ 2 mg	Respiratory paralysis (Severe spastic tetraparesis)	865	267	No
A2304/ 2 mg	Death (Unknown reason)***	380	-	No
A2304/ 2 mg	Death (Unknown reason)**a	1035	0	No
A2304	Septic shock § (colon cancer Stage IV)	716	5	Yes
A2304/ 2 mg	Pneumonia	1352	12	Yes

Days from partial dates are based on imputed dates.

Event occurred after start of alternative MS- disease modifying therapy (rituximab)/ 10 weeks after siponimod discontinuation

§ Event occurred 5 days after discontinuation from open-label siponimod

** Deaths which occurred during double-blind study treatment until safety cut-off

a Death occurred around 3 years after first dose of study medication (siponimod 2 mg). No autopsy was performed. Investigator assessed death as not suspected to study treatment (blinded study medication and open label siponimod).

*** The patient diagnosed with testicular cancer after 8 months of open-label siponimod and was reported to have died 4 months after siponimod discontinuation

The narratives of the patients, who died during the programme have been provided. There was not an imbalance between siponimod and placebo groups.

Serious adverse events (SAE)

The most frequent treatment emergent serious adverse events (TE-SAEs) are tabulated in Table 39. Since the table includes only TE-SAEs observed with the same preferred term in at least three patients, a summary of selected TE-SAEs is given below the table.

Table 39: Incidence of most frequent treatment emergent serious adverse events (at least 3 patients in the siponimod 2mg group), by preferred term – n (%) of patients with events – Controlled Pool (Safety Set Up To 30 Days of DB Last Dose)

Preferred Term	BAF312 0.25mg N=51 n (%)	BAF312 0.5mg N=43 n (%)	BAF312 1.25mg N=42 n (%)	BAF312 2 mg N=1148 n (%)	BAF312 10mg N=50 n (%)	Placebo N=607 n (%)
Number of patients with at least one SAE	0 (0)	7 (16.3)	2 (4.8)	193 (16.8)	2 (4.0)	74 (12.2)
Urinary Tract Infection	0 (0)	0 (0)	0 (0)	13 (1.1)	0 (0)	6 (1.0)
Basal Cell Carcinoma	0 (0)	1 (2.3)	0 (0)	12 (1.0)	0 (0)	6 (1.0)
Alanine Aminotransferase Increased	0 (0)	0 (0)	0 (0)	10 (0.9)	0 (0)	2 (0.3)
Aspartate Aminotransferase Increased	0 (0)	0 (0)	0 (0)	5 (0.4)	0 (0)	1 (0.2)
Atrioventricular Block Second Degree	0 (0)	0 (0)	0 (0)	5 (0.4)	1 (2.0)	0 (0)
Concussion	0 (0)	0 (0)	0 (0)	5 (0.4)	0 (0)	0 (0)
Depression	0 (0)	0 (0)	0 (0)	5 (0.4)	0 (0)	2 (0.3)
Epilepsy	0 (0)	0 (0)	0 (0)	4 (0.3)	0 (0)	0 (0)
Laceration	0 (0)	0 (0)	0 (0)	4 (0.3)	0 (0)	0 (0)
Suicide Attempt	0 (0)	0 (0)	0 (0)	4 (0.3)	0 (0)	3 (0.5)
Syncope	0 (0)	0 (0)	0 (0)	4 (0.3)	0 (0)	1 (0.2)
Appendicitis	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	0 (0)
Bradycardia	0 (0)	1 (2.3)	0 (0)	3 (0.3)	0 (0)	0 (0)
Femoral Neck Fracture	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	1 (0.2)
Hemiparesis	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	0 (0)
Macular Oedema	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	0 (0)
Suicidal Behaviour	0 (0)	0 (0)	0 (0)	4 (0.3)	0 (0)	0 (0)
Suicidal Ideation	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	1 (0.2)
Trigeminal Neuralgia	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	0 (0)
Upper Respiratory Tract Infection	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	0 (0)
Urinary Retention	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	2 (0.3)

A patient with multiple occurrences of an SAE under each treatment is counted only once in this SAE category for that treatment.
Preferred terms are sorted in descending frequency of SAEs based on BAF312 2 mg.
N is the number of patients in the treatment group at risk, n is the number of patients with at least one event in the treatment group. Incidence % is calculated by n/N.
"Up To 30 Days of DB Last Dose" means all serious adverse events reported up to and including 30 days after last dose of study drug or start of open-label BAF312, whichever occurred first.

Summary of treatment emergent serious infections not tabulated in Table 39 in the siponimod group: herpes zoster meningitis, encephalitis viral, sepsis, septic shock, pneumonia, pyelonephritis, chronic pyelonephritis, cellulitis, and three upper respiratory tract infections.

Summary of treatment emergent serious cardiac events not tabulated in Table 39 in the siponimod group: four cases of syncope, one Bundle branch block left, and one case of Heart rate decreased.

Summary of treatment emergent serious liver-related events not tabulated in Table 39 in the siponimod group: one case of hepatic enzyme abnormal, one case of hepatic enzyme increased, one case of hepatotoxicity, one case of bilirubin increased, and one case of hepatitis E.

Laboratory findings

Haematology:

Lymphocytopenia is described in the section above. Approximately half of the patients who were receiving siponimod 2 mg, in the controlled pool, had WBC decreased (53.9%; all grades) compared to 9.2% of patients in the placebo group; with no patients having grade 4 < 1.0 x109/L WBC decreased in any of the siponimod groups or the placebo group.

Assessments of CBC (complete blood count) are recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count < $0.2x10^9$/L, if confirmed, should lead to treatment interruption until recovery. In clinical studies siponimod treatment was interrupted in patients with absolute lymphocyte count < $0.2x10^9$/L. The advice of clinical monitoring to assure that the absolute lymphocyte count is above $0.2x10^9$/L is reflected in the SmPC.

There were slightly more patients who had absolute neutrophil count decreased overall (4.0% all grades) in the siponimod 2 mg group; 2.3 % in the placebo group with no patients having grade 4 < 0.5 x109/L neutrophils in any of the siponimod groups or the placebo group.

Differences observed regarding 'platelet counts decreased' between siponimod and placebo treatment groups: 7.0% all grades in the siponimod 2 mg group; 5.4 % in the placebo group with a few patients only having platelet count decreased grade 4 < 25.0 x109/L platelets (2 patients in the siponimod 2 mg group (0.2%) and 1 patient in the placebo group (0.2%).There were 6 patients (0.5%) who were reported as having had thrombocytopenia, and 3 patients (0.3%) having platelet count decreased, in the siponimod 2 mg treatment group (there were no patients having either event in any of the other treatment groups).

Liver and renal function

Changes of liver function parameters were also presented in the section of adverse events. There were no differences between patients in the siponimod and placebo groups with regard to renal parameters. A summary of renal events by treatment in the controlled pool showed no apparent difference between siponimod 2 mg and placebo treatment.

A higher proportion of patients in the siponimod groups had treatment–emergent abnormally high liver enzymes (in particular ALT, AST, GGT) compared to placebo. Levels rise within approximately 28 days of starting treatment and remains higher compared to the placebo group during the study, which return to baseline values within 1-3 months after drug discontinuation. Few patients showed elevations of > 5x ULN (grade 3) but no patient met the criteria for hepatotoxicity (Hy's law). As there are potential risks associated with elevated liver enzymes the information of monitoring of liver enzymes based on clinical symptoms are amended to the SmPC.

Triglycerides and cholesterol

Changes in triglycerides and cholesterol were presented in the section of adverse events.

Urinalysis

No major differences between the siponimod and placebo groups or discernible trends in post-baseline changes in urinalysis parameters were observed in the studies.

Safety in special populations

Age:

The patients included in the studies were up to the age of 61 years. This is reflected in *Table 36*, which does not include information on children, adolescents, or elderly.

In the siponimod 2 mg group there was a higher incidence rate (IR) of serious AEs in the >45 year age group than in the ≤ 45 year age group due to a higher incidence of infections and nervous system disorders in the older age group.

Differences of ≥ 5% in the percentage of patients ≤ 45 years and > 45 years of age with AEs were observed for the following PTs: Fall (8.4%, 16.3%), hypertension (7.3%, 14.1%). The observations in the long-term safety pools were comparable to the controlled pool.

As the age range defined in the inclusion criteria (18 to 60 inclusive years) no data of children or elderly patients are available in the safety datasets. The text in the proposed SmPC informs about the lack of data in children and elderly (section 4.2 and 5.2).

Race

There was no indication that the incidence of AEs was influenced by race. However, the robustness of the conclusions on the influence of race is limited as more than 95% of the patients treated with siponimod were Caucasian and the numbers of patients in the Asian and Black/African American subgroups were small.

CYP2C9 genotypes:

- CYP2C9*1*1 and CYP2C9*1*2→ extensive metabolizer
- CYP2C9*2*2 and CYP2C9*1*3→ intermediate metabolizer
- **CYP2C9*2*3 and CYP2C9*3*3→ poor metabolizer**

The risk 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.

Incidence rates of selected adverse events (other than macular edema) among patients with 'poor metaboliser'-genotype and 'extensive metaboliser'-genotype are presented in *Table 40*: .

Siponimod is mainly metabolised by polymorphic CYP2C9, and the genotype was found to have a significant impact on siponimod metabolism (see clinical pharmacology section). Therefore, all subjects were tested for the CYP2C9 genotype prior to study entry. Based on the expected risk of high chronic exposure those patients with **CYP2C9*3*3 (poor metaboliser)** polymorphism were not to be included in the study. Siponimod is therefore contraindicated (section 4.3 of the SmPC) for CYP2C9 poor metabolizer. Respective labelling is already included in section 4.2, 4.4 and 5.2.

In patients with **CYP2C9*2*3 or CYP2C9*1*3** genotype it is recommended to reduce the daily dose to 1 mg to achieve an exposure that is comparable to that of CYP2C9*1*1 subjects receiving a 2 mg dose and thus avoid potential long-term safety risks of chronic higher exposure. It is further specified in the SmPC that the starter pack is to be used in these subjects for treatment initiation. The starter package includes a daily dose of 1.25 mg at Day 5.

Further, the applicant has been requested to present possible differences in brady-arrhythmias according to genotype, which did not lead to further amendments to the SmPC except from the already implemented contraindication in poor metabolizers.

Table 40: Incidence rate of TEAEs, by primary system organ class, preferred term and genotype – Controlled Pool (Safety Set)

Primary system organ class	BAF312 2 mg N=968 n (IR**) (95% CI)	Placebo N=523 n (IR**) (95% CI)
Genotype: WT/WT, *2/WT, *2/*2	**N=968**	**N=523**
Number of patients with at least one AE	868 (259.2) (242.3, 277.0)	429 (192.7) (174.9, 211.8)
General disorders and administration site conditions	229 (18.7) (16.4, 21.3)	106 (16.7) (13.6, 20.2)
Fatigue	83 (5.9) (4.7, 7.4)	46 (6.5) (4.8, 8.7)
Peripheral edema	39 (2.7) (1.9, 3.7)	13 (1.8) (0.9, 3.0)
Psychiatric disorders	142 (10.6) (8.9, 12.5)	79 (11.7) (9.2, 14.5)
Depression	39 (2.7) (1.9, 3.7)	29 (4.0) (2.7, 5.7)
Primary system organ class	**BAF312 2 mg N=176 n (IR**) (95% CI)**	**Placebo N=83 n (IR**) (95% CI)**
Genotype: *3/WT, *2/*3	**N=176**	**N=83**
Number of patients with at least one AE	158 (247.8) (210.6, 289.6)	65 (141.9) 109.5, 180.8)
General disorders and administration site conditions	46 (22.5) (16.5, 30.0)	17 (18.6) (10.9, 29.8)
Fatigue	21 (9.0) (5.6, 13.8)	10 (10.3) (4.9, 18.9)
Peripheral edema	10 (4.2) (2.0, 7.7)	1 (0.9) (0.0, 5.1)
Psychiatric disorders	28 (12.4) (8.2, 17.9)	9 (8.7) (4.0, 16.5)
Depression	12 (4.9) (2.6, 8.6)	3 (2.8) (0.6, 8.1)

A patient with multiple adverse events within a primary system organ class is counted only once in the total row. A patient with multiple occurrences of an AE under each treatment is counted only once in this AE category for that treatment. N is the number of patients in the treatment group at risk, n is the number of patients with at least one event in the treatment group.
Incidence rate (IR) is calculated by n/T, i.e. the number of patients 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.

Pregnancy and lactation

Reproductive and developmental studies in pregnant rats and rabbits have demonstrated siponimod induced embryotoxicity and fetotoxicity in both species and teratogenicity in rats.

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 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.

Of the 15 pregnancies reported in 12 patients, eight resulted in successful delivery to full term with no maternal complications or neonatal abnormalities, spontaneous abortion in 2 patients (A2304 (n=2)) and elective abortion in 5 patients (randomized to 1.25mg (A2201), 1.25/2 mg, 2/2 mg (A2201E1), and

Placebo (Phase 3 DB period)). Of the above patients reported with spontaneous abortion (n=2) and elective abortion (n=5), one of the patients randomized to Placebo in the Phase 3 DB period had an elective abortion and later was reported with spontaneous abortion during open-label siponimod therapy (2 mg).

As siponimod is intended as a chronic treatment in SPMS patients, a largely (young and) female population, potential teratogenicity is a known risk. 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. Therefore, siponimod should not be used during pregnancy and lactation.

Renal and hepatic impairment

24 hepatic impaired subjects, 8 renal impaired subjects, 49 PM/DM patients and 1948 MS patients have been enrolled into the siponimod clinical program.

Hepatic impairment: Study A2122 was a single-dose, open-label, parallel-group study to assess the PK, safety and tolerability of 0.25 mg siponimod in 24 subjects with hepatic impairment and 16 healthy control subjects. Single oral doses of siponimod 0.25 mg were safe and well tolerated in subjects with mild, moderate, and severe hepatic impairment and matched healthy subjects. All reported AEs were mild in intensity; there were no SAEs. A total of three AEs of mild intensity were reported in 40 subjects (7.5%). No significant difference could be observed in the overall AE incidence between subjects with hepatic impairment (n=2, 8.3%) compared to matched healthy control subjects (n=1, 6.3%). Among the three AEs, only one asymptomatic AE (first degree atrioventricular block) was suspected to be related to study drug administration and the remaining two AEs (pain in extremity and tonsillitis) were considered to be unrelated to study drug intake. No significant bradycardia, bradyarrhythmic events or other cardiac rhythm abnormalities of clinical relevance were observed.

Renal impairment: Study A2129 was a single-dose, open-label, parallel-group study to assess the PK of 0.25 mg siponimod in 8 subjects with renal impairment and 8 subjects with normal renal function. Single oral doses of 0.25 mg of siponimod were safe and well tolerated. No AEs were reported. No significant bradycardia, bradyarrhythmic events or other cardiac rhythm abnormalities were revealed.

Overdose

Healthy subjects received siponimod as single doses (0.1 to 75 mg) or as multiple non-titrated doses (0.25 to 20 mg). The single maximum tolerated dose was determined to be 25 mg based upon the occurrence of symptomatic bradycardia after single doses of 75 mg. The highest investigated multiple dose of 20 mg over 28 days was well tolerated (9 subjects receiving 100 mg on the last day of dosing and 5 subjects receiving up to 200 mg daily for a duration of 3-4 days). Some of the 9 subjects had asymptomatic mild to moderate transient elevations of liver function tests.

In the RRMS Phase 2 Study A2201, one patient (with a history of depression) attempted suicide and overdosed on 41 siponimod 2 mg tablets. Aside from a slight elevation in liver transaminases, the patient did not experience any other AEs from the overdose.

Drug abuse

Overall, chemistry, nonclinical 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.

Immunological events

Potential effects of siponimod on the immune response/immunogenicity of selected vaccines were investigated in a dedicated study. Non inferior responder rates demonstrated that concomitant siponimod treatment does not compromise the efficacy of a PPV-23 vaccination (T cell-independent response) and therefore no siponimod treatment interruption is required. The efficacy of quadrivalent influenza vaccination (T cell-dependent vaccine) is not compromised if siponimod treatment is paused 1 week prior until 4 weeks after vaccination. The applicant has included information on uncertainties regarding disease exacerbation in relation to siponimod and the balance between the benefit of siponimod treatment and the benefit of the vaccinations.

Safety related to drug-drug interactions and other interactions

Food

Despite a delay in T_{max}, food intake has no effect on the systemic exposure of siponimod. Mean AUC and C_{max} were similar under both fasted and fed conditions (tested at 5-mg dose). Therefore, siponimod may be taken without regard to meals, as reflected in section 4.2 of the SmPC. The influence of food on the PK after a single dose is referenced in the SmPC Section 5.2.

Genotype

Under the proposed genotype-based dosing recommendations, a maximum of a ~ 1.7-fold increased siponimod exposure is expected when siponimod is combined with a moderate or strong CYP2C9 or CYP3A4 inhibitor or a dual weak inhibitor of CYP2C9 and CYP3A4. When co-administered with a moderate CYP2C9/moderate CYP3A4 dual inhibitor (e.g. fluconazole), a higher net effect is predicted, i.e. between 1.78-2.15-fold for *1*1, *1*2, *1*3 and *2*3, the highest effect being estimated for CYP2C9*2*2 patients, with a net effect of 2.73-fold.

Concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is therefore 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. Strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) and moderate CYP3A4 inducers (e.g. modafinil) are expected to significantly reduce siponimod exposure by up to 76% and up to 51% respectively. Caution should then be applied when siponimod is combined with strong CYP3A4/moderate CYP2C9 inducers in all patients regardless of genotype and with moderate CYP3A4 inducers (e.g. modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype.

Beta-blockers and other antiarrhythmic agents

Beta-blockers represent a frequently prescribed drug class in the target patient population. Patients with MS, and in particular patients with SPMS who are more advanced in average age, have co-morbidities requiring beta-blocker therapy (e.g. for hypertension or angina pectoris). The negative chronotropic effect of co-administration of siponimod and propranolol was evaluated in a dedicated PD/safety study designed to mimic typical clinical scenarios in which propranolol treatment would be initiated in patients already treated with siponimod and vice versa.

Class Ia and II anti-arrhythmic medicinal products may result at the initiation of siponimod treatment in decreased heart rate and indirect prolongation of the QT interval during the titration phase. Class Ia and

Class III antiarrhythmic medicinal products have been associated with cases of torsades de pointes (TdP) in patients with bradycardia.

In the clinical study (A2304), starting treatment with QT-prolonging or heart rate-lowering medications during study treatment initiation (i.e., the first 10 days) was to be avoided whenever possible. For patients receiving a stable dose of beta-blocker, resting heart rate was considered before starting study drug: if the resting heart rate was >50 bpm under chronic beta-blocker treatment, study drug could be introduced according to procedures for the Expanded Cardiac Monitoring Group (see above). If resting heart rate was ≤50 bpm, study treatment was not to be initiated. The investigator was to carefully evaluate the individual risk-benefit relationship and the established guidelines depending on the type of beta-blocker being used and consider potential interruption of this beta-blocker treatment until the resting heart rate was >50 bpm. If it was decided to interrupt beta-blocker treatment the investigator was to proceed with caution. Once the resting heart-rate was >50 bpm, study drug could have been initiated and after 2 weeks of treatment with study drug, beta-blocker treatment could have been re-initiated. Monitoring was not only to be limited to the heart rate-related effects but also to include symptoms related to arrhythmia and bradycardia. Introduction of beta-blocker treatment was allowed in patients who were receiving a maintenance dose of study treatment (i.e., at steady state).

If treatment with siponimod is considered in patients with cardiac disease, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended, if the heart-rate lowering medication cannot be stopped.

With respect to the reduction of peripheral blood lymphocytes by siponimod and the possible risk of bradycardia and AV block, anti-neoplastic or immunosuppressive medications, live attenuated vaccines as well as antiarrhythmic agents or beta-blockers should only be co-administered with caution and under medical surveillance, which has already been adequately addressed in section 4.4 and 4.5 of the SmPC, respectively.

Oral contraceptives

Oral contraceptives represent a frequently prescribed co-medication in female MS patients. In a dedicated PK and PD DDI study [Study A2121] co-administration of siponimod with a monophasic oral contraceptive (combined ethinylestradiol and levonorgestrel) and siponimod did not alter the PK of ethinylestradiol and levonorgestrel to a clinically significant extent (no effect for ethinylestradiol; 18 % and 28% increases for levonorgestrel $C_{max,ss}$ and $AUC_{tau,ss}$, respectively). Co-administration with siponimod (4 mg qd) did not reveal clinically relevant effects on the PD of the combined ethinylestradiol and levonorgestrel oral contraceptive, as determined by the PD markers estradiol, FSH and LH, ovarian follicle sizes, Hoogland scores of ovarian activity and SHBG. These results demonstrated that the efficacy of the tested monophasic oral contraceptive is maintained under siponimod co-administration.

Prohibited treatment

During clinical study (A2304) concomitant use of the treatments displayed in Table 41 below in combination with study drug was not allowed due to the increased risk of immunosuppression, confounding of efficacy, and/or potential interaction with siponimod. This list was modified during the course of the study. Use of excluded medications was not allowed after randomization while the patient was on study drug.

Table 41: Prohibited treatment

Medication and class	Action required
Class 1: Immunosuppressive/chemotherapeutic medications or procedures, including cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and hematopoietic stem cell transplantation	Discontinuation or interruption of study treatment, increased vigilance regarding infections Restarting study treatment was to first be discussed with the Novartis Medical Advisor
Class 2: Monoclonal antibodies targeting the immune system, including natalizumab, rituximab, ofatumumab, ocrelizumab and alemtuzumab	Discontinuation or interruption of study treatment, increased vigilance regarding infections Restarting study treatment was to first be discussed with the Novartis Medical Advisor
Class 3: Any other immunomodulatory or disease-modifying MS treatment including, but not limited to: fingolimod, interferon beta, glatiramer acetate or systemic corticosteroids (except when given for MS relapse treatment)	Interruption of study treatment, increased vigilance regarding infections
Class 4: Any concomitant medication that inhibits cardiac conduction (e.g. verapamil-type and diltiazem-type calcium channel blockers or cardiac glycosides)	Assessment of ECG and clinical status
Class 5: Potent inducers of CYP2C9	None

Discontinuation due to adverse events

The proportion of patients discontinuing drug in the 10 mg group (20%) was higher than the other siponimod groups and the proportion for the 2 mg group (8.0%) was higher than for placebo (4.9%).

The SOCs with the highest proportion of patients discontinued due to a TEAE in the siponimod 2 mg group were Investigations (1.6%) with ALT increased (0.5%) as the most common preferred term, Eye disorders (1.5%) primarily due to macular edema (1.0%), Cardiac disorders (1.2%) primarily due to second degree AV block (0.4%) and bradycardia (0.3%) and Nervous system disorders (1.1%) with dizziness (0.3%) the most common preferred term.TEAEs that led to temporary interruption of study drug occurred in a small percentage of patients, 6.8 % in the siponimod group and 2.8% in the placebo group (controlled pool). The most common TEAEs leading to study drug interruption were all in the siponimod group and included macular edema, herpes zoster, ALT increased, and vomiting.

Table 42: Incidence of most frequent treatment emergent adverse events (TEAE) leading to study drug discontinuation (at least 2 patients in any treatment group), by preferred term – n (%) of patients with events – Controlled Pool (Safety Set)

Preferred Term	Siponimod 0.25 mg N=51 n (%)	Siponimod 0.5 mg N=43 n (%)	Siponimod 1.25 mg N=42 n (%)	Siponimod 2 mg N=1148 n (%)	Siponimod 10 mg N=50 n (%)	Placebo N=607 n (%)
Number of patients with at least one AE	1 (2.0)	5 (11.6)	1 (2.4)	92 (8.0)	10 (20.0)	30 (4.9)
Macular oedema	0 (0)	0 (0)	0 (0)	11 (1.0)	1 (2.0)	1 (0.2)
Alanine aminotransferase increased	0 (0)	0 (0)	0 (0)	6 (0.5)	1 (2.0)	0 (0)
Atrioventricular block second degree	0 (0)	0 (0)	0 (0)	5 (0.4)	2 (4.0)	0 (0)
Bradycardia	1 (2.0)	0 (0)	0 (0)	4 (0.3)	0 (0)	0 (0)

Gamma-glutamyltransferase increased	0 (0)	0 (0)	0 (0)	4 (0.3)	0 (0)	0 (0)
Aspartate aminotransferase increased	0 (0)	0 (0)	0 (0)	3 (0.3)	1 (2.0)	0 (0)
Depression	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	1 (0.2)
Dizziness	0 (0)	0 (0)	0 (0)	3 (0.3)	2 (4.0)	0 (0)
Fatigue	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	4 (0.7)
Pulmonary function test decreased	0 (0)	0 (0)	0 (0)	3 (0.3)	0 (0)	0 (0)
Angina pectoris	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)
Atrioventricular block first degree	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)
Carbon monoxide diffusing capacity decreased	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)
Hepatic enzyme increased	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)
Malignant melanoma in situ	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)
Oedema peripheral	0 (0)	0 (0)	0 (0)	2 (0.2)	1 (2.0)	0 (0)
Seminoma	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)
Uveitis	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (2.0)	2 (0.3)
Lymphocyte count decreased	0 (0)	0 (0)	0 (0)	1 (0.1)	2 (4.0)	0 (0)
Lymphopenia	0 (0)	0 (0)	0 (0)	1 (0.1)	2 (4.0)	0 (0)
Multiple sclerosis relapse	0 (0)	1 (2.3)	0 (0)	1 (0.1)	0 (0)	2 (0.3)
Urinary tract infection	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	2 (0.3)
Insomnia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.5)
Prostate cancer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.3)

A patient with multiple occurrences of an AE under each treatment is counted only once in this AE category for that treatment.
Preferred terms are sorted in descending frequency of AEs based on BAF312 2 mg.
N is the number of patients in the treatment group at risk, n is the number of patients with at least one event in the treatment group. Incidence % is calculated by n/N.

Withdrawal effects

The incidence of AEs during the time period 1-30 days and > 30 days, after study drug discontinuation was low, did not show any consistent pattern that would be indicative of withdrawal effects. Newly occurring or worsening AEs that were observed after the discontinuation of siponimod treatment were generally infrequent and did not show any consistent pattern compared to placebo that would be indicative of withdrawal effects. In study 2201E1 the follow-up visit was scheduled 3 months after the last dose of study medication for patients who prematurely withdrew from the study.

Although not detected within the limited duration of the follow up studies, a possible risk for an exaggerated immune response while pausing the treatment in relation to vaccinations is addressed in the SmPC section 4.4.

2.6.1. Discussion on clinical safety

The safety database of siponimod consists of two randomized, controlled studies; a phase 3 study (Study A2304) in SPMS with a core part and extension part and a phase 2 study (Study A2201) with its long-term extension study (Study A2201E1) in patients with RRMS.

The safety profile of siponimod is described with data on AEs issued from 1784 MS patients receiving doses ranging from 0.25 to 10 mg once daily. Of these over 1737 patients were treated with at least one dose of siponimod 2 mg, the proposed dose for registration, or higher. The safety results are consistent across the different studies in the siponimod MS development program. The approaches for pooling the safety data from the above MS studies are reasonable and appropriate. The safety analysis is based mainly on data from the controlled pool with supportive evidence from the long-term safety pools. 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. Therefore, experience to long-term safety risk is not available.

Despite its more targeted selectivity for S1P receptor subtypes, the overall safety profile of siponimod is qualitatively similar to fingolimod due to the same mechanism of action. However, for siponimod duration, severity, frequency and reversibility of AEs, are more rapidly reversible and transient.

There were more adverse events in the in siponimod groups than in the placebo group, and the incidence of adverse events increased with increasing dose of siponimod. TEAEs reported more frequently in the larger siponimod 2 mg group than for placebo (by ≥ 2%) include VZV reactivation, headache, hypertension, nausea, diarrhea, liver enzymes elevated (ALT and GGT), bradycardia and peripheral edema. Headache, nasopharyngitis, urinary tract infection, and falls were the most frequent adverse events reported in more than 10 % of patients in both treatment groups. Hypertension was reported in 121 patients (10.5%) on siponimod compared with 41 (8%) on placebo. As in the controlled pool, AEs in the long-term pool were most frequently infections and infestations and nervous system disorders. Consistent with the most common events seen in the controlled pool, these were most commonly nasopharyngitis, urinary tract infection, headache and fall.

In most cases differences between siponimod and placebo were small and reversible upon discontinuation of treatment. Furthermore, the overall importance of the differences needs to take into consideration both the severity of the events and any associated sequelae. The severity of most events was rated as mild or moderate and the events were either transient, preventable or can be managed.

Grade 3 TEAEs were reported for 11.0% and 9.2% of patients in the siponimod 2 mg and placebo groups, respectively. Grade 4 TEAEs were reported for 2.0% and 1.2% of patients in the siponimod 2 mg and placebo groups, respectively. Overall, the three most common TEAEs (Grade 3 or 4) in the siponimod group were urinary tract infection, ALT increased, and depression.

With a median duration of exposure to siponimod of 63.6 months (≥ 5years), the **extension of study A2201** contributes to the characterization of the long-term safety and tolerability profile of siponimod in RRMS patients. In the long-term pool almost all patients (94.6%) reported at least one AE, with a majority (77.2 %) of patients having AEs of either mild or moderate severity; 57.6% of the patients reported AEs suspected to be study drug related. Except for the unspecific or pharmacodynamically expected AEs nasopharyngitis, headache, lymphopenia, urinary tract infection, back pain, upper respiratory tract infection, influenza, depression, insomnia, or diarrhoea, the incidence of any specific AE (in all patients) was less than 10% of the patients over the 5-year period.

Eight percent of the included patients in the siponimod 2 mg group in the controlled pool **discontinued** the study due to an adverse event as compared to five percent in the placebo group. Reasons for discontinuations included 'Investigations' with 'ALT increased' as the most common reason, 'Eye disorders' primarily due to 'macular oedema', 'Cardiac disorders' primarily due to 'atrioventricular block second degree' and 'bradycardia' and 'Nervous system disorders' with 'dizziness' being the most common preferred term. Between 11% and 14% of the patients, who discontinued, gave "physician/patient/guardian decision" as the primary cause.

There were 18 patients who died in the studies or in the time after the studies. Eight deaths during the double-blind period was divided in with four **deaths** in the siponimod group and four deaths in the placebo group, hence favoring the siponimod group, which had twice the size of the placebo group. However, the narratives did not indicate that the deaths were related to treatment with siponimod.

Serious adverse events were reported for 16.8% of patients on siponimod 2 mg versus 12.2 % placebo patients. SAEs experienced by at least 0.5% of patients in either group were increased liver transaminase concentrations, basal cell carcinoma, depression, urinary tract infection, suicide attempt, gait disturbance, multiple sclerosis relapse, and paraparesis. The numbers of patients with likely treatment

related serious or other significant events appeared higher in the siponimod 10 mg, 2 mg and 0.5 mg groups compared with the 1.25 mg, 0.25 mg and placebo groups. However, the shorter treatment duration for the siponimod 1.25 mg, 0.25 mg and part of the placebo group should be taken into consideration. Discontinuations due to adverse events followed a similar pattern.

Safety topics of interest were associated with the biologic effect of siponimod (class effect) and are therefore followed up closely during the clinical study program; infections (including reactivation of chronic viral infections other than VZV) VZV reactivation, herpes zoster, thromboembolic events, seizures, macular edema, dermatological alterations, bronchoconstriction, malignancies, lymphopenia, hepatic disorders, increased rates of liver enzymes, hypertension, and bradyarrhythmia including conduction defects during treatment initiation.

Subjects in the siponimod group had an increased risk of special infections as compared to the subjects in the placebo group. There was in increased incidence of reactivations of herpes zoster, sinusitis, and fungal skin infections in the siponimod group. One of the cases of reactivation of herpes zoster led to meningitis in one patient, who recovered following a temporary interruption of siponimod. Furthermore, there was a case of 'viral encephalitis' for which the causative agent could not be clarified and one patient developed cryptococcal meningitis. Taken together, the immunosuppressive effects of siponimod may result in more special and/or serious infections. However, the SmPC adequately advices to ascertain if patients have previously been infected with or vaccinated against herpes zoster before initiation of treatment with siponimod. The SmPC also states that siponimod cannot be initiated in patients with ongoing severe infection. Finally, previous severe infections such as multifocal leucoencephalopathy or cryptococcal meningitis have been included as a contraindication.

Before initiating treatment with siponimod, a recent complete blood count should be available. Assessments of CBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. The treatment with siponimod expectedly led to lymphopenia and, to a smaller extend, reductions in leucocytes. If an absolute lymphocyte count < $0.2x10^9$/L is confirmed, treatment should be interrupted until recovery. This topic is addressed in section 4.4 of the SmPC.

Since a severe exacerbation of disease, including disease rebound, has been reported after discontinuation of fingolimod a warning on the risk of severe exacerbation of disease after stopping siponimod treatment has been added in the SmpC. This risk is also highlithed with regards to the advice to pause siponimod treatment one week before and four weeks after vaccination.

Malignancies were generally not detected at a higher rate in the siponimod groups as compared to the placebo group. Furthermore, the incidence of malignancies was not higher in the longterm safety pool as compared to in the controlled safety pool. Nevertheless, since siponimod decreases the level of circulating lymphocytes, the immune-surveillance may be compromised, which may theoretically increase the risk of new malignancies. To address this, the applicant has agreed to include new malignancies as an important potential risk in the RMP and a warning concerning skin malignancies in section 4.4 of the SmPC. Finally, siponimod treatment is contraindicated in patients with active malignancies.

Macular oedema is a well-known risk for this drug class. The risk of macular oedema is highest at the beginning of the treatment, although it also occurs at later stages of treatment. An ophthalmologic assessment is recommended in all patients at 3-4 months after treatment initiation. Most cases were non-serious and improved or resolved spontaneously after stopping siponimod therapy. However, recurrence of macular edema upon rechallenge with siponimod is likely. Patients with a history of uveitis or (not well controlled) diabetes mellitus have an increased risk of macular edema and require careful assessment before and during the initial months of therapy with siponimod; this is addressed in section 4.4 of the SmPC. Initiation of siponimod in patients with ongoing macular edema is containdicated. Of

note, peripheral edema also occurred with a higher frequency in the siponimod groups than in placebo groups (4.4% vs 2.3%).

The initiation of siponimod treatment led to a mean decrease in heart rate. The decrease was mainly observed during the first week of treatment and most pronounced in the first six hours post-dose, therefore a titration scheme to reach the maintenance dose on day 6 is therefore applied at the start of treatment (see SmPC section 4.2). The SmPC adequately contraindicates use of siponimod in patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischaemic attack, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure, as well as patients with second degree Mobitz type II AV block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker. Further, the SmPC adequately addresses the uncertainties of siponimod treatment in patients taking medications with strong influence on cardiac conduction or function and recommends that a cardiologist should be consulted before initiation of siponimod therapy. Finally, as there are no measures to distinguish between patients, who will and will not experience symptomatic bradycardia, patients should not drive or operate machines during the first day of treatment.

Small increases in blood pressure were noticeable during treatment with siponimod. However, the increase occurred mainly during the first year of treatment and stabilised thereafter.

The siponimod treated patients showed a decreased post-baseline lung function, as assessed by FEV1, FVC, and D_LCO, as compared to the placebo groups. There is not an established mechanism for this decrease in lung function but it has been clarified that a plateau is reached following approximately one year of treatment. These decreases are slightly higher in patients with known pulmonary disease.

Liver function was affected as assessed by increased levels of ALT/AST/GGT; In the controlled pool, most ALT level rises for the siponimod 2 mg group occurred within approximately 28 days of starting treatment. No patient met Hy's law criteria for hepatotoxicity and no patient developed liver failure. However, 0.5% discontinued due to affected liver function. Patients who develop symptoms suggestive of hepatic dysfunction during treatment should have liver enzymes checked regularly and siponimod should be discontinued if significant liver injury is confirmed. This is adequately addressed in the SmPC.

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver enzyme values when taking siponimod, patients with severe liver impairment (Child-Pugh class C) should not start treatment with siponimod. The mechanism by which siponimod may cause liver enzyme elevation is unknown. An unexplained finding was a greater incidence of liver transaminase elevation in males compared to females, a gender effect which has also been seen with fingolimod, another S1P receptor modulator.

Siponimod is mainly metabolised by polymorphic CYP2C9, and the genotype has a significant impact on siponimod metabolism. Therefore, all subjects were tested for the CYP2C9 genotype prior to study entry. Based on the expected risk of high chronic exposure those patients with CYP2C9*3*3 (poor metabolizer) polymorphism were not to be included in the study. In these affected patients the clearance of siponimod is significantly reduced with 4-fold increase in drug exposure. Consequently, long-term exposure is associated with safety concerns. The risk is considered important, as clinical data related to chronic higher exposure in subjects with reduced metabolic clearance are limited as well as interactions with co-administered drugs have the potential to affect the effectiveness or safety of siponimod (e.g. coadministration of siponimod with CY2C9/CYP3A4 inhibitors and CYP2C9/CYP3A4 inducers). Siponimod is therefore contraindicated in section 4.3 of the SmPC for CYP2C9 poor metabolizer patients.

There was a possible imbalance between siponimod and the placebo groups with respect to seizures. To address this, the applicant had confirmed that seizures will be monitored continuously through routine

pharmacovigilance and steps to further characterize the risk (frequency, nature, and severity of risk) in the post-approval setting will be taken.

Suicidal attempts/ideation/behavior were more common in the siponimod group (1.6%, n=18) as compared to the placebo group (0.7%, n=4). However, the applicant's position that currently available data does not provide conclusive evidence to establish a causal role of siponimod for suicidality was acknowledged. The applicant will continue to monitor the safety topic of suicidality for changes in frequency/severity of the risk by applying routine pharmacovigilance including data-mining technologies.

As siponimod is intended as a chronic treatment in SPMS patients, a largely (young and) female population, teratogenicity is a known risk. Due to its mode of action e.g. in vascular development, it can be assumed that siponimod might cause foetal harm when used in pregnant women. Therefore, an absolute contraindication in section 4.3 of the SmPC for the use of siponimod in pregnant women taking into account the experience with fingolimod after marketing authorization as well as with siponimod during clinical trials is included in section 4.3.

There is missing information with regard to the safety in elderly patients (over 60 years old). Elderly may be more sensitive to e.g. CNS effects of siponimod or tolerate the actual adverse reaction poorly as compared to younger subjects. This is clarified in the SmPC.

The safety and efficacy of siponimod in children and adolescents aged 0 to 18 years have not yet been established. No data are available. This is reflected in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

From the safety database all adverse reaction reported in clinical trials have been included in the SmPC. The main safety issues consist of decreased heart rate and in some cases bradyarrhythmias, macular oedemas, and increased risk of infections including reactivation of herpes zoster. Additionally, since the normal surveillance system conducted by lymphocytes likely is considerably reduced, there may be a long-term increased risk of new malignancies, as is described for the related compound, fingolimod. Appropriate measures, including additional pharmacovigilance activities and risk minimisation activities have been put in place to ensure safe and effective use of the product in the recommended indication.

2.7. Risk Management Plan

Safety concerns

Table Part II SVIII.1: Summary of safety concerns

Summary of 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 metabolizers • 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

Table Part III.3 On-going 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				
CBAF312A2304 (Extension Part) Status: Ongoing	The Extension Part will allow patients to continue treatment with open-label siponimod up to 7 years and aims to provide additional long-term safety data as well as additional information on efficacy measures.	• Varicella-zoster virus (VZV) Infection reactivation • Bradyarrhythmia (including conduction defects) during treatment initiation • Macular edema • Reactivation of chronic viral infections (other than VZV), progressive multifocal leukoencephalopathy (PML) and opportunistic infections, other than cryptococcal meningitis • Cryptococcal meningitis • Potential long-term safety implications in CYP2C9 poor metabolizers • Thromboembolic events • Malignancies • Unexpected neurological or psychiatric symptoms/signs (e.g; PRES, ADEM, Atypical MS Relapses) • Long-term safety risks	Annual update	Provide periodic safety update reports (PSUR) based upon commercial use in Europe and other geographic regions where siponimod is approved and provide developmental safety update reports (DSUR) from ongoing and recently completed clinical studies to permit a comprehensive benefit-risk assessment.
			Final report	23-Sep-2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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	Interim report	Each PSUR
			Final report	PSUR 2030
Survey among health care professionals	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 (siponimod) safety measures.	To measure the effectiveness of HCP educational material	Final report	31-Dec-2025

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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 includes 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.
	Additional risk minimization measures:
	Educational materials for HCPs and patients/care givers
	-HCP checklist
	-Patient/Caregiver Guide
		Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
		None
		Additional pharmacovigilance activities:
		CBAF312A2304 (EXPAND) Phase 3 study extension part.

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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: AE follow-up checklist for adverse reaction

	SmPC Section 4.4 includes 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. -HCP checklist - Patient/Caregiver Guide	Adjudication of OIs (including CM) cases. **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase 3 study extension part.
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 treatment with Siponimod is considered in these patients, it is recommended to seek	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None. **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase 3 study extension part.

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 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 material for HCPs and patients/care givers. -HCP checklist -Patient/Caregiver Guide	
Macular edema	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects). PL section 4 (possible side effects). PL Section 2 included 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 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. • Siponimod should be discontinued if a patient develops macular edema • Siponimod therapy should not be initiated in patients with macular oedema until resolution. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. -HCP checklist -Patient/Caregiver Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase 3 study extension part.
Potential long-term safety implications in CYP2C9 poor metabolizers	**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)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase 3 study extension part

	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 should not be treated with siponimod, use in these population 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. 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: - with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients regardless of genotype. - 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). **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. -HCP checklist -Patient/Caregiver Guide	
Reactivation of chronic viral infections (other than VZV), progressive multifocal leukoencephalopathy (PML), and opportunistic infections, other than cryptococcal meningitis	**Routine risk minimization measures:** PL Section 2 includes advice on monitoring symptoms of PML and CM instruction for 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up checklist for adverse reaction Adjudication of opportunistic infections (including PML) cases.

	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. Cases of progressive multifocal leukoencephalopathy (PML) have been reported with another sphingosine 1-phosphate receptor modulator, If a patient is suspected with PML, siponimod treatment should be suspended until PML have been excluded. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. -HCP checklist -Patient/Caregiver Guide.	**Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase 3 study extension part
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 - 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities**: CBAF312A2304 (EXPAND) Phase 3 study extension part.
Malignancies	**Routine risk minimization measures:** SmPC Section 4.3 includes following recommendation: - Siponimod treatment is contraindicated in patients with active malignancies. SmPC Section 4.4 includes the following recommendations - As skin malignancies, including melanoma, have also been reported in patients treated with siponimod and in patients on long	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

	term therapy with another S1P modulator, 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. **Additional risk minimization measures:** Educational material for HCPs and patients/care givers. -HCP checklist -Patient/Caregiver Guide.	CBAF312A2304 (EXPAND) Phase 3 study extension part.
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: - 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. -HCP checklist -Patient/Caregiver Guide - Pregnancy reminder card for women of childbearing potential (WOCBP)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No. **Additional pharmacovigilance activities**: PRegnancy outcomes Intensive Monitoring (PRIM)
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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up checklist for adverse reaction. **Additional pharmacovigilance activities**:

	Additional risk minimization measures: Educational material for HCPs and patients/care givers. -HCP checklist -Patient/Caregiver Guide.	CBAF312A2304 (EXPAND) Phase 3 study extension part.
Safety in patients over 60 years old (including elderly)	**Routine risk minimization measures:** SmPC Section 4.2 includes following recommendations: - Siponimod has not been studied in patients aged 65 years and above. Clinical studies included patients up to the age of 61 years. Siponimod should be used with caution in the elderly due to insufficient data on safety and efficacy. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Use during lactation	**Routine risk minimization measures:** SmPC Section 4.6 and PL section 2 included recommendation not to breast-feed while on siponimod treatment. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None.
Long-term safety risks	**Routine risk minimization measures:** None. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None. **Additional pharmacovigilance activities:** CBAF312A2304 (EXPAND) Phase 3 study extension part

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26.03.2019. The new EURD list entry will therefore

use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of siponimod with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers siponimod to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet does not yet meet the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* The applicant will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Mayzent (siponimod) is included in the additional monitoring list as it contains a new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

MS is a chronic, immune-mediated inflammatory condition that causes neuro-axonal injury in the CNS leading to permanent and severe neurological impairment and disability. Relapsing multiple sclerosis (RMS) describes the course of MS in patients with either RRMS or secondary progressive MS (SPMS), who continue to experience relapses. Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression.

More than 50% of patients with RRMS will within a median time of 15 to 20 years from onset, develop SPMS characterized by sustained disability with or without superimposed relapses.

The aim of the treatment is to suppress relapses and disease progression. Therapies for MS include treatment for relapses (e.g. corticosteroids), symptomatic treatments (e.g. fampridine) and those that alter the course of the disease (disease-modifying therapies (DMTs).

3.1.2. Available therapies and unmet medical need

DMTs aim to modify the course of the disease by suppressing or modulating the immune responses involved in MS pathogenesis. Currently 12 DMTs are available (country/regional differences exist) for the treatment of MS (interferon beta-1a and interferon beta-1b, peginterferon beta-1a, glatiramer acetate, fingolimod, natalizumab, teriflunomide, dimethyl fumarate, alemtuzumab, ocrelizumab, cladribine, and mitoxantrone). Most are approved for RRMS or relapsing forms of MS (RMS). Products for both RRMS and RMS were approved based on treatment effect on relapses, MRI lesion activity. Interferon beta (IFNß)-1b is approved in the EU for patients with SPMS with active disease as evidenced by relapses.

There is currently no therapy available that has been shown to alter the progression of disability independent of relapses in patients with SPMS. The two trials in SPMS that provided efficacy data for marketing authorization of IFNß-1b showed a consistent 30% reduction in frequency of relapses and an inconsistent result for the primary endpoint "time to confirmed progression".

3.1.3. Main clinical studies

The clinical development program consisted of one phase 2 study in RRMS and one phase 3 study in SPMS:

Study A2201, a multicenter, randomised, parallel-group, placebo-controlled, adaptive dose ranging Phase 2 study in 297 RRMS patients that aimed to demonstrate dose-dependent efficacy of siponimod on inflammatory disease activity and to determine the optimal dose for Phase 3 based on clinically relevant effects on MRI and relapses of the selected dose (2 mg once daily).

Study A2304, a multicenter, randomised, double-blind, parallel-group, placebo-controlled Phase 3 study of variable treatment duration that aimed to demonstrate the efficacy and safety of siponimod 2 mg once daily compared to placebo in 1651 patients with SPMS. The primary endpoint in this study was the 3m-CDP based on EDSS. Six-month CDP was included as a secondary endpoint but is the preferred endpoint according to the *Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis* (EMA/CHMP/771815/2011, Rev.2).

3.2. Favourable effects

In the single pivotal study A2304, 26.3 % (288/1096) and 31.7 % (173/545) in the siponimod and the placebo arm, respectively, experienced a 3m-CDP in EDSS. The HR (siponimod/placebo) was estimated at 0.79 with 95 % CI (0.65;0.95) (p=0.0134). The risk of 3m-CDP at a given time point was approximately 21% lower for patients in the siponimod group compared to the placebo group. Most patients did not progress during the trial (percentage of patients free of 3m-CDP events: year 1: 81.82 % and 75.32 %, year 2: 69.39 % and 65.03 % year 3: 64.17 % and 56.41 % for siponimod and placebo, respectively). The Kaplan-Meier survival curves for percentage of subjects with 3m-CDP showed separation from 6 months on with a lower proportion of patients in the siponimod group with 3m-CDP events throughout the treatment period.

A hierarchical statistical testing for the key secondary endpoints was applied. No effect of siponimod was demonstrated on the time to 3-month confirmed worsening of at least 20% from baseline in T25W, the first key secondary endpoint. As for the next key secondary endpoint in the hierarchy, the change from baseline in T2 lesion volume, there appeared to be a convincing treatment effect of siponimod, even if superiority could formally not be claimed (adjusted mean over months 12 and 24 183.9 mm^3 vs 879.2 mm^3; between group difference −695.3 mm^3, 95% CI −877.3 to −513.3; p<0.0001).

The results of the analysis of the secondary endpoint "6m-CDP" were consistent with the results of the primary analysis. Siponimod led to a difference over placebo showing a risk reduction of 26% (HR 0.74, 95% CI 0.60-0.92). The secondary endpoint annualized relapse rate (ARR) was reduced by 55.5% compared to placebo (ARR ratio 0.445, 95% CI 0.337–0.587). There was no significant difference between treatment groups for self-assessed walking ability using MSWS-12. Siponimod demonstrated a rate reduction of 86% (rate ratio 0.137, 95% CI (0.098;0.190)) in the number of Gd-enhancing lesions and a rate reduction of 81% (rate ratio 0.194, 95% CI (0.155;0.244)) in the number of new or enlarging T2 lesions over 24 months. Siponimod led to a lower rate in PBVC compared to placebo (adjusted mean PBVC over months 12 and 24, −0.50% vs. −0.65%; between-group difference 0.15%, 95% CI (0.07–0.23)). All MRI endpoints were secondary endpoints and secondary endpoints other than key secondary endpoints were not corrected to maintain a family-wise error at 0.05 and thus the probability of a false positive result in at least one of these endpoints is larger than 5%.

Analysis of exploratory composite scores based on disease-relevant endpoints such as e.g. T25W, 9-HPT, and PASAT did not indicate a treatment effect of siponimod. Overall, there were no significant differences in other exploratory results including patient-reported outcomes (quality of life) and other domain-specific disability scores including cognitive and visual endpoints. The difference of 2.303 letters at Month 24 (95% CI (1.105;3.501)) for the SDMT should be interpreted with caution, considering that this was an exploratory endpoint, therefore by study design not controlled for multiciplicym and studies that suggest that 4 symbols or 10% are the minimum clinically relevant difference for patients with MS (median baseline SDMT in the trial was 41).

Pre-specified subgroup analyses of the primary endpoint 3m-CDP indicate that the treatment effect of siponimod is more pronounced in the subgroup of patients experiencing relapses during the 2 years prior to study entry (risk reduction 33.3%, HR 0.67 [95% CI 0.49, 0.91]) as compared to patients without such relapses (risk reduction 12.8%, HR 0.87 [95% CI 0.68, 1.11]), in the subgroup of patients with ≥1 Gd-enhancing T1 lesion at baseline as compared to the subgroup without baseline enhancing lesions (risk reduction 36.5%, HR 0.64 [95% CI 0.42, 0.95] versus risk reduction 17.7%, HR 0.82 [95% CI 0.66, 1.02]), and in the subgroup defined as 'rapidly evolving subjects' as compared to those who were not rapidly evolving (risk reduction 34.9%, HR 0.65 [95% CI 0.46, 0.91] versus risk reduction 13.7%, HR 0.86 [95% CI 0.69, 1.09]). In a subgroup of patients (n=827) without signs and symptoms of disease activity (defined as patients without relapse in the 2 years prior to the study and without presence of Gd-enhancing T1 lesions at baseline), the risk reduction for 3m-CDP was 7%, HR 0.93 [95% CI 0.71;1.23] and for 6m-CDP it was 13%, HR 0.87 [95% CI 0.64;1.19].

Results for subgroup analysis on the 6m-CDP endpoint were overall consistent with those on the 3m-CDP endpoint.

Post-hoc exploratory principle stratum analysis assessing the treatment effect in 'true non-relapsing patients' (i.e. those who would not relapse under any treatment) in the context of the draft ICH E9(R1) addendum resulted in a relative risk for 3m-CDP between 0.80 and 0.86 (i.e. a risk reductions between 14 and 20%) at time points 12 months, 18 months, and 24 months. The results were similar for the analysis on the 6m-CDP endpoint and similar to the results of the overall population for the primary endpoint 3m-CDP and secondary endpoint 6m-CDP. Using the "re-baselining" definition of 3m-CDP (if the EDSS value did not return to baseline EDSS after a relapse, the increased EDSS value after relapse resolution was used to establish a new EDSS baseline value), a non-significant relative risk of 0.93 with 95% CI (0.78; 1.12) was found.

Post-hoc exploratory hypothetical strategy analysis assessed the treatment effect on disability progression independent of an effect on relapses in the overall population (i.e. under the assumption that no relapse would occur and that relapses would occur in an identical rate in both treatment groups) in the context of the draft ICH E9(R1) addendum.

As a result, the point estimates for the HR for 3m-CDP were at least 0.86 (i.e. at least a 14% risk reduction, 95% CI (0.70;1.04)) and for 6m-CDP they were 0.77 (i.e. a 23% risk reduction, 95% CI (0.62;0.96)).

3.3. Uncertainties and limitations about favourable effects

Eligibility criteria and study population:

Uncertainties were raised on the representativeness of the to-be included SPMS population, i.e. the number of patients that were included based on a written summary (comprising clinical evidence of disability progression and retrospective assessment of EDSS scores). Of note, 13 patients were identified to have been randomised without documented evidence of disability progression in the 2 years prior to enrolment (neither through EDSS scores in the medical history nor through central adjudication). A sensitivity analysis of the primary endpoint excluding these 13 patients (7 from the active treatment arm and 5 from the placebo arm) was, however, in line with the primary analysis.

According to the guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2), for demonstration of prevention of disability progression independent of relapses in SPMS, it is recommended to target only SPMS patients without a recent relapse and no MRI activity suggestive of active inflammation. In this study only patients with a relapse within 3 months prior to randomisation were specifically excluded. In fact, close to 50% of the patients had either at least a relapse in the 2 years prior to study inclusion or at least a Gd-enhancing lesion at baseline. A population mainly based on patients with few or no recent relapses would have been preferable.

Blinding: A potential unblinding issue in study A2304 was communicated by EMA after being made aware of by FDA in a parallel siponimod submission procedure in the US. Apart from blinding of treatment assignment, measures were taken to ensure blinding of EDSS raters to all other clinical information (e.g. ECGs taken during the titration phase). Evaluation of the primary endpoint was assessed and managed by EDSS raters in the completely separate NESC database not accessible by other study staff. Furthermore, two separate databases were set up for the dose initiation data and the main data to preserve the blind. Nevertheless, there were raters, nurses, and investigators with unintended access to databases with potentially unblinding information. In particular, the finding that some EDSS raters and also staff from the main clinical database had access to other clinical information was of considerable concern. The applicant subsequently performed the primary endpoint analysis (3m-CDP) including only patients who could have potentially been compromised by unblinding (n=213) which resulted in a larger apparent effect size (HR ~ 0.4) as compared to the overall HR (~ 0.8). Correspondingly, the exclusion of patients affected by potential unblinding changed the treatment effect from 21.2 % (N= 1,614; HR 0.79 (0.65; 0.95)) to 15 % (N= 1,432; HR 0.85 (0.69; 1.05)).

For those patients with active disease (N= 778), defined as having had a relapse in the 2 years prior to study or focal lesion on MRI at baseline, exclusion of N=120 patients potentially affected by unblinding from the primary analysis changed the treatment effect from 31 % (N= 778; HR= 0.69 (0.53; 0.91)) to 19 % (N= 658; HR= 0.81 (0.59; 1.10)).

Upon request, the applicant identified factors that could have influenced or contributed to this imbalance in the 3m-CDP endpoints including differences in baseline characteristics (more inflammation and lower EDSS scores in this subpopulation as compared to the full population), a larger relapse rate in the potentially unblinded subgroup compared to the overall population (considering the mechanism of action this subpopulation could have experienced a greater reduction in 3m-CDP) and change in the statistical model dependence ('country' deleted as covariate). Of note, the overall HR for the 6m-CDP based on EDSS in the overall population (HR 0.74) was less different from the HR after exclusion of potentially

unblinded population (HR 0.77). For those with active disease, analysis for the 6m-CDP resulted in a HR of 0.68 [95% CI 0.48, 0.96]).

The HR for the 3m-CDP based on EDSS excluding 65 patients for whom specifically EDSS data could have been compromised, considered the main source of unblinding in this study, was 0.80 (95%CI (0.66-0.97)).

In analogy, taking into account the patient population with active diease as outlined in the proposed indication, excluding N=38 patients (out of n=778) for whom specifically EDSS data could have been compromised, resulted in a HR of 0.72 (N=740, 95% CI (0.54;0.95), risk reduction 28%, p-value 0.0222) for 3m-CDP and in a HR of 0.64 (n=740, 95% CI (0.47;0.88), risk reduction 35.8%, p-value 0.0056) for 6m-CDP.

Beyond the interpretation of the statistical significance, there was a significant difference in the change of T2 lesions volume that should have not been affected by the potential unblinding as it was quantified in a centralized reading center. Regarding the additional analyses suggesting that potential unblinding did not influence treatment decisions and ratings, the MAH provided data suggesting no association between EDSS outcomes and of heart rate changes and switching to open label rescue therapy. Although the CHMP agreed that none of them alone or in combination could completely explain this imbalance, the additional analyses and arguments underline that it is rather unlikely that the subgroup results of the patients potentially affected are solely due to a systematic bias due to unblinding.

Dose-response relationship: The dose-response relationship was elucidated in a different patient population (RRMS) using endpoints indicative of acute focal inflammatory activity and mainly with respect to MRI rather than clinical endpoints. It remains thus unknown whether the 2 mg dose is the optimal dose for the SPMS population, although with the 10 mg dose evaluated in study A2201, the incidence of adverse events was higher as compared to the 2 mg dose. Although, the RRMS study does provide information as to which doses may affect disease activity as indicated by MRI measures, it does not necessarily predict effect on disease progression in SPMS.

Participant flow: treatment discontinuations and missing data

The rate of treatment discontinuations in the pivotal study was high, but not unexpected. It is questionable if the applicant correctly describes the target of estimation as "treatment policy" strategy, considering rules for treatment switches in this study and the unclear amount of data collected after treatment discontinuation. The applicant has subsequently presented information regarding the follow-up time for different groups of patients. There were patients who did not experience a 3m-CDP but had relapses, and there were patients who suffered from relapses before the 3m-CDP. For those lost to follow-up, there were some who experienced relapses with or without onset of progression.

In a rather high proportion of subjects, the main reason for study drug discontinuation was "disease progression" and "lack of efficacy", which summed up to 12.4% of subjects on siponimod and 19.7% of subjects on placebo. Furthermore, discontinuation due to subject/guardian decision was reported as reason in 10.3% and 13%, respectively. It could not be traced back by the applicant whether subject/guardian decision was also driven by reasons in line with progressing disease. However, since the percentage of patients was higher in the placebo group, this is not of concern.

Primary endpoint: the relevance of the clinical treatment effect has been questioned in the course of this procedure: the risk of 3m-CDP at a given point in time was approximately 21% (5-35%) lower for patients in the siponimod group compared to the placebo group, and the absolute difference in event rates between the siponimod and the placebo arm at the end of the study was rather modest with 5 percentage points. A clinically relevant treatment effect can best be translated into a prolongation in time to disease progression with siponimod treatment: The Kaplan-Meier percentiles show that the longer-term benefit of siponimod over placebo could be equated with an improvement of about 25-30%

in time to 3- month CDP and of more than 50% increase in time to 6m-CDP. In other words, an additional 7 or 12 months progression free for 3 and 6m-CDP respectively, could be expected over a 2 year treatment period.

According to the guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2), the occurrence of relapses needs to be assessed during the study and taken into account when determining confirmed progression of disability. The applicant performed pre-planned subgroup analyses in patients with and without relapses during the last two years before study entry. The applicant also performed analysis to investigate the difference in time to progression accounting for lack of recovery of relapses ("re- baselining"). Subgroup analyses using baseline features (unconfounded) supported that the effect of siponimod on disability worsening is mainly driven by the effect on focal inflammatory activity. Using the "re-baselining" definition of 3-month confirmed disability progression, a non-significant relative risk of 0.93 with 95% CI (0.78; 1.12) was found. In order to theoretically estimate the treatment effect for patients who will never relapse regardless of treatment the applicant presented a principal stratum analysis and implemented a hypothetical estimand where the effect of siponimod is estimated in a situation where relapses had not occurred. The results of the HR and relative risk varies around 0.82-0.87 with wider CI including 1 for the primary endpoint 3m-CDP. All these analyses are based on quite strong and untestable assumptions and therefore the results should be interpreted cautiously. To summarise, the results of the analyses performed to estimate the effect of siponimod independent of relapses are clustered around a 0.8 – 0.9 with confidence intervals including 1, indicating a numerically small difference between placebo and siponimod in 3m-CDP for this group of patients.

(Key) Secondary endpoints:

The first key secondary endpoint 'time to 3-months confirmed worsening of at least 20% from baseline in T25W', which assesses walking speed, failed to show statistical significance of siponimod over placebo. Likewise, the effect of siponimod on the MSWS-12, a patient-reported outcome measure of walking ability, did not reach nominal statistical significance. High variability was observed in patients with higher EDSS and in need of a walking aid which may have contributed to these results.

While there was an overall robust effect on 6m-CDP based on EDSS (the preferred disability progression endpoint in the MS guideline), results on a composite endpoint for 3m-CDP (i.e., disability progression events based on EDSS, T25W, or 9-HPT scores, with time to progression defined as the time to the first of any of the 3 events), revealed a non-significant risk reduction weakening the effect robustness across the different disability progression endpoints in this study.

The treatment effect in a subgroup analysis of subjects previously treated with or without interferon beta-1b was consistent with the results in the overall population although it slightly disfavoured siponimod in patients with prior IFN beta-1b treatment, akin to the result of a post-hoc analysis that included subjects pre-treated with any IFN beta. It is unclear whether this is a chance finding. The subgroup analysis on patients previously treated with MS-DMTs was, however, more homogeneous.

3.4. Unfavourable effects

Treatment with siponimod led to brady-arrhythmias, especially during the first weeks of treatment initiation. In approximately one percent of the patients, the brady-arrythmias consisted of AV-block of first or second degree (only Mobitz type I) or other less specified types of escape rhythm. In a minority of the patients, clinical symptoms occurred in relation to the brady-arrhythmias, e.g. dizziness and chest-pain.

Macular oedema was observed in 1.7% of the siponimod treated patients as compared to only 0.2% in the placebo patients. The highest incidence of macular oedemas was observed during the first four months of treatment.

There was an increased risk of infections during treatment with siponimod consisting mainly of reactivation of herpes zoster infections, fungal skin infections, and sinusitis (sinusitis is also labelled for the related medicinal product, fingolimod). Further, a case of cryptococcal meningitis was confirmed.

Transaminase elevations and increases of GGT were listed for 7-8 % of the siponimod treated patients, approx. 1% of the population had to discontinue treatment with siponimod due to liver-related adverse events.

There were four cases of malignant melanoma in the siponimod group as compared to none in the placebo group. (An increased risk of skin malignancies is labelled for the related medicinal product, Fingolimod).

There was a small but consistent increase of 2-5 mmHg in systolic and diastolic blood pressure. Further, small reductions in lung function tests are expected over time. However, the reductions were slightly larger in the siponimod group than in the placebo group, e.g. -100 ml FEV1 per 3-6 months in the siponimod as compared to the placebo group. In patients with pre-existing pulmonary disease, the reductions in lung function were approx. two-fold the size of the reductions in patients without pre-existing pulmonary disease.

3.5. Uncertainties and limitations about unfavourable effects

There appears to be a risk of disease progression following discontinuation of treatment. Data are limited for patients discontinuing siponimod but this risk is also labelled for the related medicine, fingolimod.

The clinical consequences of combining siponimod with other medicinal products, which influence heart frequency and cardiac conduction, is unknown, since such patients have been excluded from the clinical trials. Similarly, the use of siponimod in supposedly sensitive patients, e.g. patients with existing cardiovascular disease, is unknown, since such patients have been excluded from the clinical trials.

Elderly and patients with hepatic or renal impairment may need dose-reduction and/or have a different safety profile than other patient groups due to reduced clearance or increased susceptibility (elderly) to the adverse events. Siponimod has not been properly tested in older patients or in patients with hepatic or renal impairment.

There were generally no increase in new malignancies in patients of the siponimod group compared to patients in the placebo group. However, as the immune surveillance may be compromised, new malignancies could be a long-term risk for patients treated with siponimod.

Suicidal ideation/behaviour was somewhat higher in patients treated with siponimod as compared placebo (1.6 vs. 0.7%), although most cases were confounded by relevant medical history of depression or anxiety.

3.6. Effects Table

Table 43: Effects Table for Mayzent (siponimod) 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 (data cut-off for MAA submission: 31-Dec-17).

Effect	Short Description	Unit	Siponimod	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
3m-CDP	Pts event free at 12 months (KM estimate)	%	81.82	75.32	Hazard ratio = 0.79, 95% CI (0.65;0.95) p = 0.0134	(1)
	Pts event free at 24 months (KM estimate)	%	69.39	65.03		
6m-CDP	Pts event free at 12 months (KM estimate)	%	85.51	78.30	Hazard ratio = 0.74, 95% CI (0.60;0.92) p = 0.0058	(1)
	Pts event free at 24 months (KM estimate)	%	76.41	71.48		
3m-CDP	Time to 3m-CDP based on EDSS in patients **with active disease**	No. of events/ No. of subjects included in analysis	128/515	91/263	Comparison siponimod:placebo Risk reduction 30.7%, Hazard ratio 0.69, 95% CI (0.53;0.91) p = 0.0094	(1)[a]
6m-CDP	Time to 6m-CDP based on EDSS in patients **with active disease**	No. of events/ No. of subjects included in analysis	98/515	74/263	Comparison siponimod:placebo Risk reduction 36.5%, Hazard ratio 0.63, 95% CI (0.47;0.86) p = 0.0040	(1)[a]
ARR	Adjusted ARR Neg. bin.		0.071	0.160	Rate ratio = 0.445 95% CI (0.337;0.587) p < 0.0001	(1) (2)
ARR	Adjusted ARR Neg. bin		0.093	0.171	Rate ratio = 0.544 95% CI (0.387;0.766) p = 0.0005	(1)[a]
T2 lesion volume	Adjusted mean change from baseline (av. M12 M24)	mm^3	183.9	879.2	Diff. = -695.3 95% CI (-877.3;-513.3) p < 0.0001	(1) (3)
T2 lesion volume	Adjusted mean change from baseline (av. M12 M24)	mm^3	53.4	1216.7	Diff. = -1163.3 95% CI (-1483.9;-842.78) p < 0.0001	(1)[a]

Effect	Short Description	Unit	Siponimod	Placebo	Uncertainties/ Strength of evidence	References
Gd-enhancing T1 weighted lesions	Cumulative number of Gd-enhancing T1 lesions per scan up to and including Month 24		0.169	1.088	Rate reduction 84.5% Rate ratio = 0.155 95% CI (0.104;0.231) p = 0.0001	(1)[a]
Brain volume change (PBVC)	Percentage brain volume change (PBVC) relative to baseline/ average over Month 12 and 24, adjusted mean	%	-0.623	-0.764	Difference 0.141 95% CI (0.020;0.261), p = 0.0221	(1)[a]
Cognitive processing speed	Adjusted mean change from baseline in SDMT (av. all visits)		0.705	-0.679	Diff. =1.384 95% CI (0.584;2.183) P = 0.0007	(1) (3)
						(2)
PRO	Adjusted mean change from baseline in MSWS-12 (av. all visits)		2.69	4.46	Diff. = -1.77 95% CI (-3.59;0.05) p = 0.0571	
	Adjusted mean change from baseline in MSIS-29 physical impact scale (av. All visits)		2.29	4.38	Diff. = -2.09 95% CI (-3.89;-0.29) p=0.0231	(1) (3)
Unfavourable Effects						
Infections	Infection or infestations (SOC)	%pt	48.9	49.8	Risk diff. = -0.9 95%CI [-5.8 ; 4.0]	(4)
	Herpes Zoster	%pt	2.4	0.7	Risk diff. = 1.8 95%CI [0.7 ; 2.9]	(4) (7)
Hypertension	Hypertension (SMQ Narrow)	%pt	12.2	8.7	Risk diff. = 3.5 95%CI [0.5 ; 6.4]	(4)
Liver function test elevated	Liver transaminase elevations (ALT or AST elevation above 3xULN)	%pt	5.5	1.5	Risk diff. = 4.0 95%CI [2.4 ; 5.6] No cases of Hy's law	(5)
Brady-arrhythmia		%pt	1.9	0.5	Risk diff. = 1.4 95%CI [0.5 ; 2.4] Reported during treatment initiation or treatment re-start (dose titration periods)	(4) (6)

Effect	Short Description	Unit	Siponimod	Placebo	Uncertainties/ Strength of evidence	References
Malignancies	Malignant tumours (SMQ Broad) {Skin malignancies}	%pt	1.8 {1.3}	2.3 {1.3}	Risk diff. = -0.5 95%CI [-1.9 ; 0.9]	(4) (8)
Macular oedema	Macular oedema, Cystoid macular oedema (PT)	%pt	1.7	0.2	Risk diff. = 1.6 95%CI [0.8 ; 2.4]	(4)
Seizure	Convulsion (SMQ) – Broad	%pt	1.7	0.5	Risk diff. = 1.2 95%CI [0.2 ; 2.1]	(4)

Abbreviations:
3mCDP: 3month confirmed disability progression; 6mCDP: 6month confirmed disability progression; KM: Kaplan-Meier; av.: average; ARR: annualized relapse rate; Neg. bin.: Negative binomial model; SDMT: Symbol Digit Modalities Test; PRO: Patient Reported Outcome; MSWS-12: Multiple Sclerosis Walking Scale; MSIS-29: Multiple Sclerosis Impact Scale.
SOC: system organ class; SMQ: systematic MedDRA query; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; PT: preferred term.

Notes:
(1) Data from Study A2304 – overall population
(1[a]) Data from Study A2304 – patients with active disease
(2) ARR results reported by group are estimates obtained from negative binomial model
(3) Adjusted mean change from baseline results reported by group are estimates obtained from MMRM (Mixed Model for Repeated Measures) model
(4) Data from the Controlled Pool consisting of the placebo controlled studies A2201 and A2304 (SCS Figure 1-1.1)
(5) Data from the Controlled Pool consisting of the placebo controlled studies A2201 and A2304 (SCS Table 3.4-1.1)
(6) Bradyrrhythmia is defined as: presence of hourly average below 40 as measured by Holter or MCT (mobile cardiac telemetry) during the titration phase (day 1 to day 6) or presence of one of the following during the titration phase (day 1 to day 6): 2:1 AV Block; AV Mobitz II; 3rd Degree AV Block; Advanced/ High Grade AV Block; Pause >= 3 sec.
(7) Herpes zoster is defined based on a selection of preferred terms including Herpes Zoster, Genital Herpes, Herpes zoster oticus, Ophthalmic herpes zoster, Post herpetic neuralgia.
(8) Skin malignancies is defined based on a selection of preferred terms including Basal cell carcinoma, Bowen's disease, Keratoacanthoma, Lentigo maligna, Lip squamous cell carcinoma, Malignant melanoma, Malignant melanoma in situ, Skin cancer, Squamous cell carcinoma.

From the 15 reported pregnancies in the siponimod MS clinical program, no maternal complications or infant malformations were observed. Pre-clinical reproductive and developmental studies in the rat and rabbit showed siponimod induced embryotoxicity and fetotoxicity in both species and teratogenicity in rats.

In study A2304, the first key secondary endpoint (time to 3 month confirmed worsening of at least 20% from baseline in T25W) did not reach statistical significance; additional endpoints were evaluated at nominal statistical significance level of 0.05 without correction of multiplicity or hierarchical testing. Nominal p-values for the other secondary endpoints contribute to the understanding of the totality of the evidence of the treatment effect of siponimod in SPMS.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Siponimod is a selective modulator of G-protein coupled sphingosine-1-phosphate (S1P1) and S1P5 receptors, leading to internalization and degradation of S1P1 receptors on T and B-lymphocytes, which prevents their egress and recirculation from secondary lymphatic tissue to target organs including the CNS.

The application is based on a single albeit large pivotal study (A2304). 78% of patients were recruited from the EU and thus the results are relevant for the EU-population. Close to 50% of patients did experience relapses in the 2 years prior to study or showed MRI activity at baseline and no patients older than 61 or with EDSS >6.5 were included in the study. Thus, the study population is representative of an "early stage" "active" SPMS population.

In patients with SPMS with inflammatory activity (n=778), defined as those with pre-study relapses or MRI activity at baseline, the risk reduction for the primary endpoint '3m-CDP' was 31% with siponimod compared to placebo, in line with the 37% risk reduction in 6m-CDP, although this secondary endpoint was not corrected for multiplicity. In patients without pre-study relapses and without MRI activity at baseline (N=827), the risk reduction for 3m-CDP was 7%, and for 6m-CDP it was 13%. Siponimod therefore showed clinically relevant effects on disease progression in patients with "active SPMS", whereas the effect in patients with SPMS and without signs or symptoms of active disease (n=827) was small.

Siponimod treatment was associated with a reduction of 55% in ARR, 86% in the number of Gd-enhancing lesions and a reduction of 81% in the number of new or enlarging T2 lesions over the trial in the overall population. These results on relapses and MRI lesions together with results from subgroup analyses and the mechanism of action suggested a relevant effect on focal inflammatory activity in SMPS. On the other hand, no effect of siponimod was demonstrated on the time to 3-month confirmed worsening of at least 20% from baseline in T25W and self-assessed MSW-12. Lack of statistical significance in outcomes related with walking ability could be at least partially explained by the baseline disability status of the included population (median EDSS=6) and higher variability of T25W results in the group with the greatest disability status. Similarly, results from exploratory cognitive, visual and patient-reported outcomes did not overall demonstrate a difference between siponimod and placebo arms.

Considering the study population included in study A2304, the clearly anti-inflammatory activity of siponimod and the results on disability progression in SPMS patients with and without signs and symptoms of active disease, the restriction of the indication to patients with "active SPMS" is considered justified.

Unintentional potential unblinding was detected during a GCP-inspection and considered a serious concern, esp. since the potentially unblinded subgroup of patients showed better results for the primary endpoint than the subgroup that could not have been unblinded. However, a bias due to unblinding was found rather implausible, based on the presented acceptable argumentation of the applicant and various (sensitivity) analyses that excluded potentially unblinded patients and supported the absence of a bias due to systematic unblinding. Statistical analyses with exclusion of n=213 patients from the overall study population (n=120 of the active subpopulation) were presented by the applicant as the most conservative approach of dealing with the uncertainty of potential unblinding in the trial, even though there was no indication that any indirect influence of study staff other than EDSS raters could have influenced the assessment of the primary endpoint, i.e. the EDSS ratings. The additional sensitivity analyses suggest that the better treatment effect in the potentially unblinded subgroup of n= 213 patients (overall population) (in analogy with the N=120 patients excluded from the active disease population) is rather caused by a number of baseline and disease factors that were found in these subjects owing to a relatively small subgroup which was not randomly chosen.

In the worst-case scenario with exclusion of n=213 patients, the results of the 3m-CDP endpoint lost statistical significance in the remaining n=1432 patients that could not have been affected by unblinding. However, the results for the 6m-CDP, although not the primary but the clinically more relevant efficacy endpoint, were in the same direction. Another analysis excluding only those patients (n= 65) rated by EDSS raters with temporary access to potentially unblinding information showed a risk reduction for siponimod relative to placebo of 20.0% (p =0.0236), which is in line with the risk reduction of the primary analysis in the overall study population. The same analysis in the active SPMS subjects excluding N=38 patients rated by EDSS raters with temporary access to potentially unblinding information showed a risk reduction for siponimod relative to placebo of 28% (p =0.0222). This analysis is considered the most relevant given that the so excluded patients had –if at all- a realistic risk of being potentially unblinded.

Regarding safety data, treatment with siponimod led to brady-arrhythmias, especially during the first weeks of treatment initiation. Macular oedema, another well-known class effect AE, was observed in 1.7% of the siponimod treated patients as compared to only 0.2% in the placebo patients. Other relevant AE were increased liver enzymes, SBP and DBP. An increased risk of infections during treatment with siponimod consisting mainly of reactivation of virus and fungus infection was observed. In line with evidence from other S1SP1 modulator, there were six cases of malignant melanoma in the siponimod group as compared to none in the placebo group.

Overall, the safety profile is similar to fingolimod and is considered acceptable. Patients with hepatic or renal impairment and those aged greater than 61 years were not formally included in the trial and thus safety information is missing in these subgroups. Further information on older patients are particularly relevant as subgroup analyses suggested a lower effect of siponimod in this population (likely due to advanced disease) and some of the risks could be expected to be either increased in frequency or in clinical relevance due to immune senescence (infection, malignancies) or comorbidities and polytherapy (SDB, BPD, hepatic AE).

3.7.2. Balance of benefits and risks

In SPMS, preventing or delaying the accumulation of disability is considered the most clinically relevant treatment goal. In the SPMS phase, accumulation of disability may be explained by the conjunction of pathological mechanisms including focal inflammatory activity (particularly relevant in SPMS with relapses and acute inflammatory lesions) and failure of biological compensation of the CNS damage (impaired remyelination and lack of biological redundancy).

In the opinion of CHMP and in agreement with SAG experts, the patients included in the pivotal study A2304 represent only partly the full spectrum of SPMS patients. As overall baseline characteristics and on-trial frequency of relapses indicate, the recruited population is representative of the "early" phase of SPMS where focal inflammatory activity as relevant pathogenic mechanism is still prominent.

In the overall study population, the risk of 3m-CDP at a given point in time was approximately 21% (5-35%) lower for patients in the siponimod group compared to the placebo group. However, results from subgroup analyses suggested that effect of siponimod on the rate of 3m-CDP was mainly driven by the effect on younger patients with shorter disease duration and particularly for those presenting with markers of focal inflammatory activity at entry. This is further corroborated by the finding that in the subgroup of patients without signs and symptoms of disease activity effects on 3m-CDP and 6m-CDP were small (risk reductions were 7% and 13%, respectively).

The patterns of changes in T2 lesion volume and relapse-based outcome were in line with these data. The mechanism of action of siponimod as a S1P1 modulator supports a role as immunomodulator for focal inflammatory activity in SPMS. In fact, the safety profile of siponimod is largely in line with that of fingolimod and considered acceptable. In line with SAG, the CHMP does not agree with the position of the applicant that siponimod, as an agent crossing BBB, has shown to have an additional role on neuroinflammation (microglia) and remyelination as this position is not sustained by convincing experimental or clinical data.

All above considered, the CHMP considered that an effect of siponimod independent of focal inflammatory activity was not robustly demonstrated and therefore, concluded that a positive benefit risk could only be recommended for the SPMS population with inflammatory activity. Overall, the SAG experts considered that this phenotype could be identifiable by MS treating specialist with close clinical monitoring and use of periodic standardized MRI scan. In fact, and according to the SAG experts, this population of active SPMS is usually treated off-label with a DMT authorized for RRMS or with anti-inflammatory/ immunosuppressant drugs not authorized for MS (regional variability mostly due to

reimbursements and availability factors).

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Mayzent is positive for the treatment of adult patients with SPMS with active disease, subject to the conditions listed in section '4 Recommendation'.

Divergent positions are appended to this report.

4. Recommendations

Outcome

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

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 (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to launch of Mayzent in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each Member State (MS) where Mayzent is marketed, all physicians who intend to prescribe Mayzent are provided with an updated Physician Education Pack, including:

- Summary of Product Characteristics;
- Physician's Checklist to consider prior to prescribing Mayzent;
- Patient/Caregiver Guide to be provided to all patients;
- Pregnancy Reminder Card for women of childbearing potential.

Physician's Checklist:

The Physician's Checklist shall contain the following key messages:

- <u>Potential long-term safety implications in CYP2C9 poor metabolisers:</u>
  - 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.

- <u>Bradyarrhythmia (including conduction defects) during treatment initiation:</u>
  - 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:
        a. New onset third-degree AV block occurring at any time
        b. 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.
- <u>Mayzent is contraindicated in</u>:
    - 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.
- <u>Mayzent is not recommended in</u>:
    - 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

- <u>Infections, including varicella zoster reactivation, reactivation of the other viral infections, PML and other rare opportunistic infections:</u>
    - 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 periodically during treatment.
    - 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:
    - A case of cryptococcal meningitis (CM) has been reported for siponimod. Prompt diagnostic evaluation should be performed in patients with symptoms and signs consistent with cryptococcal meningitis; appropriate treatment, if diagnosed, should be initiated. Siponimod treatment should be suspended until CM has been excluded.
    - Cases of progressive multifocal leukoencephalopathy (PML) have been reported with another sphingosine 1-phosphate (S1P) receptor modulator. 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.

- 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.
    - 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. 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. 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:

The Patient/Caregiver Guide shall contain the following key messages:

- 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.
- The signs and symptoms of infection during, and up to one month after treatment with siponimod need to be reported immediately to the prescriber.
- 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 while on treatment with siponimod and should be cautioned against exposure to sunlight without protection. Also, these patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy.
- 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:

The pregnancy-specific patient reminder card shall contain the following key messages:

- 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.
- 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.

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

Not applicable.

New Active Substance Status

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

Appendix

1. Divergent positions to the majority recommendation.

APPENDIX 1

DIVERGENT POSITION DATED 14 NOVEMBER 2019

DIVERGENT POSITION DATED 14 NOVEMBER 2019

Mayzent EMEA/H/C/004712

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation for Mayzent 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 (see section 5.1)."

The reasons for divergent opinion were the following:

In the setting of a single pivotal study, efficacy in the proposed indication has not been convincingly demonstrated.

The internal validity of the single pivotal study is compromised due to potential unblinding of study personnel. Analyses of results in potentially unblinded and not unblinded patients strongly suggests that unintentional unblinding impacted the primary efficacy results to a degree making the effect size estimated when including all patients unreliable. In the subgroup of potentially unblinded patients, there was a disproportionally large treatment effect estimated and exclusion of these patients from the overall study population led to a decrease in apparent effect size for the remaining patients not affected by potential unblinding. Once the totality of patients with active SPMS who may be potentially unblinded are excluded (120 out of 658), the primary endpoint (3-month confirmed disease progression) does not reach statistical significance (HR 0.81; 95% CI: 059, 1.10). While the 6-month CDP is statistically significant (HR 0.68; 95% CI: 0.48, 0.96), it is not corrected for multiplicity.

In order to support a claim for an effect on disability progression in SPMS, the current EMA guideline on multiple sclerosis, recommends targeting "SPMS patients without a recent relapse and no MRI activity suggestive of active inflammation and with evidence of recent progression independently of relapses. This is needed to exclude possible effects of relapse activity on disability." Nonetheless, the applicant has included a substantial proportion of patients with active disease (evidenced by relapses or imaging features of inflammatory activity) and the proposed indication specifically includes only these patients. Furthermore, on-study relapses occurred, and it was not possible reliably to assess effects of siponimod on disease progression independent of relapses in SPMS in terms of both clinical relevance and statistical significance. Thus, results are not considered compelling in terms of demonstrating clinical relevant effect on disability progression independent on an effect on relapses.

In view of the above considerations the undersigned delegates consider the benefit risk of this product to be negative.

Sinan B. Sarac

Alexandre Moreau

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